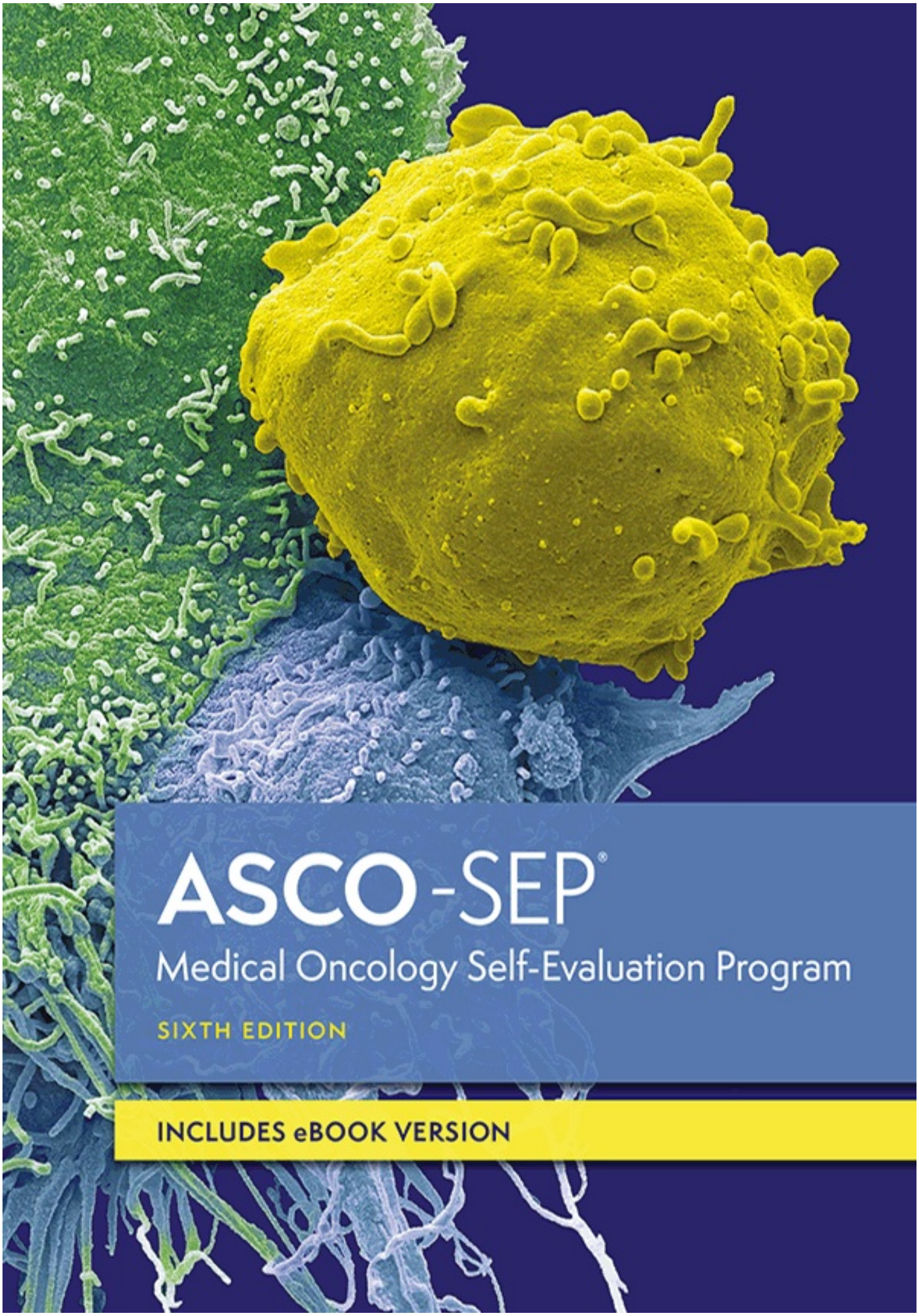
ASCO-SEP®
Medical Oncology Self-Evaluation Program
SIXTH EDITION
INCLUDES eBOOK VERSION

ASCO-SEP®

MEDICAL ONCOLOGY SELF-EVALUATION PROGRAM

SIXTH EDITION

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Cover photograph, credit to STEVE GSCHMEISSNER/SCIENCE PHOTO LIBRARY, used with permission, is of cancer cells and monocyte. Colored scanning electron micrograph (SEM) of the interaction between a monocyte and prostate cancer cells. Monocytes activated by cytokines (cell signaling proteins) or other agents are cytotoxic for cancer cells. Magnification: x 2500 when printed at 10 centimeters wide.

LETTER FROM THE EDITOR

Dear Colleague:

On behalf of ASCO, I am pleased to present the 6th edition of *ASCO-SEP®: Medical Oncology Self-Evaluation Program*. This self-evaluation resource was designed to assist you in staying current in medical oncology, to provide test questions for assessing your knowledge, and to assist you in your care of patients with cancer. In addition, through your use of *ASCO-SEP®* you may earn credit for the maintenance of certification (MOC) process. The response to the opportunity to receive MOC points for reading *ASCO-SEP®* and completing the chapter-related multiple-choice questions has been tremendous. We will continue to provide the opportunity to receive MOC points for your work with *ASCO-SEP® 6th Edition.*

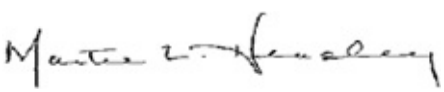
ASCO-SEP® is a comprehensive learning tool that includes 22 chapters focused on specific disease sites and oncology topics, as well as more than 180 multiple-choice questions that can be used for self-study. The "Key Points" in each chapter section facilitate review of important facts and concepts. *ASCO-SEP® 6th Edition* continues to feature vital updates at the beginning of each chapter, highlighting new data that have significantly informed practice and/or our understanding of cancer.

For this 6th edition, all of the self-assessment questions are new, providing learners with unique opportunities for review. Also available is the *ASCO-SEP® 6th Edition* Mock Examination, which can be accessed at ASCO University (university.asco.org/SEP). This convenient online study tool provides yet another resource for self-evaluation. All questions in the Mock Examination are new and do not include any test items from the book.

This *ASCO-SEP® 6th Edition* would not have been possible without the efforts of three outstanding Associate Editors who dedicated substantial time and commitment to ensure the high quality of the content: Matthew I. Milowsky, MD, Scott M. Schuetze, MD, PhD, and S. Vincent Rajkumar, MD. The success of this publication has relied on the time and talents of many contributors, including chapter authors and peer reviewers who graciously shared their time and expertise. I am also grateful for the tireless and expert support of the ASCO staff.

Thank you for participating in this worthwhile continuing medical education program. If you have comments or suggestions regarding *ASCO-SEP®*, please email ascou@asco.org.

Sincerely,



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CONTINUING EDUCATION AND MAINTENANCE OF CERTIFICATION

PROGRAM OVERVIEW

The *ASCO Self-Evaluation Program*® (*ASCO-SEP*®) is a comprehensive resource designed to help physicians assess their level of knowledge in the various areas of oncology and provide a current understanding of cancer, its treatment, and the supportive care needed to optimize the quality of life for people with cancer. This program includes 22 chapters and a companion self-assessment tool with rationales covering the full range of topics in oncology, including major cancer types, epidemiology and cancer prevention, management strategies for elderly patients, clinical trial design and statistics, molecular biology, and an overview of biologic therapy.

TARGET AUDIENCE

ASCO-SEP® is targeted to fellows, practicing oncologists, and advanced practitioners. *ASCO-SEP*® is also appropriate for use as a self-assessment tool for individual professional development, or as a teaching tool for training and continuing education purposes.

NEEDS STATEMENT

Although cancer mortality rates decreased 26% in the United States between 1991 and 2015, cancer still remains the second leading cause of death and is expected to become the leading cause in the next few years.[1] Globally, cancer is seen as an increasing burden, with 14.1 million cases diagnosed and 8.2 million cancer deaths around the world in 2012, and an estimated 32.6 million people surviving five or more years post-diagnosis.[2] To meet this challenge, the options available in medical oncology to treat patients with cancer continue to grow in both breadth and complexity. Since the launch of the Fifth Edition of *ASCO-SEP*®, for example, there have been over seventy drug approvals and safety notifications from the U.S. Food and Drug Administration.[3]

ASCO-SEP® reflects within its chapters the state of oncology today. It is not meant to be used as a textbook and does not typically include future directions for research. Rather, this publication serves as a comprehensive overview of the subspecialty of oncology for use in review, self-assessment, and teaching activities; to validate current knowledge; and to improve overall competency in oncology.

LEARNING OBJECTIVES

Upon completion of this educational activity, participants will be able to:

- Apply the basic principles of epidemiology, molecular biology, clinical pharmacology, and clinical trial design to the practice of oncology;
- Incorporate appropriate imaging and diagnostic techniques to accurately identify and stage

neoplastic disease;

- Discuss current treatment options with patients diagnosed with cancer and recommend approaches based on current evidence; and
- Assess and mitigate potential symptoms affecting quality of life and relating to treatment toxicity, comorbidities, or late effects.

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In support of improving patient care, the American Society of Clinical Oncology is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC) to provide continuing education for the healthcare team.

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Chapter	ILNA Points	ILNA Categories
1	2.25	Health Promotion/Screening and Early Detection; Survivorship
2	3	Diagnosis and Staging; Disease-Related Biology; Scientific Basis for Practice
3	1.5	Diagnosis and Staging; Scientific Basis for Practice; Symptom Management; Treatment
4	2.5	Diagnosis and Staging; Scientific Basis for Practice; Symptom Management; Treatment
5	2	Scientific Basis for Practice; Basic Concepts for Transplantation
6	2.25	Health Promotion/Screening and Early Detection
7	4.25	Disease-Related Biology; Palliative Care; Scientific Basis for Practice; Symptom Management; Treatment
8	3.75	Diagnosis and Staging; Disease-Related Biology; Health Promotion/Screening and Early Detection; Scientific Basis for Practice; Survivorship; Symptom Management; Treatment
9	3	Disease-Related Biology; Scientific Basis for Practice; Survivorship; Symptom Management; Treatment
10	4	Disease-Related Biology; Scientific Basis for Practice; Symptom Management; Treatment
11	4.5	Disease-Related Biology; Scientific Basis for Practice; Symptom Management; Treatment
12	2.75	Disease-Related Biology; Scientific Basis for Practice; Survivorship; Symptom Management; Treatment
13	1.75	Diagnosis and Staging; Disease-Related Biology; Health Promotion/Screening and Early Detection; Scientific Basis for Practice; Survivorship; Symptom Management; Treatment
14	1.5	Disease-Related Biology; Scientific Basis for Practice; Survivorship; Symptom Management; Treatment
15	2.5	Diagnosis and Staging; Disease-Related Biology; Scientific Basis for Practice; Symptom Management; Treatment
16	2.75	Disease-Related Biology; Scientific Basis for Practice; Symptom Management; Treatment
17	3	Disease-Related Biology; Scientific Basis for Practice; Symptom Management; Treatment
18	1.75	Disease-Related Biology; Health Promotion/Screening and Early Detection; Palliative Care; Scientific Basis for Practice; Symptom Management
19	1.25	Disease-Related Biology; Scientific Basis for Practice; Treatment; Basic Concepts for Transplantation; Types of Transplants and Sources of Stem Cells; Preparative Regimens; Early Post-Transplant Management; Graft-versus-Host Disease Prevention and Management; Late Post-Transplant Management
20	1	Disease-Related Biology; Professional Practice; Psychosocial; Scientific Basis for Practice; Survivorship; Symptom Management; Treatment
21	2.5	Palliative Care; Professional Practice; Psychosocial; Symptom Management
22	1.75	End-of-Life; Palliative Care; Symptom Management
Total ILNA Points	55.5	

Abbreviation: ILNA, Individual Learning Needs Assessment.

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EPIDEMIOLOGY AND PREVENTION

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Recent Updates

- A recent study in China suggested that biannual screening with ultrasound and magnetic resonance imaging (MRI) of the liver for patients with cirrhosis resulted in the detection of early-stage hepatocellular carcinomas with a high chance of curative resection and favorable survival. (Kim SY, *JAMA Oncol* 2017)
- Compliance with HPV vaccination for children and adolescents has been poor. (Jeyarajah J, *Clin Pediatr* 2016)
- Studies have shown, and guidelines now indicate, that vaccination for HPV, at least for those ages 9 to 15, can be limited to two doses of the vaccine as opposed to three doses. (Laprise JF, *J Infect Dis* 2016)
- At this time, 9% of cancer in the West is attributable to obesity; a recent International Agency for Research on Cancer Working Group report identified 13 cancers for which there is sufficient evidence and an additional three for which there is limited evidence to link them to obesity. (Arnold M, *Cancer Epidemiol* 2016; Lauby-Secretan B, *N Engl J Med* 2016)

OVERVIEW

Epidemiology is the study of disease in populations, including its distribution, determinants, natural history, and survival. Rather than focusing on the individual patient, its perspective is that of public health. The traditional focus and goal of epidemiology has been the determination of the incidence and mortality rates of cancer in different populations and subgroups, as well as the identification of risk factors for the purpose of disease prevention and control through primary prevention and screening interventions. More recently, the methods of epidemiology have been applied to clinical questions, including the assessment of treatment outcomes, such as survival, and the long-term sequelae of cancer and its treatment.

Because of its emphasis on populations, epidemiology generally uses rates (with denominator populations—rates standardized to a population—and time frames) or relative measures rather than absolute figures to measure relevant statistics. Descriptive epidemiology—the usual starting point for epidemiologists—encompasses incidence and mortality rates, survival rates, and time trends. Incidence and mortality rates are commonly expressed as the number of newly diagnosed patients or deaths per 100,000 in the group at risk.

These rates are usually age- and sex-adjusted, meaning they are mathematically adjusted to a standard population to remove the effects of a population's age and sex distribution, which may change over time. Cancer is primarily a disease of older people. Even with the increase in the number of people in the United States who are age 70 or older during the past 30 years, the number of cancer cases occurring annually has increased or diminished only slightly because many cancers are age dependent. Furthermore, because women have a life

expectancy 7 years longer than that for men, there are substantially more older women than men, so a difference in sex distribution would magnify or diminish with age as well. Thus, adjusting cancer rates for age and sex removes their effects. As a result, a true change in cancer rates because of prevention, better treatment, or new etiologic factors must be assessed by increases or decreases in age- and sex-adjusted incidence and mortality rates.[1,2]

Survival is defined as the time from diagnosis to death. A commonly used measure is the proportion of people alive at 5 years after diagnosis (Table 1-1). For some cancers, such as breast or prostate cancer, this time frame may be too short, as recurrences and deaths may continue to occur long after 5 years; thus, for these cancers, 10-year survival may be a useful measure.

The American Cancer Society (ACS) publishes an annual estimate of the absolute numbers of new cancer cases and deaths.[2] These numbers are widely quoted, especially by the lay press. As noted above, it should be emphasized that these figures are not rates and are subject to fluctuations according to the age and sex distribution of the population. ACS also publishes time trends of incidence and mortality rates for major cancers during the past 75 years; these figures can give interesting insights into the inroads made by primary prevention, screening, and treatment and changes brought about by increases or decreases in risk factors (Figs. 1-1 and 1-2).[2]

Figure 1-2 shows the changes in mortality for selected cancers since 1930. It illustrates the dramatic rise in mortality for lung cancer that accompanied the rise in tobacco use in the 20th century, peaking in men around 1985 and then falling 20 years after the Surgeon General's reports of 1964 and 1968, which publicized the hazards of cigarette smoking and its link to lung cancer. As tobacco use has fallen to around 15% in males, the lung cancer incidence and mortality rates have decreased and will continue to fall for the foreseeable future. Another dramatic change has been the fall in gastric cancer, which was the leading cause of cancer mortality in the United States prior to World War II. Most experts attribute this decline to the increased availability of the electric refrigerator and the concomitant increased consumption of fresh meat, fruits, and vegetables, as opposed to smoked and cured foods, which contain nitrites and other potentially carcinogenic agents.[3] Among women, a dramatic fall in uterine cancer, primarily in the uterine cervix, occurred; this is attributable to the widespread use of the Pap smear for screening after World War II. A decline in breast cancer mortality after the mid-1980s has been attributed to a combination of mammographic screening and advances in treatment, such as the use of adjuvant therapy.[4,5]

Table 1-1 **Definition of Terms Related to Survival**	
Survival time	Time from the initial diagnosis of cancer to death
Disease-free survival	Time from complete remission to relapse of disease
5-year survival rate	Proportion of patients who are alive 5 years after the time of diagnosis
Disease-specific survival rate	Proportion of patients who have not died of the specific disease (does not take into account deaths unrelated to the disease)
Overall survival rate	Proportion of patients who are alive at a specific time after the diagnosis (takes into account all causes of death)

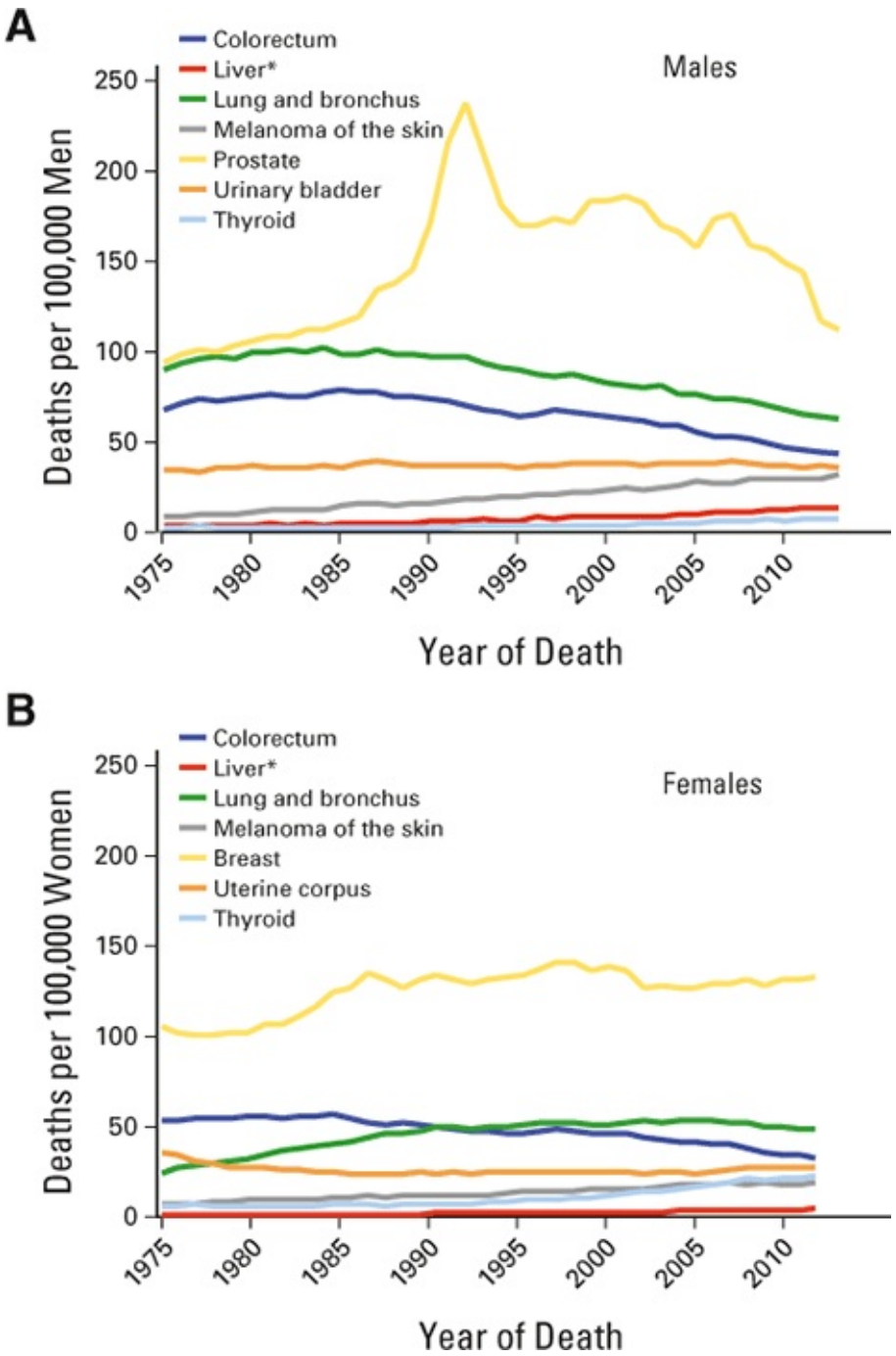

Fig. 1-1 Trends in U.S. incidence rates for selected cancers by sex (1975 to 2013).

Rates are age-adjusted to the 2000 U.S. standard population and adjusted for delays in reporting.

*Liver includes intrahepatic bile duct.

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In the incidence rates shown in Fig. 1-1, the rise in prostate cancer incidence after 1985 is the most salient curve and reflects the introduction of prostate-specific antigen (PSA) testing to the clinical laboratory and its widespread use for screening. A rise in the incidence of cutaneous melanoma in both men and women has been attributed to both a change in sun exposure patterns in the population and increased skin screening.[6,7]

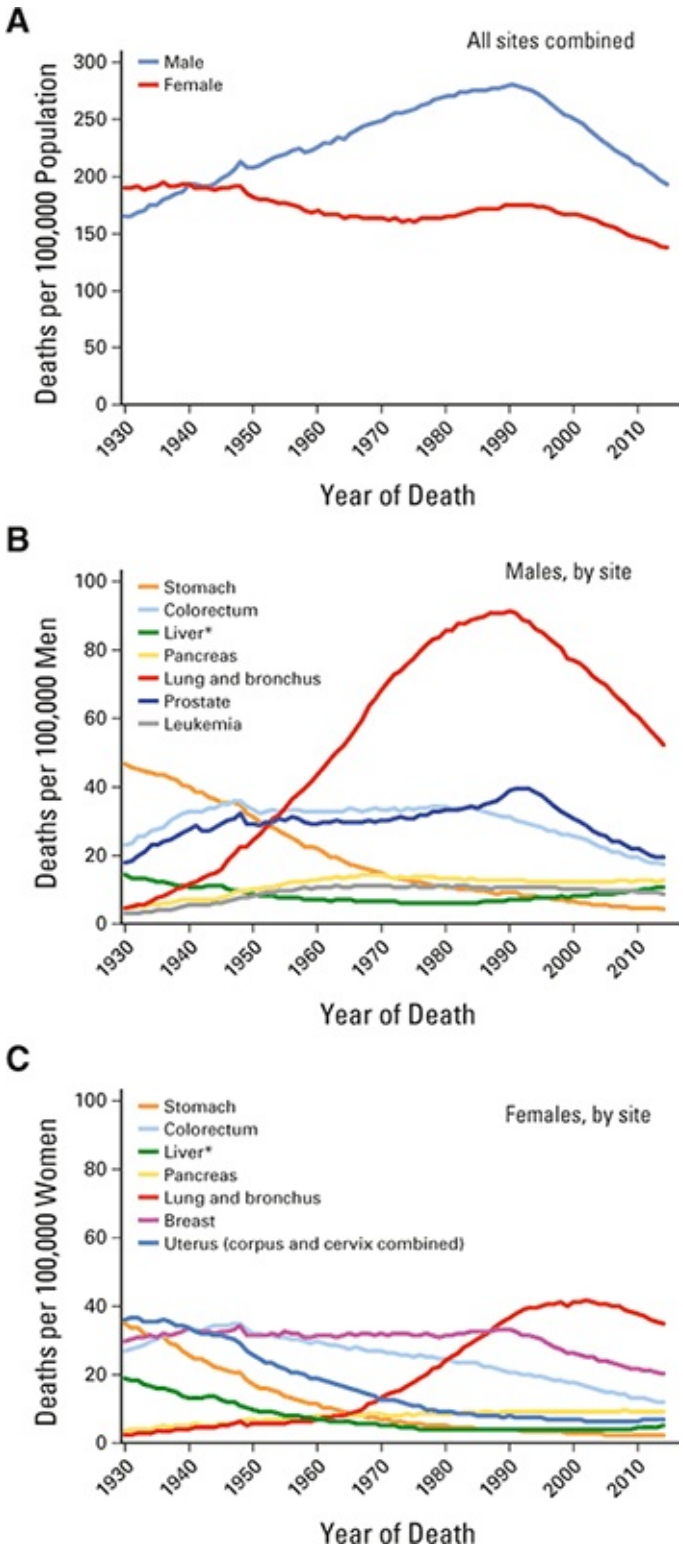

Fig. 1-2 Trends in death rates for selected cancers (1930 to 2014).

Rates are age-adjusted to the 2000 U.S. standard population. Because of changes in the *International Classification of Diseases* (ICD) coding, numerator information has changed over time. Rates for cancers of the lung and bronchus, colorectum, liver, and uterus are affected by these changes.

Mortality rates for liver, pancreas, and uterine corpus cancers are increasing.
*Liver includes intrahepatic bile duct.

KEY POINTS

- Epidemiology is the study of the distribution, etiology, and natural history of disease in populations.
- Epidemiology can include assessment of treatment outcomes, disease prevention, and disease screening.
- Epidemiology addresses these issues with a public health and public policy perspective as opposed to the perspective of the individual patient.

ASSESSING CANCER RISK

Much of epidemiology involves the assessment of cancer risk. A person can be at increased risk of cancer because of extrinsic or intrinsic factors, or a mix thereof.

- Extrinsic influences are factors outside the individual's own body, such as environmental pollutants, cultural/lifestyle habits, medication use, infectious factors, and diet.
- Intrinsic influences are factors unique to each person, such as genetics.
- To assess etiology, risk is usually reported relative to another population. For example, in 2005, the breast cancer mortality rate for black women was 35.6 per 100,000, and the rate for non-Hispanic white women was 25.8 per 100,000. During that period, the relative risk of death for black women was 1.38 times that of white women (35.6 divided by 25.8).[8]

From an epidemiologic perspective, an etiologic agent or risk factor is anything that increases the probability that an individual will develop the disease. These risk factors can include demographic characteristics (e.g., increasing age or race/ethnicity) or lifestyle and behavioral factors, such as smoking. They also include endogenous factors, such as genetic mutations that have been identified as predisposing a person for a disease, such as a deleterious *BRCA1* or *BRCA2* mutation. Most cancers undoubtedly arise from a combination of genetic and exogenous factors that interact to define certain demographic patterns. These patterns are generally recognized as the subpopulations in which a specific cancer is most likely to occur, such as breast cancer being more common in white, older, upper socioeconomic class women.

Certain genetic mutations occur with relatively high frequency, but they convey only a slight increase in the probability of the cancer occurring. These are referred to as "genetic polymorphisms" and are usually thought to provide increased susceptibility to an environmental

carcinogen or to modify risk in some other way. For example, genetic polymorphisms for the cytochrome P450 enzyme system that metabolizes carcinogens in cigarette smoke can cause variability in susceptibility to the effects of cigarette smoke. Better known are the uncommon genetic mutations that convey high risk for the development of malignancy, such as the mutations of the *BRCA* or familial adenomatous polyposis genes. *BRCA1* and *BRCA2* are genes with well-defined DNA sequences. Some *BRCA1* and *BRCA2* mutations increase the risk of breast and ovarian cancers and of certain other malignant diseases as compared with the risk for individuals without the mutations.[9] Advances in our knowledge regarding DNA methylation, histone modification, and other epigenetic phenomena may provide new insights into the effect of environmental factors on carcinogenesis and may suggest new targets for intervention.[10,11]

Knowledge regarding genetic risk factors for a particular cancer and the ability to predict the development of a particular cancer can help oncologists develop and select intervention options and to target such interventions to high-risk populations. Table 1-2 lists selected low-prevalence, high-penetrance genetic syndromes with their associated cancers. Discussion of specific genetic syndromes related to cancers of different organ sites can be found in the disease-specific chapters.

Knowledge of the risk factor also may present ethical dilemmas. Examples include whether to convey knowledge of risk to third parties in a patient's family, how to handle selection of embryos for implantation during in vitro fertilization on the basis of genetic testing, or whether such information can or should be made available to life insurance companies.[12] However, knowledge of the risk factor may allow for early interventions that could prevent disease or limit its severity.

To address risk from genetic factors, it is critical to take a good family history from patients with cancer. This is particularly important for younger patients, who are more likely to harbor a mutation. Such a history should include, at a minimum, a census of all first-degree relatives (i.e., parents, siblings, and children), with their sex, current age or age at death, any cancers diagnosed, and age at diagnosis. Family histories with cancers among the relatives that fit the pattern of a known genetic mutation or early age at diagnosis for certain cancers should lead to further evaluation and testing, possibly by a genetic specialist. The results of these evaluations have implications for the patient regarding risk of further cancers, as well as implications for other blood relatives in the patient's family. For further details on genetic cancer risk assessment and management, see Chapter 6 on Genetic Testing for Hereditary Cancer Syndromes.

Just as with genetic information, the clinician should make an effort to collect other relevant risk-factor information for patients with cancer or for healthy patients who are undergoing wellness exams. Risk information should include, at a minimum, tobacco and alcohol use, height and weight, family history, and occupational history. Other factors should be included as relevant to a specific symptom or diagnosis (e.g., exposure to organic solvents, such as benzene, in those diagnosed with leukemia; exposure to exogenous estrogens in women with postmenopausal bleeding; vaccination history in those with a human papillomavirus [HPV]–related disease). This information can be used to provide advice and guidance to the patient (e.g., regarding tobacco-use cessation), to identify patients at high risk for certain cancers, to guide early detection and prevention strategies, and to assist with the diagnosis of certain cancers.

Table 1-2 **Selected Hereditary Neoplastic Syndromes (Clinical Tests Available)**		
Syndromes	**Site(s) of Most Common Cancer(s)**	**Associated Gene(s)**
Hereditary breast and ovarian cancer	Breast, ovary	*BRCA1, BRCA2*
Cowden	Breast, thyroid	*PTEN*
Li-Fraumeni	Brain, breast, adrenal cortex, leukemia, sarcoma	*TP53*
Familial adenomatous polyposis	Large bowel, small bowel, brain (Turcot), skin, bone (Gardner)	*APC*
Hereditary nonpolyposis colorectal cancer	Colorectal and endometrium, also ovary, pancreas, stomach, small bowel	*MSH2, MLH1, PMS1, PMS2, MSH6*
Multiple endocrine neoplasia (MEN1)	Pancreatic islet cell, pituitary adenoma, parathyroid adenoma	*MEN1*
MEN2	Medullary thyroid, pheochromocytoma	*RET*
Neurofibromatosis type 1	Neurofibrosarcoma, pheochromocytoma	*NF1*
Von Hippel-Lindau	Hemangioblastoma, nervous system, renal cell	*VHL*
Retinoblastoma	Eye, bone	*RB1*
Melanoma, hereditary	Skin	*CDKN2/p16, CDK4*
Basal cell	Skin	*PTCH*
Hereditary diffuse gastric cancer	Stomach, lobular breast	*CDH1*

Chemoprevention and screening are options for certain high-risk populations, as is the modification of high-risk behavior. People at high risk for cancer often undergo intensive screening for the cancer in question. A screening test proven effective for average-risk patients is likely to be of even greater value in those at higher risk. In many circumstances, screening tests that have been shown not to be effective in screening for patients at average risk, such as CA125 for ovarian cancer, may be used by clinicians in screening patients at high risk, such as those with a *BRCA* mutation. But there would be no reason to assume it would be more beneficial for reducing mortality in high-risk patients than in those at average risk. If certain screening tests do reduce mortality, then they may be of more value in those at higher risk but would not necessarily be useful for individuals at average or low risk because of cost or other problems, such as high rates of false-positive results (discussed in more detail in the Cancer

Screening section).

Population categorization is important in epidemiology. Populations can be delineated by sex, nationality, culture, race and ethnicity, socioeconomic status, age, and other characteristics. This is the basis of descriptive epidemiology—along with time trends—and is used to provide clues to etiology. For example, a cancer that has a strong predominance in men may have a specific occupational component to it. Differences in incidence rates for various cancers found in both Japan and the United States have suggested hypotheses regarding diet and the consumption of green tea.[13]

Race and ethnicity are common ways of dividing populations in the United States. Note that race is a sociopolitical categorization.[14] The definitions used by U.S. investigators when generating population statistics are not formulated scientifically on the basis of characteristics such as genes, but rather reflect self-report by the individual and a mix of anatomical traits that often encompasses varying degrees of racial admixture. Much concern has arisen in the past 10 to 15 years with regard to outcome disparities, in particular for a wide range of cancers and for black patients compared with white patients. In some instances, these disparities also reflect differences in incidence, but in others, they may reflect differences in stage at diagnosis, access to treatment, or tumor biology. Race and ethnicity can correlate with other methods of categorization, such as poverty or prosperity, both of which may change the incidence of cancer and its related mortality.

Socioeconomic status and education also can be related to the risk of disease and death. Higher rates of breast cancer among white women in the San Francisco Bay area of California and on Long Island in New York were linked to a higher prevalence of professional women in those areas, who, as a cohort, are less likely to have a full-term pregnancy by age 30—a known risk factor for breast cancer.[15] Socioeconomic status also has been related to the type of treatment received and subsequent outcomes for various cancers, although this variable is heavily confounded with race/ethnicity and education.[16] In a classic study, Ayanian et al.[17] found that women with breast cancer who were uninsured or on Medicaid had a 49% (95% CI; 20, 84) and 40% (95% CI; 4, 89) higher risk of death, respectively, than women with private insurance. A similar effect for socioeconomic status was found for survival of patients with colorectal cancer[18] and for quality of life for prostate cancer survivors.[19]

In analytic epidemiology, observational studies are carried out to ascertain whether associations exist between an exposure and an outcome. Although a statistical association may exist between the two, there is always concern that this may reflect bias in the way the study was conducted or the presence of confounding factors. Confounding factors are factors associated with both the exposure and the outcome that can lead to an observed association, which is not truly a relationship between the two. For example, a study may show that asbestos workers have an elevated risk of lung cancer compared with the general population. However, one must keep in mind that asbestos workers may be heavier smokers than other individuals in the general population, and cigarette smoking is associated with lung cancer risk; thus, smoking may confound the observed association. Therefore, it is mandatory in a study that looks at this exposure and outcome to collect smoking information so that it can be statistically controlled and the individual effect of asbestos exposure can be appropriately measured.

Epidemiologic observational studies fall into two broad categories: cohort studies and case–control studies. Participants in cohort studies are categorized based on their exposure and then followed to determine whether the outcome develops differently in the exposed and unexposed groups. Case–control studies enroll both participants who have the outcome or disease under study and a control group of healthy participants. Both groups are then assessed for exposure.

Both cohort and case–control studies have advantages and disadvantages. In both types, one must try to avoid bias or directional error. For example, in a case–control study, a patient with cancer may be inclined to give a positive answer more frequently than a control participant to a question regarding smoking history—this is referred to as "recall bias."

As a general rule, cohort studies are preferred when the exposure is uncommon and the outcome is common, while case–control studies are preferable with uncommon outcomes. Since the incidence of most cancers, even the most common ones, is relatively low, case–control studies usually are used in cancer research. Their disadvantage is that they are often ambiguous on the temporal relationship between the exposure and the cancer. If you compare 100 patients with colon cancer to 100 patients without colon cancer for their intake of saturated fat, it can be unclear whether a decreased intake in the case patients is related to the disease or preceded the disease. In a cohort study, in which the exposure is ascertained before the cancer has developed, one can be more confident that any observed association preceded the development of disease. On the other hand, because of the low incidence of most cancers, a cohort study requires tens of thousands of subjects to be followed for years. One of the best-known cohort studies, the Nurses' Health Study, followed almost 90,000 nurses for 4 years to generate enough endpoints to determine the risk associated with dietary fat and breast cancer, the most common cancer.[20]

Molecular epidemiology—the use of sophisticated molecular and genetic markers in conjunction with the traditional tools of analytic epidemiology to investigate etiologic or other questions in cancer epidemiology—is a major field within cancer epidemiology. Biomarkers can be used to measure exposures or endpoints in place of the more traditional answers to questionnaires, and, in some instances, biomarkers can give a more objective, unbiased assessment.

Many contemporary studies use epidemiologic methodology to address clinical questions in oncology. When randomized trials may be difficult to conduct, observational studies, such as cohort or case–control studies, may be used to answer typical questions regarding the efficacy of a drug or the incidence of an adverse event from a drug and also to ascertain the cost-effectiveness of a particular intervention. Therefore, an understanding of these analytic tools is imperative for the modern oncologist.

KEY POINTS

- Cancer risk can be increased by both intrinsic and extrinsic influences.
- To assess etiology, a population risk is usually reported relative to another population.
- A key element in population statistics and rates is the presence of a denominator population.
- Germline genetic mutations, which confer an increased risk for a number of cancers, have been identified. Patients who may carry a germline heritable predisposition to cancer can be identified in the clinical setting if one is alert to the clinical manifestations of these syndromes and the patient's family history.
- A good clinical history can also identify key exogenous risk factors, such as tobacco, alcohol, hormonal, and infectious exposures and certain occupational risk factors.
- Cohort studies and case–control studies are key tools in the conduct of observational

research and the identification of risk factors for cancer.

- Differences in cancer risk exist across populations and individuals on the basis of various characteristics, such as race/ethnicity, gender, age, socioeconomic status, and education. Molecular and genetic biomarkers of cancer risk are an area of active epidemiologic research.

PATTERNS OF CARE, DISPARITIES, AND OUTCOMES RESEARCH

Although descriptive epidemiology and the determination of etiologic risk factors have been the traditional domains of epidemiology, the assessment of treatment outcomes in populations has become an important aspect of this discipline. Clinical trials demonstrate "efficacy" of a treatment. How well the intervention works in the population as a whole in routine practice is referred to as "effectiveness." A phase II clinical trial can demonstrate the efficacy of a treatment intervention (e.g., tumor shrinkage), and a phase III study compares two interventions to determine which is superior. Prevention trials usually require phase III studies to show efficacy.

The study of patterns of care or treatments that are already in clinical use is an aspect of outcomes research. Studies often demonstrate geographic and regional differences in the treatment of cancers. For example, for women with localized breast cancer, the decision to treat with lumpectomy and radiation therapy or with mastectomy may vary depending on the patient's geographic location.[21] Similar regional differences have been noted for prostate cancer screening and for the types of treatment used for localized prostate cancer.[22]

Health disparities generally can be defined as differences in outcomes related to a disease among one segment of the population compared with the general population. In current usage, the term is usually applied to subpopulations that are thought to be disadvantaged in some way, such as by race/ethnicity, increasing age, socioeconomic status, sexual orientation, rural residence, etc., and the public policy interest in disparities stems from an interest in finding avoidable and correctable causes for the disparities. For cancer-related disparities, such causes may reflect differences in risk-factor exposure, screening utilization, access to care, quality of care, or tumor biology.

The most notable example of disparities are the differences seen between blacks and whites in America with regard to cancer statistics. Estimates from the American Cancer Society in 2016 indicate that blacks had a lower projected lifetime risk for all cancers (40.8% for males, 34.3% for females) than whites (42.4% for males, 39.0% for females); despite this, blacks were at greater risk of cancer-related mortality for males (23.4% for black males vs. 22.8% for white males) and equal mortality for females (19.4% for blacks vs. 19.5% for whites).[23] Black patients are at increased risk of mortality from a wide variety of cancers.[24,25] As an example, differences in tobacco usage have been responsible for disparities in mortality from squamous cell carcinoma of the esophagus between black and white patients.[26] A study from the Southwest Oncology Group found persistent racial disparities for women with breast and ovarian cancers entered into phase III trials despite similar stage, treatment, and follow-up, suggesting that biologic differences may also play a role.[27]

Many of the disparities in outcomes among groups defined by race and socioeconomic status have been linked to differences in patterns of care. For example, treatment is less than optimal for a substantial proportion of patients with cancer who are poor or of certain ethnic backgrounds.[28] The reasons for these variations in care are complex. Some are the result of

sociocultural differences in attitudes toward therapy.[29] Patient–physician communication also can play a major role.[30] In other cases, poverty, lack of insurance, or underinsurance can make access to care difficult.[17,28,31] Logistical difficulties, such as a lack of adequate transportation to a treatment center, may play a role. Patients with severe comorbid disease or poor performance status may justifiably not be offered aggressive cancer treatments because these patients are at higher risk of a treatment-related morbidity.

To date, outcomes research on disparities has focused primarily on the identification of the circumstances under which significant disparities occur and their possible etiologies (e.g., whether they stem from biologic differences or from differences in access to care). Significant advances have occurred in this area over the past 15 years, and it is only now that interventions are beginning to be tested and to bear fruit. One good example is the New York City Department of Health and Human Services' efforts to provide colonoscopy screening to adults older than age 50. This effort has achieved a colonoscopy screening rate of 70% with no significant racial/ethnic disparities.[32] Similar mammography rates have also been achieved among racial/ethnic groups in many populations. Interestingly, although there remains a large gap between breast cancer mortality rates in whites and blacks, a recent report demonstrated that black women and white women in the United States now have nearly identical breast cancer incidence rates, possibly reflecting changes in socioeconomic status, age at first giving birth, and parity among black women.[33]

KEY POINTS

- Most clinical trials are designed to determine "efficacy," meaning how well the treatment works in a selected environment. Some larger trials and outcomes studies are designed to show "effectiveness," meaning how well the treatment works in the population as a whole.
- Epidemiologic methodology, used in the field of health outcomes research, has been active in determining areas where disparities in incidence and mortality exist and possible causes for these disparities. Having this information may lead to interventions.

CANCER PREVENTION

Prevention is intended to reduce cancer incidence and mortality. Primary cancer prevention is best defined as the use of interventions to reduce cancer incidence. Important to prevention is the fact that carcinogenesis is not a distinct event but rather a process that occurs over time. It is a cumulative continuum of discrete cellular changes resulting in uncontrolled proliferation and growth. Primary prevention involves interventions or manipulations of the genetic, biologic, and environmental factors in the causal pathway of carcinogenesis. Smoking cessation, sun avoidance, diet modification, weight loss and increased physical activity, cancer virus vaccination, and chemoprevention (e.g., tamoxifen for breast cancer prevention) are primary prevention activities.[34] Screening for asymptomatic cancers, which is intended to detect cancers earlier so that treatment can be introduced more promptly and effectively to reduce mortality, is referred to as "secondary prevention." This may be confusing, since the term *secondary prevention* is also frequently used to refer to prevention for disease survivors (e.g., tobacco cessation in lung cancer survivors). For some cancers, such as cervix cancer and

colorectal cancer, intraepithelial neoplasia is an intermediate step in carcinogenesis, and treatment of this condition is a form of cancer prevention.[35]

SMOKING CESSATION

Tobacco use is the most avoidable risk factor for cardiovascular disease, pulmonary disorders, and cancer. Smoking cessation and avoidance have the potential to save and extend more lives than any other public health activity. A smoker has a one in three lifetime risk of dying prematurely of a smoking-related disease. More human lives are lost because of cardiovascular disease caused by smoking than from smoking-related cancer. In addition to lung cancer, cigarette smoking has been linked to cancers of the upper aerodigestive tract (lip, oral cavity, pharynx, and larynx), esophagus, kidney, bladder, pancreas, small bowel, and colon.[36]

The risk from tobacco smoke is not necessarily limited to the smoker. Epidemiologic studies suggest that environmental tobacco smoke, often called “secondhand smoke” or “passive smoke,” may cause lung cancer and other pulmonary diseases in nonsmokers. The amount of smoke exposure and the degree of inhalation of cigarette smoke are correlated with the risk of mortality associated with lung cancer. Light and low-tar cigarettes are not safer because smokers tend to inhale them more frequently and more deeply. Compared with their nonfiltered counterparts, filtered cigarettes allow smaller particles to get into the peripheral parts of the lung and cause different histologic subtypes of cancer,[37-39] specifically adenocarcinomas. Those who stop smoking almost immediately stop increasing their risk of cancer, although it takes some time before their risk of cancer declines. Some carcinogen-induced gene mutations may persist for years. The use of e-cigarettes has been advocated by some as a substitute for regular cigarettes because of the much lower exposure to carcinogens; this remains a controversial approach to tobacco cessation, and it is unclear at present whether there is a total lack of risk from this form of smoking (discussed as follows).

The vast majority of adult American smokers begin smoking before age 18; two-thirds are nicotine-dependent in their high school years.[40] Therefore, communicating health messages to the pediatric and adolescent population is a major public health challenge. Studies show that a physician’s simple advice to avoid or quit smoking can improve the quit rate by two-thirds.[41] Despite this, a survey found that although more than 80% of oncologists assess their patients’ smoking behavior, fewer than 20% feel confident enough to intervene in this important area.[42]

Among the most effective smoking cessation interventions are governmental actions. Tax increases on cigarettes and restrictions on venues where smoking is permitted have been very effective in reducing smoking prevalence rates.[43] Current smoker rates are down to less than 20% in the United States, approaching 15%, and most tobacco-related cancers in this country now occur in former smokers. However, smoking remains a major factor globally, especially in Asia, and lung cancer is the leading cause of cancer mortality worldwide. Much concern has been raised in particular about smoking rates in India and China, and global efforts to reduce smoking rates are being increased.[44-47]

Smoking is an addiction. It is easier for light smokers—the less addicted—to quit. Experts believe that heavy smokers generally need an intensive, broad-based cessation program that includes counseling, behavioral strategies, and drug therapy. If drug therapy is needed, the recommended first-line therapies are nicotine-replacement therapy, bupropion, and varenicline, with clonidine and nortriptyline as possible second-line therapies.[41] Most Americans who successfully quit smoking do so on their own, without participation in an organized cessation program, but this process can be strongly enhanced by even a small amount of encouragement

from a health care provider. Smokers who stop completely are more likely to be successful than smokers who gradually reduce the number of cigarettes smoked or change to cigarettes containing lower amounts of tar or nicotine. The smoker who is quitting goes through a process with identifiable stages that include contemplation of quitting, an action phase during which the smoker quits, and a maintenance phase. As noted above, there now exist numerous effective strategies beyond counseling for advising and assisting the cooperative patient with his or her goals.[48,49]

Electronic cigarette (e-cigarette) use has recently been growing as another tool to enhance tobacco cessation. This device, which provides nicotine for the user who is addicted, but without the harmful carcinogenic exposures, is controversial in that some see it as an improvement over regular smoking, while others oppose its use because they feel that it provides a more acceptable alternative to total tobacco cessation.[50,51] In the short term, e-cigarettes do appear to be less harmful than regular cigarettes,[52] but long-term data on their carcinogenic or other harms are lacking[53]; the American Society of Clinical Oncology (ASCO) and the American Association for Cancer Research have released a policy statement recommending caution in their use until more evidence is available.[54]

Cigar smokers do not inhale, but the health risks associated with cigars are similar to those of cigarettes, especially the risks of oral cavity, laryngeal, esophageal, and lung cancers (the risk of lung cancer rises with increased depth of inhalation).[55] Smokeless tobacco, or chewing tobacco, is the fastest-growing segment of the tobacco industry and represents a serious health risk. Chewing tobacco has been linked to dental caries, gingivitis, oral leukoplakia, and oral cancer. In addition, the nitrosamines found in this product have been shown to cause lung cancer in animal studies. Esophageal cancer is linked to the carcinogens in tobacco that dissolve in saliva, are swallowed, and then come into contact with the esophagus. In certain parts of the world, smoking opium has also been associated with esophageal cancer etiology, presumably from the polycyclic aromatic hydrocarbons in the smoke.[56]

The use of marijuana is now legal in at least two states and millions of Americans are regular users. Most of the studies on marijuana use and cancer risk have focused on the upper aerodigestive tract and lung, but at present there is no clear-cut evidence of an association with marijuana use and these cancers.[57] The only cancer with which marijuana use has been consistently associated is testicular cancer, for which three case–control studies have shown an association, though a biologic explanation for this association has not been established.[58-60]

ALCOHOL

Alcohol ingestion is responsible for an estimated 5 to 10% of cancer cases in Europe and the United States, specifically for cancers of the oral cavity, pharynx, larynx, esophagus, liver, colorectum, and female breast.[61] The mechanisms by which it causes cancer vary from site to site.

The classical association of alcohol with carcinogenesis has been in the upper aerodigestive tract, where it has acted as a tumor promoter in association with tobacco use in the etiology of squamous cell malignancies. As tobacco use has declined, the incidence of these malignancies has declined as well, and it is not clear that alcohol ingestion alone has a significant carcinogenic effect for squamous cell malignancies of the oral cavity or esophagus. It does not appear to be carcinogenic alone for adenocarcinomas of the esophagus.[62]

Another tumor linked to alcohol consumption is hepatocellular carcinoma (HCC). HCC occurs in this context in heavy drinkers, as the causal chain involves the development of cirrhosis.[63] In

addition, alcohol use in moderation can act to enhance liver carcinogenesis caused by hepatitis viruses.[64]

While the relative risk is not high, but because breast cancer is so common, one of the most important effects of alcohol may be through breast cancer, in which even modest consumption is associated with elevated risk. The Nurses' Health Study found a 30% increased risk of breast cancer for women who drank 1.5 to 2 drinks per day (relative risk [RR], 1.28; 95% CI, 0.97, 1.69).[65] The Million Women Study, conducted in the United Kingdom, showed that women who consumed an average of one drink per day had a 12% increased risk of breast cancer (95% CI; 9, 14).[66] This effect appears to be due to increased estrogen and androgen levels in women consuming moderate levels of alcohol, though other plausible mechanisms have been proposed.[67]

Although there are some suggestive data, no clear associations have been established between alcohol intake and either colorectal or pancreatic cancer in the United States. It is worth mentioning that at moderate doses, many believe that alcohol ingestion has salutary effects on cardiovascular health.[68]

SUN AVOIDANCE

Results of epidemiologic studies show a correlation between the risk of nonmelanoma skin cancers (basal cell and squamous cell carcinomas) and cumulative exposure to ultraviolet radiation. Possible risk factors for melanoma include a propensity to sunburn, a large number of benign melanocytic nevi, and atypical nevi. A history of severe sunburns, especially in childhood and adolescence, is associated with increased risk of melanoma in adulthood. Recently, concern has been raised about the increasing use of indoor tanning and tanning beds, as it is increasingly clear that tanning beds increase the risk of melanoma.[69,70] Measures calling for their regulation have been proposed.[71]

Reduction of sun exposure through the use of protective clothing and a change in one's pattern of outdoor activities to avoid the most intense and direct sunlight have been advocated as ways to reduce the risk of skin cancer. Although past studies have been inconclusive, one randomized trial did confirm that sunscreen use can reduce the risk of melanoma.[72,73]

DIET MODIFICATION

Rates of cancers of the breast, colon, endometrium, and prostate are higher in North America and western Europe than in Asia. Immigrants from Asia and their offspring acquire a higher risk for these cancers after they have been in the United States for some time. These observations, as well as data from animal studies, are the basis for the hypothesis that dietary modification can significantly lower cancer risk for individuals in the United States.[74] Diet is a highly complex exposure to many nutrients and chemicals. Low-fat diets, which are usually low in red meat and high in fruits and vegetables, may render some protection through anticarcinogens found in vegetables, fruits, legumes, nuts, and grains. Potentially protective substances found in foods include phenols, sulfur-containing compounds, and flavones.[75] Although the cancer-prevention benefits are theoretical and not fully demonstrated, such a diet does lower the risk of cardiac disease. However, vitamins, minerals, or nutritional supplements in amounts greater than those provided by a good diet have not been demonstrated to be of value. Most randomized trials of vitamin supplements have not shown benefit in terms of prevention and, in some instances, have even shown harm (discussed in the section on Chemoprevention).

Despite correlative data, the dietary fat–cancer hypothesis has not been definitively

demonstrated. Case–control and cohort epidemiologic studies yield conflicting results. No prospective clinical trial has demonstrated that cancer can be prevented through lowering dietary fat or increasing fiber intake. Studies, including randomized trials, have consistently shown no effect of dietary fiber intake on colon cancer risk.[76,77] The Women's Health Initiative, which included a randomized trial with a low-fat diet intervention, also did not indicate an effect on risk of cancers of the breast or colon.[78,79] Nonetheless, a randomized trial of more than 2400 women with early-stage breast cancer showed that patients randomly assigned to a low-fat diet, in addition to standard adjuvant therapy, had a significantly improved survival compared with women on a regular diet (hazard ratio [HR], 0.76; 95% CI; 0.60, 0.98).[80]

WEIGHT REDUCTION AND PHYSICAL ACTIVITY

Many consider obesity to be the second most important risk factor for cancer in the United States, after tobacco.[81] In the West, 9% of cancers have been attributed to obesity.[82] Obesity represents the effects of an individual's net caloric intake, which is the amount consumed versus the amount expended through physical activity. Changes in either of these variables will impinge on the measure of obesity, thereby affecting cancer risk. Operationally, obesity is generally measured with the body mass index (BMI): (weight in kg)/(height in meters)^2. For U.S. adults, a BMI greater than 25 is considered overweight and obesity is defined as a BMI greater than 30.

Obesity affects cancer risk through a number of mechanisms, including hormone metabolism, thereby affecting breast, endometrial, colon, and prostate cancer risk, or by increasing esophageal reflux, which affects the occurrence of Barrett metaplasia and esophageal adenocarcinoma.[83-85] The International Agency for Research on Cancer (IARC) of the World Health Organization, a widely accepted source for the classification of cancer-causing agents, has linked 13 cancers to obesity with sufficient evidence that an elevated risk exists for those with an excess BMI (esophageal adenocarcinoma, gastric cardia adenocarcinoma, colorectal cancer, liver cancer, gallbladder cancer, pancreas cancer, postmenopausal breast cancer, uterine cancer, ovarian cancer, renal cell carcinoma, meningioma, thyroid cancer, multiple myeloma) and an additional 3 (fatal prostate cancer, male breast cancer, diffuse large B-cell lymphoma) for which there is limited evidence of a link.[85] Obesity also may increase cancer risk by inducing insulin resistance, hyperinsulinemia, oxidative stress, or inflammation—all of which are associated with increased cancer risk. These phenomena are generally observed in conjunction with obesity with an abdominal distribution of adiposity, and in those who are physically inactive—a syndrome known as metabolic syndrome.[86] There are also adipokines that arise in those who are obese, such as leptin, omentin, and others, that are associated with the promotion of cancer progression.[87]

ASCO recently issued a position statement recognizing the importance of weight and obesity and encouraging efforts to reduce weight in obese and overweight patients.[88] Although obesity does appear to be related to the incidence and prognosis of a number of cancers, there are relatively few data on whether weight loss can ameliorate the risk.[89] At least one recent study of approximately 37,000 postmenopausal women in the Women's Health Initiative showed that intentional weight loss among postmenopausal women was associated with a reduced risk of endometrial cancer; specifically, women who had a greater than 5% intentional weight loss over a 3-year period compared with women with a stable weight had a hazard ratio for endometrial cancer of 0.71 (95% CI; 0.54, 0.95) during an 11-year follow-up period. Those who gained weight had a higher risk of endometrial cancer.[90] Recent studies in this area have focused more

on weight loss among cancer survivors than on the use of weight loss to prevent cancer. Another ASCO statement has recommended that steps be taken to plan large-scale trials to assess the impact of weight loss and increased physical activity on cancer survivors in terms of reducing cancer recurrence and the incidence of new primary cancers.[91]

Physical activity has been studied for two decades and has been shown to be protective primarily for breast cancer and colorectal cancer, as well as for endometrial cancer and prostate cancer. Approximately 25% of the population is considered sedentary, and this lifestyle is considered to be responsible for up to 5% of cancers.[92] For those in whom these cancers develop, increases in physical activity appear to be helpful for survivors, although large, elegant phase III trials are lacking. Its strongest associations appear to be for cancers of the alimentary tract.[93,94]

OCCUPATIONAL CARCINOGENS

Since Percival Pott recognized an increased risk of scrotal cancer among chimney sweeps in 18th-century London, it has been understood that occupational exposures can increase the risk of certain cancers. The most important of the occupational exposures to carcinogens has been to asbestos, which is prominent among construction workers, pipefitters, and shipyard workers. Asbestos has been closely linked to the incidence of mesothelioma, lung cancer, and probably gastrointestinal tract malignancies. Another classic exposure has been radon inhalation, which occurs in uranium miners and potentially from exposure to radon in the home; radon increases the risk of lung cancer. Various other organic and aromatic chemicals are linked to the risks of leukemia and cancers of the urinary collecting system.

IONIZING RADIATION

As noted above, radon exposure through inhalation can be carcinogenic to the lungs. The effects of other sources of radiation exposure and radiation carcinogenesis, particularly on hematologic malignancies, have been well recognized since their discovery at the turn of the 19th into the 20th century. The most prominent source of such exposure stemmed from the atomic bomb explosions in August 1945 in Japan, and much of what we know about radiation dosimetry, latency, and carcinogenic effects comes from the careful and meticulous studies undertaken in the wake of those events. The other major source of radiation exposure is therapeutic radiation, mainly in the treatment of malignancies, hence the observation of second malignancies as a consequence. Exposure to ionizing radiation is associated with an increased risk of breast, lung, esophageal, and bladder cancers, leukemia, sarcoma, and brain tumors. It has also been linked to thyroid cancer when there is exposure to radioactive iodine, as in the aftermath of the Chernobyl nuclear accident, which released radioactive iodine into the atmosphere.[95] Efforts to reduce the use of radiation therapy, to minimize the size of treatment fields, and to avoid the use of an alkylating agent in combination with radiation therapy are well known in order to reduce the risk of second malignancies.[96,97]

Recently, concern has arisen about the increased use of diagnostic radiation exposure in medical care and its potential carcinogenic risks from cumulative exposure. On a population scale, sophisticated modeling has suggested that a significant increase in cancers can be anticipated from this widespread phenomenon.[98] An initial modeling study by Brenner and colleagues estimated that a single computed tomography (CT) scan in the pediatric population could raise the lifetime risk of abdominal cancer by 0.18% and of brain cancer by 0.07%—small but definitive.[99] A subsequent study in the United Kingdom confirmed that one extra leukemia

and one extra brain tumor would occur as a consequence of 10,000 head CT scans conducted in a pediatric population.[100] The risks were estimated to be similar for adults, though the evidence is not as strong. Furthermore, it is estimated that as high as 1.5 to 2.0% of cancers in the United States can now be attributable to diagnostic radiation.[101]

INFECTIOUS AGENTS

Virally induced cancer has been recognized since the early part of the 20th century, with the discovery of Rous sarcoma virus in chickens. In humans, several viruses, including hepatitis B (causing HCC), hepatitis C (HCC), Epstein–Barr virus (Burkitt lymphoma), and HPV (cervix cancer, other anogenital squamous cell malignancies, and head and neck carcinoma) have been clearly established as carcinogenic. An understanding of retroviruses has broadened our appreciation of other viral agents, such as human herpesvirus 8, which is associated with the development of Kaposi sarcoma.[102,103] In addition, the bacterium *Helicobacter pylori* (*H. pylori*) was found to be associated with certain gastric cancers, specifically non–cardia gastric carcinomas and mucosa-associated lymphoid tissue (MALT) lymphomas. These agents provide targets for vaccination as a means of primary prevention. This has been achieved for hepatitis B[104] and for HPV.[105,106] Since the hepatitis B vaccine was introduced in Taiwan in 1984, the risk of hepatoma (the leading cancer in Taiwan) has been reduced by more than 70% among those vaccinated.[107]

Another success has been the introduction of a vaccine for several subtypes of HPV. HPV vaccination is now recommended for young girls prior to becoming sexually active, which should reduce the incidence of cervix cancer by 70% or more. The Centers for Disease Control and Prevention (CDC) recommends the vaccine for boys as well. More recent studies have suggested that one or two vaccinations may suffice to give an adequate immune response versus the previously recommended three vaccinations; fewer vaccinations may increase compliance.[108,109] In fact, for the 9-to-14-year age group, the current recommendation is for two vaccinations given 6 to 12 months apart. As of 2016, HPV vaccination rates for children and adolescents, especially those in the target range of 13 to 17 years, were lagging, with vaccination rates for girls in the 55-to-60% range and for boys in the 35% range.[110] Because these same viruses are involved in other cancers, the incidence of anal, vaginal, penile, and oropharyngeal cancers may also decline, particularly if vaccination of boys becomes common.[111,112]

Another infectious cause of cancer is *Schistosoma haematobium,* which is strongly linked causally with urinary bladder cancer in Egypt.[113] The mechanism by which it causes cancer is poorly understood. Certain liver flukes are also associated with cholangiocarcinoma.

KEY POINTS

- Avoidance of carcinogens is the most efficient way to prevent cancer. Smoking is the cause of nearly one-third of all cancers in the United States. Other environmental influences, such as sun overexposure, certain chemicals, and certain infectious agents, are associated with cancer causation.
- Obesity is a risk factor for cancers, including endometrial, breast, colon, and esophageal adenocarcinoma.

- Vaccination against cancer-causing viruses can decrease the risk for developing cancer. Important examples include hepatitis B vaccination to decrease the risk of HCC and HPV vaccination to decrease the risk of cervix cancer.

CHEMOPREVENTION AND OTHER PREVENTIVE INTERVENTIONS

Cancer chemoprevention is the use of natural or synthetic chemical agents to reverse, suppress, or prevent carcinogenesis before the development of an invasive malignant process.[114] Cancers are prevented through chemoprevention or, in certain cases, through surgical removal of the organ at risk. Although the concept that pharmacologic agents can prevent a cancer is relatively new, the idea that a compound can prevent chronic disease is not. Antihypertensive agents are used to prevent heart disease, kidney disease, and stroke. Lipid-lowering drugs are prescribed to prevent coronary artery disease.

The initial genetic changes of carcinogenesis are termed “initiation.” This alteration can be inherited or acquired. Acquired genetic damage is the result of physical, infectious, or chemical carcinogens (Table 1-3). The influences that cause the initiated cell to change phenotypically are called “promoters.” Known promoters include androgens linked to prostate cancer and estrogen linked to breast and endometrial cancers. The distinction between the initiator and the promoter can sometimes blur; some components of cigarette smoke are referred to as “complete carcinogens” and serve as both initiators and promoters. Cancer can be prevented or controlled through interference with the factors that cause disease initiation, promotion, or progression.

Compounds of interest in chemoprevention include anti-inflammatory agents, antioxidants, differentiating agents, and hormone antagonists. A long-term, randomized, placebo-controlled clinical trial is generally necessary to establish the efficacy of a chemopreventive agent, and several large clinical trials have been completed.[115-117] As discussed in the following sections, tamoxifen,[115] raloxifene,[117] and aromatase inhibitors[118] have been shown to reduce the incidence of breast cancer. In addition, nonsteroidal anti-inflammatory drugs (NSAIDs), particularly aspirin, can reduce the occurrence of colorectal adenomas in various circumstances and have also been shown in long-term follow-up of randomized trials to reduce the incidence of colon cancer, breast cancer, and a variety of other cancers.[119,120] Finasteride and dutasteride reduce the incidence of prostate cancer.[116,121] Retinoids may inhibit head and neck cancers.[122] Selenium and vitamin E were shown not to reduce prostate cancer risk.[123] Other agents of interest for the chemoprevention of breast, colon, and other cancers have included calcium and vitamin D.[124,125] Most observational studies have not shown a benefit from the use of multivitamins. However, in a prospective, randomized trial of a daily multivitamin compared with placebo for U.S. male physicians, there was a small but statistically significant reduction in the incidence of cancer among the men assigned to multivitamin treatment.[126] Statin drugs have also been of interest for chemoprevention and may have some minor preventive activity for prostate cancer.[127] Table 1-4 contains a list of selected large, randomized chemoprevention trials that have been conducted.[115-118,121-123,126,128-153]

Table 1-3 **Examples of Initiators and Promoters of Cancer***

Carcinogen	Associated Cancer or Neoplasm
Alkylating agents	Acute myelocytic leukemia, bladder
Androgens	Prostate
Aromatic amines (dyes)	Bladder
Arsenic	Lung, skin
Asbestos	Lung, pleura, peritoneum
Benzene	Acute myelocytic leukemia
Chromium	Lung
Diethylstilbestrol (prenatal)	Vaginal (clear cell)
Epstein-Barr virus	Burkitt lymphoma, nasopharynx
Estrogens	Endometrium
Estrogen plus progesterone	Breast
Ethyl alcohol	Liver, esophagus, head and neck
Helicobacter pylori	Gastric
Hepatitis B virus	Liver
Hepatitis C virus	Liver
Human T-cell leukemia (HTLV)-1 virus	Adult T-cell leukemia, lymphoma
Human herpesvirus 8 (HHV-8)	Kaposi sarcoma
Human immunodeficiency virus (HIV)	Non-Hodgkin lymphoma, Kaposi sarcoma, squamous cell carcinoma of cervix
Human papillomavirus (HPV)	Squamous cell carcinoma of cervix, anogenital area, oropharynx
Immunosuppressive agents (azathioprine, cyclosporine, corticosteroids)	Non-Hodgkin lymphoma
Nitrogen mustard gas	Lung, head and neck, nasal sinuses
Nickel dust	Lung, nasal sinuses
Phenacetin	Renal pelvis, bladder
Polycyclic aromatic hydrocarbons	Lung, skin (especially squamous cell)
Schistosomiasis	Bladder (squamous cell)
Sunlight (ultraviolet)	Skin (squamous cell and melanoma)
Tobacco (including smokeless)	Upper aerodigestive tract, bladder, pancreas
Vinyl chloride	Liver (angiosarcoma)

*These agents are thought to act as cancer initiators or promoters for the cancers with which they have been associated.

CANCERS OF THE LUNG, HEAD, NECK, AND ESOPHAGUS

Tobacco smoking is the major cause of squamous cell cancers of the lung, head, neck, and esophagus. The risk of a second cancer of the lung, head, or neck is high—as great as 5% per year—for patients cured of these diseases. This is because of "field cancerization," meaning the carcinogens in tobacco smoke affect all tissues exposed to them. Even after smoking cessation, the tissues that have come in contact with smoke have residual molecular damage. For the esophagus, head, and neck, alcohol ingestion has an interactive effect with smoking. Other cancers of the lung (e.g., small cell and adenocarcinoma) also are associated with tobacco use. Very high rates of oral cancer are found in India because of the practice of chewing betel nuts. HPV infection, particularly the HPV-16 subtype, has been linked to oropharyngeal cancer[154]; a significant increase in incidence is anticipated in the coming years

as a consequence, though the introduction of HPV vaccination may reduce this effect.

Table 1-4 Randomized Chemoprevention Trials

Author (Year, Trial Name)	Study Setting/ Endpoint	Number of Patients	Intervention	Primary Outcome
Head and Neck				
Hong et al. (1990)[122]	Prior SCC	103	Isotretinoin (100 mg/m^2/day)	Positive (SPT)
Bolla et al. (1994)[128]	Prior SCC	316	Etretinate (50, 25 mg/day)	Negative
Khuri et al. (2006)[129]	Prior SCC	1190	Isotretinoin (30 mg/day)	Negative
Lung				
Virtamo et al. (2003; ATBC Cancer Prevention Study)[130]	Lung cancer	29,133	Carotene (20 mg/day); vitamin E (50 mg/day)	Negative
Omenn et al. (1996; CARET)[131]	Lung cancer	18,314	Carotene (30 mg/day); vitamin A (25,000 IU/day)	Negative
Pastorino et al. (1993)[132]	Prior NSCLC	307	Vitamin A (300,000 IU/day)	Positive (SPT)
van Zandwijk et al. (2000)[133]	Prior HNC, NSCLC	2,592	Vitamin A (300,000/150,000 IU/day); NAC (600 mg/day)	Negative
Lippman et al. (2001)[134]	Prior NSCLC	1,166	Isotretinoin (30 mg/day)	Negative
Karp et al. (2013)[135]	Prior NSCLC	1,561	Selenium (200 μg/day)	Negative
Skin				
Levine et al. (1997)[136]	Prior BCC/SCC	524	Isotretinoin (5–10 mg/day); vitamin A (25,000 IU/day)	Negative
Greenberg et al. (1990)[137]	Prior BCC/SCC	1,805	Carotene (50 mg/day)	Negative
Tangrea et al. (1992)[138]	Prior BCC	981	Isotretinoin (10 mg/day)	Negative
Moon et al. (1997)[139]	AK	2,298	Vitamin A (25,000 IU/day)	Positive
Bavinck et al. (1995)[140]	Renal transplantation	38	Acitretin (30 mg/day)	Positive
Clark et al. (1996)[141]	Prior BCC/SCC	1,312	Selenium (200 μg/day)	Negative
Elmets et al. (2010)[142]	AK	240	Celecoxib (200 mg bid)	Positive for nonmelanoma skin cancer
Chen et al. (2015)[143]	Prior BCC/SCC	386	Nicotinamide (500 mg bid)	Positive
Breast				
Fisher et al. (1998; BCPT)[115]	High risk/BC	13,388	Tamoxifen (20 mg/day)	Positive
Veronesi et al. (1998)[144]	BC	5,408	Tamoxifen (20 mg/day)	Negative
Powles et al. (1998)[145]	High risk/BC	2,471	Tamoxifen (20 mg/day)	Negative
Fisher et al. (1999)[146]	DCIS/BC	1,804	Tamoxifen (20 mg/day)	Positive
Veronesi et al. (1999)[147]	CBC	2,972	Fenretinide (200 mg/day)	Negative
Vogel et al. (2006; STAR)[117]	High risk/BC	19,747	Raloxifene (60 mg/day) vs. tamoxifen (20 mg/day)	Equal
Goss et al. (2011)[118]	High risk/BC	4,560	Exemestane (25 mg/day)	Positive
Cuzick et al. (2014)[148]	High risk/BC	1,920	Anastrozole (1 mg/day)	Positive
Colorectal				
Wactawski-Wende et al. (2006)[149]	Colorectal cancer	36,282	Calcium (500 mg bid); vitamin D_3 (200 IU bid)	Negative
Prostate				
Thompson et al. (2003; PCPT)[116]	Prostate cancer	18,882	Finasteride (5 mg/day)	Positive
Andriole et al. (2010)[121]	Prostate cancer	6,729	Dutasteride (0.5 mg/day)	Positive
Lippman et al. (2009; SELECT)[123]	Prostate cancer	35,533	Selenium (200 μg/day); vitamin E (400 IU/day)	Negative
Esophagus/Stomach				
Blot et al. (1993; Linxian)[150]	Geographic risk	29,584	Multiple vitamins/minerals	Negative
Li et al. (1993)[151]	Geographic risk	3,318	Multiple vitamins/minerals	Negative
All Cancers				
Hennekens et al. (1996; PHS)[152]	Healthy men	22,071	Carotene (50 mg qod)	Negative
Lee et al. (1999)[153]	Healthy women	39,876	Carotene (50 mg qod)	Negative
Gaziano et al. (2012)[126]	Healthy men	14,641	Multivitamin	Positive

Abbreviations: AK, actinic keratosis; BC, breast cancer; BCC, basal cell carcinoma; bid, twice daily; CBC, contralateral breast cancer; DCIS, ductal carcinoma in situ; HNC, head and neck cancer; NAC, *N*-acetylcysteine; NSCLC, non-small cell lung cancer; qod, every other day; SCC, squamous cell carcinoma; SPT, second primary tumor.

In the United States, incidence rates for esophageal adenocarcinoma are among the most rapidly increasing since the late 1970s. This cancer occurs as a sequela of Barrett esophagus and is thought to be the result of gastroesophageal reflux disease.[155] Esophagogastroduodenoscopy often is used as regular surveillance to detect Barrett esophagus among patients with gastroesophageal reflux disease; however, there is no convincing evidence that demonstrates a reduction in the subsequent incidence or mortality of esophageal adenocarcinoma.

Rates of squamous cell carcinoma of the esophagus have been declining concomitantly with the rise of adenocarcinoma, reflecting the decline of smoking prevalence. Very high rates of

squamous cell carcinoma have been identified in a belt spanning central Asia from northern Iran to China,[156] with evidence implicating local risk factors, such as the ingestion of very hot tea and the smoking of opium.[56,155,157]

Several large-scale studies have been launched to assess potential chemopreventive agents for patients at high risk for lung cancer. The Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Trial[130] and the Beta-Carotene and Retinol Efficacy Trial (CARET)[131] were prevention trials that showed the importance of testing even seemingly harmless chemoprevention agents, such as vitamins, before widespread use. The results of both trials are in contrast to numerous observational studies. The ATBC trial enrolled Finnish male smokers between ages 50 and 69. Participants received alpha-tocopherol, beta-carotene, both, or placebo in a randomized, 2×2 factorial design. After a median follow-up of 6 years, there was a significant increase in lung cancer incidence and mortality for the participants who received beta-carotene. Alpha-tocopherol had no effect on lung cancer mortality. CARET enrolled 17,000 smokers and workers exposed to asbestos. Participants were randomly assigned to four arms and received beta-carotene, retinol, both, or placebo in a 2×2 factorial design. The results of the trial demonstrated a 28% increase in lung cancer and a 17% increase in deaths for the participants receiving beta-carotene. The reason for this outcome is uncertain; it occurred despite beta-carotene's role as both an antioxidant and a precursor to retinol.

Retinoids have shown some efficacy as chemopreventive agents for squamous cell malignancies of the head and neck, possibly by promoting terminal differentiation.[128] One study randomly assigned 103 patients with a first primary squamous cell carcinoma of the head and neck to the retinoid analogue 13-*cis*-retinoic acid or to placebo.[122] At 3 years, there were two second primary head and neck cancers in the intervention group compared with 12 in the placebo group ($p = 0.005$). However, because of toxicities, two follow-up phase III trials (in curatively treated NSCLC or head and neck cancer patients) were conducted using lower doses of 13-*cis*-retinoic acid and both had negative results.[129,134]

GASTRIC CANCERS

Heavy intake of smoked and cured meats and foods, limited consumption of fresh fruits and vegetables, and infection with *H. pylori* are associated with an increased risk of gastric cancer.[3] Gastric cancer was the most common cancer in the United States prior to World War II, but it is now much less common. This decline is thought to be the result of increased consumption of fresh meats, fruits, and vegetables and decreased consumption of cured/smoked foods. Experimental evidence of causality is scarce. Gastric cancer remains a very common malignancy in Japan, Latin America, China, and in parts of the developing world. A randomized trial in China of eradication of *H. pylori* infection with a combination of omeprazole, amoxicillin, clavulanate, and metronidazole did not show a reduction in subsequent gastric cancer incidence. Nonetheless, patients who had no gastric pathology at study entry did show a significant reduction in gastric cancer incidence in subgroup analysis.[158] The rates of cancer of the gastric cardia and esophageal adenocarcinoma are rising, and there is evidence to suggest that this may be a consequence of recent declines in the prevalence of *H. pylori.*[159] It is unclear why cancers of the proximal stomach and distal stomach may have inverse associations with the presence of *H. pylori.* Nonetheless, it may be one reason the incidence of distal gastric cancer in the United States has been declining while the incidence of proximal and gastroesophageal junction cancer incidence has been rising.[160]

COLON CANCER

Findings from epidemiologic studies suggest that NSAIDs, such as piroxicam, sulindac, and aspirin, have protective effects against adenomatous polyps and invasive cancer.[119,120,161] The results of prospective intervention trials have demonstrated positive effects on the prevention of polyps. Meta-analyses of randomized trials of aspirin designed to assess other endpoints have demonstrated that these agents prevent colon cancer.[119,120] In a placebo-controlled trial, high-dose celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, was found to reduce the occurrence of colorectal polyps for patients with familial adenomatous polyposis.[162] A prospective, randomized trial of patients with a history of colorectal adenomas demonstrated a 20% reduction in recurrence of polyps for patients who received celecoxib.[163] Trials to assess COX-2 inhibitors and other NSAIDs for the prevention of colorectal adenomas have shown preventive benefits; however, these agents are associated with increased cardiovascular risk. Another study suggested that the risk of colon cancer can be reduced by doses of aspirin as low as 80 mg daily.[164] One observational study suggested that COX-2 inhibitors could improve mortality when used for patients with node-positive colon cancer.[165] This may be partly because of a beneficial effect on cancer metastasis.[166] Several subsequent studies have confirmed that aspirin used as an adjuvant therapy for stage III colon cancer could reduce mortality, and several randomized trials have been initiated.[167,168]

The Women's Health Initiative was a prospective, randomized study involving postmenopausal women randomly assigned to either combination estrogen plus progestin or to placebo. The rate of colorectal cancer was lower for women taking the study drug compared with those taking placebo.[169] However, the effect is offset by the cardiovascular and breast cancer risks associated with treatment with estrogen plus progestin.[170]

The results of epidemiologic studies indicate that diets high in calcium are associated with a lower risk of colon cancer. However, in the Women's Health Initiative study, calcium and vitamin D supplementation did not lower the incidence of colorectal cancer.[149] Evidence from prospective, randomized studies shows that calcium supplementation decreases the risk of recurrence of adenomatous polyps by approximately 20%.[171] However, a more recent trial failed to confirm these findings.[172] Calcium binds bile and fatty acids, reducing intraluminal exposure to compounds that cause hyperproliferation of the colonic epithelium.

Meat and fat intake have been linked to colorectal cancer incidence in numerous observational studies. Nonetheless, another Women's Health Initiative randomized, controlled trial found that there was no difference in the incidence of colorectal cancer among women assigned to a low-fat diet as compared with controls, though this study was relatively short-term and the difference in fat intake may have been too small.[79]

Colectomy is used as a preventive measure for individuals at extremely high risk of colon cancer as a result of a history of ulcerative colitis or of a genetic predisposition to the disease, such as familial adenomatous polyposis.[173]

No chemopreventive agent is currently recommended for the prevention of colorectal cancer for individuals at average risk, although the U.S. Preventive Services Task Force (USPSTF) has recently updated its guidelines for the use of low-dose aspirin for the prevention of coronary artery disease for adults at average risk to include the benefit of a reduction in colorectal cancer incidence as well.[174] The use of NSAIDs for patients with familial adenomatous polyposis following colectomy may be reasonable in conjunction with endoscopic screening.[162,175,176] For patients with hereditary nonpolyposis colon cancer, a randomized trial demonstrated that the use of 600 mg of aspirin for 2 years substantially reduced the incidence of colorectal cancer.[177]

LIVER CANCER

Hepatitis B–induced HCC is one of the most commonly diagnosed cancers in Asia. The use of hepatitis B vaccine has been advocated for its ability to prevent the disease. Reductions in the incidence of HCC in Taiwan and elsewhere suggest some success.[104] Although HCC is much less common in the United States, there has been a rise in incidence rates because of an epidemic of hepatitis C, which also leads to HCC, but for which no vaccine is available. For patients who are diagnosed with hepatitis C, new drug treatment to eradicate the hepatitis C virus may be expected to decrease the risk for HCC in the future. As a result, increased efforts at screening for chronic hepatitis C have been recommended; the CDC currently recommends screening all those born between 1945 and 1965 for hepatitis C, as well as those with a known elevated risk.[178]

BREAST CANCER

Tamoxifen has mixed estrogenic and antiestrogenic activities. It acts as an estrogen agonist in the endometrium and bone and as an estrogen antagonist in breast tissue. It also upregulates transforming growth factor beta, which decreases breast cell proliferation. In randomized, placebo-controlled trials to assess tamoxifen as adjuvant therapy for patients with early-stage breast cancer, this drug was found to prevent new cancers in the contralateral breast. The Breast Cancer Prevention Trial was a randomized, placebo-controlled study of more than 13,000 women at high risk for breast cancer. After a median treatment of 69 months, tamoxifen was found to decrease the risk of breast cancer by 49%. It also was associated with a reduction in bone fractures and with a small increase in the risk of endometrial cancer, stroke, pulmonary emboli, and deep vein thrombosis.[115,146] The Study of Tamoxifen and Raloxifene (STAR) trial compared tamoxifen with the selective estrogen-receptor modulator raloxifene for postmenopausal women; it was found that raloxifene decreased the risk of invasive breast cancer by rates similar to those for tamoxifen, but did not decrease the risk of noninvasive breast cancer. Compared with tamoxifen, raloxifene was associated with a lower risk of endometrial cancer, as well as with a lower risk of thromboembolic events and cataracts.[117] Further follow-up of the STAR trial for more than 6 years found that approximately 75% of the effectiveness of raloxifene versus tamoxifen was maintained with significantly less toxicity.[179] Another randomized trial showed that an aromatase inhibitor, exemestane, could also prevent breast cancer in postmenopausal women.[118] In a trial with 4560 postmenopausal women randomly assigned to exemestane or placebo, exemestane reduced the risk of breast cancer by 65% (95% CI; 0.18, 0.70) as compared with placebo. Similarly, the Second International Breast Cancer Intervention Study (IBIS-II) examined another aromatase inhibitor, anastrozole, in 1920 postmenopausal women and found the risk of breast cancer to be reduced by 53% (95% CI; 0.32, 0.68).[148] Despite these trials, uptake of these drugs for breast cancer prevention has been relatively low.[180]

The Women's Health Initiative was discontinued early in part because of the increased risk of breast cancer (odds ratio, 1.26) among women who were postmenopausal and who were taking active hormone-replacement estrogens with progestins.[181] A parallel trial of estrogen alone compared with placebo for women with a prior hysterectomy did not show an increased risk of breast cancer among women taking estrogen.[182] An analysis of the Women's Health Initiative trials concluded that there was no overall benefit of postmenopausal estrogens for women, except perhaps for short-term reduction of hot flashes.[183]

Prophylactic bilateral mastectomy to prevent breast cancer has not been assessed in a

randomized trial. In a prospective series of 139 women at high risk for breast cancer because of deleterious germline *BRCA1* or *BRCA2* mutations, 76 chose prophylactic bilateral mastectomy and 63 chose close surveillance. At 3 years, no breast cancer was diagnosed in those who chose surgery; eight women in the surveillance group had been diagnosed with breast cancer.[184] This study was small, of short duration, and by design, prone to selection biases. However, the observation that the short-term risk of breast cancer appears to be lower for women with certain *BRCA1* and *BRCA2* mutations who choose prophylactic mastectomy has been confirmed in other studies.[185,186] Because this surgery leaves some breast tissue behind, a patient's risk is not reduced to zero. When coupled with prophylactic bilateral salpingo-oophorectomy, ovarian cancer risk is markedly decreased, and there is an added benefit for breast cancer prevention.[186] Retrospective analysis of mastectomies for 214 women at high risk for breast cancer because of a family history suggests that prophylactic mastectomy can lead to a 90% reduction in risk.[187] One large study of patients from 11 centers investigated 1079 women with deleterious *BRCA* mutations and compared those who self-selected salpingo-oophorectomy with those who did not. With 3 years of follow-up, the prophylactic surgery was associated with an 85% reduction in the risk of gynecologic cancer and a 72% reduction in the risk of breast cancer in the *BRCA1* group, but there was no clear benefit for *BRCA2* carriers.[188]

A Cochrane review concluded that bilateral prophylactic mastectomy for those at very high risk for breast cancer (e.g., those with deleterious *BRCA* mutations) was effective in reducing the incidence and subsequent mortality from breast cancer.[189] One study has suggested that prophylactic bilateral oophorectomy in this setting would prevent at least 80% of ovarian cancers as well.[190]

PROSTATE CANCER

Androgens stimulate prostate cell proliferation and, in laboratory animals, cause prostate carcinogenesis. Finasteride decreases androgenic stimulation of the prostate by inhibiting 5-alpha reductase. This enzyme, which is found in high amounts in the prostate, converts testosterone to the more potent dihydrotestosterone. Finasteride was tested as a preventive agent for prostate cancer in the Prostate Cancer Prevention Trial—a 10-year, randomized, placebo-controlled study involving 18,000 men age 55 or older. Results of the study showed that this drug was associated with a 24.8% reduction in the risk of prostate cancer during the treatment period. There were some initial concerns regarding an observed increased incidence of high-grade tumors that developed while patients were treated with finasteride.[191] Later reanalyses showed that these observations were a result of the statistical methods used and that there were no true increases in high-grade tumors.[192]

A study of another 5-alpha-reductase inhibitor, dutasteride, also found a protective effect against prostate cancer.[121] Long-term follow-up of the finasteride study showed that, despite the reduction in incidence of prostate cancer, there was no improvement in overall survival.[193] Although finasteride reduced the incidence across all Gleason grades, it reduced the prevalence of lower-grade tumors disproportionately. This raises the interesting question of whether the use of a chemopreventive agent is worthwhile solely for incidence reduction if a reduction in mortality does not accompany it.

Testosterone-replacement therapy (TRT) has also become more popular over the past decade. As many as 3% of men older than age 50 receive some form of it. As a consequence, the question of its relationship to prostate cancer risk has been raised. No cohort study large

enough to adequately address the question has been conducted to date, but several small studies have shown no evidence of an increase in prostate cancer risk associated with TRT, nor has there been evidence of progression of existing prostate cancer induced by the concomitant use of TRT.[194]

Findings from epidemiologic studies indicate a correlation between a high intake of antioxidants, such as selenium and vitamin E, and a lower risk of prostate cancer. The results of a small, randomized skin cancer prevention trial of selenium compared with placebo showed a significant decrease in the number of prostate cancers among men treated with selenium compared with men receiving placebo.[195] Eight years into the ATBC Cancer Prevention Trial, which enrolled 29,000 men in Finland, 99 cases of prostate cancer were reported among men receiving vitamin E and 151 cases were reported among men taking the placebo (RR, 0.66; 95% CI; 0.52, 0.86).[196] The cancers diagnosed were almost all detected as a result of the workup of symptoms because there is no routine prostate cancer screening in Finland. However, this difference had disappeared by the 18-year follow-up of this study.[197]

The prostate cancer findings in both of these trials were incidental results of a secondary analysis. A prospective, randomized, placebo-controlled trial—the Selenium and Vitamin E Cancer Prevention Trial (SELECT)—assessed these drugs in 32,400 participants and reported no reduction in prostate cancer incidence.[123]

GYNECOLOGIC CANCER

Conization, loop electrosurgical excision procedure (LEEP), cryosurgery, electrocauterization, laser ablation, or even hysterectomy can be used to treat cervix dysplasia or intraepithelial neoplasia, both of which are precursors to invasive cervix cancer. Vaccines for HPV have been approved for young girls and boys and should lower the incidence of cervix cancer because they have already been shown to decrease the incidence of intraepithelial neoplasia.[198]

Studies have shown a strong protective effect against ovarian cancer for oral contraceptive hormone preparations.[199] However, there is no current recommendation for their routine use for prevention. For women at very high risk for ovarian cancer because of a *BRCA* genetic mutation, bilateral salpingo-oophorectomy after completion of childbearing remains the treatment of choice (including fallopian tube removal).[200] Women with Lynch syndrome, associated with large and small bowel polyps and cancers, are at elevated risk for endometrial cancer and ovarian cancer. For these women, prophylactic hysterectomy and bilateral salpingo-oophorectomy may also be recommended.

KEY POINTS

- Drugs and vitamins to be used for prevention need to undergo the same rigorous assessment of efficacy and toxicity as do therapeutic agents prior to recommendation. Indeed, because they are generally administered to a healthy population, their toxicity profile must be far safer than those of drugs used in the therapeutic setting.
- Most randomized trials of vitamins or nutritional supplements as chemopreventive agents have had negative results.
- Hormone inhibitors for hormone-dependent cancers, including tamoxifen and aromatase inhibitors for breast cancer and antiandrogens for prostate cancer, have proven

efficacious as preventive agents and may have a role in clinical practice, though the benefits must be weighed against potential side effects.

- Aspirin and other COX-2 inhibitors have also been shown to have preventive effects against colorectal cancer in particular, and possibly against other malignancies as well.
- The identification of infectious agents, such as hepatitis B and HPV, as causes of cancer has had profound consequences in terms of providing highly effective interventions, specifically vaccinations, that have led not just to reduced mortality but also to reduced incidence of their associated cancers (HCC, cervical and other anogenital cancers).

CANCER SCREENING

Cancer screening is an attempt to detect cancer or its precursors early in asymptomatic individuals, with the goal of intervening and decreasing morbidity and mortality. A screening test is not typically diagnostic for cancer; rather, it determines whether cancer might be present and whether additional testing, including a biopsy and staging, is necessary. To be of true benefit, screening must lead to earlier treatment that offers a better outcome, usually reduced mortality, compared with treatment that would occur at the onset of symptoms. Because of various biases (discussed in the following section), the ideal evaluation of a screening technology is through the assessment of disease-specific and overall mortality in a prospective, randomized clinical trial.

Early detection of an apparently localized cancer does not automatically confer benefit. There are screening tests for some diseases that have been found to be of no benefit, such as chest x-ray screening for lung cancer or urine screening for vanillylmandelic acid to detect neuroblastoma.[201] A number of common screening tests used in the United States offer undetermined benefits.

POTENTIAL BIASES

The evaluation of the benefits of a screening test is subject to several biases, including lead time, length, and selection biases, the influences of which are reduced in a randomized trial.[202] These biases can lead one to believe that there is a benefit to a screening test when, in truth, there is none; there may even be a net harm. Screening, regardless of benefit, will usually increase the number of specific cancers diagnosed. It also can produce a shift in stage toward lower stages; this will appear to improve survival statistics without reducing mortality (i.e., the number of deaths from a given cancer per number of people at risk for the disease). In such a case, the apparent duration of survival, measured from the date of diagnosis, would increase without lives truly being saved or life expectancy being changed.

When pure lead-time bias occurs, survival—the time from diagnosis to death—is increased, but treatment does not prolong life. Patients do not live longer; they are merely diagnosed at an earlier date. The screening test only prolongs the time the individual is aware of the disease and the time the individual is treated as a patient.

Length bias occurs when slow-growing, less-aggressive cancers are detected during screening. Cancers diagnosed as the result of the onset of symptoms between scheduled screenings are, on average, more aggressive, and treatment outcomes are not as favorable. An extreme form of length bias is termed “overdiagnosis bias,” or detection of pseudo-disease. Some undetected, slow-growing tumors fulfill the histologic criteria for cancer but would never

be clinically significant or cause death. This phenomenon is compounded by the fact that the most common cancers are most frequent among older people. Other competing causes of death, such as heart disease, become more relevant. This is particularly common in prostate cancer.

Selection or volunteer bias must be considered when assessing the results of any clinical trial. The group most likely to seek entry in the study may differ from the general population to which the study results might be applied. In an assessment of a group of individuals undergoing screening, individuals may have volunteered because of a particular risk factor not found in the larger population, such as a strong family history. In general, volunteers are more health-conscious and are likely to have better prognoses or lower mortality rates regardless of actually being screened; this trend is referred to as the "healthy volunteer effect."

ASSESSMENT OF SCREENING TESTS

Because of the biases described above, a screening intervention is best evaluated in a population-based, randomized, controlled screening trial with disease-specific mortality as the endpoint.[202] Because gold-standard randomized screening trials for cancer are perforce large (often involving thousands of people) and last for years, less-definitive study designs often are used to estimate the efficacy and effectiveness of screening practices. In order of strength of evidence from nonrandomized studies, efficacy can by assessed using the following:

- Findings of internally controlled trials in which intervention-allocation methods other than randomization are used, such as allocation determined by birth date or by date of clinic visit;
- Results of cohort or case–control analytic observational studies;
- Findings of multiple time series studies, with or without the intervention; and
- Opinions of respected authorities based on clinical experience, descriptive studies, or consensus reports of experts.

The last form of evidence is the weakest, because even experts can easily be misled by the biases previously described.

POTENTIAL HARMFUL EFFECTS

Subjects can be harmed as a result of screening. A harmful effect can be associated with the test itself, the workup of positive results of screening tests (both true-positive and false-positive results), and injuries from the treatment of true-positive results. Screening can detect some cancers that would never have caused medical problems; the unnecessary treatment of these cancers can be harmful. In addition to the aforementioned adverse effects of screening, there are the financial and emotional costs associated with screening and with all of the extra tests and treatments.

ACCURACY

The accuracy of any medical test is usually described using four indices: sensitivity, specificity, positive predictive value, and negative predictive value. The results of screening tests can be classified into four categories. Definitions and calculations for these terms are provided in Tables 1-5 and 1-6. Sensitivity and specificity are relatively independent of the underlying prevalence or risk of the population being screened, but the positive and negative predictive

values are highly dependent on prevalence (Table 1-7). In other words, screening is most beneficial, efficient, and economical when targeting a cancer common to the general population or groups with a high prevalence (or high risk) of the specific disease being screened. Sensitivity need not be extremely high (Table 1-7). However, it is worth reiterating that the key criterion for the public health recommendation of a screening test is that it is able to reduce cancer mortality.[203]

Table 1-5 Types of Results of Screening Tests

	Condition Present	Condition Absent
Positive Results	True positive (A)	False positive (B)
Negative Results	False negative (C)	True negative (D)

A screening test that is not efficacious in reducing mortality in an average-risk population does not become efficacious if used in a high-risk population. Conversely, if a screening test is efficacious in reducing mortality, it is certainly preferred to use this test for higher-risk populations (e.g., those with family history) or as a lung cancer screening test in smokers, but this is because the yield will be higher, and thus the cost-effectiveness and, more importantly, the positive predictive value will be better (i.e., there will be fewer false positives). But if the screening test is not effective (i.e., does not reduce mortality), it will also not reduce mortality in higher-risk populations and should not be used. A good example is chest x-ray screening, which has been shown not to reduce lung cancer mortality. It would not work any better in heavy smokers or asbestos workers, and it should not be used in those populations either. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial recently demonstrated that CA125 and transvaginal ultrasound screening are not effective in reducing mortality from ovarian cancer (discussed as follows). Thus, despite their significantly higher risk, the use of such screening would also not be indicated in *BRCA* carriers.

Table 1-6 Indices for Describing the Accuracy of Screening Tests

Term	Definition	Ability of Test	Equation
Sensitivity	Proportion of people with the disease who have a positive result on a screening test	To detect disease when it is present	A / (A + C)
Specificity	Proportion of people who do not have the disease who have a negative result on a screening test	To correctly identify the absence of disease	D / (B + D)
Positive predictive value	Proportion of people with a positive result on a screening test who actually have the disease	To accurately predict the presence of disease	A / (A + B)
Negative predictive value	Proportion of people who have a negative result on a screening test who truly do not have the disease	To accurately predict the absence of disease	D / (C + D)

Abbreviations: A, true-positive result; B, false-positive result; C, false-negative result; D, true-negative result.

Table 1-7 Influence of Prevalence on Predictive Value

Positive Predictive Value (PPV) for a Disease with Prevalence of 5 Affected Individuals per 1000 Population			Positive Predictive Value for a Disease with Prevalence of 1 Affected Individual per 10,000 Population		
	Sensitivity			Sensitivity	
	0.8	0.95		0.8	0.95
Specificity	PPV	PPV	Specificity	PPV	PPV
0.95	7%	9%	0.95	0.2%	0.2%
0.999	80%	83%	0.999	7%	9%

KEY POINTS

- Evaluation of the benefits/efficacy of a cancer screening test is far more complicated than simply performing the test and detecting localized cancers.
- The biases of screening are volunteer selection, lead time, length, and overdiagnosis. These biases can make a screening test appear beneficial when there is actually no benefit, or they may even cause harm.
- To offset these biases, a randomized trial is the best way to assess a screening test with the endpoint of reduction in cancer-related mortality.
- While not the metrics by which to decide whether a screening test should be used on a large scale, sensitivity, specificity, and positive predictive value can be important measures of the efficiency of a screening test and can inform the clinician about the rate of false positives and false negatives.

SCREENING FOR SPECIFIC CANCERS

Results from well-executed studies show convincing evidence that screening for cervix, colorectal, and breast cancers is beneficial at certain ages for people at average risk. Although special surveillance of individuals at high risk for some specific cancers because of family history or genetic risk may be prudent, few studies have been carried out to assess its true worth. Lung cancer screening with low-dose CT imaging has also been approved and recommended for those at elevated risk because of heavy smoking.

A number of organizations have evaluated certain screening tests and considered whether to endorse routine use of such measures. The USPSTF[204] and the Canadian Task Force on Preventive Health Care[205] each published screening recommendations after a rigorous review process. Each recommendation is made with a thorough, structured evaluation of the literature by screening experts. The ACS publishes the most commonly quoted screening guidelines (Table 1-8).[206]

BREAST CANCER

Studies of breast self-examination have not shown that this practice decreases mortality.[207] The results of the largest randomized, controlled study of breast self-examination reported to date showed both an increased rate of biopsy and enhanced detection of benign lesions, but little or no stage shift and no reduction in breast cancer mortality.[208] As a result, the ACS no longer recommends breast self-examination as a routine screening test.[206] Findings from several randomized trials indicate that screening women older than age 50 who are at average risk using mammography alone or mammography and clinical breast examination every 1 to 2 years decreases mortality by 20 to 30%. Each trial has been criticized for a certain aspect of its design, but there is power in the consistency of the observations.[209] A recent population analysis from Great Britain estimates that the introduction of mammographic screening to the United Kingdom starting in 1991 for women ages 49 to 64 years has led to an overall reduction in breast cancer mortality of 21%.[210]

Table 1-8 **Screening Recommendations for Asymptomatic Patients with Normal Risk**[206]

Test or Procedure	U.S. Preventive Services Task Force	Canadian Task Force on Preventive Health Care	American Cancer Society
Fecal occult blood testing (FOBT) for colorectal cancer	Annual FOBT or fecal immunochemical test (FIT), starting at age 50	FOBT or FIT every 2 years, starting at age 50	Annual FOBT or FIT, starting at age 50 (FIT preferred)
Flexible sigmoidoscopy for colorectal cancer	Flexible sigmoidoscopy every 5 years, starting at age 50	Flexible sigmoidoscopy every 10 years, starting at age 50 or older	Flexible sigmoidoscopy every 5 years, starting at age 50; consider combining with annual FOBT or FIT
Double-contrast barium enema for colorectal cancer	No recommendation	No recommendation	Every 5 years, starting at age 50
Colonoscopy for colorectal cancer	Every 10 years, starting at age 50	Insufficient evidence	Every 10 years, starting at age 50
CT colonography for colorectal cancer	Every 5 years, starting at age 50	Insufficient evidence	Every 5 years, starting at age 50
Digital rectal examination (DRE)	No recommendation	Poor evidence to include or exclude for men older than age 50	No recommendation
Prostate-specific antigen (PSA) and DRE for prostate cancer	Insufficient evidence to recommend	Insufficient evidence to include PSA in periodic health exam (PHE); poor evidence to include or exclude DRE from PHE	Shared decision between physician and patient. Annually, starting at age 50 in men with a life expectancy of 10 or more years
Pap test for cervix cancer	Starting at age 21, Pap smear every 3 years from age 21 to age 65; alternatively, Pap smear combined with HPV testing every 5 years, starting at age 30	Starting at age 25, screen every 3 years to age 69	Starting at age 21, screen every 3 years with conventional Pap tests or liquid-based Pap tests; at or after age 30, women with three normal tests in a row may screen every 3 years with cervix cytology alone, or every 5 years with HPV DNA test plus cervix cytology; women age 65 or older who have had three or more normal Pap tests and no abnormal tests in the past 10 years and women who have had a total hysterectomy stop cervix cancer screening
Breast self-examination (BSE) for breast cancer	Recommends against clinicians teaching women how to perform BSE	Insufficient evidence to make recommendation	No longer recommended
Clinical breast examination (CBE) for breast cancer	Insufficient evidence to recommend adding over and above mammography	No longer recommended at any age	No longer recommended at any age
Mammography for breast cancer	Every 2 years for women ages 50 to 74; screening before age 50 should take into account patient context and patient values regarding specific benefits and harms	Mammography every 2–3 years for women ages 50 to 74	Annually starting at age 45. Women ages 40-44 years should have the opportunity to begin mammographic screening. Women 55 or older should transition to biannual screening; clinical breast exam not recommended
Low-dose CT (LDCT) scan for lung cancer	For those ages 55 to 80 who have a 30-pack-year smoking history who currently smoke or who have quit within the past 15 years, annual LDCT	For those ages 55 to 74 with a 30-pack-year smoking history who currently smoke or who have quit within the past 15 years, annual screening up to three consecutive times	For those ages 55 to 74 with a 30-pack-year smoking history who currently smoke or who have quit within the past 15 years, discuss potential benefits and harms of screening and emphasize smoking cessation

*These recommendations are for the general population—asymptomatic people who have no risk factors, other than age or gender, for the targeted condition. Abbreviations: CT, computed tomography; HPV, human papillomavirus.

Experts disagree on whether women of average risk between ages 40 and 49 benefit from screening (Table 1-8). A meta-analysis of seven large randomized trials showed no benefit from mammography screening for women in this age group when assessed 5 to 7 years after trial entry.[211] There was a small benefit for women at 10 to 14 years after entry, which may have been the result of screening these women after they turned 50.[212] There is no consensus on the age at which to cease screening. A reanalysis sponsored by the USPSTF suggested that screening before age 50 was not necessarily beneficial.[213] Although there was a potential 18% reduction in mortality, the number needed to screen to achieve this and the concomitant number of false positives that needed to be evaluated were so high that the USPSTF argued that the risk:benefit ratio for screening before age 50 was not worthwhile. More recently, the ACS also amended its longstanding screening guidelines to recommend that screening for women at average risk begin at age 45, while women age 55 or older undergo mammography biennially.

In addition, the ACS no longer recommends clinical breast examinations.[206,214]

The results from outcomes studies show that there is substantial variation among U.S. radiologists regarding recommendations for additional testing or biopsy. This disparity is especially notable among younger women. In large cohorts, nearly half of all women between ages 40 and 49 screened annually for 10 years will have false-positive mammograms necessitating repeat mammography, ultrasound examination, MRI, or biopsy. In addition, the diagnosis of ductal carcinoma in situ has risen dramatically since the widespread introduction of mammographic screening for women younger than age 50.

Mammography may not be as sensitive for detecting breast cancers among women with *BRCA1* or *BRCA2* mutations, possibly because cancers in these women tend to develop at a younger age, when mammography is less sensitive. Studies have suggested that MRI has greater sensitivity than mammography or ultrasound. Its high cost and unproven survival benefit make it undesirable for general use, but it can increase yield in a cost-effective fashion for young *BRCA* mutation carriers,[215,216] as well as for other women at increased risk for breast cancer.[217] The ACS has developed guidelines[218] for the use of MRI for women who have a lifetime risk of breast cancer that is 20 to 25% or greater as determined by the BRCAPRO statistical model[219] or in some other way. Another category of women who are at elevated risk for breast cancer are those with dense breasts; recommendations for them vary, sometimes including ultrasound, MRI, or other tests in addition to mammography.

CERVIX CANCER

The introduction of screening with the Pap test in the late 1940s was accompanied not just by a decline in cervix cancer mortality, but also by a decline in cervix cancer incidence of at least 70%[220] (Fig. 1-1) as a consequence of its efficacy in the detection of preneoplastic lesions. This test has remained the mainstay of cervix cancer screening, though guidelines for the frequency and age range for its use have recently been revised (Table 1-8). Pap smear testing is now recommended for average-risk women in the United States starting at age 21, regardless of their sexual history, with an interval between screenings of 3 years. At age 30, the screening interval can be increased to 5 years and the cytologic testing can be combined with HPV DNA testing. If still normal by age 65 years, further screening could be stopped. Those with special risk factors, such as those who are HIV-positive, should be screened more intensively.[221]

The recognition that HPV causes cervix cancer added a new potential tool for cervix cancer screening, HPV DNA testing. However, exactly how to incorporate this test into routine screening for average-risk women in the United States remains in flux. One large study conducted in the European Union randomly assigned approximately 100,000 women ages 25 to 60 to cytology alone or to HPV testing plus reflex liquid-based cytology. The study found that HPV-based screening was more sensitive in finding cervical neoplasia than Pap smears alone and was more effective in reducing the incidence of cervical cancer (0 in the group randomly assigned to HPV screening vs. 9 in the group without HPV testing). However, no mortality benefit was demonstrated.[222] Furthermore, in women younger than age 30, transient HPV infections are common; this limits the usefulness of the test in that age range. Data from randomized trials suggest that HPV screening could provide greater protection against invasive cervix cancer than cytology screening, starting at age 30, and with screening intervals of 5 years or more.[223]

At this time, the most reasonable recommendation for HPV screening for average-risk women in the United States are that it be used in conjunction with Pap smear testing for women

over age 30 (Table 1-8). At least for now, HPV testing as a single screening modality, while recommended by some groups under some circumstances, does not appear to have sufficient evidence to support its use to the exclusion of Pap smear testing. On the other hand, HPV DNA testing as the sole means of screening has been recommended for use in resource-poor environments where Pap tests are difficult to conduct properly, such as certain African countries. In addition, HPV testing can be used to identify women at higher risk for the development of cervical intraepithelial neoplasia when the Pap test cytologic diagnosis is atypical squamous cells of undetermined significance.[224]

With regard to women who have received the vaccine for HPV, it should be noted that this does not provide immunity against all high-risk HPV types. Thus, for now, it is recommended that the standard routine screening practices be maintained in recipients of the HPV vaccine.[225]

COLORECTAL CANCER

Potential options for colorectal cancer screening include:

- Fecal occult blood testing,
- Sigmoidoscopy,
- Colonoscopy,
- Radiographic barium contrast studies, and
- CT colonography.

The results of randomized studies indicate that annual fecal occult blood testing can reduce colorectal cancer mortality by one-third.[226] The rate of false-positive results for fecal occult blood testing is 1 to 5%. Less than 10% of patients with occult blood found in stool have cancer, and approximately one-fifth to one-third have adenomas. In recent years, the fecal immunochemical test has generally been replacing the traditional guaiac-based fecal occult blood test in settings where stool testing is employed.[227]

Findings from two case–control studies found that screening sigmoidoscopy is associated with a decrease in mortality among participants age 50 or older.[228] The results from other studies show that approximately one-half of all polyps are found with the 35-cm flexible scope and two-thirds to three-quarters are found with a 60-cm scope. Diagnosis of polyps by sigmoidoscopy should lead to evaluation of the entire colon with colonoscopy.

There are three published randomized trials of sigmoidoscopy. One, from Great Britain,[229] showed a clear-cut mortality benefit for sigmoidoscopy that was quite dramatic and may justify the use of sigmoidoscopy as a routine screening test, perhaps even as an alternative to colonoscopy. A second trial, from Italy, showed an 18% statistically significant reduction in colorectal cancer incidence and a 22% reduction in overall mortality that was not statistically significant.[230] The PLCO trial in the United States has also reported the results of its randomized trial of sigmoidoscopy—the largest of the three studies, with over 150,000 participants.[231] This study showed significant 21% and 26% reductions in overall colorectal cancer incidence and mortality, respectively. All three randomized trials showed dramatic and significant reductions in distal colon cancer incidence and mortality, but no benefit for cancers in the proximal colon (which is not imaged with sigmoidoscopy).

Several recent reports, all well-conducted observational studies, explored the benefits of colonoscopy in reducing mortality. At least four such reports found that, although colonoscopy

did reduce incidence and mortality in the left colon, it did not have the same expected benefits on the right side of the colon. The reasons for these findings were unclear and may represent differences in the biology of right-sided compared with left-sided lesions or differences in the expertise of endoscopists in examining the right side of the colon.[232] A case–control study by Baxter et al.[233] demonstrated an overall reduction in colorectal cancer mortality of about 60% with the use of screening colonoscopy and showed a benefit of screening for the right colon; presumably this was because this study was done in the United States and the vast majority of colonoscopies in the United States are done by gastroenterologists who have greater expertise than surgeons or primary care doctors, who were the main endoscopists in the prior studies. The Harvard cohort studies confirmed the overall benefit of colonoscopy as well as its benefit on the right side of the colon as compared to sigmoidoscopy.[234]

Although no prospective, randomized studies have clearly demonstrated a mortality benefit for screening colonoscopy, it is considered prudent to recommend colonoscopy as a screening tool for individuals at average risk for colorectal cancer This rationale is an extension of the available data for sigmoidoscopy, which show a mortality benefit for left-sided cancers, albeit no benefit for the right side of the colon, where the sigmoidoscope does not reach.[235] Colonoscopy should be used for those at high risk, such as those with a genetic predisposition to colorectal cancer and those with inflammatory bowel disease. Little information is available on the utility of the barium enema as a screening tool. Recent interest has centered on CT (virtual) colonography as well, though no studies to date have shown that it reduces mortality. The evidence suggests that, in certain instances, it may substitute for colonoscopy.

Published guidelines for colorectal cancer screening continue to evolve. Although the ACS currently recommends the full range of screening tests listed above as options for screening, new guidelines were published in 2016 by the USPSTF.[236] These guidelines suggest sharing decision making with patients and that patients be offered a choice of screening tests. The guidelines no longer recommend the barium enema, nor do they recommend the guaiac-based fecal occult blood test. Instead, patients are encouraged to choose among the FIT test, the endoscopic procedures (sigmoidoscopy and colonoscopy), and CT colonography.

LUNG CANCER

Screening for lung cancer with chest x-ray and sputum cytologic testing was evaluated in four randomized lung cancer screening trials in the 1960s and 1970s. No reduction in lung cancer mortality was seen in those studies.[237,238] A randomized trial of chest x-ray screening was recently conducted as part of the PLCO study to reevaluate its value. The results of this study reaffirmed the absence of a mortality benefit for chest x-ray screening.[239]

Studies have shown that low-dose spiral CT scanning can diagnose lung cancers at early stages, but it was unclear whether this would save lives.[240,241] This technology was evaluated in a large, randomized clinical trial of heavy smokers, which compared CT screening with chest x-ray screening. These results were reported from the National Lung Screening Trial (NLST)[242] and showed a 20% reduction in mortality for the arm screened with CT. Spiral CT also can detect many benign processes that cause noncalcified lung radiodensities; these are false-positive findings. Spiral CT does increase the number of lesions diagnosed and, thus, will increase the number of diagnostic and therapeutic procedures performed (see Chapter 8 on Lung Cancer). Overall policy reviews conducted for spiral CT screening concluded that the benefits for certain subgroups of heavy smokers outweigh the negatives of overdetection and false positives.[243,244] The USPSTF now recommends CT screening for current or former heavy

smokers of more than 30 pack-years.[245] Several societies have added CT screening to their guidelines as well.[246]

OVARIAN CANCER

Adnexal palpation, transvaginal ultrasound, and measurement of serum CA125 have been considered for ovarian cancer screening and none has been shown to be effective. No randomized prospective trial of screening for ovarian cancer has shown an improvement in ovarian cancer mortality. The results of such screening tests could lead to futile invasive diagnostic testing that might include laparotomy. The PLCO trial randomly assigned over 78,000 women to screening with CA125 and transvaginal ultrasound for 4 years or usual care; no difference in ovarian cancer mortality was found.[247] A large British trial randomly assigned over 200,000 women to either multimodal screening with CA125 and transvaginal ultrasound, annual transvaginal ultrasound alone, or no screening. The study did not show a clear-cut benefit to screening at a median follow-up of 11 years, though follow-up continues.[248]

PROSTATE CANCER

The digital rectal examination (DRE) and measurement of serum PSA are commonly used in the United States, although most professional organizations advise caution in the use of such screening tools (Table 1-8). Prostate cancer is prone to lead-time bias, length bias, and overdiagnosis. Although screening using PSA levels and DRE clearly detects many asymptomatic cancers, its ability to reliably distinguish tumors that could be lethal but are still curable from those that pose little or no threat to health is limited. It has been estimated that 20 to 40% of localized prostate cancers diagnosed during screening are indolent and clinically nonsignificant.[249,250] Treatment of screen-detected cancers may cause morbidity, such as impotence and urinary incontinence, and carries a small risk of death.

Most expert organizations do not recommend screening for prostate cancer. The USPSTF last reviewed the evidence in support of screening in 2012 and found there was insufficient evidence to recommend it.[251] As might be expected, this decision was met with great controversy. The ACS and the American Urological Association recommend that men older than age 50 at normal risk be offered screening and be allowed to make a choice after being informed of its potential risks and benefits (Table 1-8).

The interim results of two large randomized trials of prostate screening have been reported. The PLCO trial randomly assigned 76,693 men to 6 years of annual screening with PSA or regular management according to community standards. In essence, 85% of the men in the intervention group were screened whereas more than 40% of the men in the control arm were screened. After 7 to 10 years, there was no mortality benefit (HR, 1.13; 95% CI; 0.75, 1.70).[252] The European Randomised Study of Screening for Prostate Cancer (ERSPC) randomly assigned 182,000 men in seven countries; each country had slight differences in study design. The intervention group was offered PSA screening every 4 years (every 2 years in Sweden), and 82% participated; a cutoff of 3 was used for the PSA rather than the usual 4. With a median follow-up of 9 years, the HR for mortality was 0.80 (95% CI; 0.65, 0.98). It is notable that 1410 men needed to be screened (16% of patients being screened had an abnormal PSA and required biopsy and further evaluation) to prevent 1 death, and 48 cases of prostate cancer were detected among those 1410 men to save that one life.[253]

SKIN CANCER

No randomized study has been conducted to assess whether screening for skin cancer decreases mortality, and evidence is lacking to establish the benefits of screening for skin cancer.[254] Screening programs in Scotland and Australia may have caused a stage shift in diagnosed melanomas.[255] These programs also may reinforce sun avoidance and other prevention behaviors.

OTHER CANCERS

The dramatic rise in the incidence of esophageal adenocarcinoma during the past two decades has raised concerns regarding prevention. These tumors are known to arise from Barrett esophagus—a metaplastic change in the esophageal mucosa that later progresses to dysplasia and malignancy. The main risk factor for Barrett esophagus is gastroesophageal reflux disease, a condition that has increased dramatically, perhaps in part because of the epidemic of obesity. Thus, there has been a major effort to conduct esophagogastroduodenoscopy on patients with persistent gastroesophageal reflux disease to detect early-stage Barrett esophagus and to intervene in this pathway with the use of proton-pump inhibitors and close surveillance with endoscopy. This has become a recommendation of the American Gastroenterological Association, despite the absence of a randomized trial or other high-quality evidence demonstrating a significant benefit from the point of view of cancer prevention or a mortality benefit.[256]

Although this chapter has focused on cancer screening in the United States, it is worth noting that screening for some cancers may be worthwhile in countries where these cancers are more common. One example is oral cancer, which is the most common cancer among men in India, largely because of the chewing of betel nuts. A randomized trial has shown that in one region, the use of visual screening of the oral cavity reduced mortality significantly.[257]

HCC is a common cancer in large portions of East Asia and Africa, related to chronic hepatitis B infection. A trial was conducted in Shanghai of more than 18,000 carriers of hepatitis B, who were randomly assigned to a serum alpha-fetoprotein test plus ultrasonography every 6 months or no screening. At 5 years, HCC mortality was reduced by 37% in the screened group (HR, 0.63; 95% CI; 0.41, 0.98).[258] The use of radiographic procedures to screen for HCC in patients with preexisting liver disease and cirrhosis was confirmed in another study, from Korea, which showed that the combined use of ultrasound and MRI could detect most HCC at an early stage when it was likely to be resectable.[259] Another common screening test is the use of photofluorography in Japan to screen for gastric cancer. No randomized trial has been conducted to confirm the efficacy of this test in reducing mortality.[260]

One study compared villages in China that were in an area endemic for high rates of squamous cell carcinoma of the esophagus. Fourteen villages (6827 patients) were selected for the intervention, which consisted of one-time endoscopy, while 10 villages (6200 patients) formed the controls. Ultimately, 48.6% of the intervention group underwent endoscopy, and, with a follow-up of 10 years, the mortality from esophageal cancer was 3.35% in the intervention group compared with 5.05% in the controls ($p < 0.001$), with a reduction in incidence as well.[261]

Nasopharyngeal carcinoma is a common cancer in certain parts of China and is associated with exposure to Epstein–Barr virus (EBV). A screening study from Shanghai screened 20,174 subjects for plasma EBV DNA; 5.5% tested positive, of whom about one quarter were persistently positive. They underwent further testing with endoscopy and 34 were found to have

nasopharyngeal carcinoma, mostly early stage. Only one carcinoma developed among those who were EBV-negative. [262]

KEY POINTS

- The PLCO study and the NLST have revolutionized our knowledge and approach and yielded new data on screening for four cancers. Taken together, the data have (1) shown that while chest x-ray screening is ineffective for lung cancer screening, low-dose CT scan screening is effective; (2) confirmed that sigmoidoscopy is effective in reducing mortality from colorectal cancer; (3) provided definitive evidence that CA125 and transvaginal ultrasound screening for ovarian cancer are not effective; and (4) provided negative data on PSA screening for prostate cancer.
- Although mammography screening for breast cancer among women older than age 50 is supported by evidence showing a mortality reduction, screening in women younger than age 50 remains controversial. Recent changes by the ACS reflect a more conservative approach to the use of mammography. Similarly, PSA screening among men for prostate cancer remains controversial. In both circumstances, the absolute mortality reduction is small and the number needed to screen is large, making the risk:benefit ratio a major concern from a policy standpoint.
- Low-dose spiral CT screening is an established new approach to reducing lung cancer mortality among heavy smokers.
- The use of HPV DNA testing in conjunction with Pap smear testing for women age 30 or older can allow the prolongation of the interval between screenings for cervix cancer to extend to 5 years.
- Randomized trial data are substantial enough to support the use of both fecal occult blood testing and sigmoidoscopy as screening modalities for colorectal cancer.
- There is now evidence to support the use of colonoscopy for colorectal cancer screening, albeit the benefits are modest over sigmoidoscopy and possibly over fecal occult blood testing, and the evidence for colonoscopy is not based on randomized trials.

CANCER SURVIVORSHIP

It is estimated that there are currently 15.5 million cancer survivors in the United States, representing approximately 4.8% of the population,[263] and this number is likely to grow in the coming years. This is a good thing, of course, to the degree that it reflects the increasing success of treatment in curing (or at least prolonging life for) those diagnosed with cancer. The number of cancer survivors is also increasing because of the aging of the population, with a concomitant increase in cancer cases, and because of the increased use of screening and diagnostic tests, and thus the increased diagnosis of subclinical disease.

Cancer survivors share a substantial number of issues and problems that are the subjects of intensive research efforts, including their psychologic needs, employment issues, appropriate surveillance, and management of long-term toxicities of treatment. It is also critical to note that they are at increased risk for second malignancies as an overall group. Thus, multiple primary

cancers constitute as much as 16% of tumors nowadays.[264,265] Some survivors may be at increased risk for certain specific cancers.[266] They require, at the least, special attention to make sure that they obtain the screening studies that are recommended for the general population. For those who have special risks, particular screening protocols may be required. Certain adverse effects of treatment can manifest themselves in the long term. Both thoracic radiotherapy and certain chemotherapy drugs, notably anthracyclines, may cause cardiotoxicity, usually manifesting as long-term congestive heart failure or ischemic heart disease, both of which have been described following certain treatments.[267] Peripheral neuropathy from taxanes or platinum drugs can also cause long-term issues for survivors.[268] Other toxicities include pulmonary and renal effects. There has also been growing recent interest in so-called financial toxicity: the consequences that cancer and its management have on the fiscal status of a patient and his or her family. This toxicity has become particularly stressful in an era of shifting insurance plans and growing cost of chemotherapeutic agents.[269,270]

It is mandatory that a good working relationship be established between the oncologist and the primary care physician.[271] Some studies have shown that regular wellness care may be neglected for cancer survivors under the stress and pressure of a cancer diagnosis and its treatment.[272-274] The standard protocols of good medical care, including hypertension, lipid, and other screening and vaccination protocols, should be followed for cancer survivors as they would be for any other adult. In addition, there is increasing evidence that improved lifestyle and other prevention activities, such as weight loss, tobacco-use cessation, increased physical activity, and a moderate diet, may reduce the risk of second malignancies and the risk for recurrence of the initial primary cancer. In the coming years, the medical oncologist is likely to play an increasing role as a primary and secondary prevention expert, similar to the ways in which cardiologists counsel their patients on tobacco cessation, weight loss, physical activity, and lipid management.[275]

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MOLECULAR BIOLOGY

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Recent Updates

- A new section outlining the molecular features of “Infectious Agents as Drivers of Cancer”
- An expanded discussion of “Emerging Concepts on Tumor Heterogeneity and Evolution”
- A discussion of the use of emerging liquid biopsy techniques in studies of cancer biology and therapy

OVERVIEW

Molecular oncology is evolving rapidly. Many of the genes that drive tumorigenesis, and the biologic pathways and processes affected by oncogenic mutations, have now been identified. Moreover, new molecular approaches have enabled the development of therapeutics that target specific oncogenic mutations, and advances in large-scale molecular biology are providing comprehensive descriptions of cancer genomes and allowing targeted therapies to be rationally applied to treat individual cancers. The goal of this chapter is to outline a framework for the molecular basis of cancer, and to describe established and emerging technologies being used to aid in cancer diagnosis, prognosis, and therapy.

BASIC PRINCIPLES OF MOLECULAR BIOLOGY

DNA is a macromolecule composed of four nucleotides—adenine (A), guanine (G), cytosine (C), and thymine (T) (Fig. 2-1).[1,2] Each nucleotide base is connected to a deoxyribose sugar, and phosphodiester bonds between the sugar moieties form the DNA strand. The nucleoside components of one DNA strand form hydrogen bonds with nucleosides on the complementary strand (C pairs with G; A pairs with T) to create a double-stranded DNA molecule. When DNA is replicated, the strands separate and each provides a template for an exact complement to be synthesized. The human genome contains approximately 3 billion nucleotides partitioned among 23 chromosomes. Most human cells contain a complete genomic copy of DNA, but there are exceptions. For example, erythrocytes contain no genomic DNA, mature lymphocytes delete fragments of DNA within either immunoglobulin (Ig) or T-cell receptor genes to generate antigen-recognition proteins, and megakaryocytes contain extra copies of the genome that results from the process of endoreduplication.

Although its definition continues to evolve, in its most basic form a *gene* can be thought of as a DNA sequence that encodes a protein or a functional ribonucleic acid (RNA).[3] Most genes are discontinuous and arranged in segments called “exons” and “introns.” The first step in protein

synthesis is transcription of the DNA template into a linear RNA copy; the introns are subsequently spliced out to generate a messenger RNA (mRNA) that contains a continuous coding sequence comprised of exons (Fig. 2-2). The mRNA is a template for the attachment of ribosomes, and nucleotide triplets, termed “codons,” specify which amino acids will be incorporated into a nascent polypeptide chain (translation). The 5′ and 3′ extremities of mRNA extend beyond the coding regions and have regulatory functions, such as determining mRNA stability and translational efficiency. As a result of alternative splicing, genes may encode multiple mRNAs, each of which specifies a different protein, termed an “isoform.”

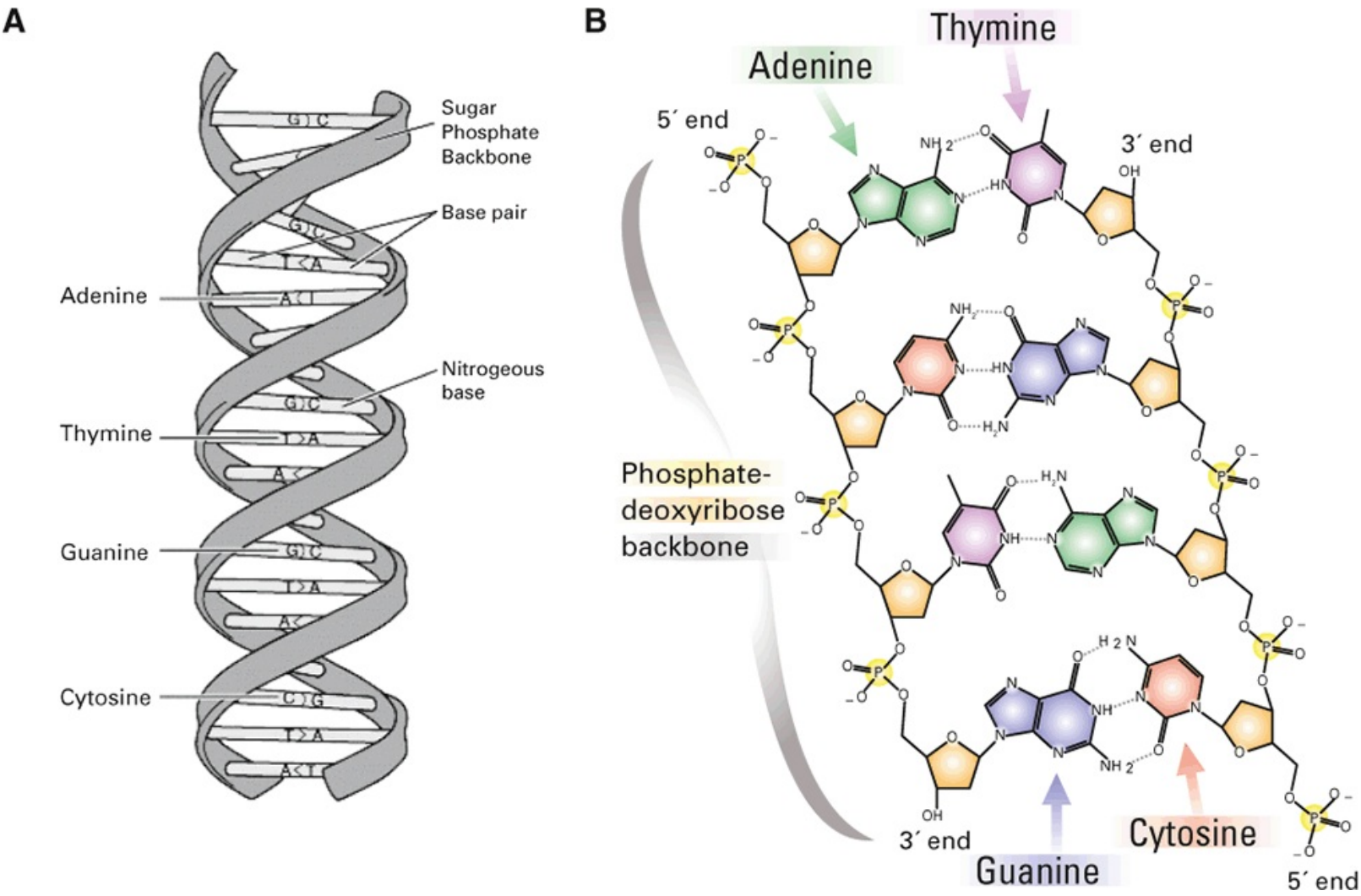

Fig. 2-1 The double helix structure of DNA includes hydrogen bonding between adenine (A) and thymine (T) bases and between guanine (G) and cytosine (C) bases.

(A) The DNA double helix. (B) A close-up of the molecular structure of DNA, showing hydrogen bonds between the two pairs of bases and the phosphodiester bonds between sugar molecules.

Source: *Wikibooks. https://commons.wikimedia.org/wiki/File:DNA-structure-and-bases.png.*

Numerous DNA regulatory elements such as promoters (which direct the site of transcription initiation) and enhancers (which increase transcription) control mRNA expression (Fig. 2-2).[4] These regulatory elements are recognized by proteins, called “transcription factors,” which establish the timing and tissue-specific characteristics of gene expression. Many transcription factors bind directly to these DNA elements and, subsequently, recruit additional regulatory proteins into the transcription complex. Proteins that mediate the assembly of active transcription complexes by recruiting factors or facilitating chromatin changes that promote

transcription are termed “coactivators,”[5] and those that inhibit transcription are termed “corepressors.”[6] Individual cell types express only a subset of the full complement of genes. Specific gene expression programs, thus, fundamentally drive many biologic processes, including growth and development, cellular differentiation, and neoplastic transformation.

Although the Human Genome Project was “completed” in 2003, the exact number of human genes remains unclear, and most estimates are in the range of 21,000. However, because most genes express alternatively spliced mRNAs leading to multiple different protein isoforms, the number of mRNAs and proteins far exceeds the number of genes. It is estimated that the full set of human proteins, known as the proteome, contains 250,000 to 1 million distinct proteins.

Epigenetic gene regulation, or *epigenetics,* refers to heritable, higher-order processes that can profoundly influence gene expression without mutating DNA. Chromatin is highly dynamic and undergoes remodeling via two central epigenetic processes, histone modification and DNA methylation.[7] DNA is compacted into chromatin by winding around proteins called “histones,” which maintain the DNA in nucleosomal complexes (Fig. 2-3A). Histones are modified covalently (e.g., acetylation, methylation, phosphorylation, and ubiquitylation) by changes in subunit composition (e.g., replacement of core histones by specialized histones) and by repositioning. Each of these modifications renders DNA more or less accessible to RNA polymerase (Fig. 2-3B).[8,9] Histone methylation occurs on lysine residues and is controlled by opposing methylating and demethylating enzymes: methylation on some sites facilitates transcription, whereas on others transcription is repressed.[10] Histone acetylation is also regulated by groups of opposing enzymes: acetylation is found in actively transcribed genes, whereas histone deacetylation correlates with repression. Epigenetic regulation also involves DNA modifications, most commonly cytosine methylation within cytosine–guanosine (CG) dinucleotides.[11] DNA regions that contain many CGs are termed “CpG islands,” and their methylation represses transcription. Indeed, promoter methylation is one way that cancer cells inactivate tumor suppressor genes. There is widespread cross talk between epigenetic modifications of DNA and histones, and genomewide analyses are revealing how complex epigenetic “marks” establish differential gene expression.[12,13]

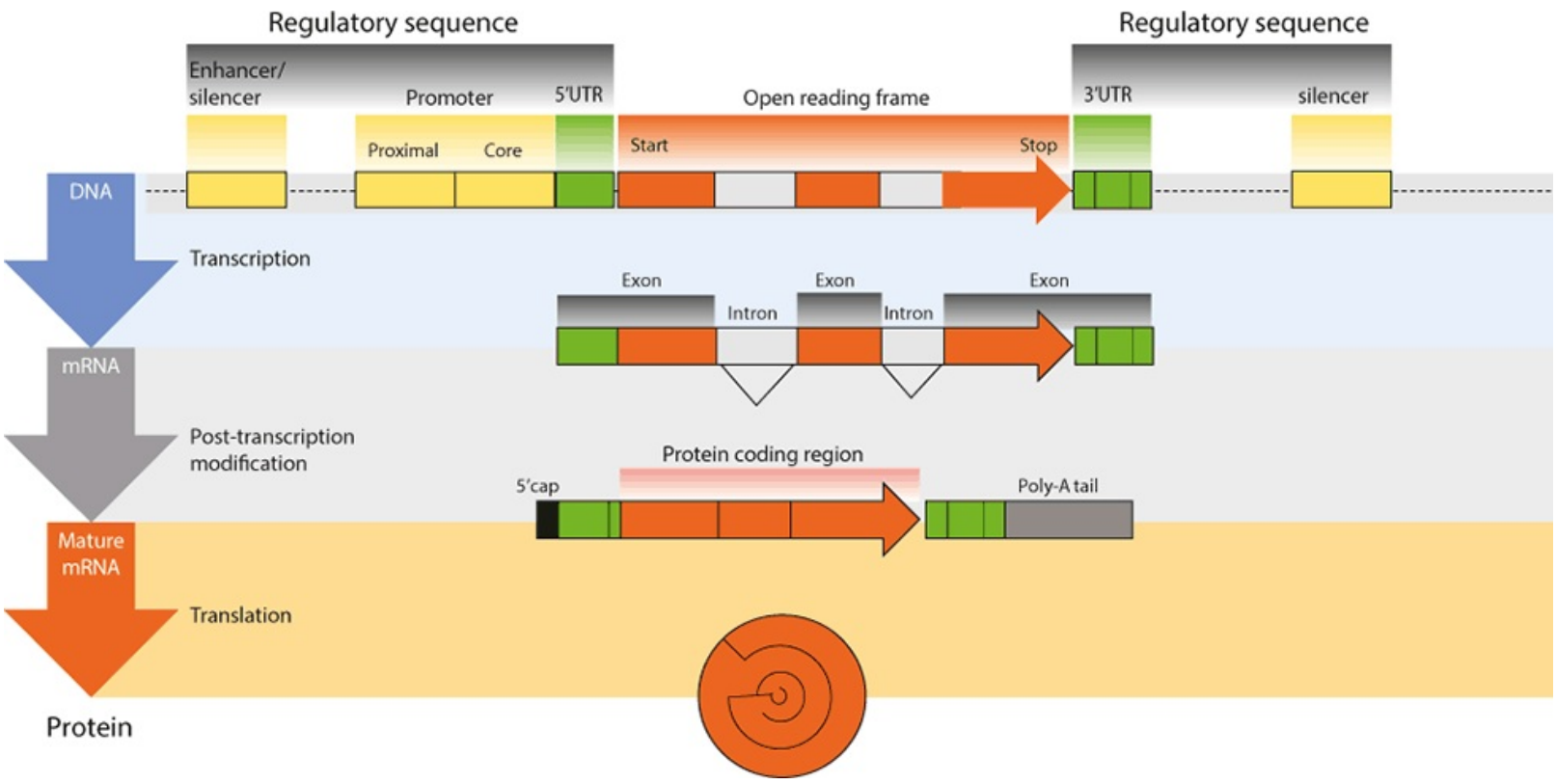

Fig. 2-2 Schematic diagram of an idealized gene, including promoter elements, an enhancer, and the transcribed region of the gene.

Promoter, enhancer, and silencer regions (yellow) regulate the transcription of the gene to generate a pre-mRNA, which contains 5' and 3' untranslated regions (green), protein coding regions (orange), and introns (light gray). Further modifications, including addition of a 5' cap (black) and 3' poly-A tail (dark gray) and removal of introns, results in a mature mRNA. The untranslated regions regulate translation of the mRNA to produce the protein product.

Source: *Shafee T, Lowe R. Eukaryotic and prokaryotic gene structure.* WikiJournal of Medicine. *2017;4(1).*

Because of their influence on gene expression, the enzymes that catalyze epigenetic modifications are important targets for cancer therapeutics.[14,15] For example, histone deacetylase inhibitors are approved for the treatment of T-cell lymphoma and multiple myeloma,[16,17] and inhibitors of the histone methyltransferase EZH2 are in clinical trials.[18-20] DNA methylation is another important drug target: 5-azacytidine and 5-aza-2′-deoxycytidine, which are approved for treatment of myelodysplastic syndrome, inhibit DNA methylation and reestablish expression of genes that were repressed by methylation.[21]

KEY POINTS

- Genes are functional units contained within DNA that specify the production of RNAs and proteins.
- Cells express only a subset of the genes contained within their genomes. Genes are transcribed into mRNA, and this is controlled by regulatory DNA elements (e.g., enhancers, promoters, and insulators).
- Gene expression is regulated by epigenetic modifications of DNA and histones. Chromatin modifications, which include methylations and acetylations, play a major role in determining the timing and extent of gene expression. The enzymes that catalyze epigenetic modifications are important targets for the development of cancer

therapeutics.

ANALYZING NUCLEIC ACIDS AND DETECTING CANCER-ASSOCIATED MUTATIONS

DNA

Polymerase Chain Reaction

The polymerase chain reaction (PCR) is a technique that can synthesize large quantities of specific DNA sequence fragments from minuscule quantities of template.[22,23] In its most basic form, PCR relies on: (1) annealing synthetic DNA primers to DNA sequences that flank the target DNA to be amplified, and (2) DNA polymerase enzymes isolated from thermophilic bacteria that can survive high temperatures. Multiple cycles of DNA-strand synthesis, heat denaturation, and primer reannealing allow for the repeated replication of the target sequence, resulting in exponential amplification of the DNA fragment (Fig. 2-4). For example, 20 PCR cycles produce approximately 1 million double-stranded copies of the original DNA, whereas 30 cycles produce more than one billion copies. A wide variety of PCR-based techniques have revolutionized virtually all methods used to manipulate, detect, and analyze nucleic acids.

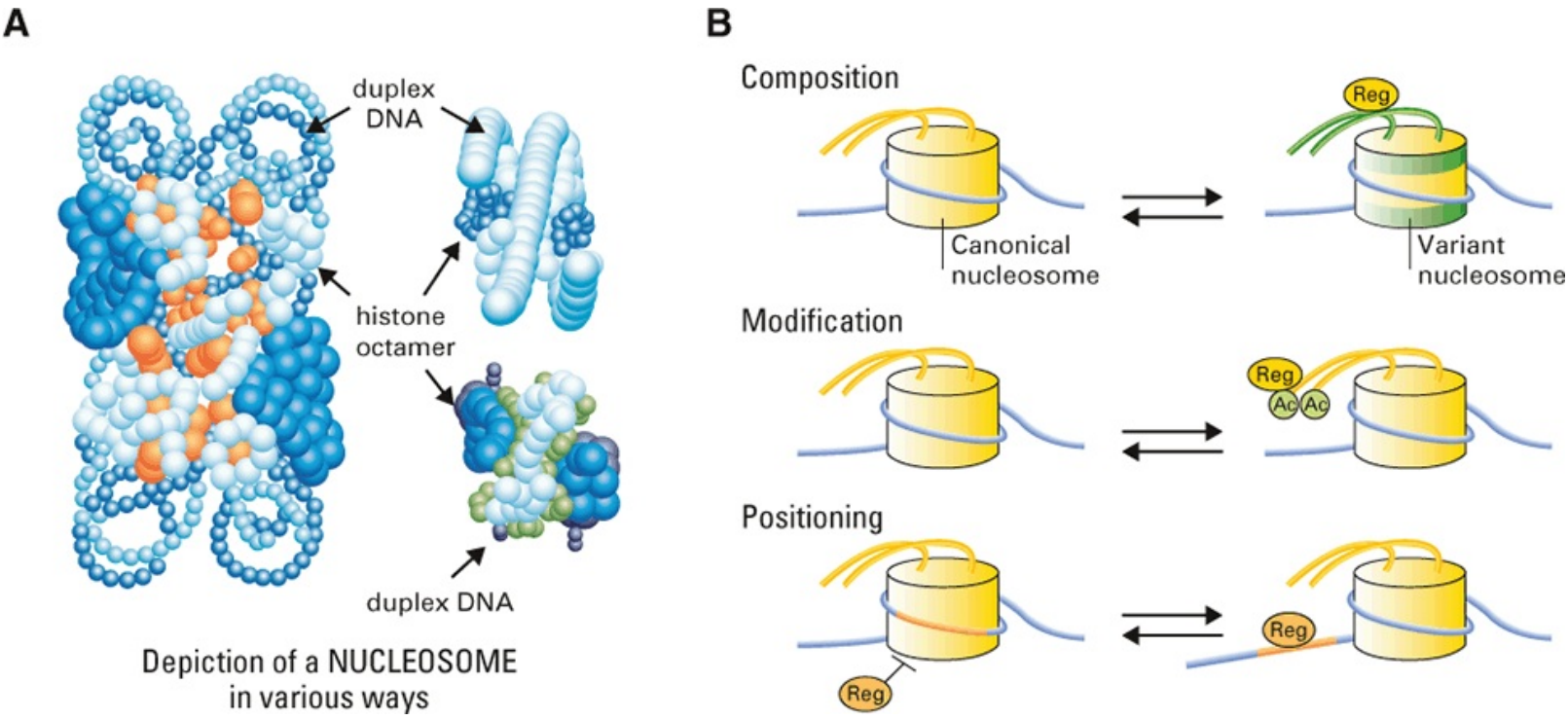

Fig. 2-3 Nucleosome structure and regulation.

(A) Nucleosome structure. The view is down the molecular 2-fold axis; DNA is represented by a tube that almost completely occludes the protein. (B) Nucleosome regulation. (top) Remodeling complexes can remove the canonical H2A–H2B dimers and replace them with variant histones (indicated in green), forming a variant nucleosome with unique tails that might bind unique regulatory proteins. (middle) Nucleosome modification (only acetylation [Ac] is depicted for simplicity) allows the binding of regulatory factors, which have specialized domains that recognize acetylated histone tails. (bottom) Nucleosome repositioning allows the binding of a regulatory factor to its site on nucleosomal DNA (orange segment).

Reprinted by permission from Macmillan Publishers Ltd: Nat Rev Mol Cell Biol. Saha A, Wittmeyer J, Cairns BR. Chromatin remodeling: the industrial revolution of DNA around histones. 2006;7:437–447. PMID: 16723979.

DNA Polymorphisms Facilitate Genetic Analyses of Complex Diseases

DNA sequences that exhibit substantial variability in a population are termed “polymorphisms” and distinguish between alleles (gene variants). Genomewide maps of polymorphic markers

were important tools in many previous analyses of genetic traits, such as cancer predisposition. Through linkage analysis of pedigrees in which early-onset cancer did or did not develop, the genetic polymorphisms that segregated with the cancer-development phenotype identified many hereditary cancer genes. Single-nucleotide polymorphisms (SNPs) are the most common polymorphisms; they represent approximately 1% of any individual's human genome sequence. Current approaches use microarray-based chips and/or DNA sequencing methods to analyze SNPs on a genomewide scale, as discussed below.[24-26] With this large volume of genetic variants, geneticists can now apply more complex methods of analysis to large populations of people who do and do not have specific phenotypes. Agnostic techniques such as genomewide association studies (GWAS) can identify the relationships among specific genes and genetic variants and health traits of interest. Alternatively, some common polymorphisms have been shown to affect phenotypes in vitro, such as metabolism of cancer therapeutics, and the relevance of these findings to clinical care can be confirmed in small patient-oriented studies.

Cytosine–adenine (CA) dinucleotide repeats, called "microsatellites," are another type of polymorphism. These regions are susceptible to imperfect replication, thus leading to variability in length. DNA mismatch repair (MMR) enzymes normally suppress these errors, but they are mutated in some familial cancers, such as hereditary nonpolyposis colon cancer (HNPCC)/Lynch syndrome. Loss of expression of MMR proteins causes altered microsatellites that form the basis of some diagnostic tests.

Next-Generation DNA Sequencing: Beyond the Human Genome Project

The completion of the Human Genome Project in 2003 heralded a new era in molecular medicine. Obtaining the human genome with 99.9% accuracy took 13 years and nearly $3 billion. The technology used to obtain the reference human genome sequence required large-scale automation and an international consortium of scientific teams. Although a remarkable achievement, the methods used for the Genome Project were not practical to apply toward goals such as sequencing cancer cell genomes to guide treatment decisions. Newer technologies, termed "next-generation sequencing" (NGS), have increased the speed and dramatically reduced the expense of genome-scale DNA and RNA sequencing.

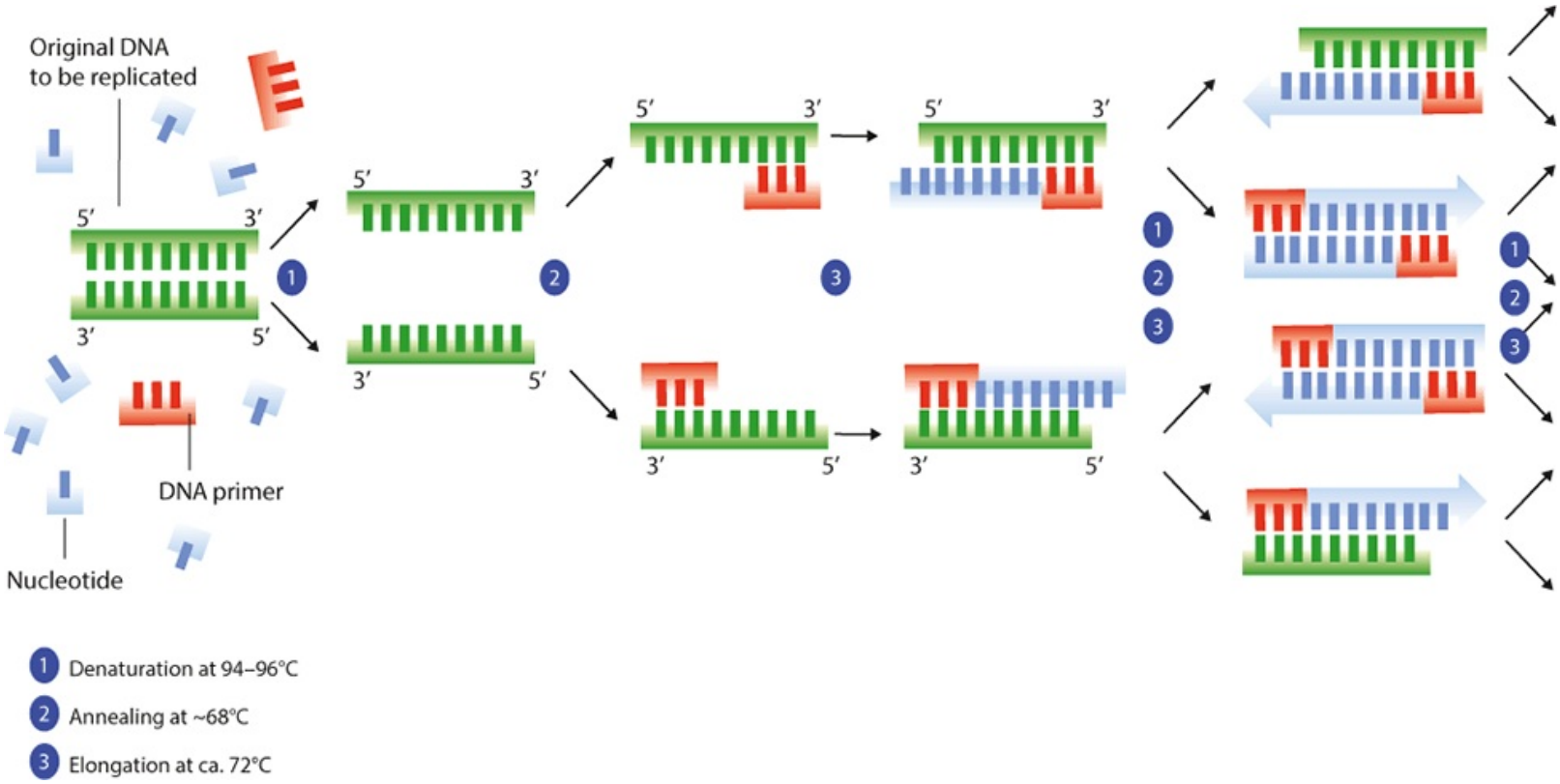

Fig. 2-4 Polymerase chain reaction (PCR).

The DNA (target) to be amplified is shown as a double-stranded DNA molecule with complementary segments (in green, far left). Also shown are sequence-specific primers (red) and nucleotides (blue). The temperature changes required for each step are indicated. The DNA is denatured and then allowed to reanneal to the primers. Taq DNA polymerase then extends from the primer using supplied nucleotides, making perfect complementary copies of the segments of DNA (in blue), yielding two copies of the target DNA after cycle 1. In subsequent cycles, the DNA is denatured and reannealed and the steps in cycle 1 are repeated, yielding exponentially increasing copies of target DNA such that with *n* cycles the yield of DNA is 2^n.

Source: *Wikipedia. Public Domain, https://en.wikipedia.org/wiki/Polymerase_chain_reaction.*

NGS methods apply massively parallel sequencing technologies to obtain millions of DNA sequence reads simultaneously using a single instrument.[27-29] Although technology platforms vary, what they have in common is that the length of the sequence read for each DNA molecule is relatively short. The power of these technologies is that they rely on sequence analysis methods that use a reference human genome sequence and sophisticated bioinformatics for positioning and alignment of millions of short reads. Because these methods are quantitative, they can also detect structural changes, such as chromosomal gains and losses and translocations in cancer cells, in addition to other types of mutations (Fig. 2-5). The cost and speed of NGS are rapidly improving. For example, in 2008, two studies reported human genome sequences that were completed in a few months, but cost approximately $1 million per genome.[30,31] As of 2016, rapid human genome sequencing was available, with costs in the range of several thousand dollars and time frames measured in weeks; this has enormous implications for understanding cancer biology, prognosis, diagnosis, and treatment. These techniques are enabling individualized treatments based on genome-scale sequence data (see the Oncogenomics and Precision Oncology section).[32]

NGS also allows epigenetic studies at a genomewide scale. For example, ChIP-Seq uses antibodies that recognize specific modifications (e.g., histone methylation) to isolate fragments of DNA associated with the modified histone; then NGS is applied to identify all DNA regions that contain the modification.[33] This strategy has produced highly detailed maps of the epigenetic marks that regulate gene expression (Fig. 2-6). Similar approaches have shown that

CpG methylation is a highly dynamic process that changes greatly during cellular differentiation.[34] The Encyclopedia of DNA Elements (ENCODE) project has used NGS approaches to catalog transcription factor binding sites as well as chromatin and histone modifications across the human genome.[35] These technologies are providing an entirely new understanding of how gene expression is regulated in health and disease.

RNA

Real-Time PCR

PCR-based methods employed for RNA analyses use reverse transcription, in which the reverse transcriptase enzyme and DNA primers first convert mRNA to a DNA copy, called "complementary DNA" (cDNA). This general strategy is termed "reverse transcription–polymerase chain reaction" (RT-PCR) to reflect both the reverse transcription and PCR steps. RT-PCR methods are widely used to precisely measure RNA abundance in cells and tissues. Real-time PCR assays use fluorescent dyes to accurately measure the amount of PCR products synthesized in various amplification cycles.[36,37] The advantages of real-time PCR include extreme sensitivity, technical ease, and the ability to accurately quantitate RNA over a very wide abundance range. Real-time PCR is often the method of choice for analyzing the abundance of specific mRNAs in tumor samples, such as monitoring the expression of the *BCR-ABL* transcript in patients undergoing therapy for chronic myeloid leukemia (CML), and for detecting minimal residual disease in leukemia and lymphoma.[38,39] RT-PCR can also simultaneously determine the expression of multiple genes. For example, one approved diagnostic test uses RT-PCR to assess the expression of 21 genes to predict recurrence risk in women with early-stage estrogen receptor–positive breast cancer.[40]

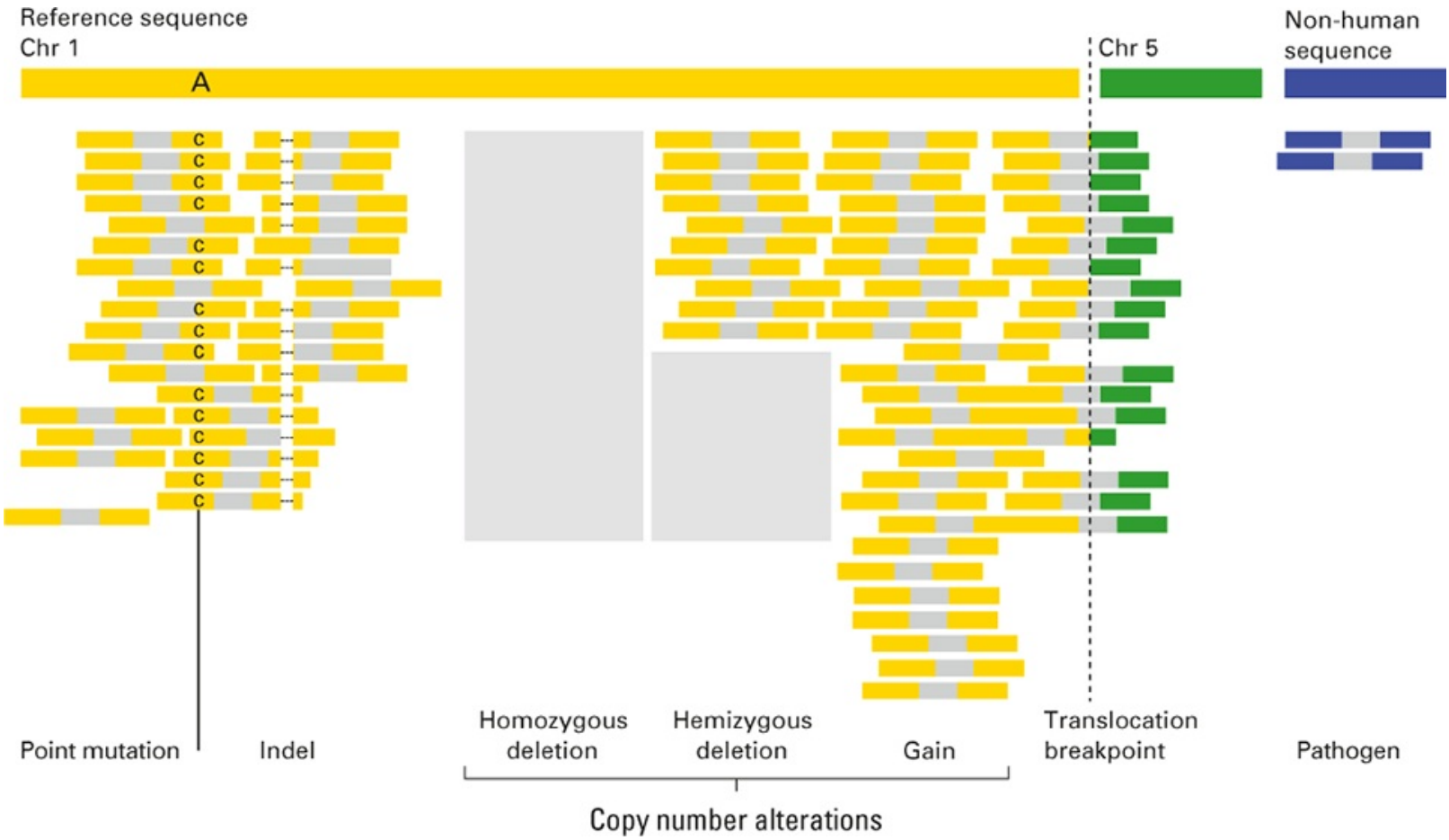

Fig. 2-5 Types of mutations discovered by next-generation genomic sequencing.

Sequenced fragments are depicted as bars, with colored tips representing the sequenced ends and the unsequenced portion of the fragment in gray. Reads are aligned to the reference genome (mostly chromosome 1, in this example). The colors of the sequenced ends show where they align with the target DNA. Different types of genomic alterations can be detected, from left to right: point mutations (in this example, A to C) and small insertions and deletions (indels; in this example, a deletion shown by a dashed line) are detected by identifying multiple reads that show a nonreference sequence; changes in sequencing depth (relative to a normal control) are used to identify copy-number changes (shaded boxes represent absent or decreased reads in the tumor sample); paired ends that map to different genomic loci (in this case, chromosome 5) are evidence of rearrangements; and sequences that map to nonhuman sequences are evidence for the potential presence of genomic material from pathogens.

Microarrays, NGS, and Global Analyses of Transcription

Some RNA analysis approaches measure the expression of thousands of genes simultaneously, and these typically utilize either microarrays or NGS. Microarray chips are small slides on which either oligonucleotides or cDNAs are spotted in a defined array.[41] Hybridization of cDNA made from tumor and control cells, each labeled with a different fluorescent dye, can show relative differences in gene expression between samples. In some cases, small amounts of RNA from limited clinical specimens are first amplified by PCR prior to hybridization. Microarray analyses of the set of genes expressed in a tumor sample, termed the “transcriptome,” have been used in diagnostic and prognostic applications. Examples include separating morphologically indistinguishable large cell lymphomas into high- and low-risk groups on the basis of their gene expression patterns (which reflect their cell of origin) and predicting risk for metastases in women with node-negative breast cancer (Fig. 2-7).[42-44] Because NGS is quantitative, it provides new ways to assess mRNA abundance at the genome scale, termed “RNA-Seq,” that are not prone to many of the technical limitations of microarrays. Thus, as NGS becomes more widely available, these approaches will replace microarrays as the method of choice for quantitating mRNAs in tumors. Indeed, RNA-Seq is becoming a vital component of cancer diagnosis and treatment.[45]

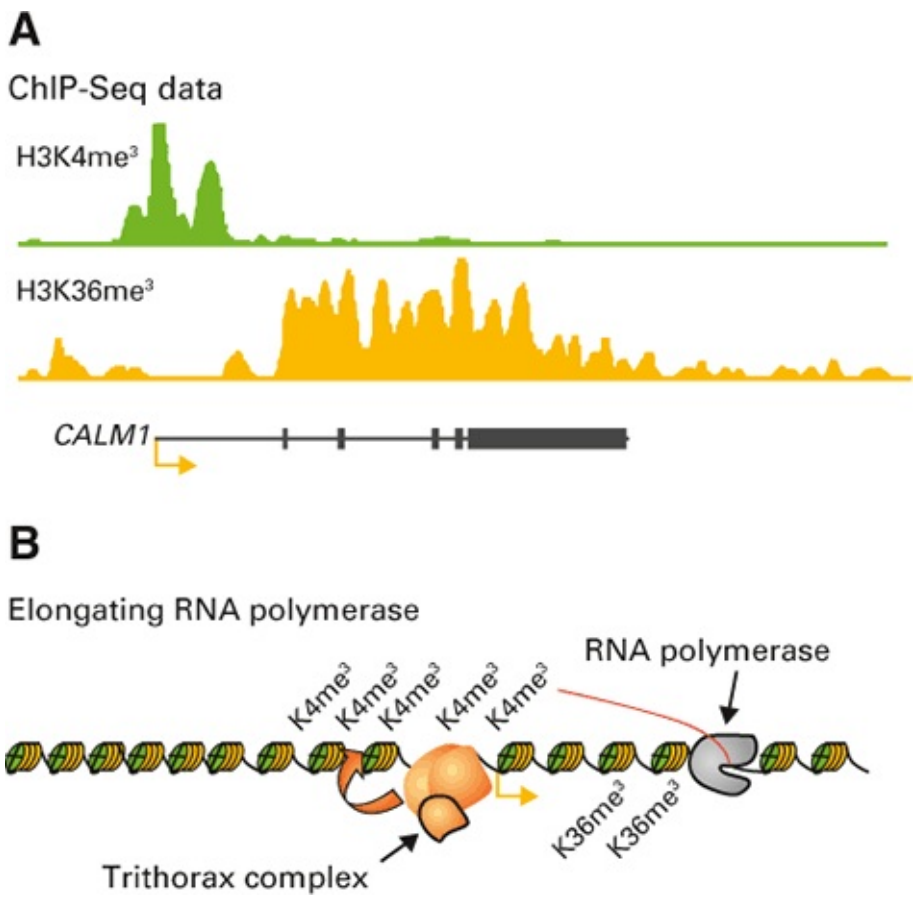

Fig. 2-6 Chromatin state maps reveal a stereotypical pattern at active genes.

(A) In mouse embryonic stem cells, the transcription start site for the *CALM1* gene (orange arrow) is marked by H3K4 trimethylation, a trithorax-associated mark, while the remainder of the transcribed region is marked by H3K36 trimethylation. (B) Evidence from model systems supports a central role for initiating and elongating RNA polymerase II in recruiting the relevant histone methyltransferase enzymes.

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MicroRNAs, Small Interfering RNAs, and CRISPR/Cas9 Genome Engineering

MicroRNAs (miRNAs) are small RNAs (18 to 24 nucleotides) that regulate the expression of other genes by base-pairing to their target mRNAs and inhibiting their expression (Fig. 2-8).[46] Most miRNAs are encoded within longer primary transcripts that are processed to form the final miRNAs. More than 400 miRNA genes regulate most human cellular processes.[47,48] Individual miRNAs target many genes simultaneously (dozens to hundreds), and many human genes are controlled by multiple miRNAs. Aberrant miRNA expression is thought to play causal roles in human neoplasia, and miRNA deregulation causes cancers in mouse models.[49-51] Because specific cancers exhibit characteristic and abnormal patterns of miRNA expression that can be detected in tissues such as blood, miRNA analyses could become another important molecular tool in cancer diagnosis and prognosis.[52]

Small interfering RNAs (siRNAs) are synthetic double-stranded miRNAs that have become common tools for molecular oncology research. Because siRNAs efficiently catalyze the degradation of their cognate mRNAs, researchers can design siRNAs that inhibit the expression of any desired mRNA transcript. These techniques, termed “RNA interference,” facilitate powerful studies of gene function, and genomewide siRNA screens are extensively used to dissect biologic pathways to ascertain gene function and identify drug targets in cancer cells.[53,54] The recent development of simple and robust genome-editing technologies using the Clustered Regularly Interspaced Short Palindromic Repeats/Cas9 (CRISPR/Cas9) system

provides a second valuable tool for whole-genome genetic screens or drug screens. While siRNA techniques can downregulate gene expression, CRISPR/Cas9 readily mutates genes such that there is a complete loss of gene expression. Thus, CRISPR/Cas9 techniques are now complementing or supplanting RNA interference in many genetic and drug screening applications.[55-58]

KEY POINTS

- DNA analysis with NGS methods, which utilize computational analysis of short nucleic acid sequence reads aligned with reference genome sequence information, can define near-complete mutational landscapes of individual tumor samples.
- Analyses of mRNA can quantitate the expression of specific genes in tumor samples, which provides insights into cancer biology as well as important diagnostic and prognostic information.
- Whole-genome genetic screens using siRNA or CRISPR/Cas9 technologies can identify genes that promote or suppress cancer or that mediate resistance to chemotherapy.

CHROMOSOME ANALYSIS

KARYOTYPING, FLUORESCENCE IN SITU HYBRIDIZATION, AND ARRAY COMPARATIVE GENOMIC HYBRIDIZATION

Cancer cells often exhibit chromosome abnormalities that are pathognomonic for specific diseases. Karyotype analyses examine an individual's entire chromosome complement, and classical analyses identify chromosomes in metaphase spreads based on banding patterns and morphology. Although these techniques are still widely used, particularly to classify hematologic malignancies, they are often augmented with newer techniques that are more sensitive and/or comprehensive. Several cytogenetic methods employ fluorescence in situ hybridization (FISH). Fluorescently labeled synthetic, prespecified sequence, nucleic acid probes are incubated with fixed metaphase or interphase cells. The probes hybridize to their complementary sequences, which allows visual inspection of the structure of specific genes. For example, chromosome- and gene-specific probes are used to determine the copy number of specific oncogenes, such as the *HER2* gene in breast cancers and gastroesophageal cancers, because significant amplification of this gene predicts sensitivity to anti-HER2 therapies. Another common FISH technique uses probes that detect gene fusions and chromosome translocations. For example, presence of the *BCR-ABL* fusion is diagnostic of CML and is sometimes found in acute leukemias. Similarly, the *EML4-ALK* gene translocation defines a subgroup of non-small cell lung cancers. Importantly, the identification of these translocations is clinically relevant, as it confers sensitivity to small molecular tyrosine kinase inhibitors. The ability of FISH-based methods to identify rare cells with abnormal karyotypes makes them useful for detecting residual disease when malignant cells harbor a cytogenetic marker. Spectral karyotyping is another FISH method for characterizing chromosome aberrations that cannot be appreciated by classic techniques; it uses a panel of chromosome-specific fluorescent probes that allow the identification of subtle and/or complex chromosomal rearrangements (Fig. 2-9).

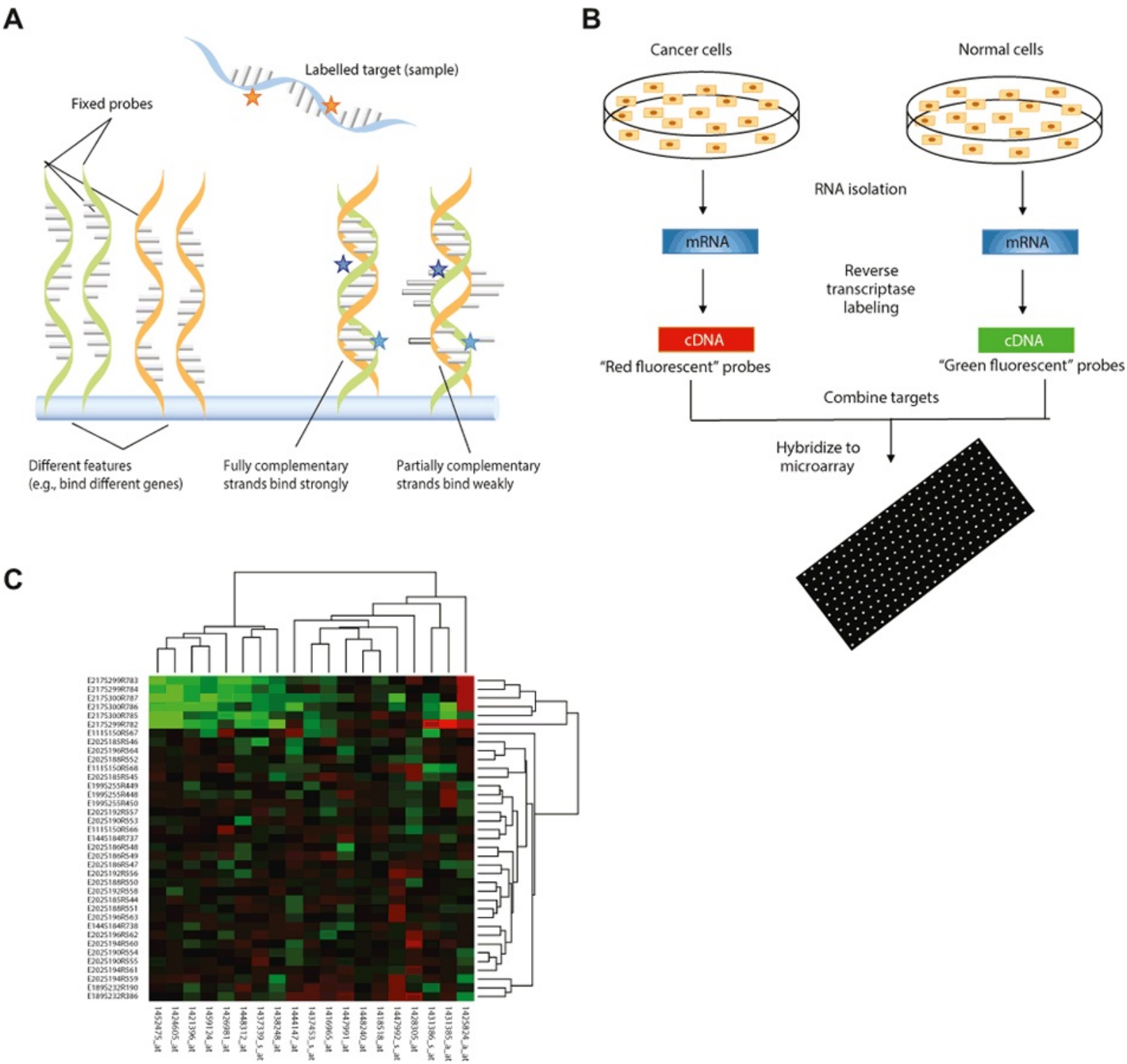

Fig. 2-7 Gene expression microarray.

(A) Microscopic dots of nucleic acid probes representing different genes are fixed to chips, where they can hybridize to labeled DNA from tissue samples. (B) Standard RNA and tumor RNA are isolated from respective samples, converted to cDNA, labeled with different fluorescent probes, and hybridized to microarrays. (C) The resulting array of fluorescent signals is read electronically and the output compares gene expression of a subset of genes between the two samples. A typical gene expression heat map is shown, where genes in green are upregulated and genes in red are downregulated.

Source: *Wikipedia. Public Domain, https://en.wikipedia.org/wiki/DNA_microarray.*

Many DNA losses or gains in tumors involve regions that are too small to be visualized by cytogenetic methods. Comparative genomic hybridization (CGH) can identify DNA gains and losses in a tumor by using DNA hybridization to compare it with a normal sample. In array CGH, labeled tumor and normal DNA are hybridized to chips containing arrays of DNA fragments representing entire genomes.[59] Because array CGH detects copy-number changes in DNA

fragments too small for detection by cytogenetic techniques and at the genome scale, it provides unique insights into the complex genomic gains and losses that drive neoplastic transformation. However, as previously discussed, NGS approaches are now becoming the preferred means of detecting copy-number changes in cancers.

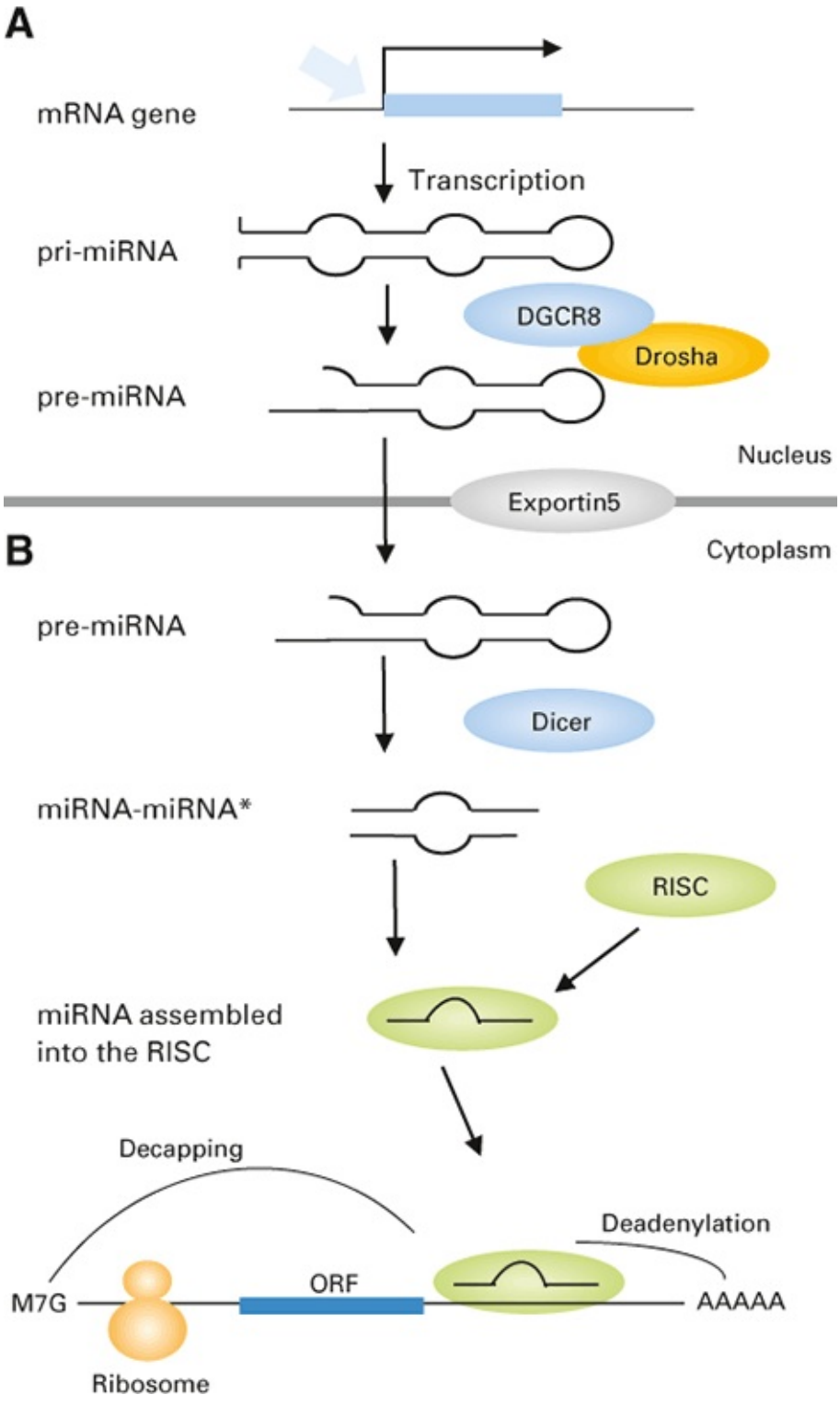

Fig. 2-8 Model of small-RNA-guided post-transcriptional regulation of gene expression.

(A) Primary miRNA transcripts are processed to miRNA precursors in the nucleus by the RNase-III-like enzyme Drosha. (B) The miRNA precursor is subsequently exported to the cytoplasm by means of the export receptor exportin-5. The miRNA precursor is further processed by Dicer to small interfering RNA (siRNA)–duplex-like intermediates. The duplex is unwound while assembling into miRNA ribonucleoproteins/RNAinduced silencing complexes (miRNP/RISC). The incorporated miRNA serves to target these complexes to mRNAs with similar sequences. This ultimately results in regulation of gene expression through translational repression or mRNA cleavage.

Source: *https://www.researchgate.net/publication/288436945_Stress_response_factors_as_hub-*

regulators_of_microRNA_biogenesis_implication_to_the_diseased_heart.

KEY POINTS

- Karyotyping reveals gross DNA structural anomalies in tumor cells, such as translocations and chromosomal deletions.
- FISH techniques detect structural abnormalities in tumor DNA, such as translocations, deletions, and copy-number variations. Genome alterations identified by FISH are clinically relevant, as they can predict sensitivity to molecularly targeted therapies and can be used to detect residual disease in hematologic cancers.
- Comparative genomic hybridization increases the sensitivity and resolution of cytogenetic analyses.

ANALYSIS OF PROTEINS: ANTIBODY-BASED METHODS

WESTERN BLOTTING, IMMUNOHISTOCHEMISTRY, AND FLOW CYTOMETRY

As previously noted, despite having ~21,000 genes, the human genome encodes >250,000 distinct proteins. Methods to study large sets of proteins simultaneously, collectively termed "proteomics," enhance the understanding of cancer and offer the potential for diagnostics that might advance cancer care beyond that achieved with NGS.

Protein-detection methods have been in common use for decades. Antibody-based methods are well established; low- to intermediate-throughput assays are routinely used in experimental and clinical laboratories to study protein expression and function. Lysis of cells or other tissue samples solubilizes proteins. These lysates can be separated by gel electrophoresis and transferred to membranes, which can then be exposed to detection probes, most commonly antibodies (Western blotting); this can detect changes in protein size, posttranslational modifications (e.g., phosphorylation), and abundance.[60] Analogous methods are used in fixed- and fresh-tissue specimens. To aid in diagnosis, pathology departments routinely employ antibody-based immunohistochemistry (IHC) methods to detect the expression of specific proteins in tumor cells, including panels of cellular markers that help to define the origins of poorly differentiated cancers or to differentiate squamous cell carcinoma and adenocarcinoma in lung cancers. Furthermore, IHC is frequently used to subclassify human tumors to refine prognosis and determine treatment. For example, p16INK4A overexpression is a surrogate for human papillomavirus (HPV)–associated head and neck cancers, which have a more favorable prognosis as compared to non–HPV-associated cancers. Ongoing studies are using HPV status to develop risk-adapted treatment algorithms for this disease. Likewise, HER2 is overexpressed in a subset of breast and gastroesophageal cancers. This overexpression has both prognostic and therapeutic significance, as these cancers frequently respond to anti-HER2 therapies. Finally, IHC for MMR proteins is commonly used to identify cancers associated with Lynch syndrome.

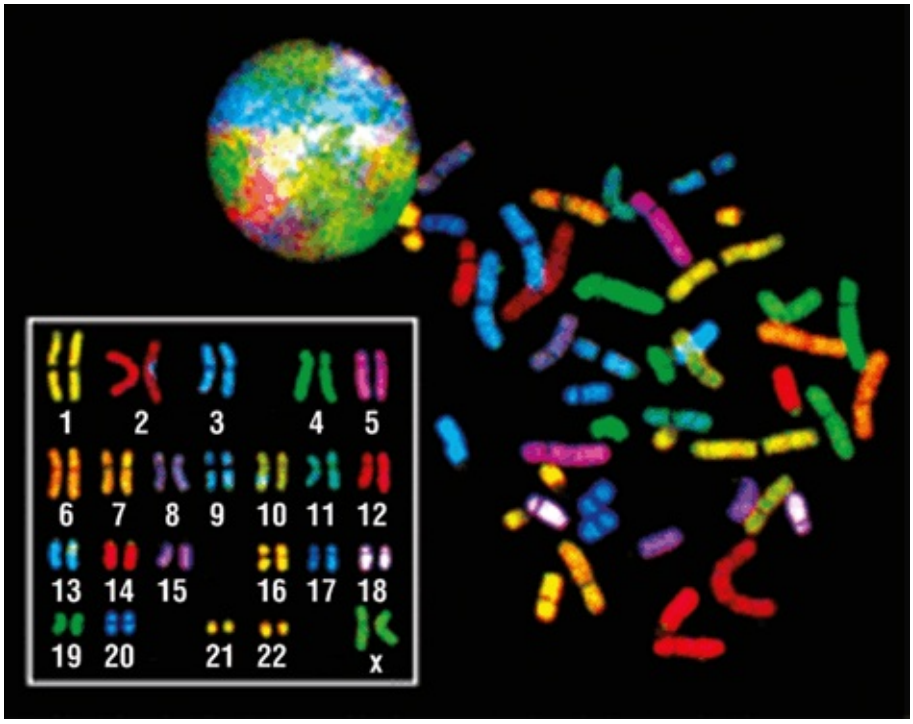

Fig. 2-9 Spectral karyotype showing different dyes characteristic for each chromosome.

This technique allows for rapid analysis of metaphase spreads for subtle chromosomal losses, gains, and translocations.

Source: *National Institutes of Health. National Human Genome Research Institute. "Talking Glossary of Genetic Terms." Retrieved November 8, 2017, from https://www.genome.gov/glossary/.*

Another important antibody-based diagnostic technique, particularly for hematologic cancers, is flow cytometry, which detects multiple cell-surface markers in complex cell populations, such as bone marrow or peripheral blood. This process, known as "immunophenotyping," can classify leukemias and lymphomas based on their cell-surface proteins. Because flow cytometry has high sensitivity and throughput it can detect small numbers of tumor cells, such as residual leukemia in normal bone marrow. Finally, flow cytometry can determine eligibility for the rapidly expanding array of monoclonal antibody–based therapies, including those targeting CD20 (for lymphoma and leukemia), CD30 (for Hodgkin and other lymphomas), CD33 (for acute leukemias), and CD38 (for multiple myeloma).

MASS SPECTROMETRY–BASED PROTEOMICS

Antibody-based methods are limited by their low throughput. Analogous to the large-scale genomic analyses of DNA sequence or RNA expression, mass spectrometry (MS) is a high-throughput technology that can assay thousands of proteins simultaneously. MS forms the core of modern proteomics and is used in combination with bioinformatics to quantitate and identify the large numbers of proteins present in complex biologic samples.[61,62] These methods are informed by genomewide sequencing that allowed construction of the comprehensive databases used to identify the peptides analyzed by MS. MS can also interrogate protein modifications, such as protein phosphorylation and ubiquitylation, on a very large scale. MS of cancer samples or serum from cancer patients can be used to generate proteomic signatures that may influence selection of therapy.[63,64] One intense area of proteomics research involves early cancer detection based on defining protein signatures indicative of early-stage cancers in tissues, such as peripheral blood.[65] Proteomic methods likely will be an important tool in cancer detection, diagnosis, and prognosis in the near future. A related area of MS that will have a

large effect in cancer biology and treatment in the near future is metabolomics, in which MS is used to measure hundreds of cellular metabolites, thus, revealing metabolic changes that have critical roles in carcinogenesis,[66] as well as potential therapeutic vulnerabilities.[67]

KEY POINTS

- Protein analyses reveal protein abundance, functional modifications such as phosphorylation and acetylation, and information such as subcellular localization.
- Immunological techniques that detect protein expression are used for a wide variety of diagnostic tests, including immunohistochemical identification and sub-classification of solid tumors and immunophenotyping for diagnosis and monitoring of hematologic malignancies.
- Mass spectrometry–based proteomics allow for large-scale analyses of protein expression and modifications in tumor tissues.

ONCOGENES AND TUMOR SUPPRESSORS: ACCELERATORS AND BRAKES ON THE ROAD TO CANCER

Transforming a normal cell into a malignant cell requires a series of mutations in genes, termed "oncogenes," which contribute to neoplasia when their functions are altered.[68,69] To date, perhaps several hundred human genes have been implicated as proto-oncogenes—genes that have the potential to be converted into oncogenes. Dominant oncogenes sustain gain-of-function mutations in cancers, whereas tumor suppressors are recessive oncogenes that sustain loss-of-function mutations in cancers.

IDENTIFICATION OF ACTIVATED DOMINANT ONCOGENES

Dominant oncogenes are activated by numerous mechanisms. Many of the first known oncogenes were discovered in experimental cancer models and subsequently found to be activated in human cancers by mechanisms such as translocation, amplification, and point mutations. These different types of mutations lead to distinct functional outcomes and often provide important diagnostic and prognostic information.

Classical Experimental Cancer Models: Retroviruses and Transfections

Many oncogenes were first discovered through studies of animal cancers induced by retroviruses, called "RNA tumor viruses." One class of RNA tumor viruses carry viral oncogenes within their viral genomes, and several dozen viral oncogenes were identified in the 1970s and 1980s. The major breakthrough with respect to human cancer came with the realization that viral oncogenes represent mutated versions of host proto-oncogenes that were captured by the viral genomes during their life cycle. Many viral oncogenes are the counterparts of extremely important human oncogenes, and the identification of their cellular homologs established the framework within which we understand the role of dominant oncogenes in tumorigenesis. A second class of RNA tumor viruses causes cancers in animals by insertional mutagenesis, in which the integration of a viral genome into a host chromosome activates a cellular proto-

oncogene. Insertional mutagenesis remains a powerful genetic tool for oncogene discovery.[70]

Another classic strategy used to identify oncogenes is DNA transfection. In this approach, DNA is extracted from tumor cells and introduced into recipient cells, which undergo morphologic and growth alterations (transformation) when they incorporate a tumor-derived oncogene. The transfected tumor cell DNA is subsequently isolated and sequenced from the transformed cells, allowing the identification of the transferred oncogene. Many critical human oncogenes, including *RAS,* were originally isolated from transfection experiments.[71]

Chromosome Translocations

Cancers often contain recurrent chromosome translocations; this is particularly true for hematologic malignancies, which are often characterized by chromosome translocations that involve Ig and T-cell receptor genes.[72] Specific translocations have important diagnostic and prognostic implications and serve as molecular markers for the detection of residual disease and relapse. The regions of DNA commonly involved with translocations are termed "breakpoints," and these often contain proto-oncogenes that are activated by the DNA rearrangement.

Chromosome translocations activate proto-oncogenes in two general ways.[73] The most common mechanism involves the creation of fusion genes when the translocation joins two genes normally found on separate chromosomes in the same translational reading frame and results in a novel protein encoded by the two fused genes. Fusion proteins often involve transcription factors or tyrosine kinases and have biologic activities that differ from the parental proto-oncogene. Indeed, several examples of this type of translocation are highly relevant to cancer biology and therapy. The *BCR-ABL* fusion that results from the reciprocal exchange of DNA between chromosomes 9 and 22, t(9;22), is known as the Philadelphia chromosome (Fig. 2-10). This translocation juxtaposes the 5′ end of the *BCR* gene on chromosome 22 and the 3′ end of the *c-ABL* oncogene on chromosome 9. The resultant novel gene produces a hybrid mRNA that codes for the BCR-ABL oncoprotein, which deregulates the tyrosine kinase activity normally associated with the c-ABL protein. This translocation is the key driver of CML and is present in other leukemias as well. Indeed, many hematologic cancers are characterized by pathognomonic chromosomal translocations that produce fusion proteins.[73]

Recurrent chromosome translocations also occur in solid tumors. In Ewing sarcoma, translocations fuse the *EWS* gene on chromosome 22 to the *FLI-1* gene on chromosome 11, and this creates a transcription factor containing a DNA-binding domain derived from *FLI-1* and a transcriptional activation domain from *EWS*.[74] Alveolar rhabdomyosarcomas also contain a pathognomonic translocation, which in this case fuses the *PAX3* and *FHK4* transcription factors. Translocations that join the androgen-responsive *TMPRSS2* gene with two *ETS* transcription factors, *ETV1* and *ERG,* occur frequently in prostate cancer and result in abnormal *ETS* expression driven by the androgen-responsive regulatory elements in the *TMPRSS2* gene.[75]

Other translocations activate proto-oncogenes by deregulating their expression without altering their protein structure. An example of this type of translocation is found in Burkitt lymphoma, which is characterized by translocations that cause the *MYC* oncogene, located on chromosome 8, to be juxtaposed to Ig genes that are located on chromosomes 14, 2, and 22 (Fig. 2-10). In each case, the translocation deregulates *MYC* expression by placing it under the control of transcriptional elements contained within the Ig locus. Other examples of proto-oncogenes that are activated by translocations involving Ig genes include *CCND1* which encodes the protein cyclin D1 (found in mantle cell lymphoma and multiple myeloma) and *BCL-2*

(in follicular lymphoma).

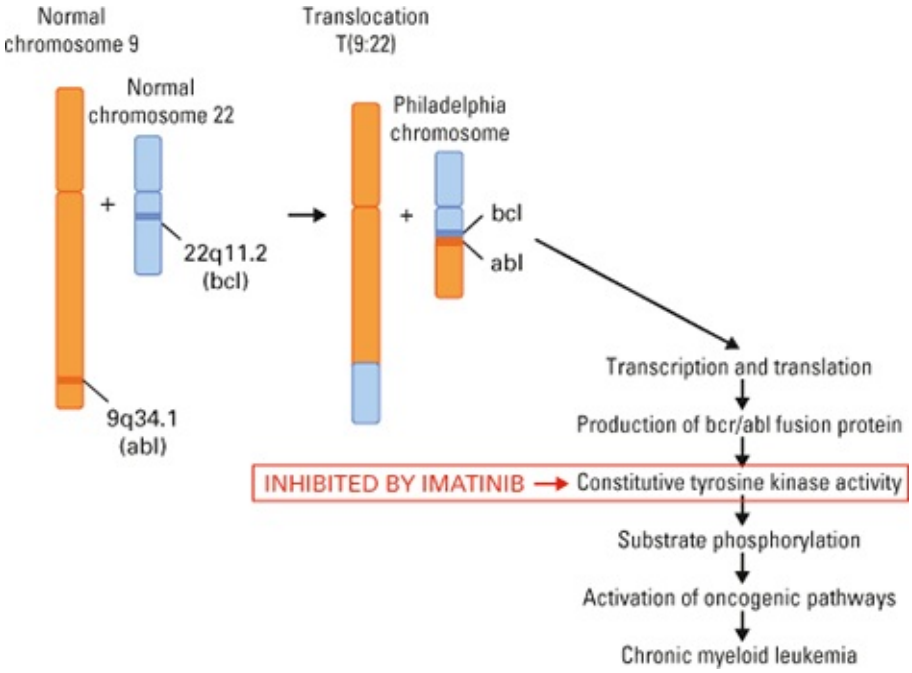

Fig. 2-10 Translocation leading to the Philadelphia (Ph) chromosome and the role of BCR-ABL in the pathogenesis of chronic myeloid leukemia.

The Ph chromosome is a foreshortened chromosome 22 resulting from an exchange between the long arms of chromosomes 9 and 22. This leads to the production of a BCR-ABL fusion protein that has constitutive kinase activity and promotes the development of chronic myeloid leukemia. The tyrosine kinase inhibitor imatinib inhibits this constitutive kinase activity and can lead to long term control of this leukemia.

Source: *Wikipedia. Public Domain, https://en.wikipedia.org/wiki/Philadelphia_chromosome.*

Other genomic rearrangements, such as chromosomal inversions, also create fusion proteins with important therapeutic implications. For example, inversions of chromosome 2 that fuse the *ALK* gene with the *EML4* gene identify a subset of patients with non–small cell lung cancer that respond to therapy with ALK inhibitors.[76]

DNA Amplification

DNA amplification results in the increased copy number of a gene and is another mechanism by which cancer cells increase the expression of a gene product, and many solid tumors exhibit proto-oncogene amplifications.[77] Gene amplification can be directly detected by many methods, including CGH, FISH, and NGS, as well as by surrogate markers, such as protein expression by IHC. In some cases, the detection of amplified genes provides important prognostic and treatment-related information, as in the case of *HER2* amplification in breast cancer and gastroesophageal cancer and *MYCN* amplification in neuroblastoma.

Point Mutations

While point mutations in cancer genes can inactivate or impair protein function, many recurrent mutations activate dominant oncogenes. Examples of this mechanism of oncogene activation include mutations of amino acids that alter *KRAS* function in colorectal cancers and activating mutations of the epidermal growth factor receptor (*EGFR*) in lung cancer. Neomorphic mutations change the function of the targeted oncoprotein, such as the altered specificity of the enzyme isocitrate dehydrogenase caused by *IDH1/2* mutations in glioma (see the

Oncogenomics and Precision Oncology section for discussion of these specific mutations). Because some common oncogenes, such as *KRAS* and *NRAS*, are activated by only a few specific point mutations, these genes were some of the first that were routinely screened for in cancer specimens. However, NGS can now identify most potentially oncogenic point mutations in primary tumor samples, and in time frames that allow genomics-based treatment decisions.[78] One common strategy uses targeted sequencing to interrogate panels of commonly mutated and actionable proto-oncogenes; this may provide genomic data with a time frame (and cost) that is more concordant with clinical interventions than broader approaches that sequence all protein coding regions or even whole genomes.

IDENTIFICATION OF INACTIVATED TUMOR SUPPRESSOR GENES

Many tumor suppressor genes were first identified by virtue of their association with hereditary cancer syndromes. Importantly, the genes responsible for familial cancers often are the same tumor suppressor genes that are inactivated in sporadic cancers. In most familial cancer syndromes, a mutant copy of a tumor suppressor gene is inherited, followed by mutation or loss of the remaining normal allele, termed “loss of heterozygosity,” in cancers that develop in these individuals. These types of recessive oncogenes, in which disruption of both alleles is associated with cancer formation, are known as two-step (Knudson) tumor suppressors, named after classic studies of the *RB1* tumor suppressor in retinoblastoma.[79]

There are important exceptions to the Knudson model that expand our understanding of how tumor suppressor genes are mutated in cancers. In some cases, loss of a single allele of a tumor suppressor is sufficient to confer cancer susceptibility or contribute to neoplastic progression, even when a normal allele persists. This is termed a “haploinsufficient tumor suppressor gene.”[80] Another situation in which a tumor suppressor will not conform to the Knudson model is when tumor suppressors are inactivated by epigenetic mechanisms, such as when the *CDKN2A* cell-cycle inhibitor is silenced by DNA methylation in cancers. So-called “dominant negative mutations” also result in noncanonical tumor suppressor inactivation because they inhibit the function of the wild-type protein produced by the normal allele, thereby removing the selective pressure to mutate both alleles. In this case, only one allele of the tumor suppressor gene will contain a mutation, such as seen with the *FBXW7* and *SPOP* ubiquitin ligases or *TP53*.

Loss of tumor suppressor gene alleles occurs commonly in cancers.[81] In classical studies, delineating a locus involved by allelic loss in a tumor type was often the first step toward identifying a tumor suppressor gene, such as the breast cancer susceptibility gene *BRCA1.*[82] Sites of allelic loss were thus determined by analyzing polymorphic markers or CGH, and disease genes were localized to within the smallest common region of allelic loss. However, this is another area of cancer genetics that is greatly affected by NGS-based technologies, which are becoming the method of choice for detecting allelic losses in tumors. NGS approaches also detect numerous other mechanisms that disrupt tumor suppressor gene function, including point mutations, deletions that lead to premature termination and/or nonfunctional proteins, and promoter methylation.

KEY POINTS

- Proto-oncogenes are normal cellular genes that can be converted into oncogenes by

mutation or by epigenetic mechanisms, which alter their normal functions or expression.

- Dominant oncogenes encode proteins that are activated in tumors by mechanisms such as amplification, point mutations, and translocations.
- Tumor suppressor genes are recessive oncogenes that are inactivated in tumors by diverse mechanisms, including deletions, point mutations, and gene silencing.

CELLULAR FUNCTIONS OF ONCOGENES AND TUMOR SUPPRESSORS

Proto-oncogenes normally function in a remarkably wide array of biologic processes. Many dominant oncogenes are found within the pathways that normally govern cell division and differentiation in response to specific signals. Other areas, cellular pathways, and/or processes are also commonly targeted by oncogene mutations in cancers, including programmed cell death (apoptosis) and protein degradation. Tumor suppressors also function within most of these cellular pathways, where they serve to counter the effects of oncogenes. Tumor suppressors also have a particularly important role in the control of DNA repair and of cellular responses to DNA damage. The major cellular pathways that contain dominant oncogenes and tumor suppressor genes, and important examples of oncogenic mutations within these pathways, are summarized below.

MITOGENIC SIGNAL TRANSDUCTION PATHWAYS

Cell division is triggered by signal transduction pathways that are stimulated when growth factors bind to specific cell-surface receptors, and these pathways contain proto-oncogenes throughout the signaling chain.[83,84] Most growth factor receptors are anchored in the cell membrane such that an extracellular domain is available for growth factor (ligand) binding and an intracellular domain interacts with downstream signaling molecules. The intracellular portion of a class of growth factor receptors—receptor tyrosine kinases (RTKs)—catalyzes the addition of phosphate to tyrosine residues. Ligand binding causes RTKs to dimerize and autophosphorylate, which recruits signaling proteins that transmit the mitogenic signal down several parallel pathways, including the phosphatidylinositol-3 kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways (Fig. 2-11). Cytoplasmic tyrosine kinases also transduce these mitogenic signals, including the c-ABL protein. The gene encoding this protein is fused with the *BCR* gene in CML. Dominant mutations in these signaling kinases found in cancer subvert the normal growth factor signals needed to stimulate these pathways.

RAS proteins transduce mitogenic signals, and their activity is regulated by whether they are bound to guanosine triphosphate (GTP) or guanosine diphosphate (GDP).[85-87] Thus, RAS activity reflects a balance of guanine nucleotide–exchange factors (GEFs), which activate RAS, and guanosine triphosphatase–activating proteins (GAPs), which hydrolyze RAS-bound GTP to GDP (Fig. 2-11). Oncogenic *RAS* mutations affect amino acids that interface with GAPs, which results in overactivity of proliferative signaling pathways. Furthermore, GAPs themselves can function as recessive oncogenes. For example, the *NF1* gene is a GAP that acquires a loss-of-function mutation in neurofibromatosis.[88]

RAS drives three parallel signaling pathways: the MAP kinase pathway (which activates transcription factors), the RAL/CDC42 pathway (which regulates membrane and cytoskeletal changes), and the PI3K pathway (which affects many cellular functions, including protein synthesis and apoptosis) (Fig. 2-12). The MAP kinase pathway is stimulated by the RAF

serine/threonine kinase, and signals to additional downstream cytoplasmic serine/threonine kinases, which ultimately activate MAP kinases and other effectors. Mutations of the *BRAF* gene are found in approximately 50% of melanomas. MAP kinase signaling ultimately activates nuclear proto-oncogenes that encode transcription factor proteins, such as *FOS, JUN,* and *MYC.* Each of these oncogenic transcription factors promotes carcinogenesis by binding to target genes and affecting their expression.

The phosphtidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway stimulates transcriptional and translational responses that affect incredibly diverse cellular processes, including cell growth and division, apoptosis, protein synthesis, and cellular metabolism (Fig. 2-13).[66,89-92] Each of these processes may be abnormal in cancers with *PI3K* mutations, which are among the most common mutations found in cancer cells.[93] AKT is a protein kinase that is downstream of PI3K and is often amplified and/or overexpressed in cancers.[94] Moreover, cancers exhibit elevated AKT activity caused by mutations in genes that regulate AKT. For example, the phosphatase and tensin homolog tumor suppressor (PTEN), which is commonly deleted in cancers, opposes PI3K and prevents AKT activation.[95] AKT phosphorylates many substrates that regulate cell division, apoptosis, and protein synthesis, and the PI3K/AKT pathway has enormously complex and important roles in controlling normal and neoplastic cellular homeostasis.[94]

Targeting Mitogenic Kinases in Cancer Chemotherapy

The concept of specifically inhibiting mutant oncoproteins in cancer falls under the umbrella term “targeted therapy” and has been heavily applied to mitogenic kinases in cancer. In cases in which the roles of individual kinases in specific cancers have been recognized for a long time, such as HER2 in breast cancer and BCR-ABL in CML, targeted therapies are already mature. However, the NGS-driven revolution in molecular oncology is now allowing these approaches to be directed against a much larger number of cancers that contain sensitizing mutations in genes that can be therapeutically targeted. Although targeted therapies will be discussed in detail in subsequent chapters in the context of specific organ sites and therapies, a general overview of these concepts is provided in this section.

Several therapeutic strategies that target aberrant RTKs are in clinical use. One approach utilizes antibodies that bind to and inhibit RTKs. Examples include trastuzumab, which antagonizes HER2 activity and is used in the treatment of breast cancers with *HER2* amplification,[96] and cetuximab, an inhibitory antibody that binds to the EGFR and is approved for use in metastatic colon cancer and head and neck cancers.[97,98]

Another important strategy to target RTKs and mitogenic kinases in cancers utilizes small-molecule inhibitors, such as imatinib, erlotinib, and crizotinib, which bind to specific kinases and inhibit their catalytic activity. These inhibitors have the greatest efficacy in tumors that contain mutations within the target kinase. For example, the efficacy of erlotinib and related tyrosine kinase inhibitors is closely associated with mutations in *EGFR* that are found in a small fraction of patients with lung cancers.[99,100] Another example is the use of BRAF inhibitors to treat patients whose melanomas harbor *BRAF* mutations.[101] The concept of directing small-molecule inhibitors against individual tumors with specific mutations is the very crux of precision oncology.

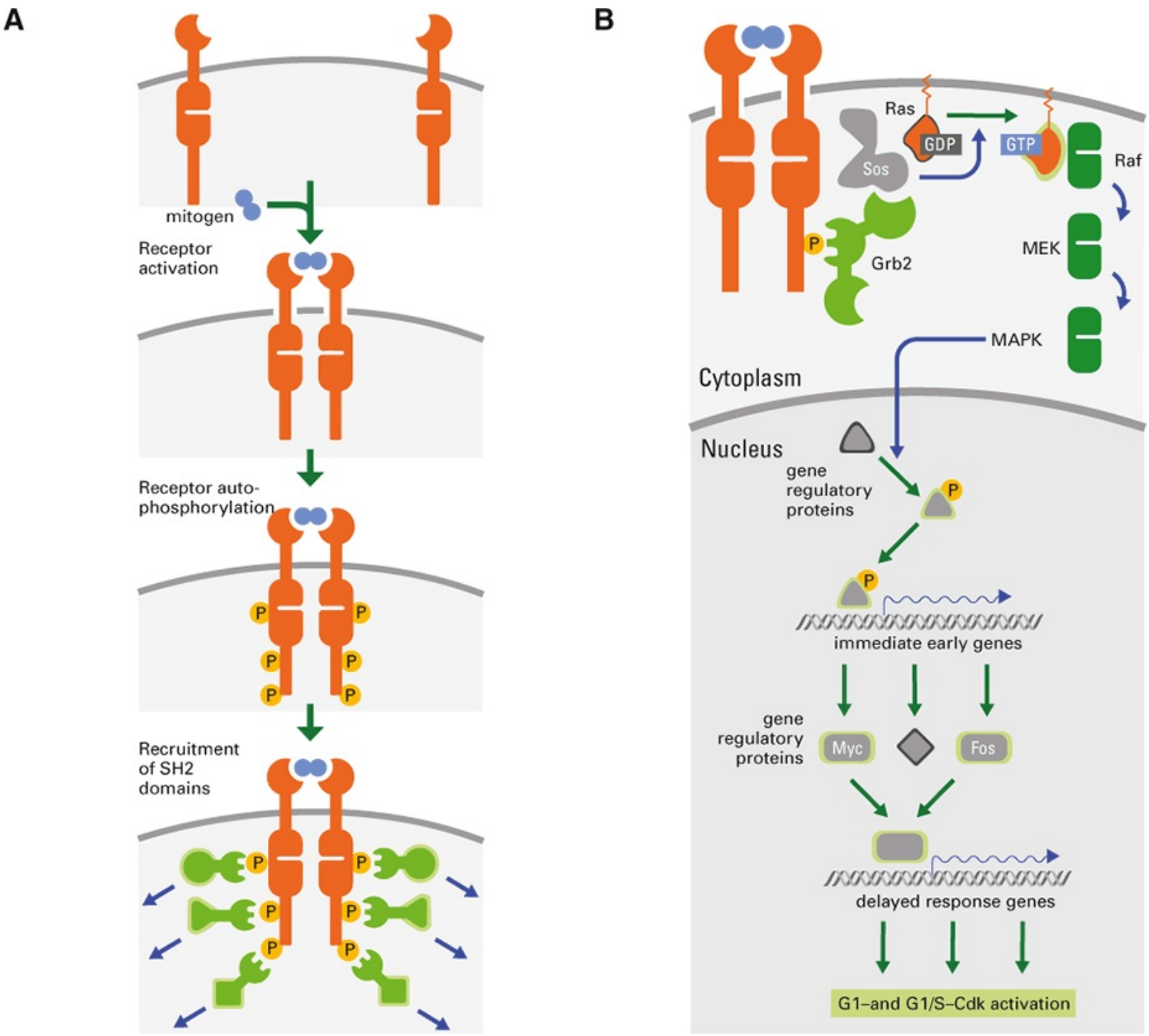

Fig. 2-11 Mitogenic signaling.

(A) Origin of the mitogenic signal at the cell membrane. The binding of growth factors to receptor tyrosine kinases causes receptor dimerization and autophosphorylation. The receptor tyrosine phosphorylation then recruits binding proteins that contain SH2 domains, and these transmit the mitogenic signal (see text). (B) Mitogenic signaling by the RAS pathway. RAS activation stimulates the mitogen-activated protein kinase pathway, which leads to the activation of downstream transcription factors such as JUN and MYC (see text).

Kinase inhibitors can also be used to treat tumors that depend on the activity of a kinase pathway but do not have mutations in the kinase itself. Examples of this approach include the treatment of chronic lymphocytic leukemia with idelalisib (which inhibits PI3K-δ) and the use of ibrutinib (which inhibits Bruton tyrosine kinase) to treat mantle cell lymphoma and chronic lymphocytic leukemia.[102] Despite their remarkable activities, the development of resistance against small-molecule kinase inhibitors limits the durability of clinical responses and may be

inevitable in solid tumors. An exception to this is the use of imatinib and related drugs to inhibit BCR-ABL in CML, for which responses are extremely durable, lasting years. In most other cancers, such as the use of BRAF inhibitors in melanoma, resistance develops much more quickly, despite impressive initial responses.

Tumors acquire resistance to kinase inhibitors in several ways. One mechanism involves mutations in the target kinases themselves, such that they are no longer inhibited by the targeted therapy. In some cases, the mutant kinases can still be effectively inhibited by related small molecules, whereas other mutations confer wider drug resistance. An example of this mechanism is the acquisition of *BCR-ABL* mutations in CML that prevent its inhibition by imatinib, but which can still be inhibited by related agents, such as nilotinib.[103,104]

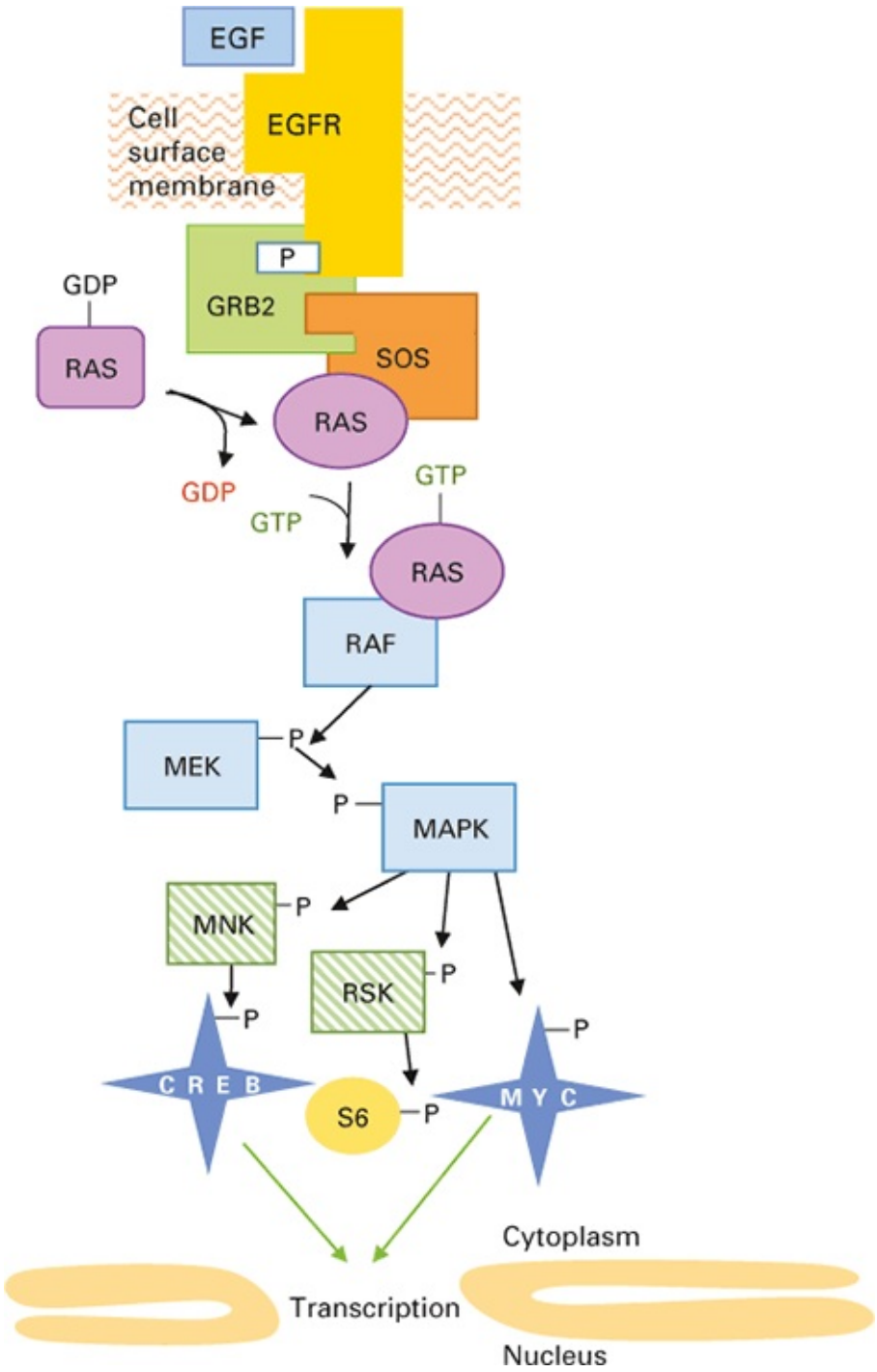

Fig. 2-12 RAS upstream and downstream signaling.

Extracellular stimuli signal through cell-surface plasma membrane receptors, for example, RTKs (EGF/EGFR shown). Through a variety of adaptor proteins, these signals cause guanine nucleotide exchange factors to replace the GDP bound to inactive RAS with GTP. GTP-bound RAS binds to a plethora of downstream effector molecules to stimulate intracellular signaling of several

pathways. Those with established roles in *RAS* oncogenesis include the RAF serine/threonine kinases (shown), as well as the PI3K lipid kinases, RAL GEFs, and Tiam1. Activating mutations in *RAS* genes are present in many tumor types and lead to constitutive RAS signaling, which drives transformation, invasion, and metastasis.

Source: *Wikipedia. Public Domain, https://en.wikipedia.org/wiki/MAPK/ERK_pathway*.

However, some mutations confer resistance to an entire class of inhibitors. The second major mechanism of resistance to kinase inhibitors involves the development of bypass pathways, in which tumor cells "rewire" their mitogenic signaling to utilize alternative pathways. In this case, although the target kinase is still sensitive to the pharmacologic inhibitors, the tumors have escaped kinase inhibition through the activation of alternative signaling pathways.[105] An example of this mechanism is the activation of alternative RTKs in lung cancers being treated with EGFR inhibitors. One therapeutic approach in this case is the use of additional kinase inhibitors to block the bypass pathway, such as targeting both the BRAF and MAPK pathways in melanoma, although additional mutations also tend to render this approach ineffective over time.

CELL-CYCLE CONTROL

Cell cycles are divided into four phases that coordinate cell growth, DNA replication, and cell division. G1 phase is a period of growth between mitosis and the onset of DNA synthesis during which cells integrate mitogenic signals and commit to the onset of DNA replication. S phase is the period of DNA synthesis during which a cell replicates its genomic complement. G2 phase follows the S phase and is a second period of cell growth. In mitosis, chromosomes are segregated to daughter cells and cell division occurs. It is critically important that cells execute the cell-division cycle faithfully, and mutations in the genes that regulate the cell cycle are among the most common genetic changes in cancer cells.[106,107]

The cyclin-dependent kinases (CDKs) orchestrate cell-cycle transitions by phosphorylating protein substrates with diverse roles in cell division (Fig. 2-14). CDKs are composed of two subunits: a catalytic subunit (the CDK) and a regulatory subunit (the cyclin) that activates the CDK. The best known G1 CDK substrate is the retinoblastoma protein (pRb), and the Rb pathway is mutated in most cancers. Early in the G1 phase, unphosphorylated pRb sequesters E2F transcription factors and represses the expression of cell-cycle genes. As the cell cycle progresses, Rb becomes phosphorylated by cyclin CDKs, which releases E2F and promotes the transcription of genes that drive cell proliferation (Fig. 2-15). Two classes of CDK inhibitor proteins prevent CDK activity. The INK4 proteins inhibit only CDK4 and CDK6, whereas the CIP/KIP proteins (p21, p27, and p57) bind to most cyclin-CDKs (Fig. 2-14).

Cyclins and CDKs can act as dominant oncogenes. The cyclin D1 gene (*CCND1*) is rearranged by chromosome inversion in parathyroid adenomas, translocated to the IgG heavy chain locus in mantle cell lymphomas, and amplified in 10 to 15% of solid tumors. Similarly, the cyclin E gene (*CCNE1*) was found to be the second most commonly amplified gene in ovarian cancers[108] and the cyclin E protein is upregulated in cancers by increased *CCNE1* transcription or prolonged protein stability.[109] CDKs themselves undergo oncogenic mutation, such as a *CDK4* mutation found in familial melanomas that prevents its inhibition by INK4 proteins.[110] Abnormal CDK4 and CDK6 activity is particularly linked to tumorigenesis, and CDK4/6 inhibitors are demonstrating great promise in breast cancer and hematologic cancers, as evidenced by the recent approval of palbociclib to treat estrogen receptor–positive breast cancer.[111-113] Small molecules that inhibit other cell-cycle kinases, such as cyclin-dependent kinase 2 (CDK2) and the Wee1 kinase, which regulates CDK activity, are also in wide clinical trials.[114,115]

Genes encoding proteins that inhibit CDKs are recessive oncogenes. p16INK4A proteins, encoded by the *CDKN2A* locus, frequently exhibit allelic loss in cancers. Another potent tumor suppressor, ARF, also is contained within *CDKN2A* and contributes to the biologic selection for its allelic loss.[116] Deletions and point mutations of the *CDKN2A* locus occur commonly in cancers such as glioblastomas.[117] *CDKN2A* is also epigenetically inactivated in tumors by promoter methylation, most notably in colon and lung cancers.[118] The p27KIP1 CDK inhibitor is a tumor suppressor whose abundance has prognostic significance in cancers.[119] This protein, encoded by the *CDKN1B* gene, is an example of a tumor suppressor that is rarely mutated, but instead is inactivated by mutations in the pathways that regulate its degradation and/or subcellular localization. *RB1* is the prototype tumor suppressor, and its role in hereditary retinoblastoma provided the basis for the Knudson two-step model.[79] Importantly, *RB1* is mutated in many sporadic cancers, including small cell lung cancer, bladder cancer, and other common tumors.[120,121]

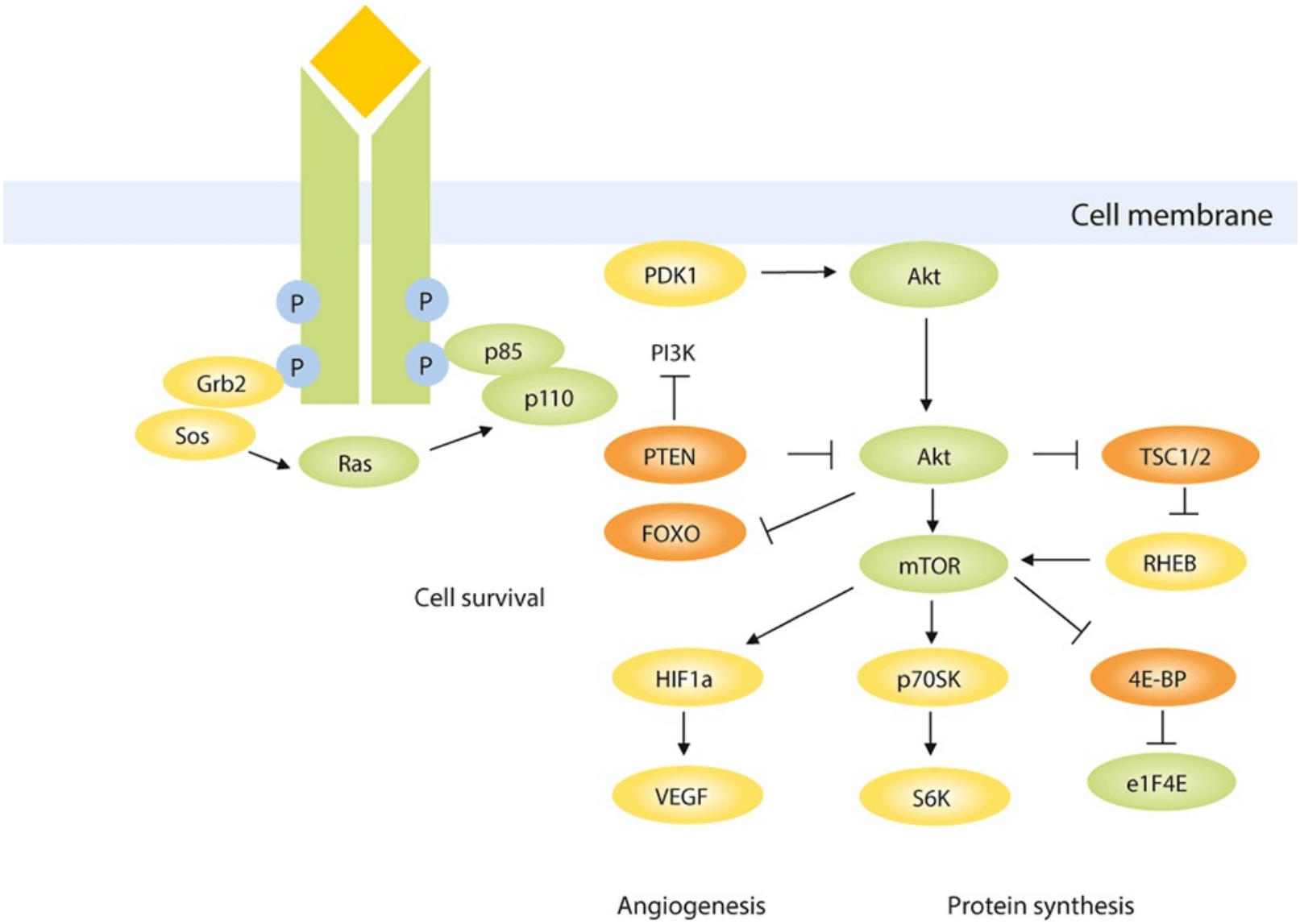

Fig. 2-13 Alterations of the AKT pathway in human cancer.

Activation of growth factor receptors such as EGFR, either by ligand stimulation or receptor overexpression/mutation, is one of the major mechanisms responsible for upregulation of AKT signaling. Other common mechanisms include activation of oncoproteins and inactivation of tumor suppressors intersecting the AKT signal transduction pathway. Proteins shown in green indicate oncoproteins for which overexpression and/or activating mutations have been implicated in many sporadic human cancers. Proteins in orange are tumor suppressors whose loss and/or inactivation have been found to contribute to deregulation of the AKT pathway and tumor formation. FOXO transcription factors have also been implicated as tumor suppressors (see text), although, to date, mutations have not been observed in any hereditary cancer syndrome. AKT signaling contributes to cancer

development by activating multiple processes, including cell survival, angiogenesis, and protein synthesis.

Source: *Wikipedia. Public Domain, https://en.wikipedia.org/wiki/Akt/PKB_signaling_pathway*.

APOPTOSIS

Tumor growth is a consequence of both unrestrained cell division and decreased cell death, and the pathways that mediate cell death contain proto-oncogenes that are mutated in cancers. Apoptosis is a physiologic process whereby complex biochemical pathways mediate cell death; it is triggered by two distinct pathways (Fig. 2-16).[122,123] Cell death through the extrinsic pathway is signaled when ligands, such as tumor necrosis factor-alpha (TNF-α) and Fas ligand, bind to cell-surface death receptors, such as TNF-R1 and Fas. Ligand binding to death receptors initiates a sequence of events leading to activation of proteases, termed "caspases," which execute the apoptotic response. In contrast, the intrinsic or mitochondrial pathway results from a number of stimuli, such as radiation therapy or chemotherapy, and involves changes in the mitochondrial membrane that affect the release of cytochrome C into the cytoplasm. The intrinsic pathway also activates a caspase cascade that ultimately leads to DNA fragmentation and cell death.

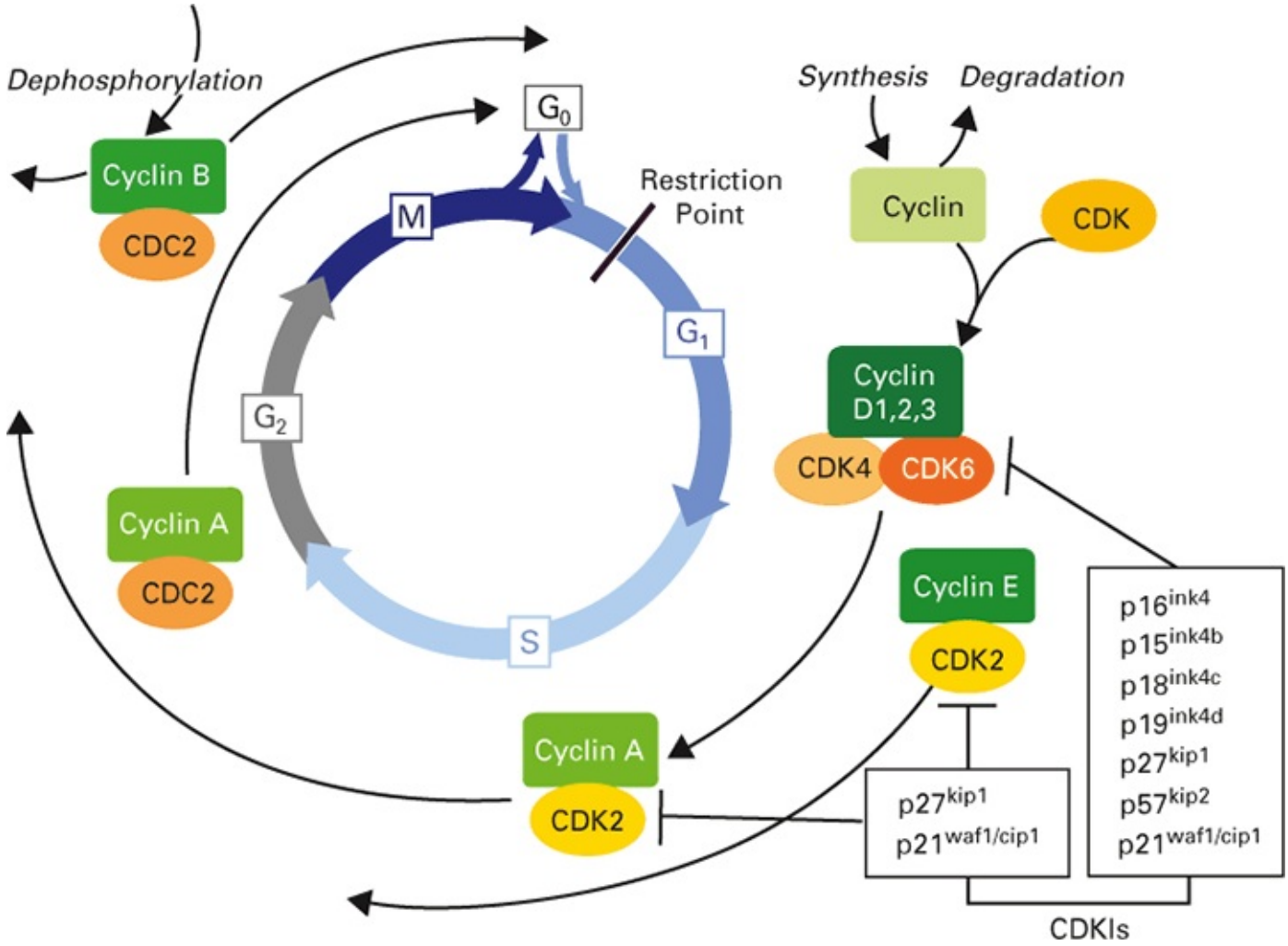

Fig. 2-14 The cell cycle.

The cell cycle is divided into four phases (G1, S, G2, and M). Progression through the cell cycle is promoted by cyclin-dependent kinases (CDKs), which are regulated positively by cyclins and negatively by CDK inhibitors (CDKIs). The restriction point is the point at which cells progress through the cell cycle independently of external stimuli.

Reproduced with permission from Schwartz G, Shah M. Targeting the cell cycle: A new approach to cancer therapy. J Clin Oncol. *2005;23:9408–9421. PMID: 16361640.*

The BCL-2 family comprises proteins that regulate apoptosis; they are either proapoptotic (promote cell death) or antiapoptotic (promote cell survival).[124] *BCL2* is antiapoptotic and was first identified as the gene activated by the t(14;18) translocation found in follicular lymphomas. The precise mechanisms by which BCL-2 prevents cell death are not fully elucidated, but they involve interactions with proapoptotic family members, as well as mitochondrial functions. One important consequence of BCL-2 overexpression in tumorigenesis is that it prevents the apoptosis normally triggered by dominant oncogenes, such as *MYC,* and this likely underlies the aggressive behavior of "double-hit" lymphomas, which contain activating translocations of both the *MYC* and *BCL2* genes.[125] The realization that BCL-2 prevents apoptosis was pivotal in the evolution of understanding the relationship between apoptosis and cancer. Because of their potential to induce apoptosis in tumor cells, drugs that target the BCL-2 family are being widely studied in clinical trials.[126-128]

Many oncogenes interact with the core apoptotic pathways. The most common mutations that impair apoptosis in tumors involve the *TP53* tumor suppressor gene. Apoptosis is one outcome of *TP53* activation by cellular stresses, and impaired cell death is an extremely important consequence of *TP53* loss in cancer. Another frequently mutated pathway that negatively regulates apoptosis is the PI3K/AKT pathway. AKT's interactions with apoptotic signaling is complex and includes direct effects on the mitochondrial membrane, as well as functional interactions with BCL-2 family members, FOXO transcription factors, nuclear factor-kappa B, and p53.

KEY POINTS

- Mitogenic signaling pathways contain many broadly acting proto-oncogenes. Many of these proteins are tyrosine kinases that can be targeted clinically by small-molecule kinase inhibitors and antibody-based therapeutics.
- The genes that regulate the cell-division cycle are commonly mutated in cancer cells.
- Many oncogenic mutations disrupt normal apoptotic responses.

UBIQUITIN-MEDIATED PROTEOLYSIS

Many short-lived proteins are degraded in a proteolytic structure called the "proteasome." Conjugation of a protein to ubiquitin is the signal for its delivery to the proteasome, and this is catalyzed by a multistep reaction in which ubiquitin is transferred to lysine side chains of the target protein (Fig. 2-17).[129-131] Ubiquitin, a 76–amino acid protein, is first attached to an ubiquitin-activating enzyme (E1), and then transferred to ubiquitin-conjugating enzyme carrier proteins (E2). In most cases, protein ubiquitylation requires an ubiquitin ligase enzyme (E3), which facilitates transfer of ubiquitin to the protein substrate. Cells contain hundreds of E3s, and these often recognize their targets after they have been modified by specific signals (e.g., phosphorylation). A family of deubiquitinating enzymes provides an additional layer of control by removing ubiquitin moieties from protein substrates. The multienzyme and signal-regulated ubiquitin–proteasome system provides an enormous amount of specificity over which proteins are degraded in various contexts. In addition to protein degradation, which is signaled by a specific type of polyubiquitin linkage to proteins, ubiquitylation also regulates processes such as

protein–protein interactions and cellular signaling, and specific types of polyubiquitin and monoubiquitin linkages mediate these alternative outcomes.

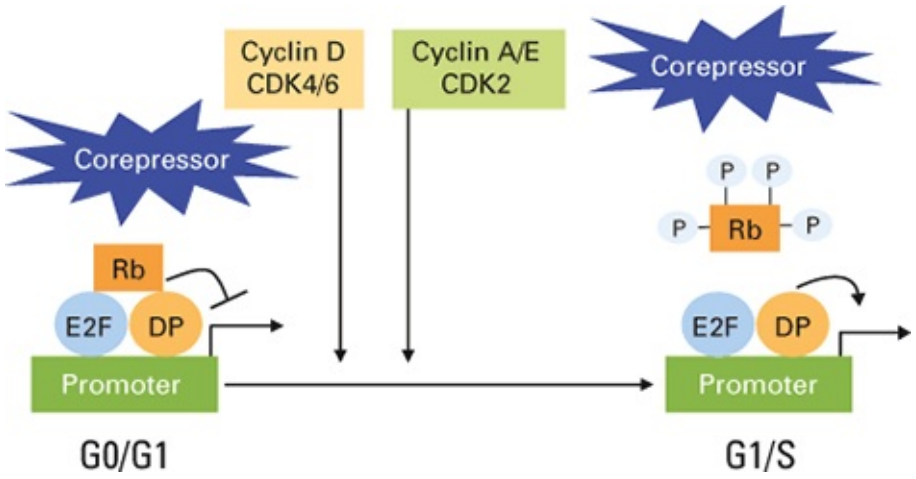

Fig. 2-15 Rb and E2F function.

Rb binds the transcription factor E2F and its associated subunit DP. Rb represses E2F-mediated transcription by recruiting chromatin remodeling complexes to the promoter in resting cells. At the G1–S-phase transition, Rb is thought to be phosphorylated by CDK2, CDK4, and CDK6. Hyperphosphorylated Rb releases E2F, allowing it to activate transcription of its target genes.

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E3 ubiquitin ligases are important oncogenes and tumor suppressors. *FBXW7* encodes an E3 ubiquitin ligase and is one of the most commonly mutated tumor suppressor genes across the cancer spectrum.[132] Fbxw7 targets numerous key oncoproteins for degradation, including cyclin E, c-Myc, Notch, and c-Jun, and inactivating *FBXW7* mutations promote tumorigenesis through the unrestrained activity of its oncogenic substrates. Cancer of some organ sites, such as T-cell acute lymphoblastic leukemias and endometrial cancers, exhibit particularly high *FBXW7* mutation rates. SPOP is another ubiquitin ligase protein recently implicated in carcinogenesis. Prostate and endometrial cancers show recurrent mutations in *SPOP* that lead to deregulation of cancer drivers, including androgen and estrogen receptors.[133,134] SPOP also appears to be involved in the DNA repair gene process, and *SPOP* mutation may predict sensitivity to DNA-damaging agents.[135] Interestingly, SPOP may act as an oncogene in clear cell renal cancer, and as such, is an example of the rare genes that can act as both tumor drivers and tumor suppressors, depending on cellular context.[136] Inactivating mutations of the Von Hippel–Lindau (*VHL*) E3 ubiquitin ligase are the cause of VHL syndrome; in this syndrome renal cell carcinomas, central nervous system hemangioblastomas, pheochromocytomas, pancreatic tumors, and other neoplasms develop. VHL syndrome is diagnosed by the presence of germline inactivating *VHL* mutations, and the remaining allele is inactivated in tumors by mutation. Inactivating *VHL* mutations are also found in most spontaneous renal cell carcinomas.[137] One critical VHL target is hypoxia-inducible factor-1 alpha (HIF1A), a transcription factor that regulates genes in response to hypoxia, including an angiogenic transcriptional program that contributes to the highly vascular tumors associated with VHL loss. In other cases, E3s are overexpressed and act as dominant oncogenes. One example of this involves MDM2, a ubiquitin ligase that degrades the p53 protein, and whose abundance is increased in cancers by mechanisms such as gene amplification.[138]

Proteasome inhibitors have emerged as important antineoplastic agents, particularly for the

treatment of hematologic cancers.[139,140] Bortezomib was the first pharmacologic proteasome inhibitor in clinical use and is approved for the treatment of patients with multiple myeloma and mantle cell lymphoma. Carfilzomib is a second-generation proteasome inhibitor approved for the treatment of multiple myeloma. However, the mechanism(s) that account for the therapeutic index associated with general proteasome inhibitors still remains unclear because these compounds affect a large number of proteins normally degraded by the proteasome. The ubiquitin–proteasome system also contributes to the actions of other chemotherapeutics, such as the striking finding that thalidomide and related drugs cause the Cereblon E3 ubiquitin ligase to abnormally degrade Ikaros B-cell–specific transcription factors and casein kinase 1 alpha and that this accounts for their efficacy in multiple myeloma and myelodysplastic syndromes with chromosome 5q deletions.[141-143] In addition to general proteasome inhibitors, activators or inhibitors of specific components of the ubiquitin ligase pathway are of great clinical interest.[144] For example, inhibitors of the SPOP ubiquitin ligase have been developed and show activity in kidney cancer models.[145]

WNT/BETA-CATENIN SIGNALING

The Wnt/beta-catenin pathway has vital roles in development and cellular self-renewal.[146] Consistent with these functions, abnormal Wnt signaling is implicated in many cancers. Reduced to their essential components, soluble Wnt proteins bind to membrane-bound receptors, and this prevents the ubiquitin-dependent degradation of beta-catenin by the proteasome. Beta-catenin then translocates to the nucleus, where it stimulates a transcriptional program in concert with members of the TCF family of transcription factors. The regulation of this pathway is quite complex, and many proteins augment or restrain Wnt pathway activation. The best-characterized role of Wnt pathway activation in human cancer is in familial adenomatous polyposis, a hereditary colon cancer syndrome caused by deletion of the *APC* tumor suppressor. *APC* loss in cancers upregulates Wnt signaling by increasing beta-catenin abundance. Although first described in familial adenomatous polyposis, *APC* mutations are found in most sporadic colon cancers, and they are an early step during the progression of colorectal cancer.[147] Many other cancers also have aberrant Wnt signaling, including uterine cancers, brain cancers, and leukemia.[120] Inhibitors of the Wnt pathway are being actively studied for use in cancer therapy.[148] For example, the finding that colorectal cancers require persistent Wnt deregulation for tumor maintenance suggests that Wnt inhibitors may be efficacious in this setting.[149]

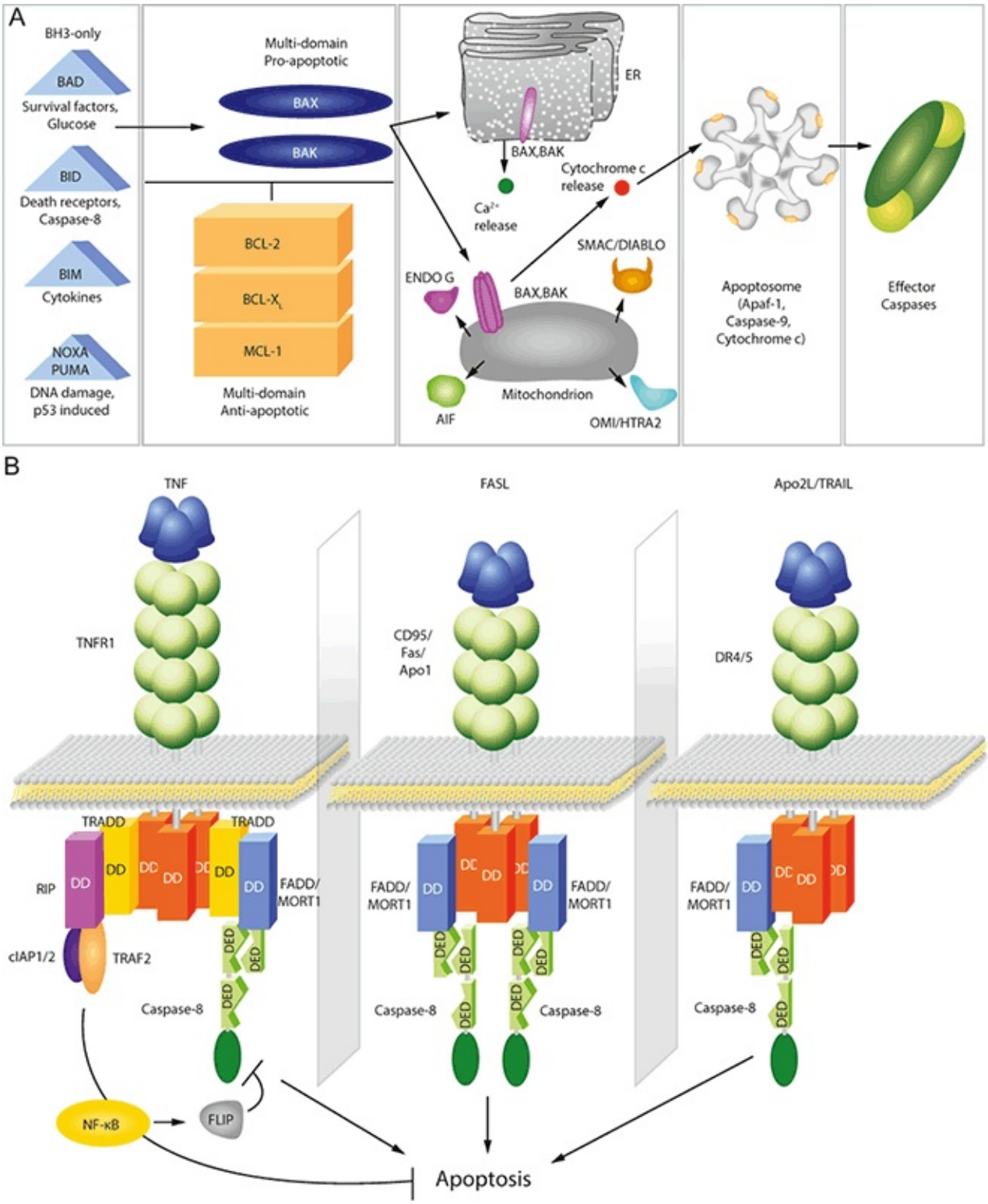

Fig. 2-16 Apoptosis pathways.

(A) The intrinsic apoptosis pathway (see text for details). (B) Extrinsic death receptor pathways. The distinct composition of the death-inducing signaling complex (DISC) downstream of the various death receptors TNFR1, CD95, and DR4/5 is illustrated.

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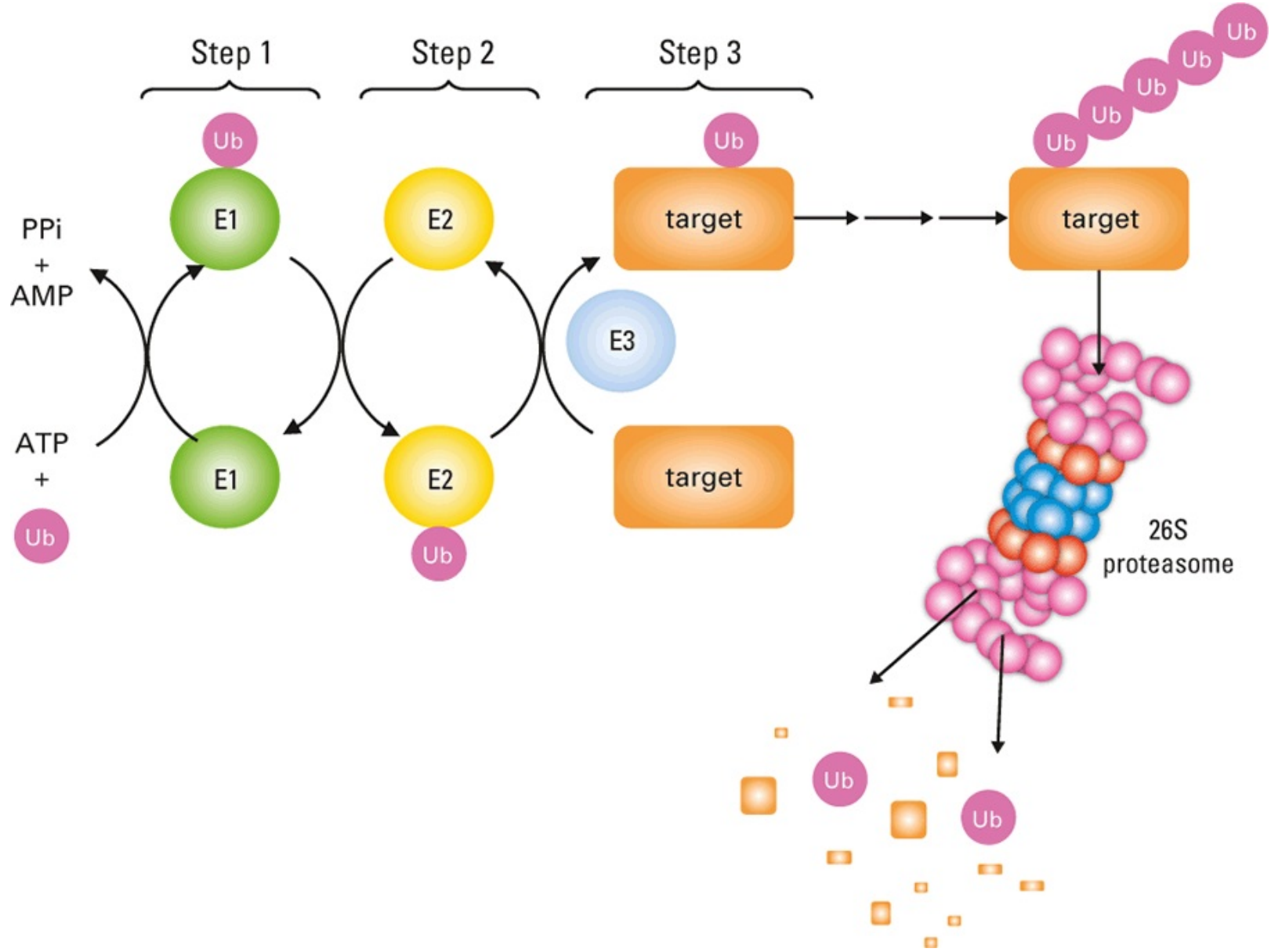

Fig. 2-17 Overview of the ubiquitin–proteasome pathway.

Ubiquitin (Ub) is a small protein that is first transferred to the ubiquitin-activating enzyme, E1, in an ATP-dependent manner. This activated ubiquitin is then transferred to the ubiquitin-conjugating enzyme, E2. Finally, the ubiquitin is covalently attached to the target protein by an E3 ubiquitin ligase, leading to formation of a polyubiquitin chain. The polyubiquitinated protein is recognized by the 26S proteasome, and is destroyed in an ATP-dependent manner.

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DIFFERENTIATION

Most somatic cells are in a terminally differentiated, postmitotic state, which is established by complex transcriptional pathways. Many proto-oncogenes affect the pathways that regulate differentiation, and these often are transcription factors and/or coactivators involved in leukemias and lymphomas.[151] For example, the gene encoding retinoic acid receptor (RAR)-alpha is deregulated by several translocations found in acute promyelocytic leukemia, most commonly t(15;17), which produces a promyelocytic leukemia (PML)–RAR-alpha fusion protein. This fusion protein acts as a dominant-negative mutant that inhibits RAR-alpha target genes by recruiting co-repressors. This dominant-negative RAR-alpha fusion is targeted by all-trans retinoic acid (ATRA), which is used in conjunction with combination chemotherapy to induce remission in patients with acute promyelocytic leukemia. ATRA binds to the fusion protein and

prevents it from bringing co-repressors to RAR-alpha target genes. Thus, ATRA treatment reverses the differentiation block caused by the translocation product and allows promyelocytes to proceed down their differentiation pathway.[151] Core-binding factor (CBF) is another transcription factor that regulates hematopoietic differentiation and genes encoding both components of CBF (RUNX1/AML1 and CBF-beta) are involved in translocations found in acute leukemia. Like RAR-alpha, these translocations produce dominant-negative proteins that inhibit CBF target gene expression, which is thought to impair hematopoietic cell differentiation.[152]

The *NOTCH* genes are involved in cell-fate and differentiation pathways and are frequently altered in human cancers. *NOTCH* genes encode transmembrane receptors that stimulate transcriptional programs after they bind to ligands.[153] Ligand binding causes Notch proteins to be cleaved, forming intracellular domains that translocate to the nucleus. Notch proteins play important roles in lymphoid differentiation and are likely drivers of hematologic cancers. *NOTCH1* was first described as an oncogene by virtue of its involvement in the t(7;9) translocation found in a subset of patients with T-cell acute lymphoblastic leukemia. However, activating *NOTCH1* mutations occur in as many as 50% of patients with this disease.[154] The precise mechanisms through which Notch proteins promote leukemia are thought to involve impaired differentiation and enhanced self-renewal, and *MYC* is a critical mediator of Notch protein activity.[155] Interestingly, Notch proteins may act as tumor suppressors in some cancers, as 20% of squamous cell carcinomas show inactivating mutations in *NOTCH* genes. How this pathway promotes cancer in some clinical situations while suppressing it in others remains poorly understood.[156]

DNA REPAIR PATHWAYS

Mammalian cells use three major DNA repair pathways to maintain genomic integrity (Fig. 2-18). Mutations that disrupt these pathways cause genetic instability and are associated with diseases characterized by sensitivity to DNA-damaging agents and cancer predisposition. Ultraviolet light–induced nucleotide dimers and other DNA adducts are recognized and repaired by the nucleotide excision repair (NER) pathway. DNA-recombination repair is involved in the restoration of double-stranded breaks induced by ionizing radiation and radiomimetic agents. Finally, the DNA MMR pathways correct errors during DNA replication by removing the mismatched strand and enabling subsequent repair of the DNA.

Nucleotide Excision Repair Pathway

NER pathways correct nucleotide lesions induced by ultraviolet light and adducts induced by chemical carcinogens.[157] There are two NER pathways: a global repair pathway and a transcription-coupled repair pathway that repairs DNA damage that occurs during transcription. Mutations affecting these pathways give rise to sun-sensitive and developmental disorders, including xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy. Xeroderma pigmentosum is an autosomal-recessive disorder leading to neurodegeneration, sensitivity to ultraviolet light, abnormalities in skin pigmentation, and cancer predisposition. Patients with this disorder have a risk for skin cancer that is estimated to be 2000 times higher than the risk in the general population. Eight genes have been associated with xeroderma pigmentosum; seven of them code for excision-repair proteins, and one is a DNA polymerase that is required for accurate replication of damaged DNA. In contrast, Cockayne syndrome is associated with two genes, *ERCC8* and *ERCC6,* which are involved in transcription-coupled DNA repair. Trichothiodystrophy is caused by mutation of either *ERCC2* or *ERCC3,* which encode helicase

subunits of the TFIIH transcription complex. Neither Cockayne syndrome nor trichothiodystrophy is associated with an increased cancer risk.

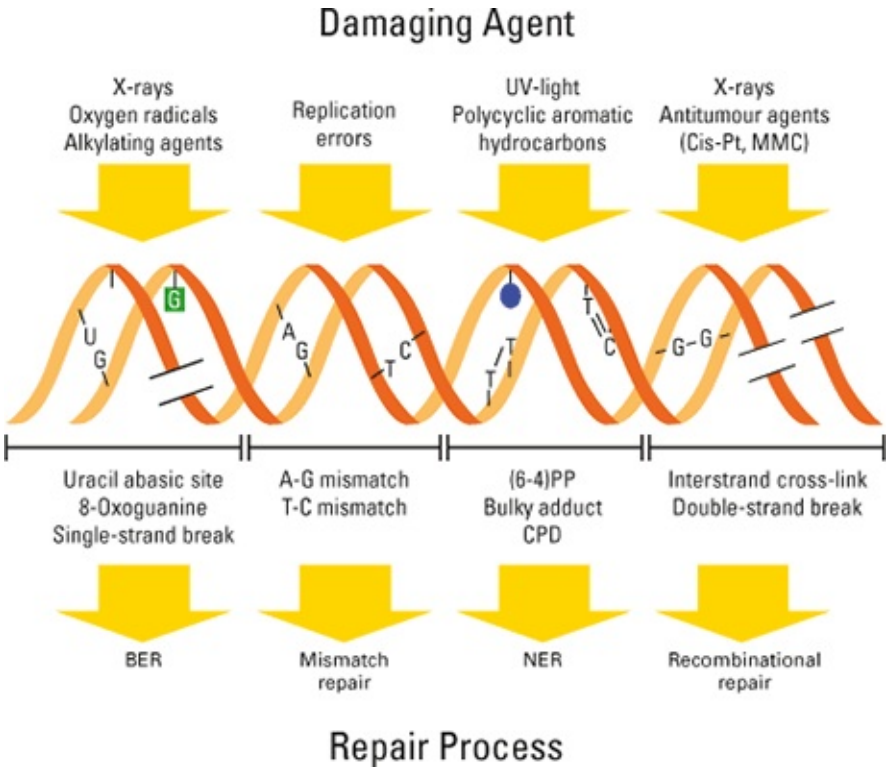

Fig. 2-18 DNA lesions and repair mechanisms.

(Top) Common DNA-damaging agents. (Middle) Examples of lesions that can be introduced into the DNA double helix by these agents. (Bottom) The most frequently used repair mechanisms for such lesions. Distinct damaging sources can induce similar types of DNA lesions, and any one agent often induces more than one type of damage. The lesion spectrum of different repair pathways may overlap.

Abbreviations: BER, base excision repair; NER, nucleotide excision repair.
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Double-Strand Break Repair

Damage to DNA by radiation, chemicals (such as chemotherapy), and other insults produces double-strand breaks that are recognized and repaired by a coordinated response that involves the proteins encoded by a wide range of tumor suppressor genes. Mutations of some of these genes cause inherited syndromes that have highly variable clinical manifestations. Ataxia telangiectasia is characterized by progressive cerebellar ataxia, telangiectasia, immunodeficiency, and increased tumorigenesis (most commonly T-cell neoplasms). The ataxia telangiectasia gene (*ATM*) encodes a large protein kinase with homology to PI3K. *ATM* is activated by serine phosphorylation in response to DNA breaks, and it phosphorylates a number of downstream substrates with critical roles in DNA repair and checkpoint pathways, including CHK2, p53, BRCA1, and NBS1 (Fig. 2-19).[158] Cells derived from patients with ataxia telangiectasia exhibit increased DNA damage after radiation therapy, as well as defects in normal cell-cycle responses to DNA damage, called “checkpoints” (discussed in more detail Checkpoints: Crossroads of DNA Repair, Cell Cycle Regulation, and Genetic Instability).

Fanconi anemia (FA) is an autosomal-recessive disease characterized by developmental abnormalities, bone marrow failure, and susceptibility to cancers, particularly acute myeloid leukemia, squamous cell cancer of the head and neck, gynecologic cancers, and esophageal cancer. Similar to ataxia telangiectasia, cells derived from patients with FA display abnormal

chromosome breakage. However, FA cells are not hypersensitive to ionizing radiation; rather, they are hypersensitive to DNA cross-linking by agents such as diepoxybutane and mitomycin C. Classic studies defined many FA complementation groups, and 13 FA genes have now been cloned. Remarkably, many of these proteins form a complex that catalyzes the monoubiquitination of two FA proteins, FANCD2 and FANCI.[159-161] Monoubiquitinated FANCD2 and FANCI become localized to nuclear foci after DNA damage, and these foci also contain FANCD1 (identical with the *BRCA2* breast cancer gene) and other proteins, including BRCA1 and NBS1 (Fig. 2-19). The striking intersection of the BRCA1 and FA pathways underscores the central importance of this DNA damage sensing and repair mechanism in carcinogenesis.

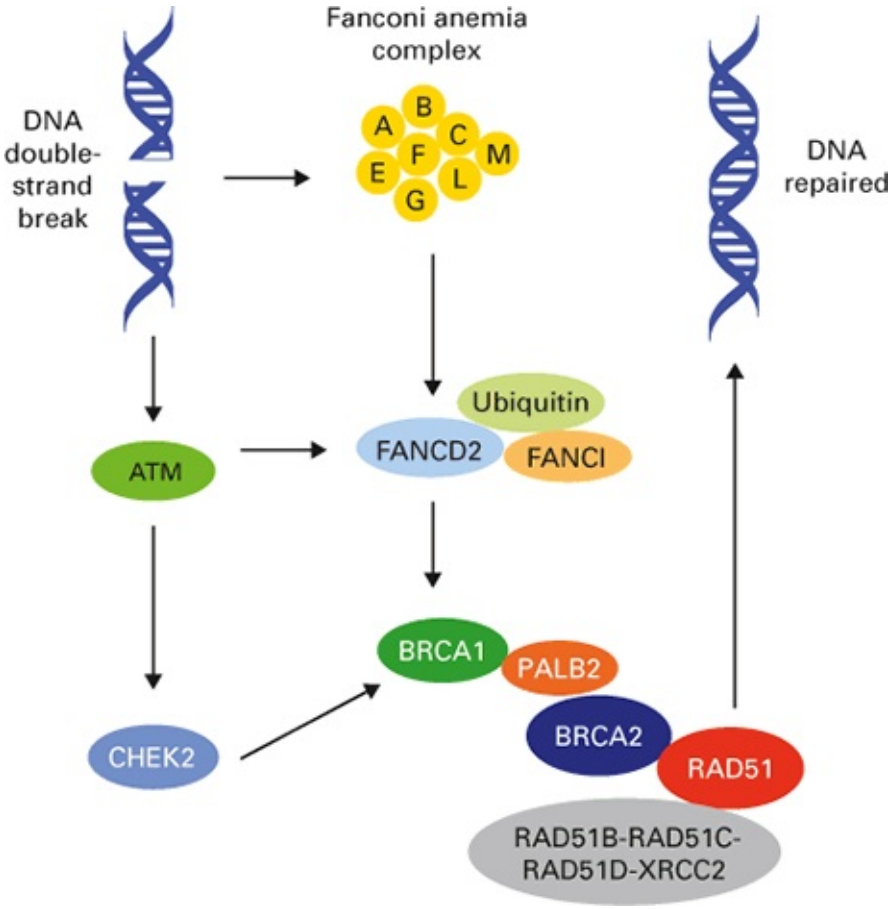

Fig. 2-19 Recombinational repair of DNA double-strand damage.

DNA double-strand breaks recruit protein kinase ATM and also activate the Fanconi anemia core complex (FANCA/B/C/E/F/G/L/M) that monoubiquitinates the downstream targets FANCD2 and FANCI. ATM activates (phosphorylates) CHEK2 and FANCD2 and in turn CHEK2 phosphorylates BRCA1. Ubiquinated FANCD2 complexes with BRCA1 and RAD51. The PALB2 protein then acts as a hub, bringing together BRCA1, BRCA2, and RAD51 at the site of a DNA double-strand break, and also binds to RAD51C, a member of the RAD51 paralog complex RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2). The BCDX2 complex recruits RAD51 or stabilizes the damage sites. RAD51 plays a major role in homologous recombinational repair of DNA during double-strand break repair. In this process, an ATP dependent DNA strand exchange takes place in which a single strand invades base-paired strands of homologous DNA molecules. RAD51 is involved in the search for homology and strand pairing stages of the process.

Source: Wikipedia. Public Domain, https://en.wikipedia.org/wiki/Fanconi_anemia#/media/File:Homologous_recombinational_repair_of_DNA_double-strand_damage.jpg.

The NBS1 protein is another component of nuclear repair foci implicated in a chromosome breakage syndrome. Nijmegen breakage syndrome is an autosomal-recessive disease characterized by microcephaly, immunodeficiency, and increased frequency of hematopoietic cancers that is caused by mutations in the *NBS1* gene. NBS1 forms a complex with MRE11 and

RAD50, which binds to BRCA1 in nuclear foci. Deficiency of the NBS1 protein blocks the formation of the MRE11–NBS1–RAD50 complex, and this impairs the S-phase surveillance responses triggered by ATM. Accordingly, many of the symptoms of this disease are identical to symptoms of ataxia telangiectasia.

Mismatch Repair

DNA MMR corrects errors that occur during DNA replication, primarily single base mismatches or short insertions or deletions.[162] A complex of proteins bind to a DNA mismatch, identify the correct DNA strand, and then excise and repair the mismatch. Several of these proteins are tumor suppressors involved in hereditary nonpolyposis colon cancer (HNPCC). Patients with HNPCC/Lynch syndrome develop colon cancer at an early age, as well as cancers in many other organ sites.[163] The two most commonly mutated MMR genes in Lynch syndrome are *MSH2* and *MLH1.* MSH2 is involved with the initial recognition of the mismatch, whereas, MLH1 helps determine which DNA strand contains the correct sequence. Mutations in other MMR genes are less commonly associated with HNPCC and include *MSH6, PMS1,* and *PMS2.* Patients with HNPCC inherit a nonfunctional MMR gene allele with subsequent loss of the remaining allele in a somatic cell that will ultimately give rise to a tumor. Importantly, impaired MMR causes a hypermutable phenotype, as evidenced by microsatellite instability, which is readily detected in tumors by PCR-based assays that reveal novel tumor-specific microsatellite fragments. Although microsatellite instability is the hallmark of HNPCC, it also is found in a subset of sporadic colon cancers. However, in these cases, *MLH1* is typically silenced by promoter hypermethylation rather than by gene mutation.

CHECKPOINTS: CROSSROADS OF DNA REPAIR, CELL-CYCLE REGULATION, AND GENETIC INSTABILITY

The fidelity of the enzymes that replicate DNA and segregate chromosomes is largely responsible for the accurate propagation of genetic information. However, these enzymes have an intrinsic error rate, and the frequency of errors is increased by genotoxic insults. Normal cells continually monitor DNA replication and mitosis and stop the cell cycle if these do not occur correctly, allowing the damage to be repaired before proliferation resumes, or initiate apoptotic and/or senescence responses if the damage cannot be repaired. The pathways that link cell-cycle progression to the accurate execution of prior cell-cycle events are called “checkpoints.”[164] (Note that this section refers to *checkpoints* as molecular processes that safeguard the genome from damage; such checkpoints are wholly distinct from the checkpoints present in the immune system that are targeted by immunotherapy approaches.)

Mammalian cells have checkpoints that operate in each phase of the cell cycle and are intricately interwoven with the cell-cycle and DNA repair machinery.[165-168] The G1 and G2 checkpoints recognize DNA damage that occurs during these cell-cycle phases and initiate responses leading to either cell-cycle arrest or cell death. In addition to DNA damage, the S-phase checkpoint also is activated by stresses that inhibit the proper function of the replication machinery, including S-phase chemotherapeutics such as hydroxyurea and cytarabine.

Checkpoint pathways may be broadly viewed as being composed of sensors/mediators, signal transducers, and effectors (Fig. 2-20). The sensors and mediators detect DNA damage and comprise protein complexes that accumulate in DNA repair foci. The DNA damage signal is then transmitted by kinases, which initially include ATM and ATR, and subsequently by kinases such as CHK1 and CHK2, which ultimately activate effectors, such as p53 and Cdc25, that

directly affect cell-cycle progression, apoptosis, and DNA repair proteins. Small-molecule inhibitors of many checkpoint kinases are being evaluated as chemotherapeutics.

Checkpoint pathways are disrupted in most cancers. One consequence of impaired checkpoint function is genetic instability, which drives tumor progression through the accumulation of additional oncogenic mutations. The p53 protein plays a central role in checkpoint pathways, and *TP53* is the most frequently mutated human tumor suppressor gene.[169-171] Although this gene is mutated in up to half of all spontaneous cancers, its role as a tumor suppressor first came to light in studies of Li–Fraumeni syndrome, a rare autosomal disorder associated with the development of a wide variety of early-onset cancers, including soft-tissue and bone sarcomas, as well as breast, brain, and colon cancers. *TP53* encodes a transcription factor that is activated by many triggers, including DNA damage and replication stress. When the p53 protein is activated by signals such as DNA damage, the outcome can be cell-cycle arrest, apoptosis, or cellular senescence; these alternative outcomes depend on many factors (Fig. 2-21). p53 accomplishes these outcomes by activating transcription of its target genes and through other actions. Tumors most commonly inactivate *TP53* through loss-of-heterozygosity, which leaves a single normal copy of the gene, followed by intragenic point mutations, which inactivate the remaining allele by altering critical functional domains of the resulting p53 protein.

Another mechanism of p53 loss in tumors involves the MDM2 ubiquitin ligase.[138] MDM2 expression is induced by p53, and it functions in a feedback loop to downregulate p53 by catalyzing its ubiquitination. The normal MDM2–p53 regulatory circuit is disrupted in many cancers. MDM2 is overexpressed in a wide spectrum of neoplasms, and this leads to decreased p53 abundance and function. A second mechanism that targets this pathway involves the *ARF* tumor suppressor. As discussed previously, *ARF* is encoded within the same gene as the p16INK4A protein and is frequently deleted in cancers.[172] ARF normally binds to MDM2, which prevents MDM2 from degrading p53. However, when *ARF* is deleted, MDM2 activity is unrestrained, causing p53 to be degraded. *ARF* expression is induced by oncogenes such as *MYC* and plays an important role in p53 activation by oncogenic signaling. Thus, loss of *ARF* disables an important protective mechanism against oncogenic transformation.

There is enormous interest in developing cancer treatment strategies that target the p53 pathway. In fact, studies in model systems demonstrating the antitumor activity of p53 restoration in tumors has reenergized this active field.[173] Strategies that target the p53 pathway range from peptides that restore p53 function in cells with mutant p53 proteins to recombinant adenoviruses that selectively kill cells with *TP53* mutations. However, the scope of these approaches is too great to be covered in detail here, and there are reviews that address this large field.[174,175]

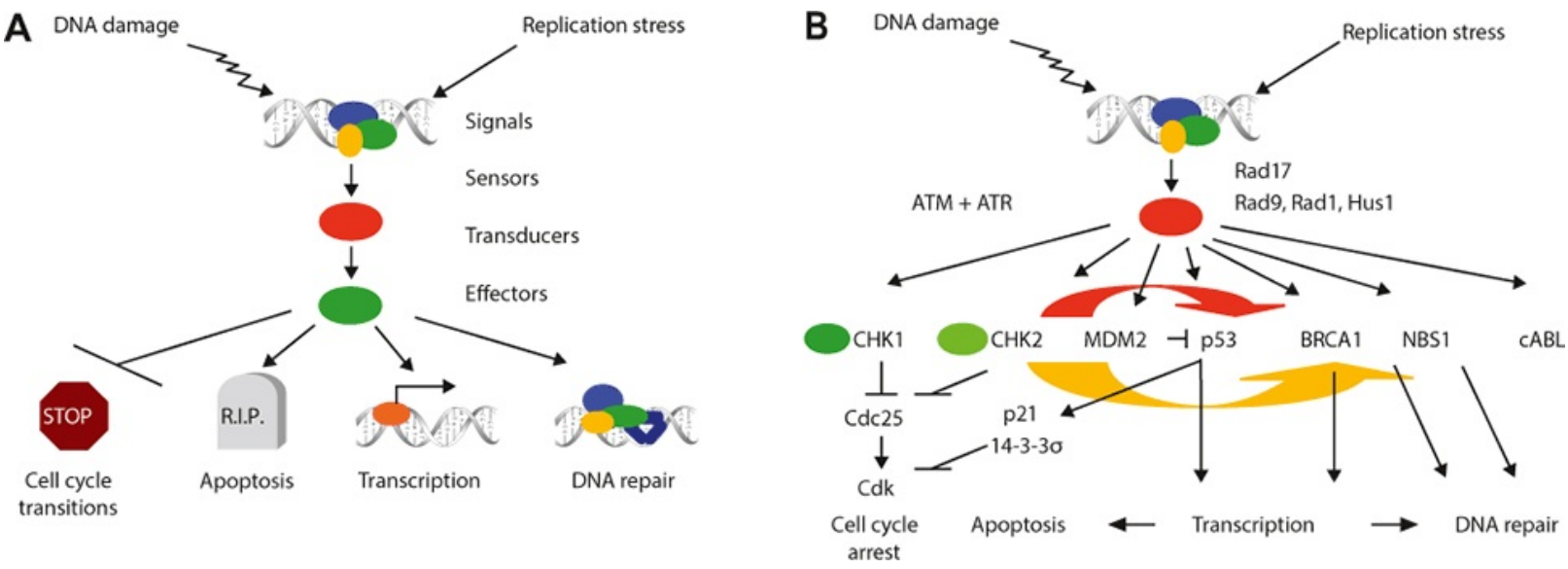

Fig. 2-20 Organization of DNA damage response pathways.

(A) A general outline of the DNA-damage response signal transduction pathway. Arrowheads represent activating events, and perpendicular ends represent inhibitory events. Cell-cycle arrest is depicted with a stop sign and apoptosis with a tombstone. The DNA helix with an arrow represents damage-induced transcription, while the DNA helix with several oval-shaped subunits represents damage-induced repair. For the purpose of simplicity, the network of interacting pathways are depicted as a linear pathway consisting of signals, sensors/mediators, transducers, and effectors. (B) Organization of the mammalian DNA-damage response pathway. Arrowheads represent positively acting steps while perpendicular ends represent inhibitory steps. Gene names are shown at the approximate positions where their encoded proteins function in the pathway. Although the general organization of the pathway is correct, some details are omitted, especially concerning the relationship between the ATR/ATM and Hus1/Rad17/Rad9/Rad1 proteins, which may participate in mutual regulation.

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The mitotic or spindle assembly checkpoint ensures that chromosomes are equally segregated to daughter cells during mitosis, and it is the key safeguard against the gain or loss of whole chromosomes, also known as “aneuploidy.” The spindle apparatus is composed of tubulin and attaches to chromosomes through their kinetochores during mitosis. In a normal cell, the signal that activates the spindle checkpoint is generated by kinetochores that are unattached or have insufficient spindle tension; this delays mitosis and ensures that chromosome separation does not occur in situations in which the daughter cells may receive an abnormal number of chromosomes because of misalignment (Fig. 2-22).[176] A number of spindle checkpoint proteins accumulate at the unattached kinetochore, including BUB1, BUBR1, MAD1, and MAD2. This complex prevents mitosis by sending a signal that inhibits the anaphase-promoting complex (APC), an E3 ubiquitin ligase that regulates mitotic entry and exit. Two critical APC targets that must be degraded for mitosis to proceed are cyclin B and securins (the latter function to hold together sister chromatids). Thus, the spindle checkpoint prevents mitosis in the setting of an improperly attached spindle by blocking the degradation of APC substrates. A number of chemotherapeutic agents target the spindle apparatus (e.g., taxanes and vinca alkaloids) and trigger the spindle checkpoint in normal cells.

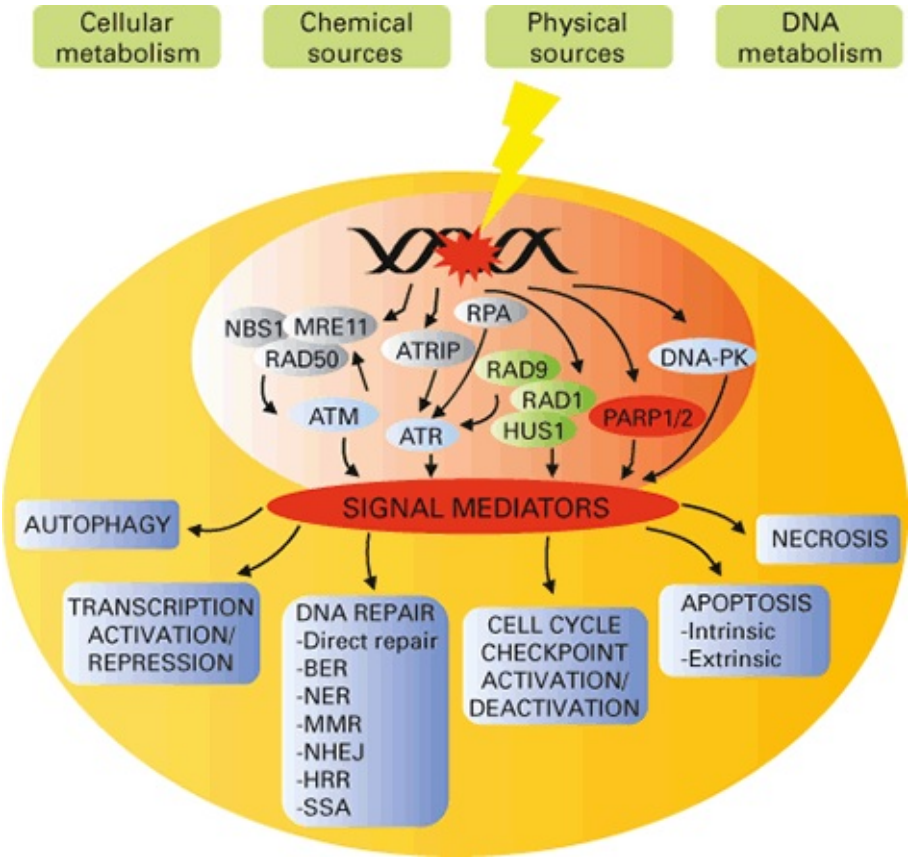

Fig. 2-21 The cellular response to DNA damage.

The activation of p53 classically occurs in response to many other cellular stresses that produce DNA damage, including oncogene-induced stress. Depending on the nature of the inducing signal, these DNA-damage responses activate myriad upstream mediators that lead to upregulation and activation of p53. This, in turn, results in activation of p53 target genes that serve to counteract the initiating cellular stress and protect the cell from further damage. When *TP53* is mutated or deleted, as it is in most cancers, these critical safeguards no longer function and cellular stress continues unabated.

KEY POINTS

- Enzymes that promote protein degradation by the proteasome can function as tumor suppressors.
- Pharmacologic proteasome inhibitors are approved for the treatment of multiple myeloma and other blood cancers.
- Genes that regulate cellular differentiation often are mutated in hematologic cancers.
- DNA repair pathways contain many tumor suppressor genes that are mutated in both familial and sporadic cancers.
- Mutations that disable different DNA repair pathways are associated with specific cancer syndromes.

MULTISTEP TUMORIGENESIS

The development of fully malignant cancers requires many independent events. Although the specific mutations that cause human cancers vary greatly between types of cancers and

individuals, the broad consequences of these mutations are abnormal phenotypes that are shared by most cancers. Hanahan and Weinberg have proposed six “hallmarks of cancer” that they define as “distinctive and complementary capabilities that enable tumor growth and metastatic dissemination” (see Fig. 2-23).[177,178] These include sustained proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. These capabilities can be acquired in different sequences, and, in some cases, a single genetic mutation might provide more than one capability. This conceptualization provides an important framework within which to consider multistep carcinogenesis.

The first three of these “acquired capabilities” involve mutations within the mitogenic signaling, cell cycle, and cell-death pathways that have been previously outlined. The fourth category involves the acquisition of cellular immortality in tumors. Normal cells are limited in the number of times that they can divide, even when they are provided with all of the normal mitogenic stimuli required for cell division. In contrast, many cancer cells have apparently limitless potential to divide. One fundamental mechanism that limits human cell division involves the ends of chromosomes, which are called “telomeres.” Telomeres normally protect the ends of chromosomes, and they shorten with each cell division. Thus, the length of a cell’s telomeres reflects the number of divisions it has undergone. Eventually the telomeres are shortened to a point at which they can no longer protect the chromosome ends; this leads to a condition termed “crisis” and, ultimately, to cell death. Unlike normal cells, cancer cells maintain their telomere length during cell division. This usually results from expression of the enzyme telomerase that adds DNA back to the telomere. Telomerase activity can be detected in 85 to 90% of cancers, and the remaining tumors maintain their telomeres through a mechanism involving recombination.

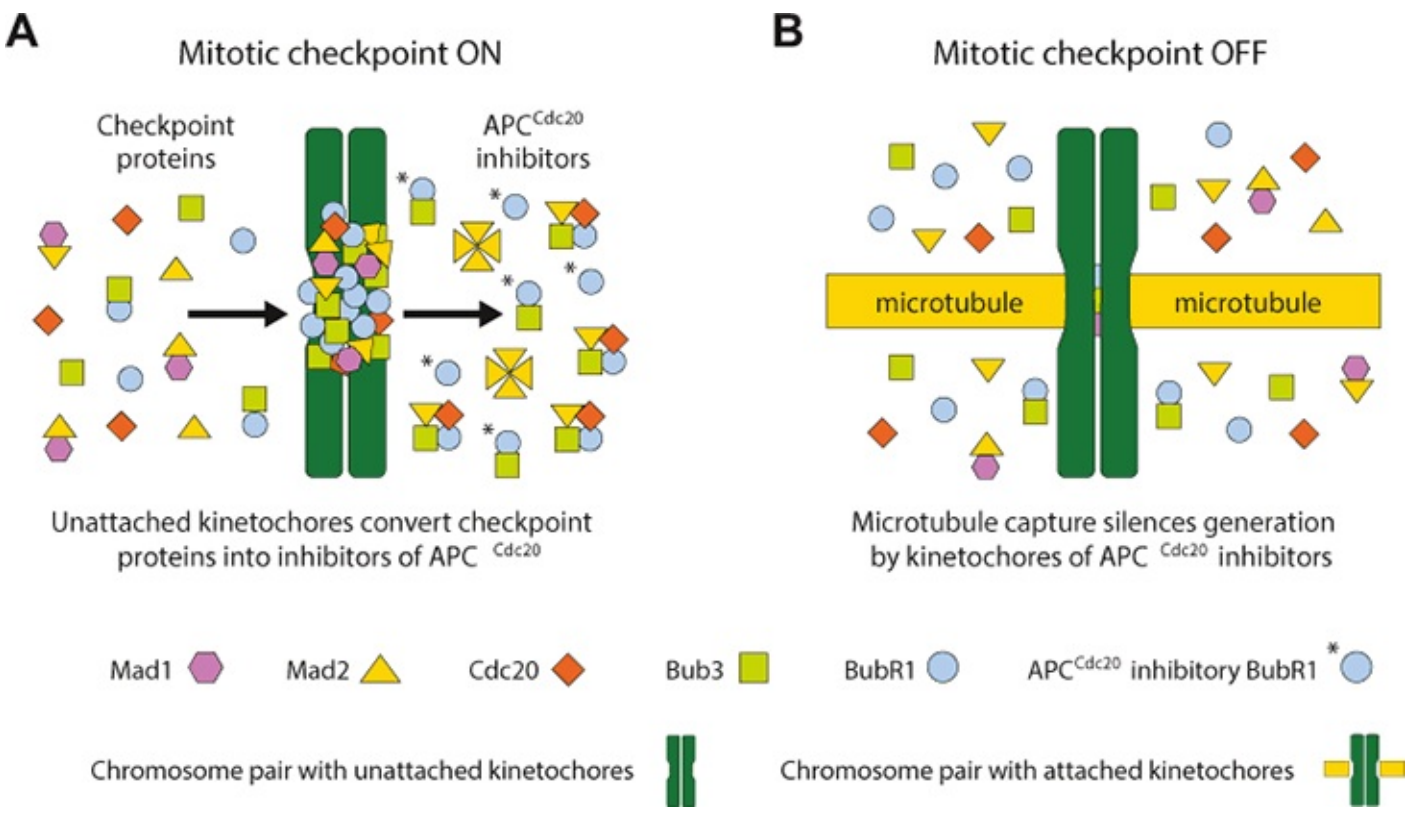

Fig. 2-22 Mitotic checkpoint signaling.

(A) Unattached kinetochores are the signal generators of the mitotic checkpoint. They recruit mitotic checkpoint proteins, including Mad1, Mad2, BubRI, and Bub3, and convert them into inhibitors of APCCdc20. (B) Once all kinetochores have made productive attachments to spindle microtubules, production of the APCCdc20 inhibitors is silenced.

The fifth capability of induced angiogenesis reflects the fact that tumors often outgrow their blood supply and must actively recruit vasculature to grow. In normal tissues, the development of new blood vessels is highly regulated by both positive and negative signals. Tumor cells promote angiogenesis by upregulating the pathways that promote blood vessel formation (e.g., increased expression of growth factors such as vascular endothelial and fibroblast growth factors) and by reducing the activity of inhibitory pathways. Some of these pathways involve transcriptional networks under the control of previously discussed genes, such as *VHL* mutations in renal cell carcinoma. The importance of these pathways in tumor cell growth has prompted the development of drugs that target angiogenesis.

The last of the six hallmarks is tissue invasion and metastasis, which is critically important because metastasis accounts for most cancer fatalities. Specific gene products are associated with the ability of tumor cells to metastasize to different organ sites. Other tissue types, such as stroma and tumor-associated cell populations, also contribute to metastasis. Elegant animal models of metastasis, as well as transcriptional profiling of human cancers, are revealing that metastasis includes alterations in genes involved in processes such as cell adhesion, integrin signaling, growth factors, chemokine signal transduction, and extracellular proteolysis.

In addition to these six hallmarks, Hanahan and Weinberg outline two emerging hallmarks and two enabling characteristics that make it possible for tumor cells to acquire the core hallmarks. The two emerging hallmarks are deregulating cellular energetics and avoiding immune destruction. The concept that tumor cells reprogram their glucose metabolism toward glycolysis, even in the presence of oxygen, was first noted more than 50 years ago. However, more recently, there has been an explosion of research into the significance and mechanisms of aerobic glycolysis in cancer, also known as the “Warburg effect.”[66] It is clear that metabolic reprogramming has critical roles in cancer cell growth and division.[179] The second emerging hallmark reflects the role of the immune system in controlling cancers and the molecular changes in cancer cells that allow them to evade immune destruction. Although discussion of immunotherapies is beyond the scope of this chapter, they are a key component of current therapy for cancer in many organ sites and are discussed in many disease-specific chapters later in this book.

The two “enabling characteristics” are properties of cancer cells that facilitate the acquisition of the hallmarks. The first of these characteristics is genomic instability, which drives the acquisition of the multiple mutations required for multistep tumorigenesis. The second enabling characteristic is “tumor-promoting inflammation,” which reflects the rapidly advancing concept that inflammatory responses can actually facilitate tumor initiation and progression. One important aspect of the “hallmark/enabling characteristics” conceptualization is that it also provides a framework for understanding the development of mechanism-based targeted therapies, which target both hallmarks and enabling characteristics. Examples of such therapies include angiogenesis inhibitors and immune checkpoint inhibitors, as previously discussed.

KEY POINTS

- Checkpoints ensure the fidelity of cell division and protect against genomic instability.

- Many tumor suppressor genes and DNA repair proteins are intimately associated with checkpoint pathways.
- The loss of checkpoint functions causes genomic instability and fosters the accumulation of multiple mutations in cancer cells.
- *TP53* is the most commonly mutated cancer gene, and it participates in diverse checkpoint responses. The p53 protein senses cellular stress and signals to pathways that regulate processes such as cell-cycle progression and apoptosis.
- Tumorigenesis is a multistep process that requires the accumulation of multiple mutations. All tumors share a number of hallmarks that contribute to their malignant phenotype, but the specific molecular events that produce these phenotypes vary greatly among tumor types and individuals.

INFECTIOUS AGENTS AS DRIVERS OF CANCER

Infectious agents contribute to the pathogenesis of approximately 15% of all cancers worldwide, affecting more than 2 million people.[180] Most of these are associated with chronic viral infection. Examples of common cancers associated with chronic viral infection include squamous cell carcinomas of the cervix, head and neck, and anus (HPV); Burkitt and other types of lymphoma, nasopharyngeal carcinomas, and some stomach cancers (Epstein–Barr virus [EBV]); and hepatocellular carcinoma (hepatitis B and C viruses). Other cancers associated with viral agents include Kaposi sarcoma and Merkel cell carcinoma. Extensive research has elucidated some of the molecular mechanisms used by infectious agents to drive carcinogenesis. As previously noted, retroviruses can cause cancer through insertional mutagenesis. Other cancer-causing viruses express proteins that interfere with the critical cancer pathways, outlined elsewhere in this chapter. For example, the HPV E6 protein promotes degradation of the tumor suppressor p53, impacting the DNA damage and repair response, while HPV E7 promotes degradation of the cell-cycle inhibitor Rb, driving cell growth, division, and proliferation. Whereas EBV-associated lymphomas are characterized by a translocation involving the *MYC* oncogene, EBV also promotes B-cell survival and transformation via molecular mimicry, as EBV gene products mimic activated cell-surface receptors and antiapoptotic proteins. Hepatitis B and C proteins promote expression of genes associated with angiogenesis, enhanced cell motility, invasion, and metastasis. In fact, many oncogenic viruses produce protein products that impact most of the hallmarks of cancer.[181] Given that viral-associated cancers frequently subvert normal cellular processes, the study of these cancers often yields insights into the biology of sporadic cancers. These insights include the identification of new oncogenes or tumor suppressor genes, as well as an increased understanding of more complex aspects of tumor biology (e.g., immune surveillance).

While viruses are most commonly associated with cancer, other pathogens also contribute to carcinogenesis. Chronic infection with the intestinal bacteria *Helicobacter pylori* is associated with some stomach cancers and low-grade lymphomas.[182] Similarly, hepatobiliary cancer, which is much more common in southeast Asian populations, is associated with endemic infection with liver flukes.[183] While less is known about the molecular mechanisms driving these cancers, chronic inflammation likely plays a major role.

Given the large number of human cancers associated with infections, there is much interest in preventing and/or treating infection with the underlying pathogen with the ultimate goal of

cancer prevention. Examples include the use of an HPV vaccine to prevent squamous cell carcinoma and universal vaccination against hepatitis B virus to decrease the incidence of hepatocellular cancers.[184] Elimination of *H. pylori* may prevent gastric cancer and often induces remission of gastric mucosa-associated lymphoid tissue (MALT) lymphomas.[185,186] As more is learned about the molecular mechanisms driving infection-related cancers, targeted agents that specifically block the function of viral gene products will likely be developed. Finally, viral proteins expressed by pathogen-associated cancers represent attractive targets for various immunotherapeutics.

KEY POINTS

- Infection-associated cancers represent a worldwide epidemic affecting more than 2 million people per year.
- Infectious agents frequently subvert molecular processes related to the hallmarks of cancer, including checkpoints, proliferation, apoptosis, and immune surveillance.
- The study of infection-associated cancers gives insights into the molecular basis of sporadic cancers.

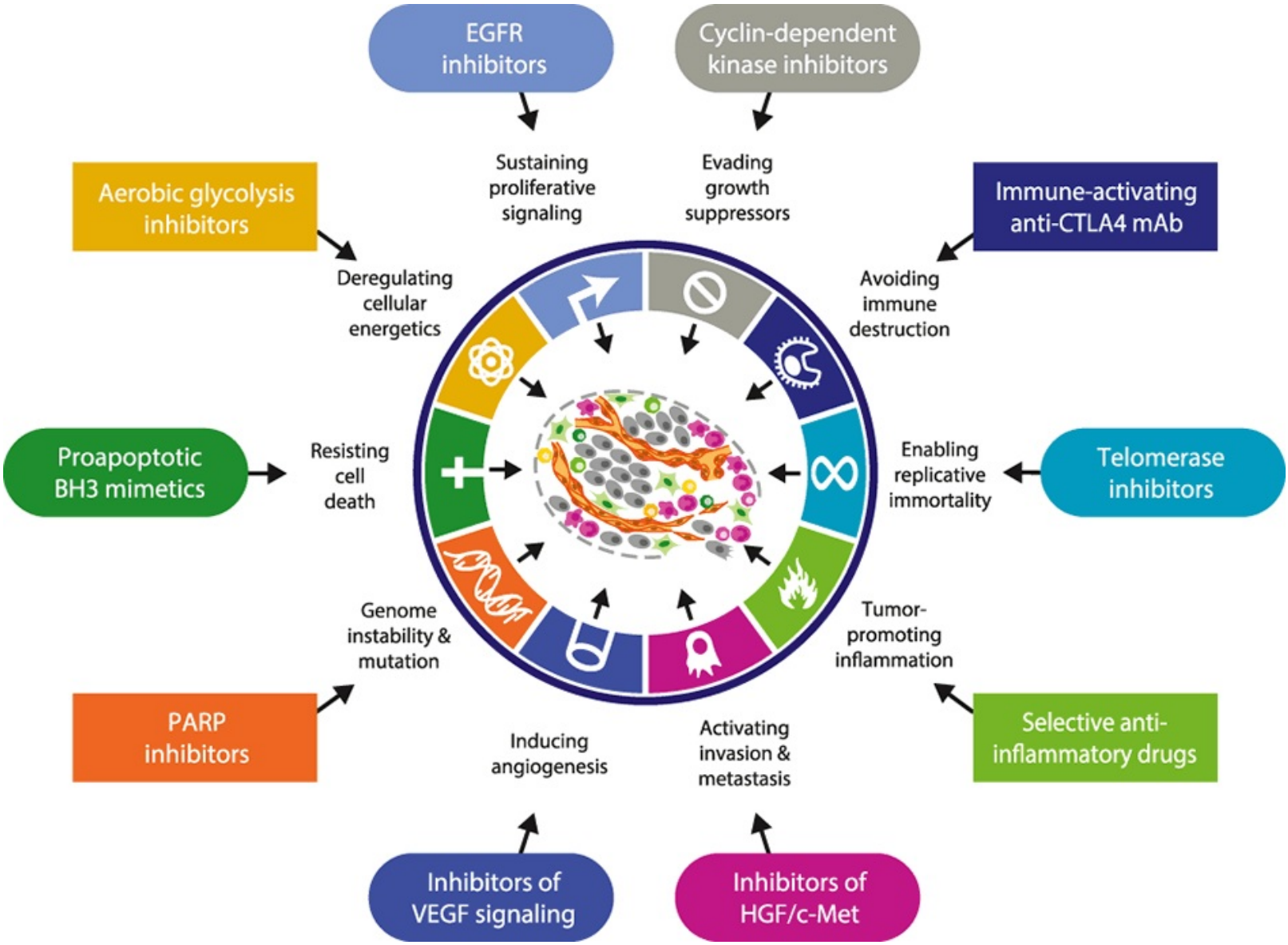

Fig. 2-23 The hallmarks of cancer.

Hanahan and Weinberg describe ten acquired capabilities necessary for tumor growth and progression (inner circle of text). Therapeutic strategies aimed at counteracting each specific hallmark are indicated. Drugs that interfere with these hallmarks have been developed and are in clinical trials, or in some cases, they have been approved for clinical use in treating certain forms of human cancer. The drugs illustrated are examples of the deep pipeline of candidate drugs with different molecular targets and modes of action in development for most of these hallmarks.

ONCOGENOMICS AND PRECISION ONCOLOGY

A plethora of studies employing NGS to study cancer genomes have radically altered our understanding of the genomic landscape of cancers and demonstrated the immediate effect of genome-scale analyses on clinical oncology. Many of these studies used integrative approaches that incorporate various types of large-scale data to discover mutations in oncogenes and cancer pathways at an unprecedented rate. This is a rapidly evolving field. A few examples are briefly described in this section to illustrate the power and importance of these approaches.

Although most current approaches to cancer genomics incorporate NGS, different strategies are used to achieve different goals. For example, when sequencing is limited to either known oncogenes or coding sequences (exomes, which comprise only 5% of the total DNA), many

tumors can be analyzed; this allows highly powered studies of genes and pathways that are targeted by mutations in cancers. Limited-sequencing approaches also rapidly characterize tumor genomes within time frames that allow treatment decisions to be made based on the presence of specific mutations; this quick turnaround is critical to the success of targeted therapies, which are often indicated only in genetically-defined subgroups of patients. In contrast, whole-genome sequencing reveals genetic alterations in regions of DNA that cannot be assessed by limited approaches and may provide entirely novel insights into the types of mutations that drive carcinogenesis. However, whole-genome approaches are more difficult to apply to large numbers of tumors, at least for the time being.

A comprehensive analysis of the explosion of cancer genomics studies enabled by NGS is beyond the scope of this chapter, but the following are some examples that highlight the power and importance of these approaches. Two examples of early studies described an integrative approach that included sequencing of protein coding regions, SNP-based array analyses of DNA copy number, and RNA-Seq to develop global views of the genes and pathways that are mutated in pancreatic cancers and glioblastomas.[187,188] The use of these combined methods helped distinguish mutations that likely played a causal role in tumorigenesis (driver mutations) from mutations that may be irrelevant (passenger mutations). Importantly, Parsons et al.[187] found that the isocitrate dehydrogenase (*IDH*) gene, previously unrecognized as an oncogene, was mutated in 12% of glioblastomas. *IDH1* and *IDH2* mutations have subsequently been found in other cancers, including acute myelogenous leukemia (AML) and chondrosarcoma. Importantly, IDH1/2 mutant proteins cause epigenetic dysregulation and DNA hypermethylation[189] and pharmacologic IDH1 inhibitors are already demonstrating efficacy in numerous clinical trials.

Dozens of large-scale cancer genomics studies, many of which have been coordinated by The Cancer Genome Atlas (TCGA; a consortium sponsored by the National Institutes of Health), have identified the molecular features of most common and many uncommon cancer types.[190] Although the data included in these remarkable publications varies among studies, the molecular features that have been cataloged include whole-exome sequencing, RNA-Seq/RNA expression, copy-number variants, DNA methylation, miRNA expression, and protein analysis. These studies have provided unprecedented insights into cancer biology and revealed many new targets for therapeutic interventions. One common theme that has emerged is that although specific organ sites exhibit unique mutational spectra, other pathways are mutated in many, or most, types of cancer.[120,191,192] Some studies have applied whole-genome sequencing to study specific cancer types, such as a TCGA analysis of adult AMLs. That work revealed that AMLs contain fewer mutations than other adult cancers, with an average of 13 mutations per sample, only 5 of which involve recurrently mutated genes.[193]

EMERGING CONCEPTS ON TUMOR HETEROGENEITY AND EVOLUTION

While initial studies from TCGA and other consortia were aimed at cataloging gene mutations and other changes in primary tumors from a wide range of organ and tissue types, more recent efforts have included multiple biopsies from the same tumor, concurrent biopsies of primary and matched metastatic lesions, or multiple biopsies over time. These data allow comprehensive studies of genetic heterogeneity within a single tumor, as well as the dynamic process of tumor evolution at various stages of disease and its treatment.[194,195] It is now apparent that tumors may exhibit heterogeneous cell populations with distinct genetic changes at their earliest stages[195] and that the idea of a linear progression of tumor evolution is overly simplistic. In one

seminal example, analysis of separate regions within a single primary renal cell carcinoma (RCC) revealed marked genetic heterogeneity.[196] While such "sampling error" has important implications for the selection of therapies based on the presence of "targetable" mutations in a single biopsy specimen, it also informs our understanding of tumor evolution. For example, this study found that inactivation of the tumor suppressor VHL was the only pathogenic genetic change present in every tumor biopsy sample taken from a presumably homogenous single RCC lesion. All other frequently mutated genes exhibited multiple and distinct mutations within different areas of the tumor. This suggests a model in which the heterogeneous landscape of primary tumors serves as the substrate for subsequent tumor evolution, during which time specific clones are enriched or lost as tumors grow, invade, and metastasize.

Molecular comparisons of metastatic lesions with their antecedent primary tumors reveals a similarly complex picture of tumor evolution, including the maintenance and/or enrichment of "founder" mutations and new mutations unique to the metastatic lesion.[197,198] Indeed, discrete metastases can have markedly different genetic profiles. Together, these types of studies are revealing complex models of tumor evolution, such as parallel evolution, in which subclones within a single tumor may evolve independently of each other, and convergent evolution, in which unique clonal populations develop molecularly distinct but functionally equivalent alterations in common cancer pathways.[195] It should be noted that many studies of tumor evolution are based on exome or genome sequencing only; thus, other molecular events, such as copy-number variation, epigenetic effects, and proteomic changes, are less well understood. Finally, large-scale genetic change, such as chromosomal instability or chromothripsis (which refers to extensive DNA rearrangements that cluster in specific genomic regions), are commonly seen in both primary and metastatic tumors. Whether these changes are a cause or a consequence of tumor evolution remains controversial, but there is much interest in targeting these processes in the clinic.[199-201]

While understanding the heterogeneity and evolution of a patient's tumor could greatly impact therapeutic decisions, serial tumor sampling via invasive biopsy techniques is generally neither feasible nor favored by patients. The emerging field of "liquid biopsy," in which circulating tumor cells or circulating tumor DNA can be isolated from routine blood draws, allows serial tumor sampling in cancer patients across the spectrum, from diagnosis, treatment, and surveillance.[202] At diagnosis, liquid biopsies may simplify the search for targetable mutations, especially when primary biopsy specimens are limited or uninformative. Because liquid biopsies allow analysis of tumor evolution in real time, they can also serve as adjuncts to standard assessments of tumor response and progression after therapy has begun. For example, Siravegna et al. used serial sampling of circulating tumor DNA from patients with *KRAS* wild-type colorectal cancer to investigate mechanisms of resistance to cetuximab.[203] This analysis showed evidence of *KRAS* mutated subclones that were enriched after prolonged cetuximab therapy. Notably, cetuximab withdrawal led to resensitization of the tumor to this agent. As the field develops, liquid biopsies are likely to become commonplace, and they should provide new insights into molecular mechanisms of chemoresistance and allow prioritization of targeted therapies based on new or evolving genetic profiles. Finally, liquid biopsy is likely to be integrated into tumor screening in asymptomatic individuals and as surveillance for recurrence following therapy, given its superior sensitivity as compared to available methods.[204,205]

MOUSE MODELS OF HUMAN CANCER

Genetic techniques developed throughout the past two decades now make it possible to create

mouse models that mimic sporadic human cancers with increasing fidelity. The first generation of genetically engineered mouse models involved expressing oncogenes from transgenes (that were injected into oocytes) or making “knockout” strains in which genes were inactivated by homologous recombination in mouse embryonic stem cells.[206] Hundreds of genes have been studied with these techniques, which led to important advances in understanding gene functions in development and tumorigenesis. In fact, these methods are still in wide use today. However, these strategies affect gene expression early in development and, in the case of knockouts, affect every cell. These characteristics limit the ability of these mouse models to replicate human cancers, which sequentially acquire rare mutations in somatic cells. Moreover, many cancer genes are lethal when disrupted in the mouse germline or lead to rapidly developing neoplasms in one tissue that preclude studies of slower-growing cancers. More recent mouse genetic engineering strategies circumvent these problems by allowing mutations to be introduced in tissue-specific and temporally controlled manners, and these have led to mouse models that much more closely resemble human cancers.[207,208] Similar to the studies in human cells previously alluded to, the use of CRISPR/Cas9 gene-editing systems to produce mouse strains with engineered oncogenic mutations is also revolutionizing the development of murine cancer models, particular in allowing the rapid development of mice with multiple mutations.[209]

In addition to murine cancers, sophisticated xenografting methods, in which human cells are grown in murine hosts, are having a major effect on cancer biology research and are already beginning to be used to help guide treatment decisions. Patient-derived xenografts (PDXs) are human tumor explants that are directly grown in immunocompetent mice, which is a much more physiologic approach than establishing tumor cell lines in vitro. PDXs can be readily subjected to sequencing and screening approaches that seek to identify therapeutic vulnerabilities. Moreover, PDX-bearing “avatar” mice can be treated with chemotherapy combinations, with the goal of determining the most effective therapy for the patient from whom the PDX was derived.[210]

KEY POINTS

- Next-generation sequencing is revealing transformative and comprehensive insights into cancer genomics.
- These technologies may allow personalized and targeted cancer therapy strategies based on specific mutations detected in a patient’s tumor cells.
- Serial tumor biopsy reveals marked tumor heterogeneity and gives insights into tumor evolution that affect the selection of cancer therapies.
- Gene targeting and transgenic methods are used to create murine models that mimic the genetic mutations found in human cancers. These models are invaluable for understanding the mechanisms underlying tumorigenesis and are used to determine the role of specific mutations in multistep tumorigenesis.

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CLINICAL PHARMACOLOGY

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Recent Updates

- In a shift from tissue-based to plasma-based genomic analysis, the FDA approved a mutation test using plasma specimens as a companion diagnostic test for the detection of exon 19 deletions or exon 21 (L858R) substitution mutations in the epidermal growth factor receptor (EGFR) gene to identify patients with metastatic non-small cell lung cancer (NSCLC) eligible for treatment with erlotinib. (www.fda.gov, June 2016)
- The U.S. Food and Drug Administration (FDA) modified the indications for erlotinib for treatment of NSCLC to limit use to patients whose tumors have EGFR exon 19 deletions or exon 21 L858R substitution mutations as detected by an FDA-approved test. (www.fda.gov, October 2016)

OVERVIEW

Medical oncologists are responsible for administering anticancer therapies to patients with malignancies. Many of these drugs exhibit a narrow therapeutic window, meaning the difference between the toxic dose and the therapeutic dose is small. Traditionally, researchers have developed antineoplastic agents to be delivered at the maximum doses to optimize their anticancer activity. However, the focus of drug development has shifted away from antineoplastic therapies that target DNA and toward molecules that target a specific “molecular target,” often a protein regulating cell growth, cancer progression, or inhibition of apoptosis. These classes of drugs are commonly referred to as “targeted cancer therapies.” Regardless of the agent, drug dosing requires a balance between the anticancer benefit and the known toxic effects these agents have on normal organs. The current era of genomic medicine has resulted in the development of drugs that target actionable somatic genetic derangements in tumors, at times leading to dramatic tumor shrinkage. This has led to a diminished focus on what the patient’s body does to the drug, as well as what the drug does to normal organs. The purpose of this chapter is to address this gap by reviewing the fundamental principles of clinical pharmacology as they relate to the practice of oncology.

PRINCIPLES OF CHEMOTHERAPY

Cytotoxic chemotherapy has been a relative success story. Cancers such as Hodgkin disease, non-Hodgkin lymphomas, testicular cancer, germ cell tumors, leukemia, Wilms tumors, retinoblastomas, and others can be cured through the effective delivery of cytotoxic chemotherapy. The objective of cancer chemotherapy is to reduce the tumor cell population to zero.

Three basic principles underlie the use of systemic chemotherapy, which generally comprises a combination of agents delivered cyclically at the highest tolerable dose. First, the fractional cell kill hypothesis states that a constant fraction of tumor cells is killed per cycle of chemotherapy, regardless of total body burden. For example, if a drug kills 99% of tumor cells per cycle of treatment, the tumor burden of 10^{11} cells will be reduced to approximately 10 cells after five cycles of therapy [$10^{11} \times 0.01^6 < 10$]. Second, neoplastic tumors are assumed to have a "steep" dose–response curve, with a linear relationship between dose of drug administered and efficacy. Thus, the highest possible dose of drugs is administered at the shortest possible time intervals. Third, the Goldie–Coldman hypothesis suggests that tumors acquire a spontaneous mutation that confers drug resistance in about one cell out of 10^5 cells. At the time of detection, with current imaging, most tumors are at least 1 gram or more in size, containing 10^9 cells, and consequently contain about 10^4 clones that are resistant to a given drug. Resistance to two drugs, however, should be seen in one cell out of 10^{10}. It, therefore, follows that multidrug therapy will be more effective than single-agent therapy.

In addition to overcoming tumor resistance, combination therapy is important in limiting drug toxicity, since several agents with nonoverlapping toxicities can be utilized. One of the first curative regimens for a solid tumor (testicular cancer) comprised bleomycin/vinblastine/cisplatin; three agents with differing mechanisms of action and nonoverlapping toxicities.

Cytotoxic chemotherapy agents are administered in the adjuvant, neoadjuvant, and combined modality and metastatic settings. Adjuvant cytotoxic chemotherapy is now the standard for breast, colorectal, ovarian, and lung cancers. In these cases, chemotherapy delivered after resection of the primary cancer can suppress or even eliminate the growth of occult cancer cells that have already metastasized, ultimately leading to cures.

Additionally, chemotherapy sometimes is used in combination with radiation therapy. Combined-modality approaches (chemotherapy and radiation together) are used to shrink the tumor in many diseases to permit surgery, to control systemic disease, or both. Chemotherapy combined with radiation therapy is also sometimes used for curative intent in, for example, lung, esophageal, anal, and head and neck cancers. Chemotherapy alone may also be used to reduce the tumor burden prior to surgery in some tumors, such as breast, bladder, and lung cancers. Chemotherapy utilized in this fashion is termed "neoadjuvant therapy." It must be noted that, in general, neoadjuvant therapy has not been shown to improve survival compared with adjuvant therapy.

Despite advances in the optimization of current cancer chemotherapy for patients with malignancies such as lymphoma and testicular cancer, classic anticancer agents that target DNA have not led to cures in most solid tumors. For example, combination chemotherapy delivered to patients with metastatic disease (e.g., metastatic breast cancer) confers little or no survival advantage compared with sequential chemotherapy. In these settings, sequential single-agent chemotherapy, with or without a biologically targeted agent, is a commonly accepted approach to treatment. This is in part because, in the metastatic setting, the balance between toxicity and efficacy is particularly important, as these patients are likely to exhibit decreases in end-organ function resulting in alterations in metabolism.[1]

KEY POINT

- Combination chemotherapy remains an important component of a majority of cancer

therapy regimens in the adjuvant and metastatic settings.

PHARMACOKINETICS

Pharmacokinetics is the relationship between time and plasma concentration following drug administration; it has been best described as “what the body does to the drug.” An understanding of the pharmacokinetics of a chemotherapy drug is critical to the optimal administration of that drug. The assessment of pharmacokinetics is an objective of most early-phase clinical trials.

From these studies, clinicians learn critical information such as:

- The range of tolerable doses,
- The relationship between drug dose and systemic exposure, and
- Differences among individuals between drug dose and systemic exposure.

The study of pharmacokinetics is classically divided into four elements: absorption, distribution, metabolism, and excretion. Absorption is defined as 100% when agents are administered through an intravenous route but varies when other routes of administration are used. The choice of drug administration route is based primarily on pharmacokinetic assessment of bioavailability—the ability of the drug to reach its target in an active form—and the formulation of an acceptable dose preparation for oral (PO), intravenous (IV), intramuscular (IM), intrathecal, or subcutaneous (SC) use. Classically, oncologic drugs have been developed using the IV route, particularly for water-soluble compounds, because complete absorption is guaranteed. Another reason for the development of IV oncology drugs in the past was the lack of reimbursement for oral oncology drugs, particularly those without a parenteral equivalent. The method of administration also is highly dependent on the ability to formulate a compound into a satisfactory pharmacologic product that can be administered by the route of choice. Several common agents (e.g., paclitaxel) are poorly soluble and must be mixed in solvents, such as Cremophor EL, a proprietary castor oil and polyethylene glycol ether emulsifier. These solvents can have their own toxic effects, as seen with the Cremophor-induced hypersensitivity reaction observed with paclitaxel administration. With current technology, a number of new formulations that reduce toxicity have been introduced. Nanoparticle albumin-bound paclitaxel is not dissolved in Cremophor; therefore, hypersensitivity is not an issue.

Bioavailability is the fraction of an administered dose of unchanged drug that reaches the systemic circulation. By definition, when a medication is administered intravenously, its bioavailability is 100%. (Similar calculations can be made for intramuscular or subcutaneous dosing compared with intravenous dosing.) Bioavailability has become more important as more cytotoxic chemotherapy agents (e.g., capecitabine), as well as biologic agents, are developed for oral dosing. The oral route has the advantage of achieving a more prolonged exposure, thereby providing coverage throughout the cell cycle when toxicity allows. In addition, oral route drug delivery allows more flexible scheduling than parenteral delivery. Agents with a high first-pass metabolism will, by nature, have poor oral bioavailability. Alterations in gastrointestinal tract absorptive capacity can alter oral bioavailability as well. Previous surgery, concomitant medications, malabsorption from other causes, and changes in motility—particularly with supportive care agents such as opiates—may alter absorption of an oral chemotherapy agent. Finally, the ingestion of drugs in either a fasting or fed state can dramatically affect drug exposure. Therefore, when considering the oral administration of drugs, it is necessary to

account for these possible variations.

Distribution identifies what happens to a drug after its administration. Typically, drugs are distributed from the plasma into extracellular and intracellular fluids. The distribution phase of pharmacokinetics may be the most complicated. In the simple two-compartment model, a drug is administered to the patient and enters the plasma compartment, followed by a distribution and redistribution of the compound to the peripheral compartment. The drug concentration in this peripheral compartment is the critical value because this is where the drug–tumor interaction will occur. It is important to recognize that drug concentration in the peripheral compartment is rarely measured in clinical trials and therefore is unknown for virtually all agents used today. The degree to which drugs distribute to the peripheral compartment alters their terminal half-life—the time required to clear 50% of an administered drug. Half-life depends on the volume of distribution (V_d) and clearance (CL). Drugs that are more highly distributed to the peripheral compartment will have a longer terminal half-life.[2] This fact has important clinical ramifications for drugs such as methotrexate, which is the classic example of a drug distributing to the third space, such as pleural effusions or ascites. This scenario can lead to substantial and prolonged methotrexate-induced toxicity.

The greatest increase in research and subsequent understanding during the past several decades has occurred in the study of metabolism of therapeutic agents (Table 3-1). In addition, cellular models have been developed that enable clinicians to define the metabolic pathways for many important chemotherapy agents. Hepatic enzymes responsible for phase I (oxidation, reduction, and hydrolysis) and phase II (conjugation) reactions prepare agents for their excretion by the liver or by the kidney. Hepatic and renal functions are critical to the excretion of most cytotoxic chemotherapy agents. When choosing dosages for patients with cancer, clinicians have typically relied on hepatic enzyme function and serum creatinine levels as the primary means to assess end-organ function. However, other factors, such as age, sex, diet, and drug–drug interactions, can lead to clinically important variability in drug effect. For some drugs, genetic variation in genes that encode enzymes responsible for drug metabolism may substantially alter pharmacokinetics and thus drug effect.

Table 3-1 **Selected Drug-Metabolizing Enzymes of Importance in Oncology**

Reaction	Substrates	Polymorphic*
Phase I Reactions		
Cytochrome P450		
CYP1A1	Benzo(a)pyrene	×
CYP1A2	Theophylline, caffeine	×
CYP2B6	Cyclophosphamide	×
CYP2C8	Paclitaxel	×
CYP2C9	Phenytoin, warfarin	×
CYP2C19	Omeprazole, diazepam	×
CYP2D6	Tamoxifen, codeine, granisetron, many antidepressants	×
CYP2E1	Ethanol	×
CYP3A4/3A5	Etoposide, ifosfamide, docetaxel, irinotecan, bortezomib, imatinib, flutamide, exemestane, lapatinib, sunitinib, sorafenib, vemurafenib, temsirolimus, nilotinib vinca alkaloids	
Ketoreductase	Anthracyclines	
Aldehyde dehydrogenases	Aldophosphamide†	
Carboxylesterases	Irinotecan	
Dihydropyrimidine dehydrogenase	Fluorouracil	×
Cytosine deaminase	Cytarabine, gemcitabine	×
Phase II Reactions		
N-acetylation		
NAT2	Isoniazid	×
Glucuronidation		
UGT1A1	SN-38‡	×
UGT2B7	Morphine, epirubicin, tamoxifen metabolites	×
Methyltransferases		
TPMT	Mercaptopurine, azathioprine	×

*Known genetic variants that influence enzyme activity.
†A cyclophosphamide metabolite.
‡Active metabolite of irinotecan.

With the advent of oral drugs targeting specific proteins in cancer, the effect of food on drug absorption and metabolic drug interactions have become increasingly important.[3] Typically, in early-phase clinical trials most oral anticancer drugs are administered on an empty stomach. Only a few agents undergo a formal food-effect study. The result is that the effect of food is sometimes identified only after the drug is in clinical use. For example, concomitant food intake can increase the systemic exposure of erlotinib, as measured by the area under the curve (AUC), by 34 to 66%, nilotinib by 82%, and lapatinib by up to 167%. Conversely, food can reduce the AUC of afatinib by 39%. A number of oral agents are relatively insoluble at alkaline pH, thus their absorption is reduced when concomitant acid-reducing agents such as proton-pump inhibitors are coadministered. These agents, such as erlotinib, should be administered at least 8 hours after ingestion of a potent acid-reducing agent in order to allow for recovery of

gastric acidity. An alternative is to utilize other agents, such as sucralfate, that do not affect gastric acidity directly.

The cytochrome P450 family enzyme system is the major catalyst of oxidative biotransformation reactions, which convert lipophilic drugs to hydrophilic forms for easy elimination. The CYP3A4 isoform is the most important with regard to metabolism of anticancer agents. A number of widely used agents, such as imatinib, sorafenib, sunitinib, vemurafenib, temsirolimus, and nilotinib, are substrates (Table 3-1). Coadministration of these drugs with strong inducers such as phenytoin and phenobarbital or strong inhibitors such as ketoconazole and grapefruit juice can affect drug levels, leading to decreased efficacy or increased toxicity. A complete listing of substrates, inhibitors, and inducers of the CYPP450 enzymes can be found on the U.S. Food and Drug Administration (FDA) website (www.fda.gov).

EXCRETION

There are two major routes of excretion: the kidneys and the biliary tract. Traditionally, chemotherapy agents were and generally still are administered using body-surface area (BSA)–adjusted doses. This method of dosing was adopted on the basis of the determination that physiologic processes such as basal metabolic rate, blood volume, and drug clearance were better correlated across animal species when BSA is utilized rather than body weight. Thus, use of BSA allowed the determination of phase I starting doses from an extrapolation of preclinical animal studies.[4] Although this method of dosing in humans was assumed to reduce the interpatient variability of drug exposure and thus drug effects, the interspecies correlation of BSA with clearance and other physiologic processes is not necessarily translatable to intraspecies correlation. BSA dosing has been shown to be associated with high pharmacokinetic variability and is a poor indicator of drug exposure. For example, Baker and colleagues reviewed 33 investigational agents and found that BSA-based dosing reduced interpatient variability for only 5 (15%) agents. Interestingly, the reduction in clearance variability was between 15% and 35%, indicating that only one-third of the clearance variability was attributable to BSA.[5] Despite these deficiencies, BSA-based dosing continues to be used for most cytotoxic agents. However, for some agents, such as carboplatin, several methods have been proposed for calculating drug doses considering the AUC and its subsequent hematologic toxicity and also the direct relationship between glomerular filtration and carboplatin clearance. However, this approach has been criticized because the calculated creatinine clearance methods, which are based on random serum creatinine measurements, are not accurate. Thus, the glomerular filtration rate (GFR) used to calculate the carboplatin dose is inaccurate.

Inulin clearance is widely regarded as the gold standard for measuring GFR. The classic method of inulin clearance requires an intravenous infusion and timed urine collections, making it cumbersome. As a result, a number of alternative measures for estimating GFR have been devised. The most frequently used estimation for GFR in adults is the Cockcroft–Gault equation, which was developed for estimating creatinine clearance; its prediction of GFR has been tested widely.[6,7] Another equation for estimation of creatinine clearance, by Jelliffe, has been used extensively.[8] The Modification of Diet in Renal Disease equation provides estimates of GFR standardized for BSA.[9] The abbreviated version is easy to implement, since it requires only serum creatinine, age, sex, and race. However, no single formula for estimating GFR has been deemed accurate for carboplatin dosing to achieve an optimal therapeutic index. This is because in the past, multiple assays were used to measure serum creatinine, resulting in

considerable interlaboratory variability in the reporting of creatinine values. In 2006, in an effort to standardize serum creatinine reporting across North America, the National Kidney Disease Education Program published recommendations to recalibrate serum creatinine assays to an isotope dilution mass spectrometry (IDMS) traceable reference method. This method has been in worldwide use since 2011. For some patients with normal renal function, the new standardized IDMS method produces creatinine values that are on average 10 to 20% lower than older, non-IDMS values. Therefore, for patients with relatively low serum creatinine, the IDMS method generates abnormally low values, leading to an overestimation of creatinine clearance and consequently higher calculated carboplatin doses, which could result in significant toxicity. To avoid such potential toxicity, the FDA recommends capping the carboplatin dose for a desired AUC. The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function.

The clearance of an agent is an important aspect of accurate drug dosing. Clearance can be calculated as the dose divided by the AUC or the dose rate divided by concentration at steady state. Few clinicians memorize the values of clearance for agents, but it is necessary to be aware of the variability in clearance. Most of the compounds used have a variation in clearance of approximately 20 to 40%, although some agents have high variability (75 to 100%). Some of the important factors affecting variability in clearance include changes in end-organ function, drug–drug interactions, and genetic variation leading to alterations in enzymes, which activate or clear a particular drug.

Variability in the metabolic or excretory organs because of dysfunction or the concomitant administration of medications that affect enzyme function is common and must be recognized. Many agents are highly protein-bound, and variability in the amount and function of proteins involved in drug metabolism will influence clearance. Many agents currently used in clinical practice must be adjusted for either renal or hepatic dysfunction (Table 3-2). Additional variables that affect excretion include enterohepatic circulation, wherein, after biliary excretion, reabsorption of either the parent drug or its metabolites may take place in the small intestine.

Genetic polymorphisms that lead to a reduction or an increase in the function of enzymes involved in the uptake, metabolism, and distribution of drugs can account for a substantial portion of the variability in drug response phenotypes (toxicity and clinical response). Lastly, it is important to know which drugs form active metabolites (Table 3-3). Many agents are metabolized into active forms. These include antimetabolites such as 5-fluorouracil (5-FU), pemetrexed, and gemcitabine. Others are prodrugs, in which the parent compound is essentially inactive. Metabolic enzymes convert these compounds to the active moiety. These include irinotecan (activated to SN38), cyclophosphamide (phosphoramide mustard), tamoxifen (endoxifen), temsirolimus (rapamycin), and temozolomide (MTIC). An important noncytotoxic prodrug that is used widely in oncology is codeine (3-methylmorphine), which is metabolized by CYP2D6 to morphine.

Table 3-2 **Drugs Requiring Dose Modification for Organ Dysfunction**

Liver Dysfunction	Renal Insufficiency	Glomerular Filtration Rate of Less than 25%
Cyclophosphamide	Bisphosphonates	Bleomycin
Cytarabine Dactinomycin	Capecitabine Carboplatin	Cyclophosphamide
Docetaxel	Cisplatin	Daunorubicin
Doxorubicin	Etoposide	Epirubicin
Epirubicin	Fludarabine	Idarubicin
Etoposide	Hydroxyurea	Ifosfamide
Fluorouracil	Methotrexate Pemetrexed	Mercaptopurine
Gemcitabine	Pentostatin	Streptozocin
Ifosfamide	Topotecan	
Irinotecan		
Paclitaxel		
Thiotepa		
Vinblastine		
Vincristine		
Vindesine		
Vinorelbine		

Modified from Hendrayana T, Wilmer A, Kurth V, Schmidt-Wolf IG, Jaehde U. Anticancer dose adjustment for patients with renal and hepatic dysfunction: from scientific evidence to clinical application. *Sci Pharm*. 2017;85:8. doi:10.3390/scipharm85010008.

Table 3-3 **Examples of Oncology Drugs with Active Circulating Metabolites**

Chemotherapy Drugs	Other Oncology Drugs
Alkalating Agents	Analgesics
Cyclophosphamide	Morphine
Ifosfamide	Codeine
Procarbazine	Hydrocodone
Dacarbazine	Protein Kinase Inhibitors
Temozolomide	Imatinib
Hexamethylmelamine	Sunitinib
Thiotepa	Sorafenib
Anthracyclines	Dasatinib
Doxorubicin	Dabrafenib
Idarubicin	Alectinib
Epirubicin	Crizotinib
Camptothecins	Imatinib
Irinotecan	Sunitinib
Antimetabolites	Sorafenib
Tegafur, uracil, and fluorouracil (UFT)	Dasatinib
Methotrexate	Dabrafenib
6-Mercaptopurine	
Antiestrogens	
Toremifene	
Tamoxifen	
Retinoids	
All-trans retinoic acid	

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In summary, when choosing a drug and a dose, oncologists must consider factors known to affect the activation and/or clearance of a given drug, including (1) route of administration, recognizing factors that influence absorption (e.g., gastric motility, food effect, prior surgery); (2) organ function; (3) drug–drug interactions; and (4) pharmacogenetics. Following consideration of these factors, the clinician must then develop a plan for careful monitoring of drug-response phenotypes, namely toxicity and response. Although classic toxicities, such as myelosuppression, are not commonly seen with newer targeted therapies that do not directly target DNA, substantial toxicity (e.g., trastuzumab- or sunitinib-induced cardiomyopathy) is not rare, and therefore close observation is necessary.

TOXICITY OF SYSTEMIC THERAPIES

Cytotoxic Therapy

Most cytotoxic drugs target DNA or proteins that are commonly expressed by both malignant and normal host tissues. Therefore, their therapeutic index—the ratio of efficacious concentrations to toxic concentrations—are very narrow, leading to significant toxicity. Because of their broad effects on DNA and associated synthetic proteins, there are several common toxic effects of cytotoxics, in addition to unique effects based on specifics of their mechanisms of cytotoxicity. Commonly seen toxicities with most cytotoxic drugs related to effects on rapidly proliferating cells include alopecia, myelosuppression, mucositis, diarrhea, and fatigue. Nausea and vomiting is also common. In addition, unique toxicities that need to be noted by oncologists include cardiotoxicity with doxorubicin, pulmonary toxicity with bleomycin, renal toxicity with cisplatin, and peripheral neuropathy with the antitubulin agents and platinum compounds.

Targeted Therapy

Recent basic science advances have led to the identification and elucidation of the mechanisms of action of aberrant proteins that are differentially expressed in cancer cells compared to normal cells, and these drive malignant transformation and maintenance of the malignant phenotype. Targeting these cancer-specific aberrations with small-molecule inhibitors and monoclonal antibodies started the era of “targeted therapies.” Because of the differential expression or overexpression of these proteins in cancer cells, targeted therapies were assumed to be relatively nontoxic. However, the incidence and severity of adverse events with targeted therapy appears to be similar to those of standard cytotoxic agents. The major difference is the various types of toxicity observed. Toxic effects of these agents can be divided into “mechanism-based” effects related to inhibition of the target protein, such as hypertension with angiogenesis inhibitors, skin rash with epidermal growth factor receptor (EGFR) inhibitors, and hyperglycemia with phosphatidylinositol-3-kinase (PI3K) inhibitors. Other toxicities are structurally based or “off-target” effects. As an example, ceritinib is an inhibitor of ALK kinase with significant gastrointestinal (GI) side effects of nausea, vomiting and abdominal pain, while another anaplastic lymphoma kinase (ALK) inhibitor, alectinib, has minimal GI toxic effects. Common toxicities of targeted agents are dermatologic, vascular, coagulation, endocrine, ocular, and pulmonary (Fig. 3-1). Because of the continuous, prolonged administration of these agents, such toxicities can be challenging to manage, and are exhaustively discussed in a publication by Dy and Adjei.[10]

Immunologic Agents

Immune checkpoint inhibitors of cytotoxic T-lymphocyte antigen 4 (CTLA-4), PD-1 (programmed death 1), and programmed death ligand 1 (PDL-1) are having a significant impact on a number of malignancies (see Chapter 4: Principles of Immuno-Oncology and Biologic Therapy). The immune activation induced by these compounds have led to the advent of immune-related adverse events, which can affect any organ in the body and, if not treated quickly, can lead to death. These toxicities have included colitis, hepatitis, pneumonitis, pericarditis, hypophysitis, uveitis, rash, and activation of infections such as tuberculosis.[11] Management involves cessation of treatment and rapid institution of high-dose corticosteroids.

TREATMENT OF PATIENTS WITH TOXIC DRUG LEVELS

For some chemotherapy drugs, the drugs themselves may be intrinsically toxic to either the liver or kidneys. In this case, toxic levels of the drug can build up, leading to prolonged and severe side effects. Some drugs can be removed by dialysis. For other drugs, specific antidotes have been developed. Leucovorin has been the standard treatment for reversing methotrexate toxicity for several decades. Glucarpidase is another antidote to treat patients with toxic levels of methotrexate in their blood, defined as levels exceeding 1 µmol/L, as a result of reduced clearance because of renal impairment. Glucarpidase, a recombinant form of the bacterial enzyme carboxypeptidase G2, converts methotrexate into glutamate and 2,4-diamino-N(10)-methylpteroic acid, which are inactive metabolites that can be eliminated from the body via nonrenal pathways.[12]

Clinicians need to be aware that leucovorin should not be administered within 2 hours before or after a glucarpidase dose because leucovorin is a substrate for glucarpidase. Toxic levels of 5-FU can build up after an overdose or in patients with dihydropyrimidine dehydrogenase (DPD) deficiency who receive full doses of 5-FU. This can lead to severe neutropenia, colitis cardiac dysfunction, or encephalopathy. Uridine triacetate has been approved to treat patients after an overdose of 5-FU or capecitabine or for patients exhibiting severe toxic effects within 96 hours after the end of 5-FU or capecitabine administration. Uridine triacetate is an acetylated form of uridine. Following PO administration, uridine triacetate is deacetylated by nonspecific esterases present throughout the body, yielding uridine in the circulation.

KEY POINTS

- A broad understanding of the metabolism of cytotoxic and biologic agents is necessary.
- Bioavailability is important when using oral chemotherapy agents.
- Food can alter bioavailability and thus drug exposure.
- Drug–drug interactions are an important—but often unrecognized—factor influencing drug effects.

PHARMACOGENOMICS

Pharmacogenetics has been defined as the study of variability in drug response because of heredity. In this context, there are germline aberrations (occurring in host cells) in drug-metabolizing pathways or drug targets that are inherited and can affect individual responses to drugs, both in terms of therapeutic effect and adverse effects.[13] More recently, the term “pharmacogenetics” has been introduced. Although the former term is largely used in relation to genes determining drug metabolism, the latter is a broader term that encompasses all genes in the genome that may determine drug response.[14] These aberrations can therefore be somatic (occurring in tumor) or germline. The distinction, however, is arbitrary, and the two terms can be used interchangeably.

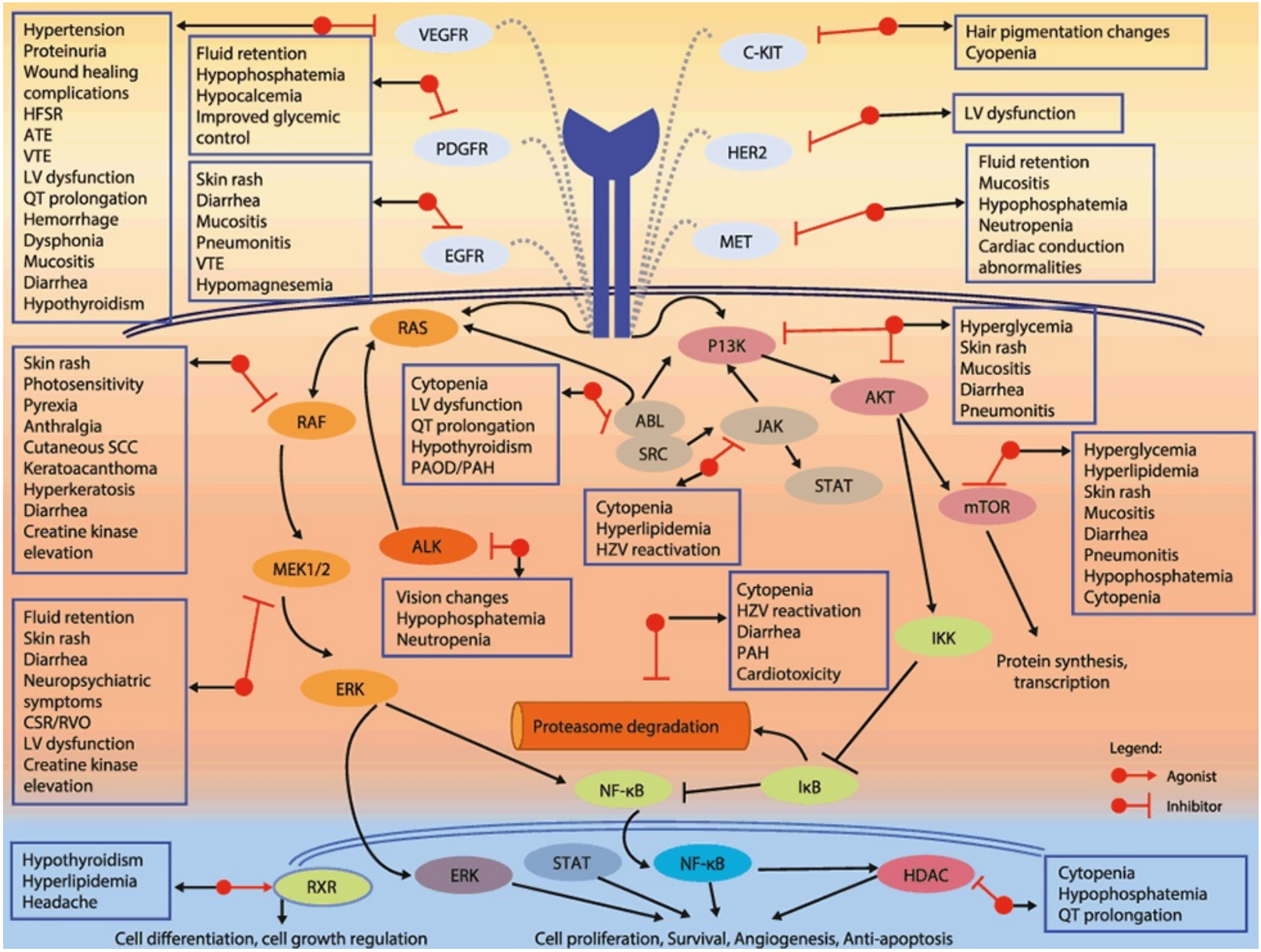

Fig. 3-1 Toxicities of targeted anticancer agents.

Reprinted with permission from Dy GK, Adjei AA. Understanding, recognizing, and managing toxicities of targeted anticancer therapies. *CA Cancer J Clin.* 2013;63:249–279. PMID: 23716430.

Much of this genetic variation is in the form of single-nucleotide polymorphisms (SNPs). SNPs are defined as variants with population frequencies of 1% or greater, which can alter the amino acid sequence of the encoded protein or alter RNA splicing, leading to altered kinetics and catalysis of the protein.

Technologic advances enable rapid and accurate assessment of tumor gene expression and deduced function, both at the level of individual genes and by global gene analysis. In the latter case, massive parallel sequencing of the entire genome is now possible (see Chapter 2: Molecular Biology). This type of research has been critical in identifying specific biologic subsets of cancer that are more or less likely to relapse (prognostic) in the absence of systemic treatment, as well as in identifying genes or gene patterns associated with response (predictive for specific therapies or agents). For breast cancer, many gene expression array tests are commercially available in which the expression patterns of a subset of genes important in proliferation identify tumors that are associated with a higher risk of recurrence (see Chapter 7: Breast Cancer).[15] This same technology may identify a subset of tumors more likely to benefit from chemotherapy.[16]

Mutations in genes that encode transmembrane receptor tyrosine kinases as well as proteins involved in downstream signaling cascades are important for response to tyrosine kinase inhibitors. For example, lung cancers that harbor mutations that activate the EGFR tyrosine kinase domain lead to high response rates to the drugs gefitinib, erlotinib, and afatinib. Similar situations exist for *ALK* gene rearrangements and response to crizotinib and ceritinib, as well *BRAF* mutations and response of melanoma to vemurafenib and dabrafenib. Furthermore, in the case of colorectal cancer, mutations in the important oncogene *KRAS* are predictive of lack of response to the EGFR-inhibiting drugs panitumumab and cetuximab. In the latter example, retrospective studies have demonstrated that monoclonal antibodies that target EGFR appear to be effective only in tumors with wild-type *KRAS.*[17]

In the specialty of oncology, clinicians must take into account all sources of genetic variation that influence drug effects. This includes both somatic and germline genetic variations. The following sections illustrate important examples in which genetic variation at the level of both the tumor and the host leads to substantial changes in drug effect.

The promise of pharmacogenetics to individualize treatment according to gene sequence variation is well illustrated in the treatment of patients with cancer. Administration of “standard” doses of chemotherapy to patients with inherited deficiencies in enzymes responsible for their metabolism and disposition can result in marked toxicity, which can be lethal. Conversely, patients who have increased enzymatic activity may be at risk for treatment failure—also an undesirable outcome when dealing with a potentially fatal illness. The traditional method by which individualized anticancer drug doses are developed and determined has involved the use of BSA measurements and weight-based dosing.[18] However, multiple studies have indicated that dosing in this manner does not reliably account for the variability in exposure to most chemotherapeutic drugs.[19]

Examples of the role of pharmacogenetics have been clearly illustrated with both cytotoxic chemotherapy and targeted therapies, including the two endpoints most important to patients with cancer: response and toxicity. The three examples discussed below have led to relabeling or hearings by the FDA to reflect the importance of pharmacogenetics.

THIOPURINES

The thiopurine drugs mercaptopurine and azathioprine (the latter of which is a prodrug that is converted to mercaptopurine in vivo) are purine antimetabolites used clinically to treat both pediatric and adult leukemias and as immunosuppressant agents.[20] Thiopurines are metabolized in part by *S*-methylation, catalyzed by the enzyme thiopurine *S*-methyltransferase (TPMT).[21,22] A group led by Richard M. Weinshilboum first identified three groups of patients on the basis of the level of TPMT activity in their red cells and found that the level of activity was inherited in an autosomal-codominant fashion.[21,23] Subsequently, it was shown that patients who received standard doses of thiopurines and who were homozygous for very low levels of TPMT activity or for no activity ($TPMT^{L}TPMT^{L}$) had greatly elevated concentrations of active drug metabolites, 6-thioguanine nucleotides, and a markedly increased risk of life-threatening, drug-induced myelosuppression.[24] As a result, the phenotypic test for the level of TPMT activity in red cells and, subsequently, DNA-based tests were among the first pharmacogenetic tests to be used in clinical practice. The result of *TPMT* gene resequencing has demonstrated that the most common variant allele responsible for low levels of activity among white populations encodes a protein with two alterations in the amino acid sequence as a result of SNPs.[25,26] These sequence changes result in a striking reduction in the quantity of TPMT,[25] at least in part

because the variant protein is degraded rapidly.[20] A series of less frequent *TPMT* variant alleles has also been described.[23]

UGT1A1 AND IRINOTECAN

Irinotecan is a prodrug, metabolized in vivo to 7-ethyl-10-hydroxycamptothecin, SN-38 (Fig. 3-1), which is a potent inhibitor of topoisomerase I.[27-29] In humans, both gastrointestinal (e.g., diarrhea) and hematologic (e.g., neutropenia) toxicities are dose-limiting following the administration of irinotecan. SN-38 is inactivated by glucuronidation to form the glucuronide conjugate (SN-38G) in a reaction catalyzed by the polymorphic hepatic enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) (Fig. 3-2).[30] A dinucleotide repeat polymorphism in the TATA box in the promoter for *UGT1A1* results in reduced hepatic *UGT1A1* expression and is considered the most common cause of Gilbert syndrome (mild unconjugated hyperbilirubinemia).[31-33] Patients homozygous for the *UGT1A1*28* polymorphism have substantially lower SN-38 glucuronidation rates and substantially higher rates of grade 4 or 5 neutropenia than those who do not carry this genetic variant.[34] In addition, it has been demonstrated in a Japanese population that 80% of patients who suffered from life-threatening irinotecan toxicities had variant sequences because of *UGT1A1*6* (211G→A) and *UGT1A1*27* (686C→A).[35] The importance of *UGT1A1* pharmacogenetics in mediating irinotecan-related toxicity was recognized by the FDA when the irinotecan label was modified to recommend a dose reduction for patients homozygous for the *UGT1A1* polymorphism. Recent studies have demonstrated that not only do patients homozygous for the *UGT1A1*28* polymorphism require lower doses of irinotecan, but also that patients who do not carry the genetic variant tolerate substantially higher doses of irinotecan.[36]

TAMOXIFEN AND CYP2D6

Tamoxifen can be considered a prodrug that requires metabolic activation to elicit its pharmacologic activity. Tamoxifen undergoes activation to metabolites that are 100 times more potent suppressors of estradiol-stimulated breast cancer cell growth (4-OH tamoxifen and endoxifen) compared with tamoxifen or its primary metabolite, *N*-desmethyl tamoxifen. Endoxifen is the most abundant active metabolite in most individuals and results from the CYP2D6-mediated oxidation of *N*-desmethyl tamoxifen (Fig. 3-3).[37] In separate studies of women treated with tamoxifen, genetic variation in *CYP2D6* and/or coadministration of CYP2D6 inhibitors were associated with a significant reduction in the mean plasma endoxifen concentrations, with the reduction in endoxifen concentrations directly related to inhibitor potency.[38,39] Multiple studies have evaluated whether genetic polymorphisms that alter CYP2D6 enzyme activity or the coadministration of CYP2D6 inhibitors are associated with disease recurrences, including conflicting data from large secondary analyses of prospective adjuvant tamoxifen trials.[40-42] One meta-analysis demonstrated that the *CYP2D6* genotype was associated with recurrence or death, but only among patients taking 20 mg/day for 5 years for the adjuvant treatment of estrogen receptor–positive breast cancer.[43] Clinicians should avoid the concurrent use of potent CYP2D6 inhibitors and tamoxifen. Ongoing prospective studies should provide definitive data as to the role of selecting hormonal therapy according to CYP2D6 genotype.

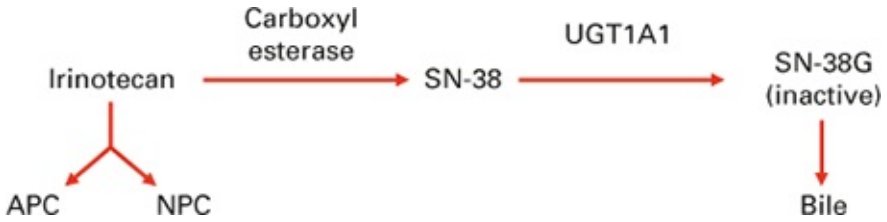

Fig. 3-2 Metabolic pathway of irinotecan, a prodrug that is activated by carboxylesterase to the active metabolite SN-38.

SN-38 is glucuronidated by uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*), forming the inactive metabolite SN-38 glucuronide (SN-38G), which is eliminated by the bile.

Abbreviations: APC, aminopentanecarboxylic acid; NPC, 7-ethyl-20-(4-amino-1-piperidino)carbonyloxycamptothecin.

KEY POINTS

- *Pharmacogenetics* is the study of the role of genetic inheritance in individual variation in (1) drug response and (2) toxicity.
- FDA-recognized examples of oncologic drugs for which toxicity or response is influenced by pharmacogenetics, include the thiopurine drugs mercaptopurine and azathioprine *(TPMT)* and irinotecan *(UGT1A1).*

PHARMACODYNAMICS

Pharmacodynamics is the study of the effects of drugs in the body, including the drug target. It is often summarized as the study of "what a drug does to the body." In early-phase clinical research, it is important not only to define the pharmacokinetic parameters of a given drug but also to determine the effect of the drug on the tumor or on the target endpoints. These types of studies are best done in late phase I or early phase II clinical trials, in which the drug dose is fixed and the variability in target modulation can be assessed more easily. One of the greatest challenges in pharmacodynamic studies is selecting the endpoint. Ideally, endpoints can be measured reliably and are easily quantified and clinically meaningful. Also, the most reliable and relevant samples for assessing biomarkers are tumors, but access to tumors may be difficult. Clinical trials may also be designed to study changes in a circulating blood factor, to determine its correlation with disease endpoints. Determining such a relationship in early phases of clinical research simplifies the clinical development pathway for a particular agent. Examples include inhibition of phosphorylated extracellular signal regulated kinase (phospho-ERK), phosphoprotein kinase B (Akt), and retinoblastoma (Rb) phosphorylation in tumors. Additionally, a drug may exhibit effects on normal tissues, which may be associated with efficacy. Examples include, EGFR-1–induced skin rash (associated with a higher rate of tumor response) and aromatase inhibitor–induced arthralgias (associated with lower recurrence rates in the adjuvant treatment of estrogen receptor–positive breast cancer).

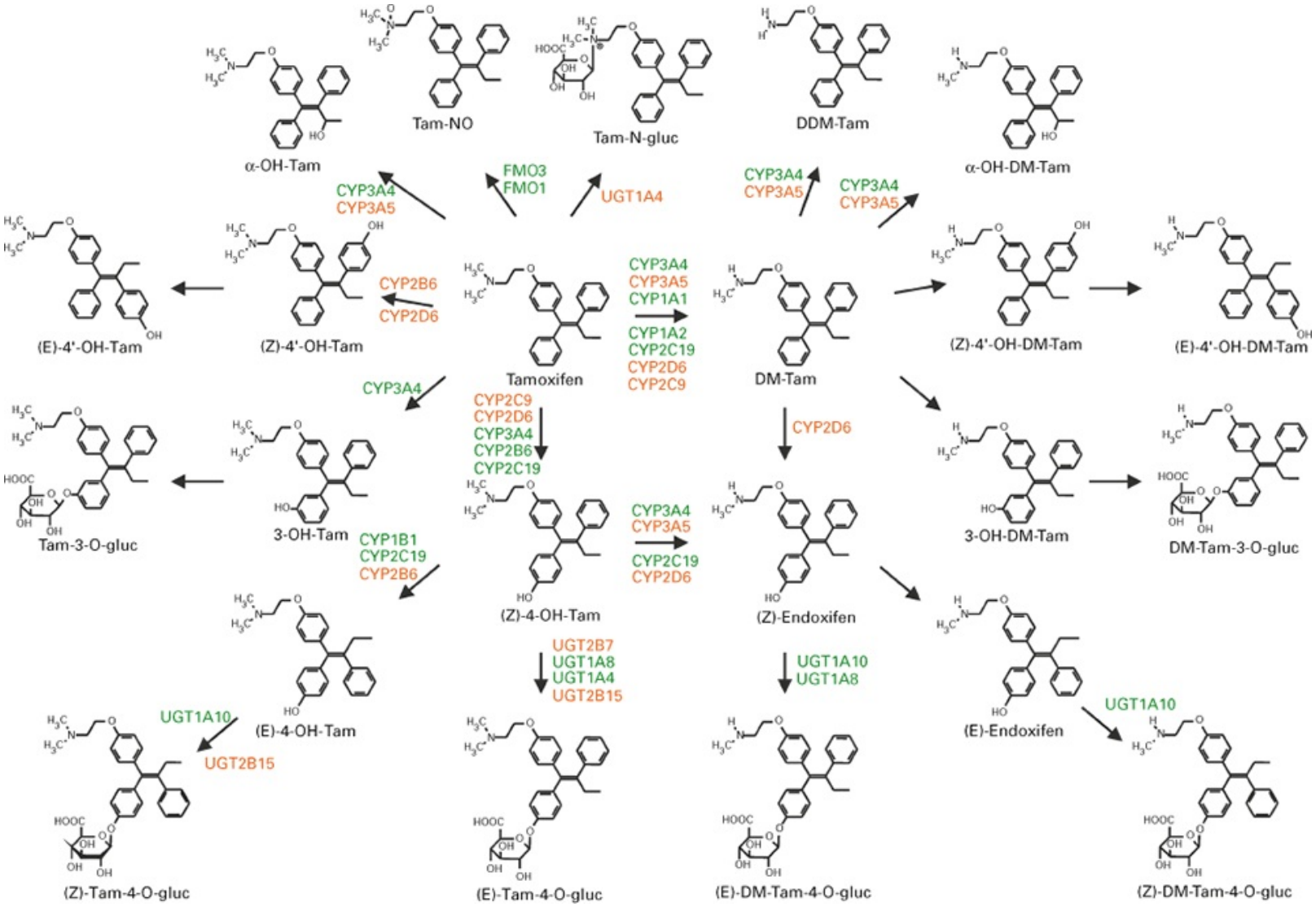

Fig. 3-3 Metabolism of tamoxifen.

Reprinted by permission from Macmillan Publishers Ltd.: Murdter TE, Schroth W, Bacchus-Gerybadze L, et al. Activity levels of tamoxifen metabolites at the estrogen receptor and the impact of genetic polymorphisms of phase I and II enzymes on their concentration levels in plasma. *Clin Pharmacol Ther.* 2011;89:708–717.

BIOLOGIC AGENTS AND PREDICTIVE BIOMARKERS

Hundreds of novel biologic agents are in development for the treatment of cancer. Many of these agents bind a particular receptor or protein within a tumor. Therefore, the expression of the target is critical when using such an agent. Examples include *HER2*-targeting drugs such as trastuzumab, ado-trastuzumab emtansine, pertuzumab, and lapatinib, which target the *HER2* oncogene as well as critical other members of the EGFR system (*HER1* and *HER3*). In the metastatic setting, expression or amplification of the *HER2* receptor is critical for the activity of *HER2*-targeting drugs.[44] More recently, the FDA has approved biologic agents along with a companion biomarker (vemurafenib and the BRAF V600 Mutation Test; crizotinib and the Abbott Vysis ALK Break Apart FISH test).

DRUG RESISTANCE

Drug resistance has been seen as a major cause of the lack of cure with systemic cancer therapies. Cancer cell killing by a drug depends on transport of drug to the tumor and engagement with the drug target. Drug resistance could be due to any step in the process of absorption, transport, metabolism, and modification of the drug target. With classic

chemotherapy drugs, resistance mechanisms due to efflux pumps that extrude drugs from cells and multidrug resistance have been well characterized. Multidrug resistance is conferred by the expression of ATP-binding cassette family proteins that include P-glycoprotein (P-gp), multidrug resistance protein (MRP), and breast cancer resistance protein (BCRP). Tumors expressing these proteins exhibit resistance to several chemotherapeutic agents, which tend to be natural products but may have different targets. Examples are anthracyclines, vinca alkaloids, taxanes, and epipodophyllotoxins for P-gp.[45] With the dramatic clinical responses being seen with targeted agents that inhibit oncogenic kinases, the emergence of resistance has become a major problem. Multiple mechanisms of resistance, including target modification through secondary mutations, gene amplification and development of bypass tracts have been identified.[46] Based on these findings, a number of second- and third-generation kinase inhibitors have been identified that can overcome resistance to EGFR inhibitors, BCR-ABL inhibitors, and ALK inhibitors, for example (Fig. 3-4).

KEY POINTS

- Pharmacodynamics is the study of the effects of drugs in the body, including the drug target. Pharmacodynamic studies have been useful in documenting the mechanism of action of drugs, but have not been useful biomarkers.
- Predictive biomarkers such as gene mutations, translocation, and amplification have been useful in developing highly effective drugs, with a number of molecular aberrations such as *EGFR* mutations being approved as companion biomarkers to drugs.
- An emerging problem with therapy with molecularly targeted drugs is the relatively rapid development of resistance. There are several research efforts aimed at identifying and targeting mechanisms of resistance.

DRUG DEVELOPMENT: CLINICAL TRIAL DESIGN

The goals of clinical research are to expand knowledge about new anticancer agents through the conduct of well-designed clinical trials, to rapidly gain approval by regulatory bodies, and to obtain adequate clinical information for safe and effective drug delivery. The medical literature is focused on clinical research and clinical trial design, which makes the comprehension of trial design critical for practicing physicians.

NONCLINICAL DRUG TESTING

New compounds are discovered primarily by two means. First, there is rational design of new therapeutic agents. When a target is known, drugs can be tailored to fit the target (e.g., vemurafenib for V600E melanoma). Second, compounds are discovered as a result of high-throughput screening, in which multiple compounds with unknown activity are tested against a series of cancer cell lines (e.g., rapamycin, the active moiety of temsirolimus). Those with the best activity are selected for further development. From either source, new agents with promise are tested in vitro and subsequently in vivo to determine whether the drug can kill cancer cells. During in vivo testing, toxicity, dosing schedule, and route of administration are investigated. Subsequently, drugs are formulated for a specific route of administration (e.g., PO

or IV), and the administration schedule is again optimized (e.g., daily, weekly, or via infusion). Although schedules often are based on expected toxicities, mechanisms of action, and animal studies, patient and physician convenience are also factors.

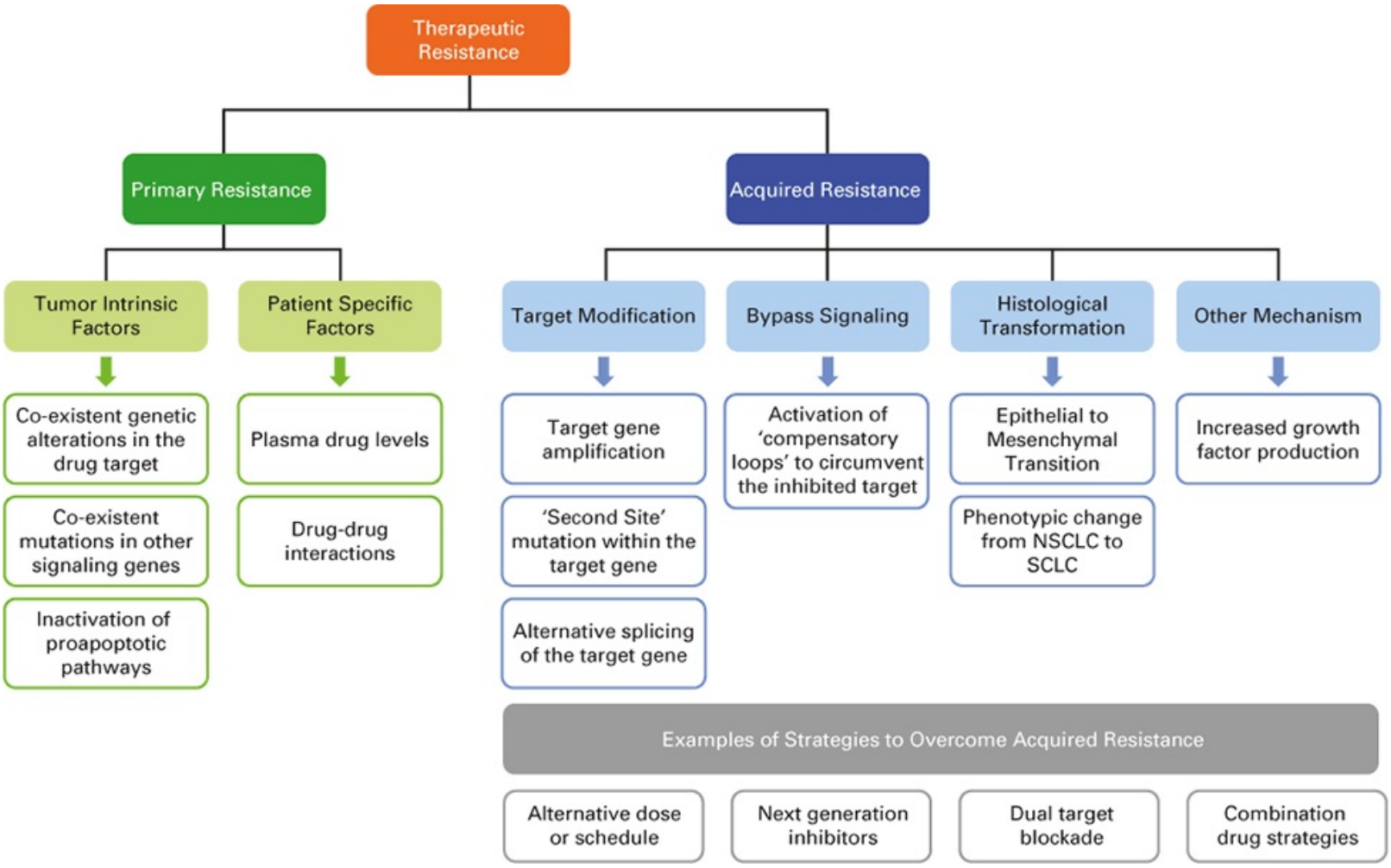

Fig. 3-4 Resistance mechanisms to kinase inhibitors.

If the agent yields positive results in nonclinical testing, clinical trials are performed. Based on toxicology studies involving animals, a starting dose is determined for phase I clinical trials using one of two standard techniques. The more common method is to take one-tenth of the dose that kills 10% of the most sensitive animal species. An alternative strategy is to use one-third of the toxic dose–low (defined as the lowest dose of a substance at which any toxic effect is produced). Once the phase I dose has been selected and appropriate regulatory measures have been met, phase I clinical trials are then performed.

PHASE I TRIALS

The primary goal of a phase I clinical trial using classic cytotoxic chemotherapy has been to determine the maximum tolerated dose (MTD): the highest dose of a drug or treatment that does not cause unacceptable side effects. However, the MTD may not be the optimal dose, especially for drugs that target a specific receptor or growth factor pathway. However, the small sample sizes in a phase I trial do not allow for an accurate assessment of an "optimal dose." This can be ascertained only through randomized dose-ranging studies. Secondary goals are to determine the optimal administration schedule, the toxicity profile of the agent, and

the pharmacokinetics and pharmacodynamics, as discussed previously, as well as to observe for any clinical activity. Typically, patients with cancer who enter phase I clinical trials have advanced cancer that has not responded to standard therapy. To be eligible for these trials, patients' disease must have a good performance status and they must have relatively normal end-organ function so that adequate pharmacology can be determined.

The classic phase I design for cytotoxic chemotherapy agents has been developed largely empirically. In this design, three patients are treated at each dose level. The first cohort is treated at a starting dose that is considered to be safe based on extrapolation from animal toxicologic data, and the subsequent cohorts are treated at increasing dose levels that have been fixed in advance. The size of the cohorts is expanded if severe (grade 3 or 4) toxicities occur. Pharmacokinetic measurements are typically obtained for all patients, as are toxicity and tumor assessments. Historically, dose escalation using this trial design typically followed a modified Fibonacci sequence, in which the dose increments become smaller as the dose increases (e.g., the dose first increases by 100% of the preceding dose, and thereafter by 67%, 50%, 40%, and 30 to 35% of the preceding doses).

In recent years, a number of alternative designs for phase I studies have been investigated. Adaptive or Bayesian designs are increasing in popularity. The primary goal of all these designs is to shorten the duration of phase I trials and to enhance the precision of the phase II dose recommendation. These methods are typically based on the concept of using toxicity as the endpoint of the trial. A mathematical function is created that describes the hypothesized relationship (curve) between the incidence of dose-limiting toxicity (DLT) and dose. This curve is reasonably predicted to assume a sigmoid shape for which the MTD must be estimated first. As information regarding the presence or absence of toxicity accumulates, the original estimate of the MTD is updated to more accurately fit the hypothesized curve to the actual data. Under these types of trial designs, the occurrence of toxicity results in an adjustment of the curve to match the probability that one is now approaching the MTD. Conversely, the absence of toxicity results in adjustments of the curve to match the probability that one is not yet at the MTD. Therefore, the occurrence of no DLT in several sequential patients results in a statistical prediction that the dose can be more rapidly escalated in a safe manner.[47]

Typically, phase I clinical trials, utilizing the standard 3+3 designs as well as the newer Bayesian designs, have been performed in patients with multiple tumor types; however, these trials may focus on a single tumor or a particular group of tumors known to express a specific receptor or mutation. A newer focus in phase I trials is to treat genomic subsets. Thus, eligibility for the trial includes the presence of specific genetic aberrations in the tumors. One example includes mutations in the p110-alpha subunit of PI3K, called *PIK3CA,* responsible for activation of the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway, which can cause neoplastic transformation and promote cancer progression. One report demonstrated that, in a phase I population of patients, *PIK3CA* mutations were detected in 18% of tested patients, and patients with *PIK3CA* mutations treated with PI3K/AKT/mTOR inhibitors demonstrated a higher response rate than patients without mutations.[48]

With agents that are not expected to be overly toxic or when clinical effects are expected before toxic effects are likely to develop, other designs can be used. The phase 0 design is one example in which small numbers of patients are treated with the goal of determining early on whether a given drug will affect its intended target.

Phase I clinical trials involving combination agents have the added emphasis of evaluating the interaction between the two agents. This is particularly important when there might be a pharmacologic interaction resulting in a substantial change in the toxicity profile. These trials

can be complex. Such trial designs were examined by a National Cancer Institute task force, which recommended that proposed drug regimens should be selected on the basis of a biologic or pharmacologic rationale supported by clinical and/or robust and validated preclinical evidence and accompanied by a plan for subsequent development of the combination. The design of the phase I clinical trial should take into consideration the potential pharmacokinetic and pharmacodynamic interactions as well as overlapping toxicity. Depending on the specific hypothesized interaction, the primary endpoint may be dose optimization, pharmacokinetics, and/or pharmacodynamics.[49]

Investigators are discouraged from making definitive decisions regarding the efficacy of a given cancer drug tested in a phase I study. However, observed tumor activity in the phase I setting is usually the impetus for studying the drug in subsequent phase II studies.

PHASE II TRIALS

The primary goal of phase II clinical trials is to better determine the preliminary efficacy and toxicity of an agent. Although traditional phase II trials have used a single-arm design, researchers increasingly use randomized trial designs, which allow for preliminary comparisons of efficacy and toxicity. Typically, a fixed dose and schedule of the therapy are selected and patients have only one tumor type and have similar characteristics, including similar exposure to previous therapies.

The choice of tumor type is based on preclinical and early clinical research, as well as the molecular biology of the mechanism of the agent's action. Many studies involve patients who have untreated metastatic cancer; however, in order to quickly evaluate efficacy and obtain regulatory approval, some studies involve patients who have highly refractory tumors. Phase II clinical research is typically the point at which decisions are made about the subsequent development of a given compound. If minimal or no clinical activity is observed or there is excessive or unmanageable toxicity in phase II studies, development of the drug is usually not continued.

Although the classic statistical design for a phase II single-arm trial relied on drug response (complete or partial), newer targeted therapies are often cytostatic; therefore, time-to-disease-progression endpoints are now more commonly employed. Additionally, randomized phase II trials are sometimes performed to establish proof of efficacy of a biologic agent. The randomized phase II discontinuation design was used to test the drug sorafenib, ultimately contributing to its approval for the treatment of renal cell carcinoma. In this design, after a 12-week run-in period, patients with tumor shrinkage of less than or equal to 25% continued with the drug. These patients were randomly assigned to sorafenib or placebo for an additional 12 weeks, and patients with tumor growth of more than or equal to 25% discontinued treatment.[50,51] The study effectively demonstrated that sorafenib significantly prolonged progression-free survival compared with placebo. Similar to what was done for phase I studies, the Clinical Trials Design Task Force of the National Cancer Institute has developed formal recommendations about aspects of phase II trial design—endpoints, randomization, inclusion of biomarkers, biomarker-based patient enrichment strategies, and statistical design—that are the subject of frequent debate. In general, the recommendations encourage the use of progression-free survival as the primary endpoint and support randomized phase II trials, inclusion of biomarkers, and incorporation of novel designs. However, it is acknowledged that using objective response as an endpoint and single-arm designs remain relevant in certain situations.[52]

PHASE III TRIALS

The ultimate goal of phase III clinical research is either to gain approval of a new agent by a regulatory body or to replace the current standard of care. These trials are typically large, ranging from as few as 300 patients to as many as several thousand. By definition, these trials are randomized clinical studies. The design and size of each trial hinges specifically on the selected endpoints. The gold-standard endpoint is survival, which is recognized by all regulatory agencies. However, survival endpoints may not be optimal for all cancers, especially those in which multiple active agents are available to patients after completion of the clinical trial. For breast and colorectal cancers, the FDA now recognizes disease-free survival, defined as the time to the first event of relapse, development of a second primary cancer, or death. Additionally, response rate, time to disease progression, quality of life, and other nontraditional endpoints have been incorporated into phase III clinical trial designs and have provided support to the approval process of many new agents in oncology.

NOVEL TRIAL DESIGNS

With molecular characterization of tumors becoming routine in clinical practice, the notion of treating tumors according to molecular aberrations rather than histologic classification is becoming more widespread, leading to new study designs. The most common designs are the so-called umbrella and basket trials. In umbrella trials, multiple aberrations in a single tumor type is targeted by different drugs. An example is a current National Cancer Institute (NCI) clinical trials network study in second-line squamous cell cancer of the lung in which aberrations in MET, PI3K, CDK4/6, and others are targeted by different agents.[53] Basket studies involve the treatment of different tumor types that have a specific molecular aberration with specific drugs. In this fashion, therapy is targeting a specific molecular aberration regardless of the tissue of origin. An example is the NCI MATCH trial.[54] While these designs are critical proof-of-concept studies generating important clinical information, the path to regulatory approval of an agent using these designs still remains unclear.

KEY POINTS

- Traditional oncology drug development has comprised phase I pharmacology studies, phase II initial efficacy studies, and phase III randomized comparisons against standard of care.
- With the emergence of molecularly targeted agents, novel study designs such as Bayesian designs, seamless phase I/II designs, basket, and umbrella studies have been introduced.

NEW MEDICINES AND NOVEL MECHANISMS OF ACTION

A growing understanding of the molecular, genetic, and biochemical changes that occur during the processes of carcinogenesis, progression, and metastasis has shifted oncology drug development away from traditional chemotherapeutic agents that target DNA and toward therapeutics that act on specific molecular targets that drive tumor growth and metastasis. Moreover, these same basic science advances in synthetic chemistry, immunology, and

molecular biology have led to novel approaches to inhibiting these targets. In addition to small-molecule kinase inhibitors and antibody therapy (monoclonal, polyclonal, and bispecific antibodies), one area of recent progress is in antibody-drug conjugate (ADC) technology. This approach involves an antibody directed against a surface antigen of the cancer, which is conjugated to a toxin (typically a tubulin such as a maytansine derivative) by a linker. The antibody binds the cell-surface antigen, the complex is internalized by endocytosis, the linker dissociates, and the toxin is released intracellularly, leading to apoptosis. Earlier approaches had led to significant toxicity, particularly hepatotoxicity, as the linker disintegrated significantly in the peripheral circulation. Improvements in linker technology, together with a number of available toxins and identification of tumor antigens with limited normal tissue expression, has advanced this field. Ado-trastuzumab emtansine (TDM-1) links the toxic antitubulin emtansine to trastuzumab; in 2013, it was approved for the treatment of HER2-positive breast cancer that showed progression on treatment with trastuzumab.[55] A number of ADCs are in clinical testing now, with two of the more promising ones being anetumab ravtansine, which targets mesothelin-expressing tumors[56] and rovalpituzumab tesirine, which targets the notch family receptor delta-like ligand 3 (DLL3). The DLL3 antibody is conjugated to a toxic pyrrolobenzodiazepine DNA-damaging agent, tesirine. DLL3 is expressed in about 80% of small cell lung cancers, and phase III trials are ongoing.[57] In terms of novel targets, efforts continue to target signal transduction proteins such as ERK kinase, TRK kinase, cell-cycle regulating proteins (the cyclins, the cyclin-dependent kinases, and inhibitors of cyclin-dependent kinases), epigenetic targets, and tumor metabolic targets (see Chapter 2: Molecular Biology).

Immunotherapy is a third area in which important advances have been made over the past couple of years (see Chapter 4: Principles of Immuno-Oncology and Biologic Therapy). Clinicians have known for many years that using nonspecific enhancers of the immune system, such as interleukin-2 (aldesleukin) and interferon, can generate immune responses that lead to clinical responses for patients with kidney cancer or melanoma. More recently, there has been increased interest in the development of immune-based therapy for more common solid tumors, such as cancers of the breast, bladder, head and neck, lung, and gastrointestinal tract and for hematologic malignancies such as lymphoma. Recent advances in understanding the mechanisms of immune tolerance of the host to tumor-specific antigens have led to the development of immune checkpoint proteins such as monoclonal antibodies against anti-PD-1 and anti-PDL-1. The anti-PD1 inhibitors pembrolizumab, nivolumab, and atezolizumab have been approved by the FDA for multiple solid tumors.

The rapid pace of drug development is evidenced by 22 approvals of novel entities, as well as by expanded indications for previously approved entities by the FDA in 2016. A current list of FDA-approved drugs in oncology can be accessed at https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs. Two recent FDA approvals warrant mention. The first approval of a plasma-based genomic analysis occurred when the FDA approved the cobas EGFR Mutation Test v2 using plasma specimens as a companion diagnostic test for the detection of exon 19 deletions or exon 21 (L858R) substitution mutations in the *EGFR* gene to identify patients with metastatic non-small cell lung cancer NSCLC eligible for treatment with erlotinib. The approval was based on a multicenter, open-label, randomized, phase III study, to evaluate the efficacy and safety of erlotinib versus gemcitabine plus cisplatin as first-line treatment for patients with stage IIIB/IV NSCLC. The agreement between the cobas EGFR Mutation Test v2 in plasma and the cobas EGFR Mutation Test v1 in tissue was evaluated for detection of *EGFR* mutations in patients with NSCLC who were screened for participation in the study. In 76.7% (95% CI; 70.5, 81.9) of tissue-positive specimens, plasma

was also positive for an *EGFR* mutation. Plasma was negative for *EGFR* mutation in 98.2% (95% CI; 95.4, 99.3) of tissue-negative cases.[58]

In the second approval, the FDA modified the indication for erlotinib for treatment of NSCLC to limit use to patients whose tumors have EGFR exon 19 deletions or exon 21 L858R substitution mutations as detected by an FDA-approved test. This labeling supplement is based on the results of a randomized, double-blind, placebo-controlled trial of erlotinib administered as maintenance therapy in patients with advanced NSCLC who had not experienced disease progression or unacceptable toxicity during four cycles of platinum-based first-line chemotherapy. Patients whose tumors harbored activating *EGFR* mutations (exon 19 deletions or exon 21 L858R mutations) were excluded from this trial. Results demonstrated that survival following treatment with erlotinib was not better than placebo administered as maintenance in patients with metastatic NSCLC tumors not harboring *EGFR*-activating mutations.[59]

KEY POINT

- Substantial gains have been realized in the development of drugs that inhibit novel cancer targets. These targets include, but are not limited to, angiogenesis, signal transduction growth pathways, and immune checkpoints.

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PRINCIPLES OF IMMUNO-ONCOLOGY AND BIOLOGIC THERAPY

Rodrigo Ramella Munhoz, MD, and Michael A. Postow, MD

Recent Updates

- A large number of biologic agents that promote antitumor immune and nonimmune responses have been approved for clinical use since the 5th edition was published.
- In collaboration with the National Comprehensive Cancer Network, the American Society of Clinical Oncology issued its first clinical practice guideline on management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy. (Brahmer JR, *J Clin Oncol* 2018)
- The clinical indications for the use of antibodies blocking the immune checkpoint PD-1 and its ligand PD-L1 continue to expand. In addition to advanced melanoma and non-small cell lung cancer, nivolumab has been approved for the treatment of patients with advanced renal cell carcinoma, relapsed/refractory classic Hodgkin lymphoma, recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma following platinum-containing chemotherapy, and mismatch repair–deficient advanced colorectal cancer. Nivolumab is also approved for clinical use in combination with ipilimumab in advanced melanoma. (Ansell SM, *N Engl J Med* 2015; Younes A, *Lancet Oncol* 2016; Ferris RL, *N Engl J Med* 2016; Sharma P, *Lancet Oncol* 2017; Overman MJ, *Lancet Oncol* 2017; Larkin J, *N Engl J Med* 2015; Postow MA, *N Engl J Med* 2015)
- Pembrolizumab is now approved for treatment in the first-line setting of patients with PD-L1–positive non-small cell lung cancer or in combination with chemotherapy irrespective of PD-L1 expression, metastatic SCCHN, classic Hodgkin lymphoma, urothelial carcinoma, and for patients with mismatch repair–deficient solid tumors, expanding prior indications for metastatic melanoma and refractory non-small cell lung cancer. (Reck M, *N Engl J Med* 2016; Langer CJ, *Lancet Oncol* 2016; Seiwert TY, *Lancet Oncol* 2016; Chen R, *J Clin Oncol* 2017; Bellmunt J, *N Engl J Med* 2017; Le DT, *N Engl J Med* 2015;)
- Atezolizumab has been approved for the treatment of patients with advanced urothelial carcinoma and metastatic non-small cell lung cancer. (Rosenberg JE, *Lancet* 2016; Balar AV, *Lancet* 2017; Rittmeyer A, *Lancet* 2017)
- Avelumab became the first systemic agent to be approved for the treatment of advanced Merkel cell carcinoma, and the indication of this agent was subsequently expanded to advanced urothelial carcinoma. (Kaufman HL, *Lancet Oncol* 2016; Apolo AB, *J Clin Oncol* 2017)
- Durvalumab has been approved for the treatment of patients with advanced urothelial carcinoma. (Massard C, *J Clin Oncol* 2016)
- Ipilimumab resulted in significant overall survival improvement when used in the adjuvant setting for patients with stage III melanoma and is approved as adjuvant therapy. (Eggermont AMM, *N Engl J Med* 2016)
- Necitumumab has been approved for use in combination with gemcitabine and cisplatin for patients with advanced squamous non-small cell lung cancer. (Thatcher N, *Lancet Oncol* 2015)
- Olaratumab has been approved for use in combination with doxorubicin for the treatment of patients with advanced soft-tissue sarcomas. (Tap WD, *Lancet* 2016)
- Obinutuzumab in combination with bendamustine, followed by obinutuzumab monotherapy has been approved for the treatment of patients with rituximab-refractory indolent non-Hodgkin lymphoma. (Sehn LH, *Lancet Oncol* 2016)
- Daratumumab, an anti-CD38 monoclonal antibody, has been approved for use as a single agent and in combination with lenalidomide or bortezomib and dexamethasone for the treatment of patients with refractory multiple myeloma. (Palumbo

A, *N Engl J Med* 2016; Dimopoulos MA, *N Engl J Med* 2016)

- Elotuzumab, an immunostimulatory monoclonal antibody targeting SLAMF7, has been approved by the FDA for use in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma in whom prior therapies have failed. (Lonial S, *N Engl J Med* 2015)

OVERVIEW AND GENERAL CONCEPTS OF IMMUNO-ONCOLOGY

Biologic therapy—whether for neoplastic, infectious, immunologic, or other diseases—refers to the use of biologic products or substances that are made by living organisms, such as cytokines, antibodies, and cells. For cancer, these substances are administered primarily to generate or restore host immune responses or to mediate nonimmunologic antitumor activities. Since the introduction of interferon (IFN) more than 25 years ago, progress in biologic therapy for cancer has been rapid. Several cytokines have been approved by the U.S. Food and Drug Administration (FDA). An increasing number of monoclonal antibodies are being used clinically. The introduction of immune checkpoint blockade with monoclonal antibodies has had a major impact in the management of a growing number of malignancies and has paved the way for the development of combined approaches, already in clinical use for the treatment of patients with melanoma. Cellular therapy based on artificially engineered antigen receptors (either chimeric or modified T-cell receptor) produced remarkable results in patients with refractory hematologic malignancies, and in combination with cell-based vaccine approaches already approved for clinical use, are expanding the applicability of cancer immunotherapy, or immuno-oncology. This chapter will focus on the immunology, pharmacology, and toxicology of biologic therapy in clinical use to treat cancer. More detailed review of the clinical application of specific agents is provided in tumor-specific chapters.

The immune system protects against microbial pathogens while simultaneously maintaining tolerance to “self.” The “innate” response forms the first line of defense. Innate immune cells (e.g., macrophages, dendritic cells, and natural killer [NK] cells) express receptors (e.g., toll-like receptors [TLRs]) involved in the recognition of conserved molecular patterns (pathogen-associated molecular patterns [PAMPs]), such as unmethylated CpG DNA motifs, found on exogenous organisms, and cell damage-associated molecular patterns (DAMPs) (e.g., high-mobility group box 1 [HMGB1]) but not on normal, uninflamed human tissues. Stimulation through these receptors triggers a cascade of events that includes the production of cytokines, activation of cellular cytotoxicity, an increase in nitric oxide synthesis, and activation of the complement system. These events promote the elimination or lysis of microbial pathogens and promote recruitment and activation of other immune cells.

Microbial/cellular fragments that result from the destruction produced by the innate immune response are taken up by antigen-presenting cells (e.g., macrophages, dendritic cells, B cells), which then process the fragments and present these antigens to generate the “adaptive” response, largely though the activation and mobilization of T cells and antibody-producing B cells. These cells express highly diverse antigen-specific receptors—the T-cell antigen receptors (TCRs) and the B-cell antigen receptors (BCRs)—generated by random rearrangement of the TCR and immunoglobulin (Ig) gene segments, respectively. The adaptive response allows generation of extremely diverse T- and B-cell repertoires that, compared with the innate response, provide a more specific but also broader and more flexible responses that include the capacity for generating “memory.”

Immune responses are highly regulated. Many types of cells and molecular factors, including

cell-surface molecules, are involved in modulating (either positively or negatively) both the innate and the adaptive response. A key step in the generation of adaptive immunity is the presentation of antigens by antigen-presenting cells to T-helper cells, which promote cellular effectors (e.g., cytolytic T lymphocytes [CTLs]) or humoral effectors (e.g., antibodies) through the production of specific cytokines. Regulatory cells and cytokines also serve to suppress the immune response to maintain tolerance to self and limit immune-mediated damage to normal tissues.

KEY POINTS

- Cells of both the antigen-nonspecific innate and antigen-specific adaptive responses have been implicated in antitumor immunity.
- Specific immunity to tumors requires uptake of tumor antigens by antigen-presenting cells and presentation to T-helper cells, which coordinate the generation of cellular (cytotoxic T cells) and/or humoral (antibody-producing B-cell) responses.
- Immune responses are highly regulated to maintain tolerance to self and limit immune-mediated damage to normal tissues.

IMMUNE CELLS

A wide variety of hematologic and nonhematologic cells are important in innate and adaptive immunity. The following are considered to play prominent roles in antitumor immune responses.

T Cells and Immune Checkpoints

T cells are paramount in the adaptive immune responses as effectors and as regulators. The signaling complex of T cells includes the TCR dimer, the accessory molecules (CD4 or CD8), and the CD3 signal transduction module. Unlike antibodies, which can react to intact proteins, T cells, through the TCR, react only to peptide fragments of antigens that are noncovalently complexed with major histocompatibility complex (MHC) molecules, which are integral membrane glycoproteins. There are two types of MHC molecules. Class I MHC (e.g., human leukocyte antigens A, B, and C) are expressed on all cell types and serve as the antigen-presenting molecule for CD8+ T cells. Class II MHC (e.g., HLA-DR) is recognized by CD4+ T cells and is present primarily on antigen-presenting cells but also can be present on other cells, including tumor cells. Polymorphisms within MHC molecules determine whether a peptide fragment will complex with the MHC molecule and thus whether a T cell from an individual will respond to a specific epitope of an antigen, resulting in the phenomenon referred to as “MHC restriction.” Because of this phenomenon, some peptide cancer vaccines can be applied only to patients with specific HLA types.

T-cell activation requires not only the presentation of an antigen within the context of an MHC molecule and stimulation through the CD3 module but also “costimulatory” signals. Activation is in turn regulated by “coinhibitory” signals, essential in limiting the magnitude of the immune response and autoimmunity, but also exploited as immune evasion mechanisms by tumor cells. The CD28 family of receptors includes the stimulatory receptor CD28 and the inhibitory receptors cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death 1 (PD-1).

Receptors of the CD28 family interact with the B7 family of ligands, which include B7-1, B7-2, programmed death ligands 1 (PD-L1 also called B7-H1), and 2 (PD-L2 also called B7-DC). These interactions are referred to as “immune checkpoints.” A simplified diagram for the CTLA-4 and PD-1 immune checkpoints is shown in Figure 4-1. Several other receptor–ligand engagements can act as modulators of the immune response, including those mediated by the costimulatory and coinhibitory molecules listed below.

Costimulatory receptors:

- CD28
- CD137
- CD27
- OX40 (or CD134)
- Inducible T-cell costimulator (ICOS)
- Glucocorticoid-induced tumor necrosis factor receptor [TNFR]–related protein (GITR)

Coinhibitory receptors:

- CTLA-4
- PD-1
- B- and T-cell attenuator (BTLA),
- Lymphocyte-activation gene 3 (LAG3)
- T-cell immunoglobulin and mucin-domain containing 3 (TIM3)
- PD-1H (also named VISTA [V-domain Ig suppressor of T cell activation]).

Cytolytic T Lymphocytes

Cytolytic T lymphocytes (CTLs) are primarily CD8+ T cells and thus recognize, through their unique TCR, antigens presented within the context of MHC class I. Two mechanisms are involved in their cytolytic effector activity. The predominant mechanism is granule exocytosis and the release of perforin and granzymes. The second mechanism is mediated by the death activator Fas ligand, which is expressed on the cell surface of CTLs. Both mechanisms cause cells to undergo apoptosis (Fig. 4-2). When appropriately activated, these cells also produce cytokines, such as interferon-gamma, interleukin-2 (IL-2), and tumor necrosis factor α (TNF-α), that also can mediate or enhance antitumor effects. CTL can move to another cell and, by reorienting its granules to another region of contact, destroy it. In this manner, CTL can kill many tumor cells, resulting in a very robust and very specific “serial killing” response that is considered to play a central role in immune-mediated tumor rejection. Tumor-infiltrating CD8+ lymphocytes can be associated with improved clinical outcome.[1]

T-Helper Cells

T-helper cells secrete cytokines that regulate all immune cells. They are essential in generating CTLs, regulating B-cell antibody production, and activating phagocytes. Most T-helper cells express CD4 and thus recognize antigens presented by class II MHC. Depending on the nature of the peptide and the activation status of the antigen-presenting cells, several types of

responses can be promoted, including a cellular immune response mediated by CTLs and by macrophages, referred to as T-helper cell type 1 (Th1) response, or a humoral response mediated by antibody, referred to as Th2 response (which also includes activation of eosinophils). Predominant cytokines produced in a Th1-associated response are interferon-gamma and IL-2. Predominant cytokines produced in a Th2-associated response are IL-4 and IL-5. CD4+ T cells are required in an antitumor response largely to help naive CD8+ T cells, leading to their differentiation and activation into tumor-specific CTLs and the development of antigen (Ag)-specific memory. Cytokines produced by T-helper cells also may mediate antitumor effects by activating macrophages and NK cells. T-helper cytokines (e.g., interferon-gamma) may also directly suppress tumor growth.

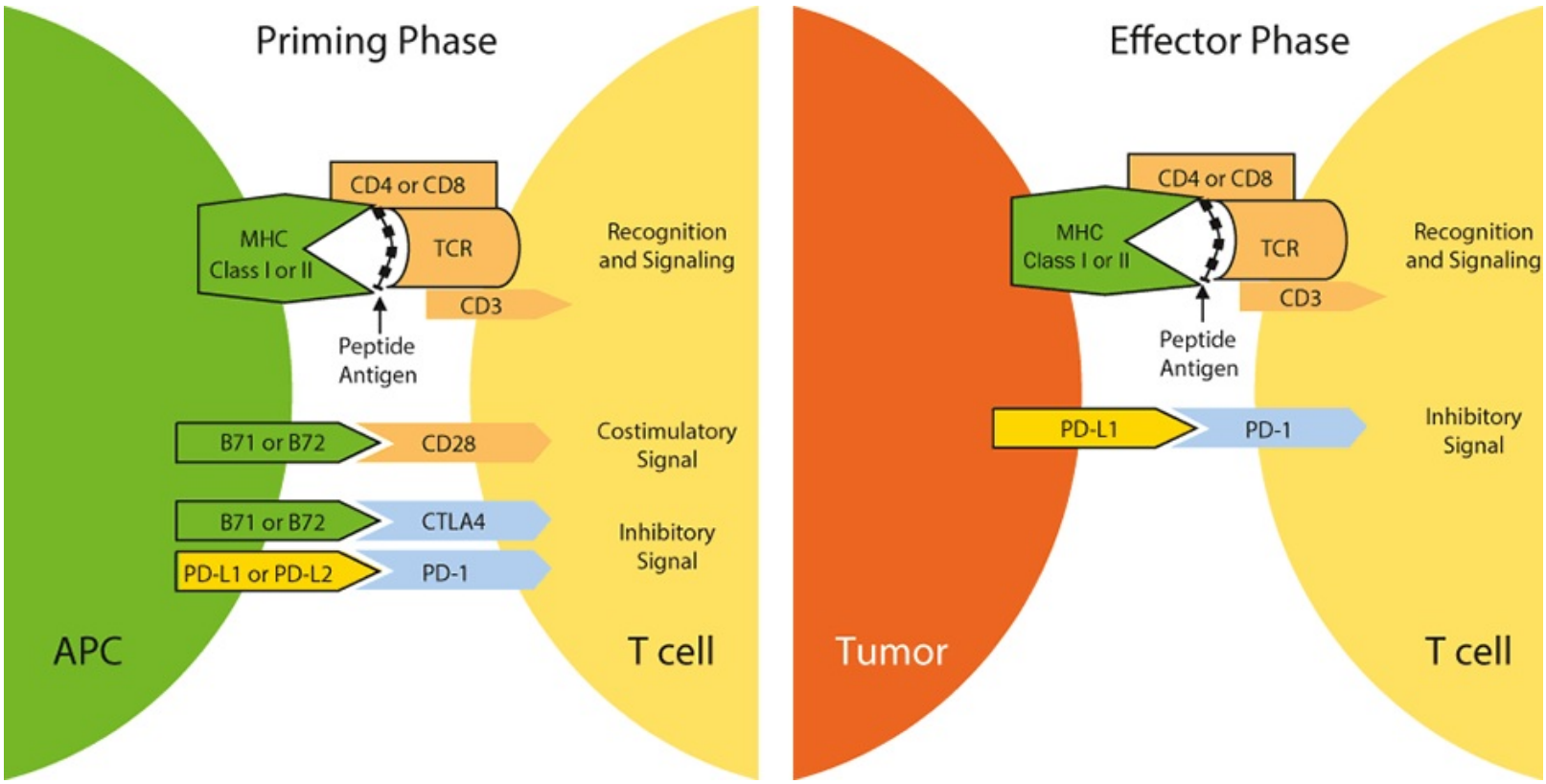

Fig. 4-1 Regulation of T-cell priming and effector function.

During the priming phase of T-cell activation, antigens are presented to the T-cell receptor (TCR) as peptide fragments within major histocompatibility complex (MHC) molecules on antigen-presenting cells (APCs). The primary costimulatory signal is delivered through the CD28 receptor on the T cell after engagement of its ligands, B7-1 or B7-2, on the APC. Fully effective engagement also depends on the interactions among several other molecules, such as adhesion molecules (not shown). Failure of the costimulatory B7/CD28 complex to be engaged results in either a nonactivating T-cell event and/or anergy. Engagement of the cytolytic T-lymphocyte antigen 4 (CTLA-4) receptor (CD152) on the T cell by the same B7-1 or B7-2 ligands results in inhibition of the response. Engagement of the programmed death 1 (PD-1) receptor with one of its two ligands, PD-L1 or PD-L2, on APC also results in inhibition of the response. PD-L1 is also expressed by tumors. During the effector phase, engagement of PD-1 on the activated T cell by PD-L1 on the tumor results in inhibition of T-cell function.

Regulatory T Cells

Regulatory T cells (Tregs) are subsets of T lymphocytes capable of discriminating self-antigens from non–self-antigens. In healthy individuals, Tregs maintain tolerance by suppressing expansion of effector cells directed against self-antigen. Tregs that express CD4, CD25, and forkhead box P3 (FOXP3; a forkhead family transcriptional regulator) play a central role in maintaining immune self-tolerance. The mechanism of suppression of self-reactive lymphocytes is not clear but does appear to involve direct cell-to-cell contact or the production of IL-10 or of

transforming growth factor β (TGF-β). Given that many tumor-associated antigens are normal self-constituents, CD4+CD25+FOXP3 Treg cells engaged in the maintenance of self-tolerance may impede tumor-reactive T cells. Their role in cancer, however, is not established, and the prognostic significance of intratumoral Treg cells may be context-dependent and affected by the tumor type, the other cells in the tumor microenvironment, and soluble molecules that vary with time and treatment. In cancers, such as breast cancer, data show that intratumoral Treg cells confer a poorer prognosis[2]; however, in colorectal cancer, there is a better prognosis.[3]

Natural Killer Cells

Natural killer (NK) cells are a relatively small population (less than 10%) of circulating lymphocytes and are distinct from T cells and B cells. They are part of the innate or immediate non–Ag-specific response to pathogens and transformed cells. Although their cytotoxic mechanisms are similar to those of CTL, NK cells do not require recognition of MHC molecules, and thus killing by NK cells is designated as non-MHC-restricted lysis. In fact, class I MHC molecules send a negative regulatory signal through receptors on the NK cells (killer inhibitory receptors [KIRs]) that inhibit NK cell lytic function. Conversely, loss of class I MHC on tumor cells may result in NK cell killing of cells that could otherwise escape T-cell recognition. Under normal homeostatic conditions, multiple families of NK cell receptors that inhibit their activation exert the predominant effects, while inflammation and infection, as well as malignancy, may lead to activation through a number of other activating receptors that recognize soluble and cell-membrane ligands on tumors and infected cells. Also in contrast to CTLs, NK cells express Fc receptors and thus can mediate antibody-dependent cell-mediated cytotoxicity (ADCC). When activated, NK cells also produce interferon-gamma. Although NK cells do not require activation for lytic activity, the stimulation of NK cells with interferons and IL-2 markedly enhances their antitumor activity. In contrast to CTLs, which can kill multiple cells, there is evidence that NK cells must rearm themselves by exposure to IL-2 before they are effective against new targets. Furthermore, there is, for the most part, no memory component to the NK response.

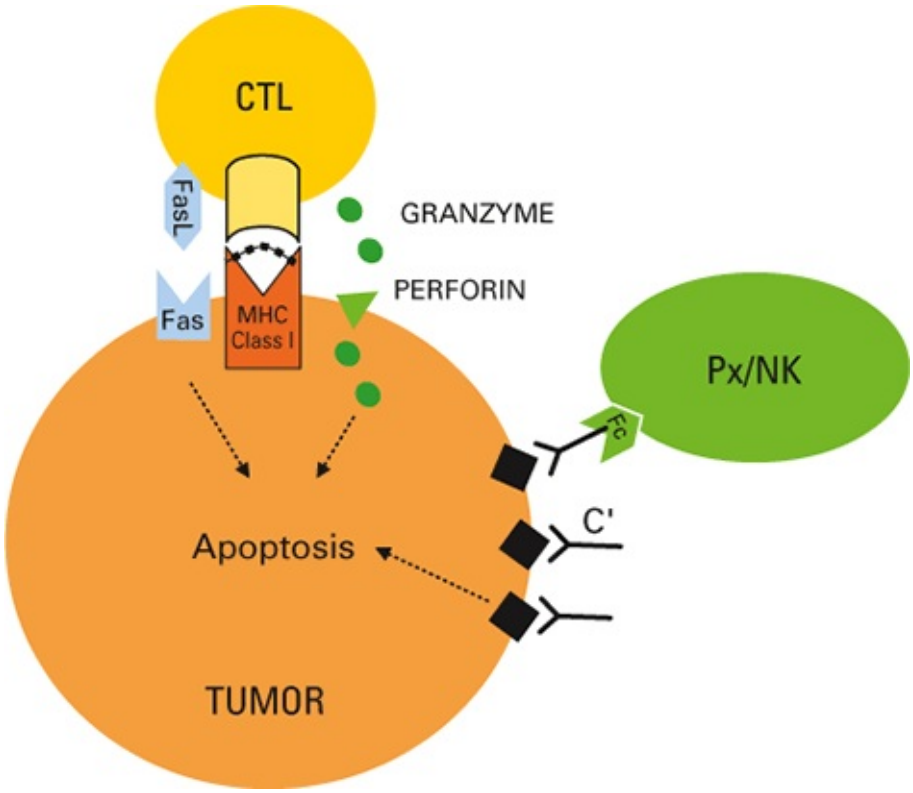

Fig. 4-2 Mechanisms of cell killing by cytolytic T lymphocytes and antibody.

After attaching to the major histocompatibility complex (MHC)–peptide complex, cytolytic T lymphocytes (CTLs) discharge cytoplasmic granules containing perforin and granzymes by exocytosis. Perforin molecules insert themselves into the plasma membrane of target cells, which enables granzymes to enter the cell. Granzymes are serine proteases that, once inside the cell, activate caspases that cause the cells to undergo apoptosis. When CTLs bind to their target, they also upregulate Fas ligand (FasL) on their surface, which binds with the Fas receptor on the surface of the target cell, leading to its death—also by apoptosis. Antibody recognizes antigen in its native conformation. After binding, a complement reactive site on the antibody is activated that sets into motion a cascade of reactions, including the activation of many molecules of the complement system, which in turn activate increasing amounts of enzymes resulting in complement-mediated cytotoxicity (CMC). A product of the complement cascade also strongly activates phagocytosis by macrophages and neutrophils. These phagocytes (Px) and also natural killer (NK) cells bind their Fc receptor (CD16) to the antibody and destroy the antibody-bound cell (antibody-dependent cellular mechanisms). Antibody-recognizing cell-surface molecules that regulate cell signaling/growth can directly elicit apoptosis. Abbreviations: C′, complement.

B Cells

Antibody-producing B cells are involved in adaptive immunity and also serve as antigen-presenting cells. The BCR binds soluble antigens, which are then internalized by receptor-mediated endocytosis and processed into peptide fragments that are then displayed at the cell surface within class II MHC. T-helper cells specific for this structure (i.e., with a complementary TCR) bind the B cell and secrete cytokines that stimulate the B cell to proliferate into cells with identical BCRs and ultimately to differentiate into plasma cells that secrete antibodies (i.e., the soluble version of the BCR). In contrast to T cells, which recognize only processed peptide antigen, antibodies produced by B cells recognize the intact protein antigen in its native conformation. Antibodies also can recognize polysaccharides and nucleic acids. Antigen-binding specificity is encoded by three complementarity-determining regions on the Fab (fragment-antigen binding) region, whereas the monomorphic Fc (fraction-crystallizable) region of the antibody is responsible for binding to serum proteins (e.g., complement) or to cells such as macrophages and NK cells that express Fc receptors that transmit signals leading to ADCC. Complement-mediated cytotoxicity (CMC) may develop in the case of complement-fixing Fc classes of IgG and multimeric antibodies such as IgM, and subsequent activation for the complement protein cascade. Central to CMC is the ability of the antibody to redistribute the target on the cell membrane into large glycolipoprotein microdomains known as “lipid rafts.” Antibodies also can directly mediate antitumor effects by interacting with cell-surface receptors that regulate cell growth (Fig. 4-2). Although cellular immune responses appear to be central in the generation of effective antitumor immunity, a substantial body of data indicates that antibodies are also important. Furthermore, the antitumor effects of antibodies have been validated by the clinical efficacy of monoclonal antibodies specific for tumor-associated molecules.

Dendritic Cells

Dendritic cells are a widely distributed, heterogeneous population of antigen-presenting cells that are derived from bone marrow progenitors and circulate in the blood as immature precursors prior to migration into peripheral tissues. Within different tissues, dendritic cells differentiate and become active in the uptake and processing of antigens via MHC class I and II molecules, which require distinct intracellular processing pathways, termed the “antigen-processing machinery” (APM), generally using class I for endogenous antigens and class II for exogenous antigens, but with substantial overlap. Dendritic cells function at the intersection of the innate and adaptive immune responses. Upon stimulation provided by microbes (via TLRs), cytokines, and/or T-cell signals (e.g., CD40 ligand), dendritic cells undergo further maturation

and migrate to secondary lymphoid tissues, where they present antigen to T cells. The nature of the immune response elicited depends on a variety of factors, including the mode and duration of activation and the cytokine milieu.

Two distinct dendritic cell lineages have been described in humans: myeloid dendritic cells (mDCs) express the receptor for granulocyte–macrophage colony-stimulating factor (GM-CSF) and other myeloid markers. mDCs reside in tissues and are the most efficient antigen-presenting cells, particularly with regard to the primary activation of naive T cells. They stimulate tumor-reactive CTLs through an IL-12–dependent mechanism. Plasmacytoid dendritic cells (pDCs) lack myeloid cell markers and express the receptor for IL-3 (CD123). They reside in peripheral blood, and after encountering a virus, they secrete large amounts of interferon-alpha, a cytokine with immunomodulatory as well as antiviral properties. The role of pDCs in antitumor immunity is under investigation.

Macrophages

Macrophages, which derive from peripheral-blood monocytes, are widely dispersed throughout the body and mediate a variety of functions. Macrophages are specialized phagocytes. Phagocytosis is mediated through surface receptors for complement and other opsonins and through the uptake of particles into phagosomes that then fuse with cytoplasmic lysosomes. Macrophages express Fc receptors for antibodies and can mediate antibody-dependent cellular uptake and cytotoxicity. Similar to dendritic cells, macrophages function at the intersection of the innate and adaptive immune responses and can process antigen via the APM and present peptides within MHC molecules to activate specific T- and B-cell effector mechanisms. Macrophages also are potent secretory cells. They are major producers of the pro-angiogenic vascular endothelial growth factor (VEGF). Distinct activation states of macrophages have been described: M1 macrophages produce high levels of inducible nitric oxide synthase, IL-12, and TNF, whereas M2 macrophages produce arginase, IL-10, TGF-beta, and prostaglandin E_2. M1 macrophages are potent effector cells that kill tumors through nitric oxide and TNF, whereas M2 macrophages limit Th1 immune responses and promote angiogenesis, processes that promote tumor growth. Whereas M2 macrophages are associated with a decrease in survival for patients with cancer, M1 macrophages have been associated with an improved survival.[1,2]

Myeloid-Derived Suppressor Cells

A number of investigations have identified immature myeloid cell populations present in tumors and lymphoid organs, referred to as myeloid-derived suppressor cells (MDSCs), which inhibit T-cell functions and play a role in tumor-associated immune suppression. They have been described in patients with many types of solid tumors.[3-5] Human MDSCs are still poorly defined but have been reported to lack the expression of markers of mature myeloid and lymphoid cells (i.e., lineage-negative) and HLA-DR. MDSCs do express the common myeloid marker CD33. The precise nature of this regulatory cell population and whether they are precursors of granulocytes, macrophages, or dendritic cells appear to depend on the tumor and tumor-derived factors of the host. This highly plastic population suppresses T-cell functions through different molecular pathways, mostly involving arginase metabolism products, inducible nitric oxide synthase, reactive oxygen species, and/or production of soluble inhibitory factors such as TGF-beta, IL-10, prostaglandin E_2, and nitric oxide.

KEY POINTS

- T cells recognize antigens presented to the T-cell antigen receptors as peptide fragments within MHC molecules. T-cell activation requires stimulation not only through the T-cell antigen receptor but also through immune costimulatory receptors.
- Interactions with coinhibitory receptors on T cells, referred to as “immune checkpoints,” suppress unwanted and harmful self-directed immune activities.
- T-helper cells promote Th1–associated CTLs through the production of cytokines, such as interferon-gamma and interleukin-2 (IL-2), and promote Th2-associated antibodies through production of cytokines, such as IL-4 and IL-5.
- CTLs kill tumors by apoptosis through granule exocytosis and Fas-mediated mechanisms.
- B cells produce antibodies that recognize antigens in their native conformation. Antibodies can react against tumors by complement-mediated and ADCC mechanisms.
- Dendritic cells are the most efficient antigen-presenting cells.
- Several lymphoid and myeloid cell populations act to suppress immune responses, including regulatory T cells and MDSCs.

IMMUNE SURVEILLANCE

Several lines of evidence support the existence of cancer immune surveillance—that the innate/adaptive immune system continually recognizes and removes malignant cells that arise throughout an individual’s lifetime. Individuals with suppressed immune systems, such as organ transplant recipients or patients affected with primary or acquired immunodeficiency disorders, are at increased risk for the development of malignancy. The rare spontaneous regression of cancer and the responses to withdrawal of immunosuppression in some cases, as well as waning of the incidence of Kaposi sarcoma in AIDS with the advent of highly active antiretroviral therapies, are further evidence in favor of immune surveillance in cancer control. Brisk infiltration by subpopulations of lymphocytes, especially CD8-T cells, in tumor specimens is an independent positive prognostic factor for some cancers, such as melanoma and ovarian cancer.[1,6,7] Likewise, the natural occurrence of a humoral immune response to a tumor-associated antigen is associated with a favorable clinical outcome in cancers such as breast cancer.[8] Human T cells that accumulate within the mass of a tumor can be shown, in some instances, to proliferate in response to autologous tumor cells in vitro. Most importantly, pharmacologic modulation of the immune response with cytokines and with various types of antibodies has produced objective tumor responses in patients.

Effective surveillance requires that the tumor express determinants, capable of being recognized by the immune system (i.e., tumor antigens), and that are associated with the tumor intrinsic antigenic potential. Numerous tumor-associated antigens (TAAs), including the differentiation antigens carcinoembryonic antigen (CEA), tyrosinase, and prostate-specific antigen (PSA), as well as peptides that result from genes overexpressed in tumors (e.g., *erbB2*), have been defined with antibodies and applied in diagnosis and in monitoring response to therapy. As outlined previously, antigens that are recognized by the T cells differ substantially

from those defined by antibodies. To function as a T-cell rejection antigen, the tumor must express the associated peptide determinant in the context of MHC molecules. Failure of antigen processing or binding to MHC molecules—or inadequate expression of costimulatory or adhesion molecules—may lead to poor immunogenicity. Several targets that can potentially serve as tumor rejection antigens have been identified by a variety of techniques (Table 4-1). Many of these have been targeted in vaccine approaches. Oncofetal, cancer-testis (a group of oncofetal antigens), and differentiation/lineage-specific antigens are expressed by normal adult tissues and, therefore, are not tumor-specific. In contrast to those that are overexpressed and not mutated (e.g., *erbB2*), oncogenes/tumor suppressors that are mutated can be considered tumor-specific and even patient-specific (e.g., *p53*). The tumor immunogenicity and response to treatment with monoclonal antibodies targeting immune checkpoints can be also influenced by peptides and antigenic neoepitopes generated from aberrant gene products and increased number of somatic missense mutations, also defined as tumor mutational load.[9-11] As a demonstration of this principle, significant antitumor effect from PD-1 blockade has been demonstrated in patients with mismatch repair (MMR) deficiency–related tumors, marked by genomic instability and a high mutational burden.[12] Other factors that drive the capacity of mounting an adequate immune response include the expression of proinflammatory chemokines (type I interferons, CCL2, CCL3, CCL4, CCL5, CXCL9, and CXCL10) and mutations involving pathways that are part of the immune activation cascade, including disruptive mutations or, conversely, amplifications of JAK1 or JAK2 (implicated in interferon-dependent signaling), phosphatase and tensin homolog (*PTEN*) loss, and activation of the WNT/beta-catenin pathway.

KEY POINTS

- Several lines of evidence, including clinical responses with pharmacologic modulation of the immune response, support the role of the immune response in cancer regulation, both in immune surveillance against nascent malignancy and in therapy for established malignancy.
- Recognition of tumor cells by the immune system can be influenced by a variety of factors, including the tumor intrinsic antigenic potential (e.g., mutational burden and neoantigen signature, strength of immunogenicity of tumor antigens), preexisting host immune condition and products of genomic aberrations affecting pathways driving the immune response.
- This continuous interaction between tumor cells and immune cells, not always successful in terms of tumor control, is characterized as immune surveillance.

IMMUNE ESCAPE

Animal models have demonstrated the existence of “immunoediting,” in which activation of immune mechanisms initially controls the tumor, but over time leads to the selection of tumor cells that escape the immune pressure, grow progressively and then contribute to the establishment of an immunosuppressive tumor microenvironment.[13] Because most of the tumor antigens identified are nonmutated self-antigens, a high degree of immunologic tolerance exists,

limiting the generation of immune effectors. As noted, Treg cells engaged in the maintenance of self-tolerance may impede tumor-reactive T cells. Tumors are heterogeneous, and the repertoire of tumor antigens on the cells of one tumor may be variable, even within the same patient. Downregulation of MHC class I molecules and other components of the antigen-presentation process can occur. Membrane-associated factors expressed by tumor cells that directly inhibit T-cell function have also been identified, and tumors can exploit inhibitory immune checkpoints as evasion mechanisms. Tumor expression of PD-L1 and PD-L2, ligands of the coinhibitory receptor PD-1, is considered to be a significant mediator of immunosuppression within the tumor microenvironment. However, a large part of the role played by PD-1–expressing T cells may be to secrete interferon-gamma (IFNγ) upon initial T-cell activation, and this in turn upregulates PD-L1 on tumor cells, conferring on the tumor and T cell interaction a dependence on this ligand-receptor association that can be therapeutically targeted by antibodies. The expression of Fas ligand by some tumor cells may help to maintain a state of immune privilege by inducing apoptosis of Fas-sensitive T and NK effector cells—the “Fas counterattack”. There is also evidence that a tumor's expression of antiapoptotic molecules, which prevent perforin or death receptor dependent cytotoxicity, can result in escape despite expression of the target antigen. In addition, tumor-associated factors, such as underglycosylated tumor-associated mucins, have been shown to reduce binding of antibodies to tumor cell surfaces.

Table 4-1 **Potential Immunotherapy Targets**		
Antitumor Antigens	**Example**	**Associated Malignancies**
Oncofetal	CEA	Colorectal, breast, non-small cell lung
	Beta-human chorionic gonadotropin (hCG)	Colorectal, pancreatic, non-small cell lung
Cancer-testis	MAGE	Melanoma, lung, ovary, bladder, liver
	NY-ESO	Melanoma, lung, bladder, liver
Oncogene/ tumor suppressor	*HER2*	Breast, gastric
	p53	Multiple
	RAS	Multiple
	WT1	Multiple
	BCR-ABL	Chronic myeloid leukemia
Differentiation/ lineage-specific	Prostate-specific antigen (PSA)	Prostate
	Prostatic acid phosphatase	Prostate
	gp100	Melanoma
	Tyrosinase	Melanoma
	MART/Melan-A	Melanoma
	Ig (idiotype)	B-cell malignancies
Aberrantly glycosylated molecules	MUC1 (mucin)	Pancreatic, breast
	GM2 (ganglioside)	Melanoma, neuroblastoma
	GD2 (ganglioside)	Melanoma, neuroblastoma
Viral	E6, E7 (HPV)	Cervical cancer
	EBNA (Epstein-Barr virus)	Burkitt lymphoma, nasopharyngeal carcinoma

Tumor cells and the surrounding stroma may release a number of suppressive cytokines and other soluble factors, such as prostaglandin E_2, that are not conducive to antitumor immunity. Cancer-associated factors have been shown to inhibit the production and stimulatory capacity of dendritic cells.[14] The T-helper cell response also may be skewed toward a Th2 phenotype, which inhibits Th1 response and the cellular immunity that is critical in mediating tumor rejection.[15] TGF-beta is produced not only by host cells but also by tumors and can inhibit the differentiation of T cells into CTLs and T-helper cells and promote the generation of Treg cells. By producing cytokines (e.g., GM-CSF), cancers can promote the infiltration of M2-polarized macrophages and MDSCs that can inhibit T-cell function. Downregulation of the CD3 zeta-chain of the TCR complex and impairment of function have been shown for T cells isolated from patients with cancer.[16]

KEY POINTS

- The ability of cancer to evade the immune response is aided by the fact that most tumor antigens are self-proteins, which impede the generation of immunity via tolerogenic mechanisms, such as the elaboration of Treg cells and the central elimination of autoreactive T cells by thymic selection.
- While immune checkpoints are a necessary function to prevent unchecked autoimmunity, tumors can co-opt these mechanisms to escape immune responses.
- Cancer evasion of the immune system results not only from immunosuppressive factors secreted by or expressed on the tumor, but also from the ability of the tumor to modulate antigen expression and to be endowed with or later evolve mechanisms of resistance to immune effectors.
- The recognition of evasion mechanisms involved in tumor immune escape can be exploited therapeutically.

IMMUNE SUBVERSION

Although effective antitumor immunity has been demonstrated in experimental systems and in patients, immune responses are abundantly present in tumor-bearing hosts that provide no apparent protection to the host and may contribute to the oncogenic process. Not only can tumors escape immune response, but they can also exploit or subvert the immune response to promote their growth, invasion, and metastasis. Local tumor growth within the stroma is promoted by angiogenesis. Immune cells, including macrophages, T cells, and neutrophils, fully participate in tumor angiogenesis by secreting cytokines, such as IL-1, IL-8, and VEGF, that directly affect endothelial cell functions including endothelial cell proliferation, migration, and activation. In addition to angiogenic factors, macrophages also produce matrix metalloproteinases that degrade the extracellular matrix involved in tumor cell invasion and metastasis. Accumulating data show that many tumor cells express chemokine receptors and respond to chemokine gradients in vitro. Experiments in vivo also have indicated that certain chemokines can serve as tissue-specific attractant molecules for tumor cells, promoting tumor cell migration/metastasis to particular sites. Several cytokines produced by immune cells have been shown to transmit cell growth signals in tumor cells and directly promote tumor cell growth. TGF-beta, TNF-alpha, and IL-6 are able to promote the growth of some tumors while suppressing the growth of others.

KEY POINTS

- The interaction between tumor cells and immune cells is not unidirectional.
- Tumors can subvert the immune response by stimulating the production of immune cell factors that promote angiogenesis, invasion, and metastases.
- Immune cell cytokines also may function as tumor growth factors.

BIOLOGIC AGENTS

Many cytokines, monoclonal antibodies, and cell therapies for cancer have been developed and are applied clinically, acting through either immune or nonimmune effector pathways.

The immune response can be activated to mediate tumor destruction through one of several mechanisms. These include increasing immune effectors and modifying tumor cells to increase their susceptibility to immune effectors. A highly effective strategy is to block one or more of the negative immunoregulatory host checkpoints involved in evasion mechanisms. The elimination of cells or cytokines that promote immune escape may permit a more effective and persistent antitumor immune response. This approach cannot be effective unless there is a simultaneous positive immune response to the tumor. This may occur naturally, as is observed among select patients (e.g., patients with malignant melanoma with regressed primary lesions). Alternatively, it may have to be induced (e.g., by a cancer vaccine).

There are two general immunotherapy approaches. “Active” immunotherapy attempts to stimulate (in vivo) an intrinsic immune response to the tumor, either nonspecifically with cytokines or specifically with antibody or vaccine approaches. “Passive” or “adoptive” immunotherapy involves the preparation of antibodies and cells outside the body (ex vivo) followed by administration to patients.

Biologic agents can also be used to mediate antitumor effects by nonimmune effector mechanisms. Some biologics are administered not to promote antitumor responses but rather to ameliorate the side effects of therapy and progressing cancer. These include hematopoietic growth factors. They also include cytokines that are produced by nonimmune cells and that do not directly activate antitumor immune effector mechanisms. For example, human recombinant erythropoietin is used to manage anemia.[17] The human recombinant keratinocyte growth factor palifermin is used to decrease the risk of severe mucositis associated with very high-dose chemoradiotherapy such as in hematopoietic stem cell transplantation. Denosumab is a fully human monoclonal antibody that targets receptor activator of nuclear factor kappa B (RANK) ligand, a protein that acts as the primary signal to promote bone removal by osteoclasts. It is used for the prevention of skeletal-related events for patients with bone metastases and myeloma as well as in the management of giant cell tumor of bone.[18,19]

The pharmacokinetics of biologic agents are quite variable. Elimination half-lives for most cytokines are measured in minutes to hours and, for most antibodies, in days to weeks. Infused cells can persist for months. Unlike chemotherapy, which acts directly on the tumor, cancer immunotherapies exert their effects on the immune system and demonstrate kinetics that involve generating an antitumor immune response. The approach to assessing and managing response and toxicity can also differ. Immunotherapy may induce patterns of antitumor response not adequately assessed by Response Evaluation Criteria in Solid Tumors (RECIST) or World Health Organization (WHO) criteria. Patients may have a transient worsening of disease before the tumor regresses. Responses can take appreciably longer to become apparent as compared with those for cytotoxic or targeted therapy. Continued disease regression is frequently observed well after immunotherapy is suspended. Furthermore, some patients who do not meet criteria for objective response can have prolonged periods of stable disease that are clinically relevant. New immune-related response criteria designed to more comprehensively capture all response patterns are under investigation.[20] As the goal of many approaches is to break immune tolerance by the removal of negative immunoregulatory mechanisms, evidence of autoimmunity as a side effect of treatment is predicted and has been associated with clinical benefit in some, but not all, studies.

KEY POINTS

- Biologic agents may elicit an antitumor effect through either immune mechanisms or nonimmune pathways.
- Immunotherapies may stimulate components of an existing tumor-immune interaction ("active immunotherapies"; e.g. cytokines, antibodies targeting immune checkpoints) or harness cells or antibodies engineered ex vivo ("passive immunotherapies"; e.g., adoptive cell therapies).

CYTOKINES

Cytokines are a diverse group of small proteins released by immune and nonimmune cells distributed throughout the body. Cytokines play integral roles in innate and adaptive immunity as effector and regulatory molecules. They also play an integral role in a variety of other biologic processes. Cytokines, which are active physiologically at very low concentrations, may act locally (autocrine or paracrine) or at a distance (endocrine). They are characterized by pleiotropy (one cytokine, multiple effects), redundancy (multiple cytokines, one effect), and synergy (the sum of the response together is greater than the sum of the individual responses). The administration of a cytokine will initiate a cascade of cytokine production and both stimulatory (amplification) and inhibitory/antagonistic effects. Cytokines act on their target cells by binding specific membrane receptors that contain cytokine-specific and signal-transducing subunits. They can be divided into groups based on function (e.g., chemokines are cytokines that are chemoattractants to immune cells) or on cellular source (e.g., lymphokines are cytokines produced by lymphocytes). Study of the structure and function of cytokine receptors, however, has led to improved understanding of cytokine action and a more useful classification (Table 4-2). Cytokines can lead to tumor destruction by one of two general mechanisms. They can function indirectly and enhance the activity of antitumor cellular or humoral immune effector mechanisms, or they can interact directly with tumor cells; cytokines, such as TNF-α, interferon-α, interferon-gamma, IL-4, and IL-6, have been shown to initiate tumor cell apoptosis or cell cycle arrest. Recombinant cytokines in clinical use are shown in Table 4-3.

Table 4-2 **Examples of Cytokines Involved in Immune Regulation**

Group	Function	Receptor	Examples
Hematopoietic	Leukocyte proliferation, differentiation, and activation	▪ Multimers with Trp-Ser-X-Trp-Ser motif ▪ Signals primarily by receptor-associated JAK and STAT	IL-2, IL-3, IL-4, IL-6, IL-7, IL-11, IL-12, G-CSF, GM-CSF
Interferon	Inhibit virus replication	▪ Two polypeptide chains with tandem fibronectin domains ▪ Signals primarily by JAK-STAT	Interferon-alpha, interferon-beta, interferon-gamma
TNF	Inflammation and other biologic processes	Four extracellular domains activate caspases that mediate apoptosis ("death receptor") or pathways that promote cell survival and inflammation	TNF-α
Chemokine	Attract leukocytes to inflammatory sites	Seven transmembrane helices interact with G proteins	MIP-1α, IL-8
IL-1	Inflammation and hematopoiesis	▪ Extracellular Ig domain and cytosolic toll-IL-1 receptor (TIR) domain ▪ TIR activates signaling pathways	IL-1β
Growth factor	Growth and differentiation of nonimmune cells	Multimeric complexes with intrinsic tyrosine or serine/threonine kinase activities	TGF-β, VEGF

Abbreviations: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; IL, interleukin; JAK, Janus tyrosine kinase; MIP-1α, macrophage inflammatory protein 1α; STAT, signal transducer and activator of transcription; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α; VEGF, vascular endothelial growth factor.

INTERFERONS AND INTERLEUKIN-2

Interferons-alpha and beta (referred to as type I interferons), produced by many cell types, and interferon-gamma (referred to as type II interferon), synthesized primarily by lymphocytes, mediate a wide variety of biologic effects, including inducing the transcription of a diversity of genes, and affect nearly all phases of the innate and adaptive immune responses. Interferons, type I in particular, inhibit virus replication in infected cells. All enhance class I MHC and thereby promote CD8+ CTL responses; interferon-gamma is capable of inducing class II MHC. Interferons enhance NK cell cytotoxicity, upregulate Fc receptors, and promote ADCC mechanisms. They regulate the balance between Th1 and Th2 cells, promoting, for the most part, Th1 responses. In addition to affecting humoral immunity by modulating T-helper cells, interferons can have direct effects on B cells, including regulating proliferation and Ig production. Interferon-gamma also plays an important role in macrophage activation.[21] Interferons can directly inhibit the growth of tumor (and normal) cells and produce antiangiogenic effects.

Among the more than 20 different known interferons, only interferon-alpha 2 has been extensively and clinically evaluated for cancer. Two recombinant interferon-alpha 2 preparations have been approved: interferon-alpha 2a and interferon-alpha 2b. The pleiotropic effects of interferons have led to their evaluation in almost all malignancies, alone or in combinations.[22] However, for the most part, the use of interferon in cancers has been supplanted by more active and potentially less toxic drugs. Toxicities, which are highly diverse, include flu-like symptoms, such as fever, chills, and myalgia, neuropsychiatric side effects (fatigue and depression), liver dysfunction and myelotoxicity. Novel applications of interferons are being tested in both solid tumors and hematologic malignancies, and there is growing interest in the

possibility of combining interferon with antibodies against immune checkpoints.

Table 4-3 Recombinant Cytokines in Clinical Use for Cancer

Cytokine	Effects	Cancer Indications
Interferon-α; PEG-interferon alpha	▪ Immune (upregulate MHC, activate NK cells) ▪ Antiangiogenesis ▪ Direct antiproliferative	Melanoma, hairy cell leukemia, chronic myeloid leukemia, follicular lymphoma, Kaposi sarcoma, renal cell carcinoma
Aldesleukin (IL-2)	Activate cytotoxic T lymphocytes and NK cells	Melanoma, renal cell carcinoma
Sargramostim (GM-CSF)	Stimulates the development and function of neutrophils, monocyte–macrophages, and dendritic cells	Shortens chemotherapy-induced neutropenia in elderly patients with acute myeloid leukemia, promotes myeloid reconstitution after HSCT, mobilizes stem cells
Filgrastim (G-CSF) Pegfilgrastim (G-CSF)	Stimulates the development and function of neutrophils	Shortens chemotherapy-induced neutropenia, promotes myeloid reconstitution after HSCT, mobilizes stem cells

Abbreviations: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; HSCT, hematopoietic stem cell transplantation; MHC, major histocompatibility complex; NK, natural killer; PEG, pegylated.

IL-2 is a T-cell growth factor. Antigen binding to the TCR stimulates the secretion of IL-2 and the expression of high-affinity IL-2 receptors (CD25). The interaction between IL-2 and the IL-2 receptor stimulates the growth, differentiation, and survival of antigen-selected T cells. IL-2 is a major activator of CTL and NK cytotoxicity, and is necessary for the development of memory T cells. It also indirectly regulates B cells and hematopoiesis and the generation and maintenance of Treg cells, which, as noted, has been implicated in abrogating antitumor activity.[23] Furthermore, IL-2 is involved in activation-induced cell death, a process that leads to the elimination of self-reactive T cells.

Recombinant IL-2, aldesleukin, has been applied in a variety of doses, routes, and schedules.[24-26] Aldesleukin was approved as treatment for patients with metastatic renal cell cancer and melanoma on the basis of experience with the high-dose regimens. Objective responses occur in a minority of patients, approximately 15%, at a cost of significant toxicity. However, in approximately 5% of all treated patients, the response is complete and often of prolonged duration.[24] High-dose IL-2 is also used to support the persistence and activity of tumor-infiltrating lymphocyte (TIL) therapies for melanoma and other malignancies. Administration of aldesleukin requires particular expertise, and patients must be treated in an inpatient monitored or intensive care unit setting, as the use high doses is comparable to inducing a controlled state of septic shock with fever, hypotension, decreased renal function, hyperbilirubinemia, rash, and marked malaise.

KEY POINTS

- Cytokines can function indirectly and can enhance the activity of antitumor immune effectors.
- Cytokines, such as the interferons, also have been shown to directly inhibit tumor cell growth.
- IL-2 was approved and is occasionally used for metastatic renal cell cancer and melanoma on the basis of the experience with a high-dose IV bolus of the agent, a

regimen limited by toxicity and very low antitumor activity.

ANTIBODIES

Adoptive therapy with monoclonal antibodies, which can mediate antitumor activities by a variety of mechanisms (Fig. 4-2), has been one of the major advances in cancer immunotherapy. Most of the approved antibodies in oncology are of the human IgG1 subclass, the subclass that is the most effective at engaging Fc receptors on NK cells and macrophages and mediating CMC and ADCC. Antibody constructs designed not to mediate CMC and ADCC have also been developed, as have antibody-based constructs that target more than one epitope. The monoclonal antibodies used in initial clinical trials were mouse-derived and usually generated a vigorous human–antimouse antibody (HAMA) response. Therapeutic monoclonal antibodies come in the following forms:

- chimeric (i.e.,mouse variable chain fused to a human constant chain, termed “ximab,” and are 65 to 90% human);
- humanized (i.e., mouse hypervariable/complementarity-determining regions grafted to human Ig, termed “zumab,” and are 95% human);
- fully human (termed “umab”).

Most antibodies naturally have long serum half-lives. Limitations, however, have been identified. Triggering of tumor antigen-specific cellular immunity by monoclonal antibody, in conjunction with immune escape mechanisms used by tumor cells, may contribute to differential clinical responses to monoclonal antibody-based immunotherapy.[27] The antigenic heterogeneity of most tumors presents challenges, as do the small fraction of injected antibodies that actually bind to tumors, because of the occasional inability of antibodies to penetrate into large tumor masses. Furthermore, binding of antibodies to circulating antigens also can limit delivery to the tumor. Although now rare, immune responses to artificial humanized antibodies can still be problematic, causing hypersensitivity reactions or neutralization of the antibody. Whether they target tumor cell membrane determinants, factors involved in tumor progression such as angiogenesis, or immune checkpoints, monoclonal antibodies are mainstays of cancer therapy (Table 4-4).

IMMUNE CHECKPOINT ANTIBODIES

Monoclonal antibodies against immune checkpoints resulted in an initial paradigm shift in the management of melanoma and non-small cell lung cancer; more recently, approvals have expanded the clinical application of immune checkpoint antibodies to the treatment of patients with squamous cell carcinoma of the head and neck, clear-cell renal cell carcinoma, Hodgkin lymphoma, and urothelial carcinoma, with additional approvals likely.

Increased activation of the immune system and significant (and occasionally, sustained) antitumor effect has been demonstrated in randomized trials investigating the efficacy of monoclonal antibodies targeting CTLA-4, PD-1, and PD-L1. Conceptually, the mechanisms of these immune checkpoints are not redundant: CTLA-4, a CD28 homolog, is induced by exocytosis upon initial activation of naive T cells, primarily in nodal structures. The PD-1–PD-L1 pathway, however, is implicated in tolerance and evasion mechanisms that involve previously activated T cells with cytotoxic capabilities, acting predominantly but not exclusively in the

effector phase within the tumor microenvironment in peripheral tissues. Nevertheless, the complete spectrum of activity of these immune checkpoint inhibitors is not understood. As an example, the efficacy of CTLA-4 blockade has been associated with the elimination—via ADCC mediated by the anti-CTLA4 antibody—of Tregs with immunosuppressive effects.[28]

Table 4-4 Unconjugated Monoclonal Antibodies in Clinical Use for Cancer

Antibody	Type	Target	Indication
Immune Checkpoint			
Ipilimumab	Human	• Blocks CTLA-4	Melanoma
Pembrolizumab	Human	• Blocks PD-1	Melanoma, squamous cell carcinoma of the head and neck, non-small cell lung cancer, Hodgkin lymphoma, urothelial carcinoma, MMR-deficient solid tumors
Nivolumab	Human	• Blocks PD-1	Melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, MMR-deficient advanced colorectal cancer
Atezolizumab	Humanized	• Blocks PD-L1	Non-small cell lung cancer, urothelial carcinoma
Avelumab	Human	• Blocks PD-L1	Merkel cell carcinoma, urothelial carcinoma
Durvalumab	Human	• Blocks PD-L1	Urothelial carcinoma
Antitumor Antibodies			
Rituximab	Chimeric	• Binds CD20 • CMC/ADCC • Direct antiproliferative	Follicular lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia
Ofatumumab	Human	• Binds CD20 • CMC/ADCC • Direct antiproliferative	Chronic lymphocytic leukemia
Obinutuzumab	Humanized	• Binds CD20 • Mediates antibody-dependent cellular mechanisms • Direct antiproliferative	Chronic lymphocytic leukemia, follicular lymphoma
Alemtuzumab	Humanized	• Binds CD52 • CMC/ADCC	Chronic lymphocytic leukemia
Daratumumab	Human	• Binds CD38 • CMC/ADCC	Multiple myeloma
Elotuzumab	Humanized	• Targets SLAMF7 • Immunostimulatory effect	Multiple myeloma
Anti-epidermal Growth Factor Family			
Trastuzumab	Humanized	• Binds HER2 • CMC/ADCC • Direct antiproliferative • Antiangiogenesis	Breast cancer, gastroesophageal cancer, gastric cancer
Pertuzumab	Humanized	• Binds HER2 and blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4 • Direct antiproliferative effects • CMC/ADCC • Antiangiogenesis	Breast cancer
Cetuximab	Chimeric	• Binds EGFR • CMC/ADCC • Direct antiproliferative • Antiangiogenesis	Colorectal cancer, head and neck cancer
Panitumumab	Human	• Binds EGFR • CMC/ADCC • Direct antiproliferative • Antiangiogenesis	Colorectal cancer
Necitumumab	Human	• Binds EGFR • Direct antiproliferative • Antiangiogenesis	Squamous non-small cell lung cancer
Antiplatelet-Derived Growth Factor			
Olaratumab	Human	• Binds PDGFR • Direct antiproliferative	Soft-tissue sarcomas
Angiogenic Factor			
Bevacizumab	Humanized	• Binds VEGF • Antiangiogenesis	Colorectal cancer, nonsquamous non-small cell lung cancer, renal cell carcinoma, glioblastoma, ovarian cancer, cervical cancer
Ramucirumab	Human	• Binds VEGF receptor 2 • Antiangiogenesis	Gastric or gastroesophageal junction adenocarcinoma, colorectal cancer, non-small cell lung cancer

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; CMC, complement-mediated cytotoxicity; CTLA-4, cytotoxic T-lymphocyte antigen 4; EGFR, epidermal growth factor receptor; MMR, mismatch repair; VEGF, vascular endothelial growth factor; PD-1, programmed death 1; PDGFR, platelet-derived growth factor; PDL-1, programmed death ligand 1.

Despite the unequivocal efficacy, toxicity from immune checkpoint inhibitors can be problematic and results from activation of the immune cells against “self” antigens. These immune-related adverse events (irAEs), include dermatitis, pruritus, colitis/diarrhea, hepatitis, pneumonitis, and endocrinopathies (thyroiditis, hypophysitis, adrenalitis, etc.), among others.[110] Virtually any organ or tissue can be targeted by activated immune cells, and cases of Guillain–Barré syndrome, nephritis, pure red cell aplasia, and myocarditis have been reported. Because

of the potentially serious and life-threatening implications of irAEs, including colonic perforation, Stevens–Johnson syndrome, and myocarditis, active surveillance, and continuous monitoring is advised, and risk evaluation and mitigation strategies and algorithms for the management of adverse side effects have been developed. In general, toxicities are more pronounced with ipilimumab in comparison to monoclonal antibodies targeting PD-1/PD-L1 when used as single agents, particularly colitis/diarrhea, fatigue, rash, and hepatitis. Doses are generally withheld for any moderate irAE or for symptomatic endocrinopathy. The management of symptomatic or severe irAEs usually involves the use of systemic corticosteroids (prednisone, methylprednisolone, or equivalent) and, for patients with irAEs that fail to resolve with steroids, additional immunosuppressive agents (e.g., infliximab [anti-TNF], mycophenolate mofetil [an inhibitor of purine synthesis]). Permanent treatment discontinuation must be considered in situations of a persistent grade 2 or grade 3 irAE and is usually recommended in the setting of a grade 4 irAE. It is important to highlight that the appropriate management of immune-related side effects with immunosuppressive agents, such as corticosteroids, does not appear to impair an established antitumor response, but steroid therapy prior to beginning immune checkpoint blockade is not advised.

The particularities involved in the clinical use of corticosteroids extend beyond the plethora of adverse events. The unique mechanisms of action of immune checkpoint inhibitors makes the assessment of response by conventional criteria difficult, and aberrant patterns of response have been documented. Patients receiving either anti-CTLA-4 or anti-PD-1/PD-L1 agents may experience delayed responses or durable stable disease even after apparent disease progression. Although the immune-related response criteria (irAE) have been proposed, the applicability and, more importantly, interpretation in clinical practice remain challenging. [20] As a general principle, although infrequent, the possibilities of early or delayed pseudoprogression (i.e., initial enlargement of target lesions and/or appearance of new lesions, followed by subsequent response) must be considered, and treatment beyond the first documented progression may be acceptable in select situations, particularly in the setting of clinical stability or symptomatic improvement.

Ipilimumab

Ipilimumab, the first immune checkpoint inhibitor approved by the FDA, blocks the effects of the negative T-cell regulator CTLA-4 (Fig. 4-1), which then, in turn, augments T-cell responses to tumor cells. It was the first drug shown to improve overall survival in metastatic melanoma in randomized clinical trials in both pretreated (as monotherapy) and treatment-naive (in combination with dacarbazine) patients.[29,30] Objective response rates have been low, on the order of 10 to 15%; nevertheless, long-lasting responses have been demonstrated: in a combined analysis of more than 1800 patients treated with ipilimumab in phase 2 and phase 3 trials, long-term overall survival rates of approximately 20% were demonstrated, with an apparent plateau in the survival curves beyond 3 years.[31] Ipilimumab is FDA-approved for the treatment of melanoma, not only in the metastatic setting but also in the adjuvant setting, where it has been shown to improve relapse-free and overall survival.[32]

Ipilimumab is administered intravenously over 90 minutes every 3 weeks for 4 doses, with additional maintenance doses every 12 weeks for up to 3 years when used in the adjuvant setting. Nevertheless, the optimal dose recommended for patients with advanced disease remains debatable, in view of a randomized trial that demonstrated an improvement in overall survival with a higher dose (10 mg/kg) in comparison to the standard, FDA-approved dose (3

mg/kg).[33] The higher dose was accompanied by an increase in treatment-related adverse events, including grade 3 to 5 adverse events (34.3% vs. 18.5%), and its acceptability for treating metastatic disease remains uncertain.

Ipilimumab has also shown preliminary activity for patients with non-small cell lung, renal cell, and castrate-resistant prostate cancers, but has not been approved for these indications. In addition, the combination of ipilimumab and nivolumab is approved to treat patients with melanoma and is discussed in more detail in the following section.[34,35] Combinations with other immune modulators are also being tested, as are combinations with targeted, cytotoxic, and radiation therapies, to potentially improve the efficacy of therapy.[36]

Pembrolizumab

Pembrolizumab is an IgG4 kappa isotype monoclonal antibody against PD-1 which blocks this major immune checkpoint. Pembrolizumab is approved for the treatment of metastatic melanoma, squamous cell carcinoma of the head and neck, and refractory non-small cell lung cancer. It is also indicated for the treatment in the first-line setting of patients with metastatic non-small cell lung cancer whose tumors express PD-L1 on at least 50% of tumor cells and no sensitizing mutation of the *EGFR* gene or translocation of the anaplastic lymphoma kinase (*ALK*) gene.

Pembrolizumab produced a response rate of 33% among patients with advanced melanoma in a large phase I trial that randomly assigned 655 patients with various prior therapies to a variety of doses and schedules.[37] In a randomized trial, pembrolizumab resulted in improved response rates and 6-month progression-free survival when compared to chemotherapy in ipilimumab-refractory cases[38]; pembrolizumab, administered on two different schedules, also demonstrated significant improvement in 2-year overall survival rates and progression-free survival rates at 6 months when compared to ipilimumab, with a more favorable toxicity profile.[39]

Analyses performed in tumor samples of patients treated in the phase I trial of pembrolizumab studied PD-L1 expression in the tumor as a predictive marker for responsiveness in patients with melanoma.[40] Although these studies suggested that PD-L1 positivity correlated with increased responsiveness, absence of PD-L1 expression did not preclude a clinical response. Pembrolizumab should therefore be considered for patients with melanoma regardless of their PD-L1 status.

In non-small cell lung cancer, the superiority in terms of overall survival of pembrolizumab over docetaxel in previously treated patients with PD-L1–positive tumors was demonstrated in a randomized, phase 3 trial.[41] In addition, pembrolizumab was associated with significantly longer progression-free survival and overall survival and fewer adverse events (grade 3, 4, or 5 treatment-related adverse events, 26.5% vs. 53.3%) in comparison to platinum-based chemotherapy in treatment-naive patients with advanced non-small cell lung cancer and PD-L1 expression on at least 50% of tumor cells.[42] Also in the first-line setting for patients with nonsquamous, non-small cell lung cancer and with no *EGFR* or *ALK* genomic tumor aberrations, pembrolizumab used in combination with carboplatin and pemetrexed resulted in an objective response rate of 55%, compared to 29% with chemotherapy alone, and improved progression-free survival in a randomized, phase 2 study, with a similar incidence of grade 3 or worse treatment-related adverse events.[43]

Although phase III trials are ongoing, pembrolizumab was also approved for patients with recurrent or metastatic head and neck squamous cell carcinoma who have had progression

after platinum-based chemotherapy based on results of a phase Ib trial.[44] Among 60 patients with PD-L1–positive tumors (expression of at least 1% of tumor cells or stroma), objective responses occurred in 8 of 45 evaluable cases (18%); the median duration of response was not reached.[44]

Pronounced activity leading to FDA approval was also documented in classic Hodgkin lymphoma,[45] urothelial carcinoma refractory to platinum-based chemotherapy,[46] and solid tumors with microsatellite instability–high (MSI-H) or mismatch-repair deficiency (dMMR). Of note, the biomarker-directed use of pembrolizumab for this latter subgroup of patients is supported by the results of at least five single-arm clinical trials that showed an objective response rate of 39.6% among almost 150 patients with MSI-H or dMMR, including those accrued in the pilot trial by Le and colleagues published in 2015.[47]

Pembrolizumab is administered intravenously over 30 minutes every 3 weeks until disease progression or unacceptable toxicity occurs. Its half-life is approximately 26 days. Treatment toxicity has been minimal. The most common toxicities are fatigue, pruritus, rash, diarrhea, and arthralgia. Approximately 10 to 25% of patients experienced grade 3 or 4 toxicity, with significant variability among different indications and trials. Pembrolizumab is being studied in phase III trials as adjuvant therapy after complete resection of high-risk melanoma and in other cancers.

Nivolumab

Nivolumab is a fully human IgG4 PD-1 immune checkpoint inhibitor antibody that selectively blocks the interaction of the PD-1 receptor with its two known programmed death ligands, PD-L1 and PD-L2. In a phase I study, nivolumab was associated with promising antitumor activity and a favorable safety profile for patients with several solid tumors, including advanced melanoma.[48] Nivolumab is approved to treat metastatic melanoma, alone and in combination with ipilimumab. As a single agent, nivolumab is approved in non-small cell lung cancer, renal cell carcinoma, classic Hodgkin lymphoma, and squamous cell carcinoma of the head and neck.

Randomized trials involving patients with ipilimumab-refractory melanoma demonstrated a higher rate of objective responses from nivolumab when compared to chemotherapy.[49] Nivolumab also improved overall survival when compared to dacarbazine among untreated patients with melanoma who did not have a *BRAF* mutation.[50] Nivolumab has been approved for use in combination with ipilimumab, as discussed in other sections. This combination is associated with greater toxicity than either ipilimumab or nivolumab alone.

Nivolumab was approved for patients with advanced squamous cell non-small cell lung cancer whose disease has progressed on or after platinum-based chemotherapy, irrespectively of PD-L1 expression, based on a randomized trial that demonstrated improved overall survival and a nearly doubled 12-month overall survival rate (42% vs. 24%) compared to docetaxel.[51] Nivolumab also has been shown to improve survival over docetaxel in advanced nonsquamous non-small cell lung cancer.[52] In both trials, the use of nivolumab was associated with a favorable toxicity profile when compared to standard chemotherapy.

In November 2015, the FDA approved nivolumab to treat patients with advanced/metastatic renal cell carcinoma. The safety and efficacy of nivolumab were demonstrated in a randomized, phase 3 study that compared nivolumab to everolimus in 821 patients with advanced clear cell renal cell carcinoma whose disease progressed on prior antiangiogenic therapy.[53] Both overall survival and objective response rate (25% vs. 5%; odds ratio, 5.98; 95% CI; 3.68, 9.72; $p < 0.001$) were improved.

Nivolumab has also been approved for recurrent or metastatic SCCHN based on overall survival improvements demonstrated in a randomized, phase 3 trial.[54] In addition to prolonged overall survival and a higher 1-year survival rate (36% vs. 16.6%), nivolumab resulted in a lower incidence of treatment-related grade 3 or 4 adverse events (13.1% vs. 35.1%) when compared to standard-therapy (methotrexate, docetaxel, or cetuximab) in patients whose disease had progressed within 6 months after platinum-based chemotherapy.[54]

Nivolumab was the first immune checkpoint inhibitor to be incorporated into the management of hematologic malignancies. The approval for the treatment of patients with classic Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation and brentuximab vedotin was based on single-arm, multicenter trials that demonstrated response rates of 66 to 87%.[55,56]

Subsequently, the indications of nivolumab have been expanded to other solid tumors. In metastatic urothelial carcinoma following platinum-based therapy, objective responses occurred in 52 of 265 patients (objective response rate, 19.6%), including 23 of 81 patients (28.4%) with a PD-L1 expression of at least 5% and a median duration of response not yet reached.[57] The most recent approval was for patients with metastatic colorectal cancer and DNA mismatch repair–deficient tumors or tumors harboring microsatellite instability. In a phase 2 study that accrued 74 pretreated individuals with the previously described characteristics, nivolumab resulted in an objective response rate of 31.1%, with 51 of 74 (64%) achieving disease control for 12 weeks or longer.[58]

Nivolumab is administered intravenously over 60 minutes every 2 weeks until disease progression or unacceptable toxicity occurs; the FDA modified the dosage regimens for the currently approved indications to a flat dose of 240 mg IV, and a new regimen of 480 mg administered every 4 weeks is under evaluation. Nivolumab's half-life is approximately 27 days. The spectrum of toxicity of nivolumab is comparable to that of pembrolizumab. Again, irAEs are less frequent than with ipilimumab; the most serious of these include pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, and thyroid dysfunction.

Nivolumab is being studied in phase III trials as adjuvant therapy after complete resection of high-risk melanoma. It is anticipated that additional approvals will be forthcoming for several cancers.

Atezolizumab

Atezolizumab is a humanized monoclonal antibody that blocks the PD-L1 protein on tumor cells, disrupting the PD-1–PD-L1 checkpoint pathway. Atezolizumab is currently approved for the treatment of patients with non-small cell lung cancer that has progressed after platinum-based chemotherapy (and targeted therapy against *EGFR* or *ALK* genomic aberrations, in patients with tumors harboring these target mutations), as well as for advanced bladder cancer.

This anti-PD-L1 agent was initially approved for the treatment of patients with urothelial carcinoma previously treated with a platinum-containing regimen. In a single-arm, phase 2 trial, atezolizumab produced objective responses in 15% of the cases in a preliminary analysis, reaching 26% with longer follow-up.[59] Of note, grade 3 or 4 treatment-related adverse events occurred in 16% of the patients, with fatigue being the most common. Atezolizumab was also investigated as first-line treatment for patients with advanced urothelial carcinoma that is ineligible for platinum-based therapies, resulting in durable response rates, good tolerability, and a median overall survival of 15.9 months.[60]

Following a breakthrough therapy designation by the FDA based on preliminary results, a

randomized, phase III trial confirmed the superiority of atezolizumab when compared to docetaxel in patients with previously treated non-small cell lung cancer.[61] Among patients with both squamous and nonsquamous lung cancer, atezolizumab resulted in prolonged overall survival and fewer grade 3 or 4 adverse events regardless of PD-L1 expression or histology.

Avelumab

Avelumab is a fully human anti–PD-L1 IgG1 antibody. In 2017, avelumab was granted accelerated approval by the FDA and became the first systemic therapy approved for the treatment of patients with advanced Merkel cell carcinoma (MCC). This agent was evaluated in an open-label, single-arm, phase 2 study that included 88 patients with advanced MCC refractory to cytotoxic chemotherapy.[62] Among 28 patients with objective responses, resulting in an objective response rate of 31.8%, there were 8 complete responses. The proportion of responses with a duration of at least 6 months was 92%, with a median duration of response not reached. Of note, only five grade 3 treatment-related adverse events were reported (5%) and there were no grade 4 adverse events or treatment-related deaths.[62] Avelumab has also been approved for the treatment of patients with advanced urothelial carcinoma who progressed on a platinum-based therapy.[63]

The recommended dose of avelumab is 10 mg/kg administered intravenously over 60 minutes every 2 weeks, and patients should be premedicated with acetaminophen and an antihistamine for the first four infusions and subsequently as needed because of the risk of infusion-related reactions, which can manifest in up to 25% of the patients.

Durvalumab

The fully human, anti–PD-L1 human monoclonal antibody durvalumab received accelerated FDA approval for the treatment of patients chemotherapy-refractory disease with advanced urothelial carcinoma. In the preliminary publication of the phase I/II multicenter, open label trial that subsequently supported the approval, 61 patients with advanced bladder cancer were treated with durvalumab; the incidence of grade 3 treatment-related adverse events was 4.9%, and there were no grade 4 or 5 toxicities. The objective response rate was 31% in the entire evaluable study population, and 46.4% among those with PD-L1 expression of at least 25% in tumor cells or tumor-infiltrating immune cells by immunohistochemistry.[64] The recommended dose of durvalumab is 10 mg/kg administered intravenously over 60 minutes every 2 weeks, without premedication.

Combinations of Immune Checkpoint Inhibitors

The combination of ipilimumab and nivolumab is also approved for clinical use in patients with advanced melanoma. In two randomized trials, the combination demonstrated superior response rates and progression-free survival in comparison to ipilimumab.[34,35] Exploratory analysis also demonstrated that patients whose tumors expressed low PD-L1 levels benefited from the combination over nivolumab alone, but because of the limited size, unplanned retrospective subset analysis, and technical limitations of current methods for PD-L1 testing, the use of this marker to select therapy is not advised. The combination also had a significant increase in the incidence of immune-mediated adverse events requiring experience and very close communication between the treating physician, the patient, and other members of the health care team to offer this highly active regimen to patients with advanced melanoma. Long-

term results and data regarding overall survival, as well as the identification of predictors that will allow patients to be selected for single or combined therapy, are awaited, and clinical trials are ongoing for immunomodulators that will enhance antitumor activity with less immune-related toxicity. The same combination with different doses and intervals of therapy is being investigated in patients with non-small cell lung cancer, breast cancer, head and neck carcinoma, and other solid tumors and hematologic malignancies.

Despite the advances achieved with the use of immune-checkpoint blockade, disease progression develops in a significant proportion of patients as a result of mechanisms involved in primary and secondary resistance. Although these mechanisms are yet to be properly characterized, their understanding may pave the way for a rational development of combinations and treatment sequencing in the near future.

KEY POINTS

- Immunologic checkpoint blockade with antibodies against CTLA-4 and PD-1 is an effective method for reversing cancer immunosuppression and promoting immune responses against several cancer types.
- Checkpoint inhibition is associated with a unique spectrum of side effects called irAEs, which include dermatologic, gastrointestinal, hepatic, endocrine, and other less common inflammatory events.
- The patterns and kinetics of response to immune checkpoint inhibitors can differ from those observed with conventional cytotoxic chemotherapy or targeted therapy.
- The clinical applications of anti–PD-1 and anti–PD-L1 agents continue to expand.
- The combination of immune checkpoint inhibitors may result in improved response rates and disease control at a cost of greater toxicities; nevertheless, long-term effects and the impact on survival are still unknown.

MONOCLONAL ANTIBODIES THAT DIRECTLY TARGET THE TUMOR

Rituximab

The first monoclonal antibody to receive FDA approval for therapeutic use was rituximab, a human/mouse chimeric IgG1 directed to CD20, a transmembrane protein expressed on malignant and normal B cells. CD20 is expressed on more than 90% of cells in B-cell non-Hodgkin lymphoma and to a lesser degree on chronic lymphocytic leukemia (CLL) cells. CD20 function is not established. The intracellular portion of CD20 contains phosphorylation sites for signaling kinases. It may affect the cell cycle through calcium-channel regulation. The cytotoxic effects of rituximab appear to involve CMC, ADCC, and induction of apoptosis.

Rituximab is approved for the treatment of CD20-positive non-Hodgkin lymphoma (low-grade or follicular B-cell and diffuse large B-cell) and CLL. Dosing of rituximab is dependent on the clinical setting. Rituximab is usually administered IV for 4 or 8 doses weekly. Manageable infusion-related reactions occur for the majority of patients, thus premedication with acetaminophen and diphenhydramine is recommended. Mild to moderate flulike symptoms are also common. Severe infusion reactions, such as bronchospasm and hypotension, occur in 10%

of patients and are usually reversible with appropriate interventions. Transient hypotension may occur; therefore, withholding antihypertensives 12 hours before infusion should be considered. To address infusion reactions, the initial infusion is administered slowly. If hypersensitivity or infusion-related events do not occur, the infusion rate is increased incrementally. Subsequent infusions also are administered more slowly initially, with incremental rate increases. The incidence of hypersensitivity reactions decreases markedly with subsequent infusions. Rituximab can elicit a tumor lysis syndrome. It also induces B-cell lymphopenia, which lasts for approximately 6 months. Full recovery occurs in 9 to 12 months. CD20 is not expressed on hematopoietic stem cells. Rituximab therapy has been associated with reactivation of hepatitis B and with progressive multifocal leukoencephalopathy due to opportunistic viruses, including the JC papovavirus.[65,66] Screening patients for hepatitis B prior to therapy is recommended. Antiviral therapy and comanagement with infectious disease specialists are recommended for patients with serologic evidence of virus.[67] When used in combination with a variety of chemotherapeutic regimens, rituximab does not add to the toxicity of chemotherapy, with the exception of a slightly higher rate of neutropenia. This does not, however, translate into a higher infection rate.[68] Laboratory assays are being developed to identify patients who are likely to have a response to rituximab, including assays of Fc receptor polymorphisms and tumor apoptotic regulators.[69]

Ofatumumab

Ofatumumab is a human IgG1 monoclonal antibody also directed against the CD20 protein currently approved for the treatment of patients with recurrent or progressive CLL. Ofatumumab targets an epitope different from that for rituximab and most other CD20-directed antibodies. Ofatumumab binds to both the small and large loops of the CD20 molecule on B cells. Its location is in closer proximity to the membrane, which in theory allows for more effective complement deposition and subsequent B-cell killing. Preclinical data suggest improved CMC and ADCC compared with rituximab. Direct effects on B-cell proliferation have also been demonstrated.

Ofatumumab is administered as an IV infusion weekly for the first 8 doses, then every 4 weeks for the remaining 4 doses. The first dose of ofatumumab is reduced (300 mg) to lessen the risk of serious infusion reactions; all subsequent doses are 2000 mg. Ofatumumab can be used in combination with fludarabine and cyclophosphamide for relapsed CLL. Infusion reactions can be problematic, and premedication with a PO or IV antihistamine, PO acetaminophen, and an IV corticosteroid prior to each dose is recommended. In addition to infusion reactions, which occurred in 44% of patients with the first infusion and 29% with the second infusion, adverse reactions have included infections, neutropenia, and pyrexia. The most serious side effect of ofatumumab is an increased chance of infections. Progressive multifocal leukoencephalopathy is a rare but also serious side effect. As with rituximab, screening of patients for hepatitis B and comanagement with infectious disease specialists for patients who test positive are recommended.

Obinutuzumab

Obinutuzumab is a humanized, type II CD20 monoclonal antibody that has been glycoengineered to reduce core fucosylation, conferring enhanced affinity for the human FcγRIIIa receptor on effector cells and, hence, enhanced ADCC. As a type II monoclonal antibody, obinutuzumab has lower capacity to relocalize CD20 into lipid rafts upon binding

compared with the type I antibodies rituximab and ofatumumab and is less potent in inducing CMC. It is, however, more potent in mediating cell adhesion and direct cell death. Obinutuzumab and rituximab bind adjacent and partially overlapping epitopes on CD20 but acquire different orientation upon binding, which most likely contributes to different biologic characteristics of type I and II antibodies. In preclinical studies, obinutuzumab showed superior induction of direct cell death and enhanced ADCC with less CMC compared to rituximab.

Obinutuzumab has been approved for the treatment of patients with rituximab-refractory follicular lymphoma and in combination with chlorambucil for CLL. Premedication with glucocorticoid, acetaminophen, and antihistamine is recommended. The FDA-approved regimen for treatment of CLL is obinutuzumab as outlined above in combination with chlorambucil on days 1 and 15 of each cycle; in patients with refractory non-Hodgkin lymphoma, obinutuzumab is used in combination with bendamustine, followed by obinutuzumab monotherapy.[70] The most common adverse reactions with obinutuzumab in combination with chlorambucil were infusion-related reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, and musculoskeletal disorders. As with other CD20 targeted antibodies, hepatitis B virus reactivation and progressive multifocal leukoencephalopathy are also risks that require surveillance and treatment, including screening for hepatitis B as for the other B-cell–directed antibody therapies.

Alemtuzumab

Alemtuzumab is a humanized IgG1 directed against CD52, a nonmodulating glycoprotein expressed on the surface of normal and malignant B cells, including the malignant B cells of CLL. It is also expressed on T cells, NK cells, monocytes, macrophages, and tissues of the male reproductive system. CD52 function is unknown. The cytotoxic effects of alemtuzumab are presumed to involve ADCC and CMC mechanisms.

Alemtuzumab is approved for the treatment of CLL, cutaneous T-cell lymphoma, and T-cell lymphoma. Alemtuzumab administration can be limited by infusion-related toxicities such as hypotension, rigors, fever, dyspnea, bronchospasm, chills, and/or rash. Premedication with diphenhydramine and acetaminophen before infusion is recommended, as is hydrocortisone if infusion-related events occur. Alemtuzumab induces profound B- and T-cell lymphopenia, and a variety of opportunistic infections have been reported.[71] Severe and prolonged myelosuppression also can occur. Infection prophylaxis, trimethoprim–sulfamethoxazole for pneumocystis prophylaxis, and famciclovir (or its equivalent) for herpetic infections are necessary and must be continued for 2 months after completion of therapy or until CD4 cell counts are greater than 200, whichever occurs later. Alemtuzumab is also being tested as part of the conditioning regimens for allogeneic hematopoietic stem cell transplantation (HSCT) to support engraftment.

Daratumumab

Daratumumab is a human IgG1k monoclonal antibody that targets CD38, a protein that is overexpressed in multiple myeloma cells. Daratumumab binds to CD38, resulting in complement-dependent and antibody-dependent cell-mediated cytotoxic effects.

Daratumumab was initially approved as single agent for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy; in November 2016, the FDA expanded the indication of daratumumab in combination with lenalidomide or bortezomib and dexamethasone for the treatment of patients with refractory multiple myeloma

and at least one prior therapy.[72-74]

As a single agent, daratumumab is administered intravenously at 16 mg/kg weekly for 8 weeks, and then less frequently. Most common toxicities include infusion reactions, fatigue, nausea, pyrexia, and respiratory symptoms. Pre- and postinfusion medications (acetaminophen, steroids, and antihistamines) are advised to prevent infusion reactions. Daratumumab is associated with anemia, lymphopenia, neutropenia, and thrombocytopenia. Prophylaxis for herpes zoster reactivation is also recommended.

Elotuzumab

Elotuzumab is an immunostimulatory humanized IgG1k monoclonal antibody targeting the signaling lymphocytic activation molecule F7 (SLAMF7), a cell-surface glycoprotein involved in inhibitory signaling of NK cells. SLAMF7 is expressed on multiple myeloma (MM) cells, NK cells, plasma cells, and subsets of cells of hematopoietic lineage. Binding of elotuzumab to the extracellular domain SLAMF7 results in antitumor activity against MM cells through antibody-dependent cellular cytotoxicity and lysis of tumor cells through the activation of NK cells. Elotuzumab is currently approved by the FDA for use in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma in whom prior therapies have failed.[75]

The recommended dose of elotuzumab is 10 mg/kg intravenously every week for the first two cycles and every 2 weeks thereafter, in combination with lenalidomide and dexamethasone. The most frequent adverse events include lymphopenia, neutropenia, fatigue, pyrexia, peripheral neuropathy, respiratory symptoms, upper respiratory tract infection, and pneumonia. Infusion reactions and hepatotoxicity may also occur.

Trastuzumab

Trastuzumab is a humanized IgG1 directed against the extracellular domain of HER2, also known as ErbB2, a member of the epidermal growth factor (EGF) family of receptor tyrosine kinases. HER2 may be overexpressed by breast, gastroesophageal, and many other cancers. Overexpression is implicated in the malignant transformation process, is an independent adverse prognostic factor in breast cancer, and may predict response to both chemotherapy and hormonal agents, depending on other characteristics of the tumor cells. Trastuzumab exerts antitumor effects by several mechanisms that are not yet completely understood. Immune effector mechanisms, namely ADCC and CMC, are considered to be central. Trastuzumab has direct antiproliferative effects, which include cell-cycle arrest and/or induction of apoptosis; it markedly accelerates HER2 endocytosis and degradation. Trastuzumab also can mediate antiangiogenic effects, including the inhibition of VEGF production.

Trastuzumab is approved for use in breast, gastric, and gastroesophageal junction cancers. It is administered IV, with an initial loading dose followed by weekly administration. Other regimens, such as dosing every 3 weeks, also have been effectively applied. Trastuzumab is generally well tolerated. Infusion reactions do occur, but premedication is usually not required. Cardiac dysfunction may be problematic. It was observed in almost 30% of patients who received an anthracycline and cyclophosphamide; thus, concurrent therapy with anthracyclines is not recommended. Cardiac dysfunction also has been observed in approximately 15% of patients receiving trastuzumab plus paclitaxel and in approximately 5% of patients receiving trastuzumab alone. Patients should undergo monitoring for decreased left ventricular function before trastuzumab treatment and frequently during and after treatment.

Ado-trastuzumab emtansine (TDM-1), a HER-2-targeted antibody-drug conjugate of trastuzumab and mertansine, a microtubule inhibitor, is also approved for the treatment of patients with HER2-positive, advanced breast cancer as single agent.

Pertuzumab

Pertuzumab targets the extracellular dimerization domain (subdomain II) of HER2 and thereby blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGF receptor (EGFR), HER3, and HER4. Pertuzumab was the first drug approved in the breast cancer neoadjuvant treatment setting. Approval was based on the pathologic complete response rate, defined as the absence of invasive cancer in the breast and lymph nodes, observed in a phase II study involving women with early HER2-positive breast cancer who were randomly assigned to receive to one of four neoadjuvant treatment regimens.[76]

Pertuzumab is administered IV; an initial loading dose is administered, followed by infusions every 3 weeks. Its half-life is approximately 3 weeks. There are specific dosing recommendations for drugs, such as trastuzumab and docetaxel, when administered with pertuzumab. The most common adverse reactions observed among patients who received pertuzumab in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy. Cardiac dysfunction can occur; however, pertuzumab in combination with trastuzumab and docetaxel was not associated with increases in the incidence of symptomatic left ventricular systolic dysfunction or decreases in left ventricular ejection fraction compared with placebo in combination with trastuzumab and docetaxel. Other significant adverse reactions reported with pertuzumab included infusion-associated reactions, hypersensitivity reactions, and anaphylaxis.

Cetuximab

Cetuximab is a human/mouse chimeric IgG1 to the extracellular domain of the EGFR, also known as ErbB1. It is approved for treatment of colorectal cancer and squamous cell carcinoma of the head and neck. Cetuximab competitively inhibits the binding of EGF and other ligands, such as TGF-alpha. It blocks activation of receptor-associated kinases, resulting in inhibition of cell growth, apoptosis, and decreased VEGF and matrix metalloproteinase production. EGFR is expressed in many normal epithelial tissues, such as skin. Many different human carcinomas overexpress EGFR, including colorectal and head and neck cancers. EGFR protein overexpression, which can be accompanied by gene amplification, or copy number gains, is associated with a negative prognosis across different cancers. In animal studies, cetuximab inhibited tumor cells that overexpress EGFR as well as increased the activity of chemotherapy and radiation. The presence of mutations in the *KRAS* oncogene, which encodes a signal transducer that mediates response to stimulation of cell-surface receptors, including EGFR, has been associated with lack of response to cetuximab.[77] *KRAS, NRAS,* and *BRAF* testing is recommended for all patients with metastatic colorectal cancer who are candidates for anti-EGFR antibody therapy, and it is recommended that patients with *KRAS, NRAS,* or *BRAF* mutations should not receive anti-EGFR antibody therapy.[78]

Cetuximab is administered IV; an initial loading dose is administered, followed by weekly infusions. The plasma half-life is approximately 5 days. Every-other-week infusions have also been used. In general, cetuximab has been well tolerated. Infusion reactions do occur and can be severe, particularly with the initial infusions, and premedication with diphenhydramine is recommended. The most common side effect has been an acnelike skin rash, which develops in

up to 75% of patients and which probably represents the biologic effects of the blocking EGFR present in the skin. The rash develops rapidly following cetuximab initiation, peaks between weeks 2 and 4, and thereafter tends to steadily abate in severity with continuation. The development of a rash has been associated with greater therapeutic effectiveness.[79] Life-threatening toxicities, such as interstitial lung disease, have been observed rarely.

Panitumumab

Panitumumab is a recombinant, human IgG2 monoclonal antibody that also binds specifically to EGFR with identical target specificity to that of cetuximab. IgG2 is less efficient than IgG1 in mediating ADCC. In contrast to cetuximab, panitumumab is fully human. The theoretical advantage conferred by this agent, compared with its chimeric counterpart, is that there is less potential for an antigenic response against the therapeutic antibody, since panitumumab is fully human. The antitumor effects are considered to be identical to those of cetuximab. Efficacy has been confined to patients whose tumors do not express *KRAS* mutations.[80] Panitumumab is administered IV, without a loading dose, every 14 days. As was predicted, the development of human antihuman antibodies has not been detected with treatment. Approximately 1% of patients exposed to panitumumab, however, experienced severe infusion reactions, whereas approximately 3% of patients treated with cetuximab experienced severe infusion reactions. Other toxicities appear to be similar. Skin rash with variable presentation is common. An association between the development of rash and response has also been suggested. Rare but serious adverse events, such as pulmonary fibrosis, have been observed. Anecdotal reports have suggested that patients whose disease is considered intolerant to cetuximab may be safely treated with panitumumab, but their disease is not considered non–cross-resistant, so antitumor activity cannot be rescued with a switch in antibodies. Panitumumab was approved on the basis of a phase III trial in which patients with metastatic colorectal cancer were randomly assigned to receive either panitumumab with best supportive care or best supportive care alone.[81] No patients who had been previously treated with cetuximab were included, and in a randomized comparison trial, panitumumab and cetuximab demonstrated similar antitumor activity and toxicity.

Necitumumab

Necitumumab is a recombinant, fully human IgG1 monoclonal antibody directed against the extracellular region of EGFR that blocks the binding of EGFR to its ligands, also leading to ADCC. In preclinical models, necitumumab resulted in EGFR binding activity similar to that of cetuximab, both IgG1 class antibodies, and higher than that of panitumumab, an IgG2 class antibody with less pronounced ADCC activity. The FDA granted approval to necitumumab in combination with gemcitabine and cisplatin for first-line treatment of patients with metastatic squamous non-small cell lung cancer. In a randomized, phase III trial, the addition of necitumumab to chemotherapy resulted in longer overall survival.[82]

Necitumumab 800 mg (absolute dose) is administered intravenously over 60 minutes on days 1 and 8 of 21-day cycles. The most common adverse events include skin rash and hypomagnesemia. Cardiopulmonary arrest and/or sudden death (3%) have been reported in patients receiving necitumumab. Close monitoring of serum electrolytes is recommended.

Olaratumab

Olaratumab is a recombinant human monoclonal antibody against platelet-derived growth factor receptor alpha (PDGFRα), a receptor tyrosine kinase expressed on mesenchymal cells involved in cell growth, chemotaxis, and differentiation. Olaratumab is indicated for use in combination with doxorubicin in patients with advanced soft-tissue sarcomas not amenable to curative treatment, and it was the first therapy approved by the FDA for the treatment of soft-tissue sarcomas in the first-line setting in more than four decades. Approval was based on results of an open-label, phase Ib and a randomized phase II trial that included patients with diverse soft-tissue sarcomas not previously treated with an anthracycline.[83] In comparison to doxorubicin alone, the addition of olaratumab to doxorubicin resulted in prolongation of both progression-free survival and overall survival. A phase III trial of olaratumab in combination with doxorubicin has been completed and results are awaited.

Olaratumab is administered intravenously at 15 mg/kg on days 1 and 8 of each 21-day cycle in combination with doxorubicin on day 1 for up to eight cycles, and then as single agent until disease progression or unacceptable toxicity occurs. Most common adverse events include nausea, vomiting, diarrhea, fatigue, lymphopenia, neutropenia, mucositis, neuropathy, decreased appetite, and abdominal pain. Infusion reactions can occur, and premedication with diphenhydramine and dexamethasone is recommended.

KEY POINTS

- The effectiveness of monoclonal antibodies has been established for both hematologic malignancies and solid tumors.
- Targets have included tumor cell membrane determinants and factors involved in tumor progression.
- Monoclonal antibodies can mediate antitumor activity via immune mechanisms (e.g., antibody-dependent and complement-mediated cellular mechanisms) and by nonimmunologic mechanisms (e.g., direct induction of apoptosis).
- Although active as single agents in some cases, monoclonal antibodies are most often administered with chemotherapy or radiation therapy.
- Because of infusion reactions, premedication is required for treatment with many monoclonal antibodies, particularly those that are used to treat hematologic diseases.
- Unique and often severe organ toxicity related to the molecule being targeted can be seen.

ANTIANGIOGENIC ANTIBODIES

Bevacizumab

Bevacizumab is humanized IgG1 directed against vascular endothelial growth factor (VEGF). Often overexpressed by tumor cells as well as by tumor-associated macrophages, VEGF has proven to be a pivotal stimulator of endothelial cell development and angiogenesis. Bevacizumab binds the VEGF isoform and prevents the interaction with its receptors (Flt-1 and KDR) on endothelial cells. Bevacizumab has been shown to inhibit new blood vessel formation in in vitro models and to reduce tumor vascularity and progression in in vivo animal tumor

models. Bevacizumab has been shown to have a direct and rapid antivascular effect in the tumors of patients with colorectal cancer.[84] Most of bevacizumab's indications (colorectal cancer, lung cancer, ovarian cancer, cervical cancer) are in combination with chemotherapy. Bevacizumab is also approved in combination with interferon-alphaa for the treatment of patients with metastatic renal cell carcinoma and as a single agent or in combination with irinotecan for the treatment of patients with glioblastoma, although it is rarely used now for either indication because of its toxicity and low antitumor activity.[85]

Bevacizumab is administered intravenously every 14 days. The plasma half-life is approximately 20 days (free plus bound to circulating VEGF). Clinical toxicities include hemorrhagic complications, which are more common among patients with squamous cell histology non-small cell lung cancer than with adenocarcinoma. Other important toxicities also include hypertension, proteinuria, gastrointestinal perforations, thrombohemorrhagic events, and wound healing complications that make it advisable to avoid bevacizumab for several weeks prior to any major surgical procedure and to delay its administration until the surgical incisions are fully healed. Administration also should be suspended several weeks prior to elective surgery. Hypertensive crisis, nephrotic syndrome, and congestive heart failure have been observed. Bevacizumab must be suspended for patients with gastrointestinal perforation, wound dehiscence, serious bleeding, nephrotic syndrome, or hypertensive crisis. The risk of continuation or temporary suspension for patients with moderate to severe proteinuria is unknown. Infusion reactions are relatively uncommon. Other rare complications, including a reversible posterior leukoencephalopathy syndrome, have been observed among patients treated with bevacizumab.[86]

Ramucirumab

Ramucirumab is a monoclonal antibody that binds to VEGF receptor 2 (VEGFR-2) and blocks the activation and downstream signaling mediated by the receptor. It is the first biologic treatment given as a single drug that has survival benefits for patients with advanced gastric or gastroesophageal junction adenocarcinoma that progressed after first-line chemotherapy.[87] Ramucirumab is also approved for use in combination with paclitaxel for advanced gastroesophageal junction adenocarcinoma following prior fluoropyrimidine- or platinum-containing chemotherapy, in combination with folinic acid, fluorouracil, and irinotecan (FOLFIRI) for patients with advanced colorectal cancer whose disease progressed while on prior bevacizumab- and oxaliplatin-containing regimens (second-line setting) and in combination with docetaxel for patients with metastatic non-small cell lung cancer with disease progression following platinum-based chemotherapy.

Ramucirumab is administered by IV infusion every 2 weeks. Premedication with antihistamines is recommended to decrease the risk of infusion-related reactions. Patients who suffer a grade 1 (mild) or 2 (moderate) infusion-related reaction should also be premedicated with acetaminophen and dexamethasone or its equivalent before each infusion, and the infusion rate should be slowed by 50%. The most common adverse reactions of ramucirumab are hypertension and diarrhea. Other important risks include hemorrhage, arterial thrombotic events, infusion-related reactions, gastrointestinal perforation, impaired wound healing, clinical deterioration among patients with cirrhosis, and reversible posterior leukoencephalopathy.

BISPECIFIC ANTIBODY THERAPY

A bispecific monoclonal antibody is an artificial protein that is composed of fragments of two

different monoclonal antibodies and consequently binds to two different types of antigen. Bispecific monoclonal antibodies have been developed to simultaneously bind to a cytotoxic cell and to a tumor cell in order to destroy the tumor cell.

Blinatumomab

Blinatumomab belongs to a class of constructed antibodies known as bispecific T-cell engagers (BiTEs). It consists of genetically engineered, murine tandem single-chain variable fragments (scFvs), which are not actually a fragment of an antibody but instead a fusion protein of the variable regions of the heavy- (V_H) and light- (V_L) chains of Igs, connected with a short linker. scFvs lack the antibody Fc domains and thus do not mediate CMC or ADCC. One scFv binds T-cell–specific CD3 and the other B-cell–specific CD19. By targeting CTL against the CD-19–expressing B cells, the T cells become activated within minutes and induce perforin-mediated death to the targeted B cells. In contrast to CD20, CD19 is expressed on the earliest B-precursor lymphocytes that undergo malignant transformation in acute lymphocytic leukemia. Blinatumomab is approved by the FDA for the treatment of Philadelphia chromosome–negative relapsed/refractory B-lineage acute lymphocytic leukemia in adult patients, specifically for eradication of minimal residual disease.[88]

Blinatumomab has a short serum half-life of 1 to 2 hours. As a consequence of the short elimination half-life, blinatumomab is administered as a 4-week continuous IV infusion. Shorter infusion times had also been explored but seemed to result in higher incidences of adverse effects, including neurologic symptoms, such as seizures, and a cytokine-release syndrome—a symptom complex that can be life-threatening and includes fever, nausea, chills, hypotension, tachycardia, headache, rash, and dyspnea that results from the release of cytokines from cells targeted by the antibody as well as immune cells that are recruited.[89] Although blinatumomab was derived from murine sources, HAMA is rare; HAMAs develop in less than 1% of patients during therapy. Absence of the Fc region along with B-cell depletion resulting from therapy are assumed to be the critical components for this low immunogenicity.

KEY POINTS

- The efficacy of antiangiogenic agents, particularly of monoclonal antibodies against VEGF and VEGFR, has been demonstrated in different solid tumors.
- Bowel perforation, hemorrhagic complications, and thromboembolic events may develop in patients receiving antiangiogenic drugs, and treatment suspension is advised in those undergoing surgical procedures.
- Bispecific monoclonal antibodies, such as blinatumomab, have been developed to simultaneously bind to a cytotoxic cell and to a tumor cell in order to destroy the tumor cell.

IMMUNOTOXINS AND RADIOIMMUNOCONJUGATES

Biologic agents have been used to deliver toxins or radiation to malignant cells, as opposed to activating host antitumor mechanisms. Denileukin diftitox is a recombinant immunotoxin consisting of IL-2 fused to the enzymatically active domains of diphtheria toxin. It is internalized

into IL-2–receptor-bearing cells (CD25) by endocytosis. Diphtheria toxin activation is controlled by its intracellular cleavage from the bispecific molecule and then inhibits protein synthesis, leading to apoptosis. Denileukin diftitox is indicated for the treatment of patients with persistent or recurrent CD25+ cutaneous T-cell lymphoma.[90] Cytokine release may occur, the result of the killing of T cells, and can result in capillary leak syndrome. Vision loss has also been observed.

Brentuximab vedotin is an antibody-drug conjugate approved to treat anaplastic large cell lymphoma and Hodgkin lymphoma. The compound consists of the chimeric monoclonal antibody brentuximab, which targets the cell-membrane protein CD30, linked to 3 to 5 units of the antimitotic agent monomethyl auristatin E (MMAE, designated “vedotin”). The antibody portion of the drug attaches to CD30 on the surface of malignant cells, delivering MMAE, which is responsible for the antitumor activity. Brentuximab vedotin is usually well tolerated, with manageable side effects including peripheral sensory neuropathy.[91]

Ado-trastuzumab emtansine, which consists of trastuzumab linked to the cytotoxic agent mertansine, an antitubulin, has demonstrated activity for patients with breast cancer that has not responded to prior treatment with trastuzumab.[92] Although ado-trastuzumab is well tolerated in clinical trials, thrombocytopenia has been reported, and liver and cardiac toxicity can develop. The drug is approved for treatment of advanced breast cancer.

Two mouse monoclonal antibodies to CD20 conjugated to radioisotopes, ^{131}iodine-tositumomab and ^{90}yttrium-ibritumomab, have demonstrated clinical effectiveness for patients with lymphoma. Both are indicated for the treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin lymphoma, with or without transformation, including rituximab-refractory disease. Toxicity is typically quite mild. The main side effect is reversible myelosuppression, and exposure is limited to a single dose because of the radiation exposure as well as to the high incidence of HAMA development.[93,94]

KEY POINTS

- Biologic agents can be engineered to deliver toxins and radiation to malignant cells in the form of immunotoxins and radioimmunoconjugates.
- Examples of effective immunotoxins include brentuximab vedotin, approved for the treatment of patients with anaplastic large cell lymphoma and Hodgkin lymphoma, and ado-trastuzumab, a molecule that incorporates trastuzumab and a cytotoxic agent, used in the treatment of breast cancer.

CELLULAR THERAPY

A distinct immunotherapy approach, termed “adoptive cell therapy,” is to infuse immune cells expanded, engineered or generated ex vivo. A variety of immune effector cells have been explored for adoptive cellular therapy and tested in clinical trials. Early efforts examined the infusion of LAK cells, which had little activity and required the coadministration of high-dose IL-2 to maintain their activity. Initial studies of patients with advanced melanoma and renal cell carcinoma demonstrated antitumor activity. Comparable results, however, were subsequently seen with IL-2 alone. Methods of generating antitumor CTLs by culturing peripheral blood, lymph node, or TILs with cytokines and tumor antigens ex vivo also have been evaluated clinically. Response rates of 50% or more among patients with metastatic melanoma

accompanied by long progression-free survival have been observed with the infusion of TIL in nonrandomized studies.[95] The infusion of T cells that have been genetically modified either with a reprogrammed, recombinant chimeric antigen receptor (CAR) or with an engineered TCR have demonstrated encouraging results in clinical trials. CARs redirect T-cell specificity toward antibody-recognized antigens expressed on the surface of cancer cells and are composed of an extracellular antigen-recognition domain, a transmembrane domain, and an intracellular T-cell signal domain. Of note, CARs are able to recognize a variety of antigens without restriction of their MHC determinants, since the target cell antigen is not processed and presented but is there in its entirety on the malignant cell surface, and costimulatory signals can be incorporated into the intracellular domain in order to enhance cellular responses. CAR-redirected T cells specific for the B-cell differentiation antigen CD19 have demonstrated significant activity in the treatment of B-cell malignancies.[96,97] Similarly, CAR-T cells targeting the B-cell maturation antigen (BCMA) appear promising in the treatment of relapsed refractory myeloma. TCR-modified T cells have demonstrated activity in the treatment of selected solid tumors but are structurally dependent on HLA type and antigen expression on MHC molecules of the target cell.[98,99] The toxicities of adoptive T-cell therapies can be severe; they include cytokine release syndrome, hypotension, pyrexia, and neurologic adverse events. Dendritic cells also have been generated ex vivo and are under investigation in vaccine approaches (including Sipuleucel-T, detailed below), as have monocytes/macrophages as potent antigen-presenting cells.

DONOR LYMPHOCYTE INFUSION

Cells infused in allogeneic HSCT represent an effective adoptive cellular therapy in clinical use. An allogeneic graft-versus-leukemia (GVL) effect, which is a restricted form of graft-versus-host disease (GVHD), has been suggested by the increased relapse rate for recipients of T-cell–depleted allografts, higher relapse rates after either syngeneic or autologous transplantation, and the lower frequency of relapse for patients with more severe GVHD. Given these clinical observations, donor leukocyte infusion (DLI) was tested among patients whose malignancies relapsed after allogeneic transplantation. Numerous reports have documented success of DLI for patients with chronic myeloid leukemia; the majority of these patients achieved durable complete molecular remission.[100] Acute myeloid leukemia has only modest response rates, and acute lymphoblastic leukemia rarely responds. DLI also can eradicate Epstein–Barr virus–associated posttransplantation lymphoproliferative disease following allogeneic transplantation. More recent studies have identified potential target antigens among patients responding to DLI. The major drawback of DLI is GVHD, which is a major source of transplantation-related mortality, and methods of promoting GVL over GVHD are under investigation. New investigational approaches aimed at improving the efficacy of DLI under investigation include priming of donor lymphocytes to recipient tumor antigens ex vivo and infusions of alloreactive NK cells. The effects of lymphocyte infusions in the setting of myeloablative and nonmyeloablative treatment are also under investigation in solid tumors.[101]

SIPULEUCEL-T

Sipuleucel-T is an autologous cellular immunotherapy designed to stimulate an immune response to prostate cancer. It is approved for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer. Sipuleucel-T is manufactured from peripheral-blood mononuclear cells (PBMCs) isolated during leukapheresis. PBMCs are cultured ex vivo with PA2024, a fusion protein consisting of prostatic

acid phosphatase (PAP) and GM-CSF for 2 days and then reinfused into the patient. The approach is designed for the GM-CSF portion of the fusion molecule to activate blood monocytes and dendritic cells to present PAP as a tumor antigen.[102,103] The final cell product, however, includes a variety of leukocytes, including T and B cells. Median overall survival was improved for patients treated with sipuleucel-T compared with those receiving similarly prepared autologous dendritic cells not exposed to the antigen–GM-CSF fusion protein.[102] Adverse events more commonly reported in the sipuleucel-T group were chills, pyrexia, headache, flulike illness, myalgia, hypertension, hyperhidrosis, and groin pain. These events were generally mild or moderate in severity and usually resolved within 1 to 2 days. Investigations are ongoing to enhance the benefits of Sipuleucel-T by the addition of other immunomodulators, and the technology also is being explored in the treatment of other malignancies.

KEY POINTS

- Many cells of the immune system generated and/or modified ex vivo can be administered to an individual to effect an antitumor immune response.
- The use of reprogrammed CAR- and TCR-endowed lymphocytes has produced promising results in both hematologic and solid malignancies; nevertheless, the applicability of these approaches remains restricted to specialized centers and toxicities can be limiting.
- An autologous cell-based vaccine and donor leukocyte infusion after allogeneic hematopoietic cell transplantation are examples of cellular therapies in clinical use and under active investigation.

SUPPORTIVE CARE BIOLOGIC AGENTS—HEMATOPOIETIC GROWTH FACTORS

Many cytokines affect hematopoiesis either directly or indirectly. Cytokines that serve as hematopoietic growth factors are now in common use for the prophylaxis of febrile neutropenia for patients receiving cytotoxic treatments, and in the setting of HSCT, where they are used to mobilize hematopoietic progenitor cells for transplantation.

GM-CSF

GM-CSF stimulates the development of neutrophils and monocytes/macrophages and promotes the proliferation and development of early erythroid, megakaryocytic, and eosinophilic progenitor cells. It is produced by endothelial cells and fibroblasts as well as by T cells and monocytes/macrophages. GM-CSF produces a variety of effects on cells of the neutrophil and monocyte/macrophage lineages, including augmentation of monocyte/macrophage MHC class II expression and enhancement of granulocyte and macrophage cellular cytotoxicity and ADCC mechanisms. GM-CSF also serves as the principal mediator of the proliferation and differentiation of mDC. It enhances dendritic cell antigen uptake, MHC, and costimulatory molecule expression, as well as the ability of dendritic cells to stimulate T cells.

Recombinant GM-CSF (sargramostim) can be used in the prophylaxis of neutropenia. Because of the sensitivity of rapidly dividing myeloid cells, sargramostim is typically initiated 1

to 3 days after completion of chemotherapy and administered daily through postnadir recovery. Sargramostim is generally well tolerated; however, side effects include pain and inflammation at the injection site, bone pain, myalgia, arthralgia, and low-grade fever. Nausea, fluid retention, dyspnea, pericarditis, pleuritis, pulmonary emboli, splenomegaly, and hypersensitivity reactions have been reported but are rare.

The ability of GM-CSF to function as an immunoadjuvant and to stimulate DC and tumor-specific T-cell responses has led to its evaluation in a number of clinical trials as anticancer therapy. Various cancer vaccine approaches that incorporate GM-CSF have been tested clinically, including combination with immune checkpoint inhibition with favorable effects on both survival and toxicity in melanoma that are undergoing further investigation.[104] There also is evidence that administering sargramostim as monotherapy has antitumor activity for patients with prostate cancer or melanoma, in whom increases in DC have been observed.[105-107] The ability of sargramostim to promote phagocyte-mediated ADCC is also being tested in clinical trials in which it is being administered with monoclonal antibodies.[108]

Granulocyte Colony-Stimulating Factor (G-CSF)

G-CSF is produced by macrophages, lymphocytes, fibroblasts, and endothelial cells. It induces the production and release of neutrophilic granulocytes in the bone marrow and enhances their functional capacity in the periphery. Moreover, G-CSF possesses essential neutrophil-activating functions, such as the oxidative burst, degranulation, phagocytosis, and chemotaxis. G-CSF markedly stimulates neutrophil ADCC mechanisms. As a regulator of neutrophil activity, G-CSF plays a role in innate immune responses. There is growing evidence that G-CSF also exerts immunoregulatory effects in adaptive immunity. G-CSF mediates anti-inflammatory reactions accompanied by Th2 differentiation and promotes tolerogenic antigen-presenting cell–T-cell interactions.

Recombinant G-CSF (filgrastim) may be used to decrease the risk of febrile neutropenia associated with cytotoxic chemotherapy treatment. It is usually administered SC daily for up to 2 weeks, until postnadir neutrophil recovery is at normal or near-normal neutrophil levels. Because filgrastim stimulates myeloid cells to divide and because dividing cells are sensitive to cytotoxic chemotherapy, filgrastim should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy and no earlier than 24 hours before the administration of chemotherapy to lessen the risk of aggravating leukopenia. Recently, two biosimilars to filgrastim, filgrastim sndz, and tbo-filgrastim, have been approved for the same indications as those for filgrastim.[109] A pegylated form of recombinant G-CSF, pegfilgrastim, has a variable plasma half-life of 15 to 80 hours, which allows administration once per chemotherapy treatment cycle rather than daily. Pegfilgrastim should not be administered in the period between 14 days before and 24 hours after the administration of cytotoxic chemotherapy. The safety data appear to be similar between filgrastim and pegfilgrastim. The most commonly observed adverse effects are mild to moderate bone pain after repeated administration and local skin reactions at the site of injection. Fever, diarrhea, edema, dyspnea, skin rash, splenomegaly (with rupture), and hypersensitivity reactions also may occur but are very rare. The G-CSF receptor, through which filgrastim and pegfilgrastim act, has been found on tumor cell lines. The possibility that pegfilgrastim acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim is not approved, cannot be excluded. The immunomodulatory effects of G-CSF, such as the ability to promote ADCC mechanisms and to promote T-cell tolerance in pathologic conditions associated with a

Th1–Th2 imbalance, are under investigation.

KEY POINTS

- Hematopoietic factors, recombinant G-CSF, and GM-CSF are commonly used for the prophylaxis of febrile neutropenia and in hematopoietic stem cell transplantation.
- The ability of G-CSF and GM-CSF to modulate antitumor immune responses is under investigation, with particular interest in combinations with immune checkpoint inhibitors.

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CLINICAL TRIALS AND BIOSTATISTICS

Brent R. Logan, PhD

Recent Updates

- Increasingly, clinical trials are being conducted in a biomarker driven fashion. (Redig AJ, *J Clin Oncol* 2015)
- Adaptive designs are being used more frequently to improve trial efficiency. (Bhatt DL, *N Engl J Med* 2016)

OVERVIEW

Both practicing oncologists and cancer researchers are aware of the heterogeneity that appears in almost every dimension of cancer and its treatment: among types of cancer, among patients with cancer, and in the response of disease to treatment. Although this challenge can be met in part by gaining a better understanding of the underlying factors that affect the disease and its response to treatment, the complexity of the underlying biology makes it almost certain that randomness and unpredictability will continue to be a significant component of cancer research and treatment.

Statistics is the branch of mathematics that deals with the collection and analysis of data in the face of uncertainty and random variation. “Biostatistics” is a term commonly used to refer to statistical methods and applications related to medical research, although the distinction is not necessary and not used here. The term “biometry” more commonly refers to nonmedical biologic applications. Not surprisingly, statistics plays a significant role in medicine as a whole and in oncology in particular, and statistical concepts and ideas will be encountered repeatedly in the medical literature relevant to the oncologist. This chapter is intended to cover topics that an oncologist will encounter and for which he or she will need a basic understanding in order to read and interpret current articles in medical journals. The intention of this chapter is not to detail the how of statistics (i.e. no formulas or equations) but rather to elucidate the what and why of biostatistics in oncology.

Of course, it is impossible to summarize in any depth or breadth an entire scientific discipline in a single chapter, even when focused on its application to clinical oncology; therefore, there is a focus on topics that are either commonly encountered or frequently misunderstood. In addition to reviewing basic statistical concepts and analytic methods common in clinical research, the chapter includes a section on clinical trial design. Although perhaps not a purely statistical topic, clinical trials are an essential part of clinical research, and they are the means by which one attempts to control systematic sources of variation. Properly designed clinical trials help one to isolate the random components of variation, which can then be quantified

using appropriate statistical analysis. Taken together, proper design and analysis allow one to make an objective evaluation of treatment options, reflecting both the strengths and uncertainties of the evidence at hand.

BASIC CONCEPTS

Basic statistical concepts are reviewed in this section,[1,2] with a focus on terms and issues that commonly arise in the analysis of medical data, especially those that are most commonly misunderstood and starting with the notion of sample and population, for which basic descriptive statistics are relevant. Then the chapter moves to topics in inferential statistics, where one attempts to relate characteristics of the sample to characteristics of the population. This is the crux of using statistics in medical research, and includes the concepts of hypothesis testing, p values, and confidence intervals. Finally, the chapter covers a somewhat different point of view relating to these concepts, that of Bayesian statistics.

SAMPLE AND POPULATION

Two terms that occur early in a discussion of statistics are “sample” and “population.” In general terms, the data that are generated in medical studies (e.g., in a clinical trial) represent an observed sample from an idealized larger population, such as all patients with a particular diagnosis and stage of disease. The sample data are described and subjected to statistical analysis in hopes of making inferences about the larger population from which they came. In practice, the sample is rarely drawn randomly from the population, but it is assumed that the behavior of the sample, and statistics calculated from it, are governed by parameters that characterize this hypothetical larger population.

A “statistic,” as compared with the discipline called “statistics,” is a quantity summarized from a set of data—for example, the mean or median. These are commonly referred to as “descriptive statistics.” They may describe quantitative variables, such as age or tumor size; ordinal variables, such as stage of disease; or categorical variables, such as sex or race.

Table 5-1 defines some common descriptive statistics. Most of these terms refer also to characteristics of a population, but are considered here as statistics calculated from a sample of data. In some cases, a simple description of the sample characteristics is all that is intended; however, a common use of sample statistics, either explicitly or implicitly, is to estimate their counterparts in a population. For example, the mean is a statistic computed from a sample. At least conceptually, the mean of the population from which the sample arose could be determined by enumerating and averaging all the values in the population. Instead, the sample mean (a statistic whose value varies from sample to sample) is used to estimate the population mean (a parameter with a fixed value). Such usage is a part of inferential statistics.

HYPOTHESIS TESTING

The two basic components of inferential statistics are estimation, which was previously noted and hypothesis testing.[3] Whereas estimation attempts to ascertain the value of a population parameter, hypothesis testing attempts to decide only whether the parameter has a particular value (or range of values). Many aspects of clinical trial design are framed in terms of hypothesis testing. This framework is sometimes somewhat artificial, but it is often used to plan the size of clinical trials and is the origin of many commonly encountered statistical terms.

Table 5-1 **Basic Descriptive Statistics**	
Statistic	**Definition and Description**
Mean	The average value of the sample.
Median	The value dividing the ordered values of the sample in half; equivalent to the 50th percentile. For an odd sample size, the median is the middle value; for an even sample size, the median is the average of the two middle values.
Percentile	The value below or equal to which a specified percentage of ordered observations fall. Tertiles, quartiles, and quintiles are values dividing an ordered sample into thirds, fourths, and fifths, respectively.
Mode	The most frequent value in the sample. Not often used.
Standard deviation	A measure of the variation of a sample distribution, based on the average squared distance from the sample mean. Most of a sample from a normal distribution is contained within two standard deviations above and below the mean.
Standard error	A measure of variation of the sample mean, or other estimated parameter describing a distribution. Unlike the standard deviation, the standard error gets smaller with larger sample sizes.
Range	The difference between the maximum and minimum value. In practice, the maximum and minimum are usually given, not the difference.

The statistical hypothesis test involves three basic steps: (a) formulation of the null hypothesis, (b) collection and analysis of data, and (c) a decision to reject or not reject the null hypothesis. The term “not reject” is deliberately used here, rather than the term “accept,” for reasons that are elaborated as follows. The null hypothesis is a semantic concept that is not at all the same as a scientific hypothesis. For example, in a trial of a new therapy, there is likely a scientific belief or hypothesis that the new therapy will be more effective than a standard therapy currently in use. However, the null hypothesis in such a setting would be just the opposite: The new therapy has the same effectiveness as the standard therapy. In the clinical trial setting, the desired scientific outcome is usually to reject the null hypothesis.

If one formulates the problem such that the only outcomes are to reject or not reject the null hypothesis, then there are two possible errors that can be made. One is that the null hypothesis is true and is incorrectly rejected (false-positive); the other is that the null hypothesis is false and is incorrectly not rejected (false-negative). The first of these is called a “type I error,” and the rate of type I error is usually designated α and referred to as the significance level; the second is called a “type II error,” and the rate of type II error is usually designated β. The rate

of type II error requires specification of exactly how the null hypothesis is false, which is referred to as the “alternative hypothesis.” It is more commonly specified by the probability of correctly rejecting the null hypothesis when a particular alternative to the null hypothesis is true; this is called “power” and is designated $1 - \beta$.

Hypothesis tests are carried out by calculating a test statistic from one or more samples. In years past, one then referred to a table of critical values for the test statistic, calculated from the theoretical distribution of the test statistic under the null hypothesis for a given sample size and type I error rate. If the test statistic was larger than the critical value (or smaller, depending on the type of statistic and test), then one rejected the null hypothesis. Although this can still be done, the computation of a test statistic now almost always involves the automatic computation of an associated p value, whose use, and misuse, is discussed in the next section.

Table 5-2 describes some common statistical tests. These all relate to simple comparisons of a quantitative or categorical characteristic, between groups or within a group. The table includes examples of both parametric and nonparametric tests. Parametric tests are derived using a specific assumption about the distribution of the data (e.g., normal, binomial, or exponential), whereas nonparametric tests make fewer such assumptions. Although the latter feature is desirable, a nonparametric test will generally have somewhat less statistical power than a parametric test that is correctly matched to a specific distribution. Fortunately, these considerations usually become less important with increasing sample size, and the choice of a parametric or nonparametric test is not critical. More complex statistical methods that relate to other types of endpoints, or that consider multiple variables simultaneously, are described later in this chapter.

INTERPRETING P VALUES AND CONFIDENCE INTERVALS

One of the most widespread concepts related to the statistical analysis of medical data, and possibly the most often misunderstood, is the p value. The p value is calculated after data have been collected, and it measures the strength of the evidence against the null hypothesis. For a given statistical model and assumptions, the p value is the probability, if the null hypothesis were true, that a result as different from (or more different than) the one observed could be produced by chance alone. If the p value is small, then one can reasonably infer that chance is not a good explanation for the observed data under the null hypothesis and that, therefore, it is a consequence of some systematic effect. Whether the systematic effect has been designed into the study, as in a randomized trial, or is a result of bias or selection factors is a different question.

What constitutes a small p value? In the world of clinical research, a p value of less than 0.05 is commonly used to indicate statistical significance. This number is arbitrary but is as good as any other if one wants only to establish a minimum threshold of evidence for something that is being measured on a continuous scale. In the formal hypothesis testing paradigm, it is equivalent to rejecting the null hypothesis when the type I error rate is set at 5%. The major error in interpretation of the p value involves outcomes for which the p value is large. The fact that a result is not statistically significant means only that chance is at least a reasonable explanation for the observed data. It does not mean that it is the only explanation and that the null hypothesis is true. The 0.05 level of significance (or any other level) does not discriminate truth from falsehood, and the p value is most certainly not the probability that the null hypothesis is true.

Table 5-2 **Basic Statistical Tests**

Setting	Test	Definition and Description
Comparing means	Two-sample t	Used to compare means between two groups for a quantitative variable. Generally robust to small sample size and nonnormal distributions, but sensitive to outlying values, which inflate estimates of variability.
	Paired t	Used to compare paired quantitative data; for example, a quantitative characteristic measured before and after treatment in each patient. Same sensitivity to outlying values as the two-sample t-test.
Comparing medians or distributions	Wilcoxon rank sum (Mann–Whitney)	A nonparametric alternative to the two-sample t-test. Less sensitive to outlying values than the two-sample t-test, although somewhat more conservative.
	Wilcoxon signed rank	A nonparametric version of the paired t-test. Less sensitive to outlying values than the paired t-test, although somewhat more conservative.
Comparing proportions	Chi-square	Used to compare proportions between two or more groups. Fairly robust to small sample sizes, unless there is an imbalance between groups. The "continuity correction" sometimes applied to the chi-square test is conservative and generally unnecessary.
	Fisher exact	Used to compare proportions with small sample size. A conservative test compared to the chi-squared.
	McNemar	Used to compare paired proportions; for example, a binary characteristic assessed before and after treatment in each patient. It is based only on the discordant pairs (where outcome is different) and is not used to assess concordance.

What, then, does a large p value mean? In the absence of any other information, and assuming that the data arise from a properly designed study, the safest and most accurate interpretation is that "there is insufficient evidence that the null hypothesis is false." Whether a nonsignificant p value provides useful information will depend on considerations such as how well powered the study is to detect important clinical effects, as described further in the next section. The reality is that the p value, whether small or large, actually carries very little information. It conveys no information about the direction or magnitude of an effect, no information about the uncertainty in the estimated effect, and no information about the clinical significance of the effect. Even a small p value is no guarantee that an effect has clinical significance. In studies with a very large sample size, even a modest departure from the null hypothesis can be associated with a high degree of statistical significance, but the departure from the null hypothesis may have little practical meaning.

The quantity that contains this missing information is the confidence interval.[4] The confidence interval represents a range within which the true population value likely lies. An interval with a 95% confidence level will be expected to contain the true value of an effect 95% of the time, and miss it 5% of the time. Of course, for any particular confidence interval it is unknown whether it does or does not contain the true value. In contrast, the p value provides information only about a single value. Figure 5-1 shows a variety of scenarios for the outcome of a statistical analysis and illustrates how confidence intervals relate to the concepts of statistical and clinical significance.

When a p value is not less than 0.05, the associated null value will be contained within the 95% confidence interval. The fallacy that this is, therefore, the true value is readily apparent, since the null value is only one among a range of possible values that could reasonably have produced the observed data.

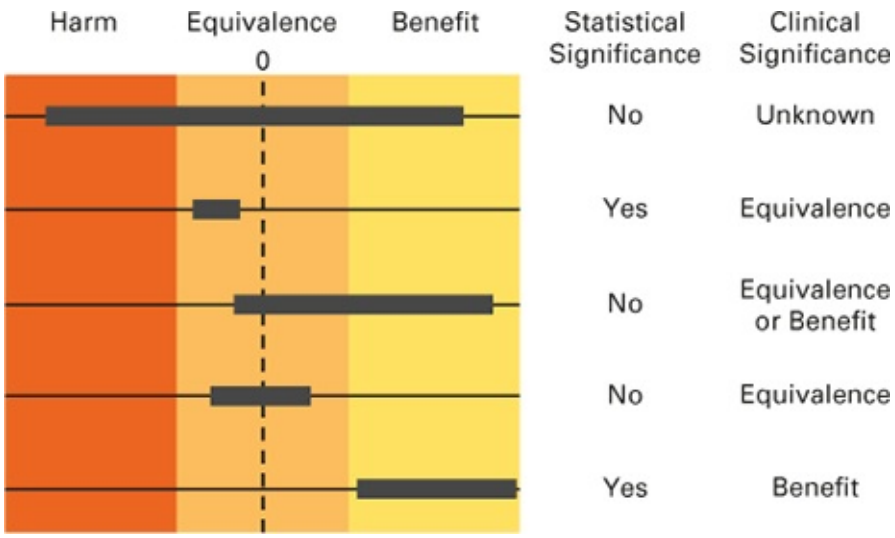

Fig. 5-1 Interpreting confidence intervals with respect to statistical and clinical significance.

Heavy black lines illustrate 95% confidence intervals that could arise from a comparative clinical trial of an experimental therapy compared with standard therapy. The vertical dashed line indicates exact equality between arms, and the light orange area indicates a difference close to equality that is considered clinically insignificant. The yellow area indicates a difference between arms that would be considered a clinically significant benefit for the experimental arm; the dark orange indicates clinically significant harm for the experimental arm. The determination of statistical significance (at the $\alpha = 0.05$ level) is based only on whether the confidence interval includes 0. The full range of the confidence interval must be examined to determine what conclusions are reasonable with respect to the clinical significance of the study.

SAMPLE SIZE AND POWER CALCULATIONS

The calculation of sample size for a clinical trial depends on a variety of factors, including the endpoint to be evaluated and the particular method of statistical analysis; however, all such calculations depend on the same basic considerations: the acceptable rates of type I and type II error (or power); a null hypothesis and the particular alternative to the null hypothesis for which power is calculated; and the variability of the outcome. In some cases, the latter is determined by the null hypothesis and a specified alternative, in other cases, it can vary independently. These factors influence the calculation of sample size or power in a reasonably intuitive way, summarized in Table 5-3.

The most common value specified for the α level is the ubiquitous 5%, especially in comparative clinical trials, and a common value for power is 80% or 90%, but of course these can vary depending on the situation. The factor with the greatest influence in the design of a clinical trial is the particular alternative to the null selected for use in the calculations. This is frequently referred to as the effect size that one is (scientifically) hypothesizing or would be of interest. Depending on the outcome of interest in the study, the effect size may be, for example, a difference in proportions, a difference in means, or a hazard ratio (HR). In most cases, with all else being equal, a halving of the effect size used in the calculation results in roughly a fourfold increase in the sample size requirement. Conversely, doubling the effect size results in roughly a 75% lower sample size. Thus, it is critically important to make realistic assumptions about the effect size for which a clinical trial is designed.

As previously noted, the hypothesis testing framework is useful for formulating the calculation of power and sample size, but is an artificial and oversimplified view of the clinical trial as a whole. In the real world, interpreting a clinical trial and acting on its results is a far more complex undertaking than simply rejecting or not rejecting a statistical null hypothesis.

BAYESIAN STATISTICS

Most of the familiar statistical concepts and applications encountered in medical research are based on what is called the “frequentist view” of statistics and probability. In the frequentist perspective, probability is a quantity that, in principle, reflects the underlying long-term frequency with which an event will occur under repeated observation. This frequency is governed by unknown but fixed parameters that define a probability distribution. For example, the mean and standard deviation of a normal distribution determine how frequently, on average, a value from that distribution will exceed a certain value. The statistical procedures derived from this perspective are all based on relating observed data to the fixed parameters of the probability model that generates the data.

Table 5-3 **Factors Influencing Sample Size in a Comparative Study**

Quantity	Effect
Type I error rate	Decreasing error rate increases sample size
Type II error rate	Decreasing error rate increases sample size
Effect size*	Smaller effect size increases sample size
Variability	Smaller variability decreases sample size

*Difference between null and alternative hypothesis values.

Bayesian statistics also seek to relate observed data to the probability model that generates the data. The term “Bayesian” derives from a basic theorem known as “Bayes rule,” which was formulated by the Reverend Thomas Bayes in the mid-18th century. Although partly just a matter of mathematics, the Bayesian formulation allows the incorporation of a more subjective notion of probability—the notion of probability as a measure of the strength of one's belief in a single outcome—for example, the probability that your team will win the Super Bowl this season or that the moon is made of green cheese. It further allows the application of this view of probability to unknown parameters governing a probability distribution—for example, the probability that the rate of response to a treatment exceeds a fixed value. This is not a meaningful concept in a frequentist framework, because the response rate is viewed as a fixed number.

The Bayesian approach to statistical inference involves three basic steps: (a) specification of a prior distribution for the unknown parameter, based on existing knowledge; (b) collection of data; and (c) use of the data to update the prior distribution, resulting in a posterior distribution. A simple example involves a card game such as poker. In a fair game, it is presumed that any particular hand of cards is equally likely to be dealt to any particular player (the prior distribution). After the cards are dealt, one observes one’s own hand and perhaps parts of the hands of other players (the data). This information can be used to recalculate the probability that other players hold particular hands, which are no longer equally likely (the posterior distribution).

Although the mathematical basis of Bayesian statistics is not in question, the first of the steps previously noted is one that has the potential to generate controversy in applying Bayesian methods to medical research. This is because the prior distribution is allowed to incorporate subjective judgments about the quantity under investigation. Many statisticians argue that prior beliefs about an unknown quantity represent a form of bias that should be avoided in scientific research; others argue that ignoring prior knowledge is in itself a bias. It is

possible to employ a Bayesian framework in a way that minimizes the use of information contained in prior beliefs, thereby letting the data speak for themselves. This is done by choosing a prior distribution that is said to be uninformative with respect to the quantity under study (also sometimes called a "flat prior"). Interestingly, and reassuringly, statistical procedures conducted within the latter framework are often very similar, or even identical, to those conducted within a frequentist framework, and they produce very similar results. They simply use different mathematical machinery and terminology.

Some clinical trial designs make use of Bayesian concepts, and these are described briefly in the next section, on clinical trial design. Although less common, some forms of data analysis may also employ Bayesian methods. In situations in which Bayesian methods have been employed in the design or analysis of a research study, one should always be able to ascertain the nature of the prior distribution. If a subjective or informative prior distribution has been used, its rationale and appropriateness should be carefully considered, and it should be recognized that the choice of a prior distribution can influence the interpretation and conclusions of the study.

KEY POINTS

- Statistical significance and clinical significance are different concepts.
- Large p values, by themselves, are not evidence for a lack of effect; they should generally be regarded as uninformative.
- Confidence intervals provide information about both statistical and clinical significance.
- Sample size requirements for comparative trials are extremely sensitive to the assumed effect size (difference in outcome between arms); for example, halving the effect size results in a fourfold increase in the total number of patients required for a trial.
- Frequentist and Bayesian methods provide alternative frameworks for viewing the parameter of interest in a statistical model.

CLINICAL TRIAL DESIGN

Clinical trials are a fundamental part of the process of medical science leading to the development of treatments for cancer, as well as its prevention and detection.[5-8] In oncology, clinical trials have historically been classified according to the general phases of drug development. Although this classification by no means accounts for all of the clinical trials relevant to oncology, it is a useful starting point for describing the key elements of trial design, which necessarily vary according to the objectives of the trial.

Phase I trials focus on toxicity, with a goal of determining a dose and treatment regimen that would have acceptable toxicity if the drug were effective. Phase II trials are designed to provide a preliminary indication of whether that therapy is effective. The result is considered preliminary because the study is uncontrolled, uses a surrogate endpoint (such as tumor response instead of survival), or is not large enough to rule out chance effects. The phase III trial is typically a controlled, randomized trial large enough to distinguish chance effects from true treatment effects. It is also not uncommon to see trials that are classified in other ways: e.g., as phase I/II, phase Ib, or phase II/III. There is no single governing body for trial nomenclature, and trial

sponsors are free to attach whatever labels they wish to a particular study. Sometimes this is driven by regulatory or insurance considerations: for example, the Food and Drug Administration offers definitions of trial phases for studies that it regulates, and insurers may decline coverage for patients participating in certain phases of trials.

PHASE I

The initial phase of human experimentation in the development of chemotherapeutic agents involves finding a dose that produces an acceptable level of toxicity. What is acceptable obviously depends on the disease in question: in diseases like cancer, with significant morbidity and mortality, the acceptable level of toxicity may be quite high. Indeed, with cytotoxic drugs, the toxicity of the drug may be, to some extent, a measure of its potential efficacy. With newer cytostatic or targeted agents, however, the presumed correlation of toxicity and efficacy may not hold, and the design of appropriate phase I trials for such agents can be challenging.

Traditionally, the objective of a phase I trial is to determine the maximum dose of an agent, either alone or in combination with other agents, that will produce an acceptable level of toxicity when administered on a specific schedule and by a specific route. This dose is usually referred to as the maximum tolerated dose (MTD) or the recommended phase II dose. For example, a simple definition of acceptable toxicity might be “toxicity of grade 4 or worse in not more than one out of six patients,” where grade 4 toxicity is defined according to standard criteria. The toxicity that defines the MTD is said to be dose-limiting toxicity (DLT). Once an MTD is established, one presumes that this dose will be used in further evaluations of efficacy in phase II trials; however, this logical progression is complicated by the fact that patient populations in phase I and II trials are likely to be dissimilar.

Phase I Endpoints and Patient Population

Since agents or regimens being tested in phase I trials have unproven efficacy, ethical considerations necessarily limit the patient population that can be enrolled in these trials. Typically, these are patients for whom multiple lines of therapy have failed and for whom no standard treatment options remain. The patient population is generally heterogeneous with respect to disease diagnosis, but may be restricted to specific cancers, depending on the type of agent being tested and its mechanism of action. For example, it would have been inappropriate to test a highly targeted agent like imatinib mesylate in a phase I trial in cancers that do not have the specific mutation targeted by this drug.

The most important endpoint to specify in a phase I trial is the definition of DLT. Although certain definitions are relatively common, the definition can vary considerably and may be tailored to reflect toxicities expected on the basis of the mechanism of action of the agent. The most common standard for rating the severity of toxicities is the National Cancer Institute’s Common Toxicity Criteria, which provides specific criteria for grading a wide range of toxicities on a numeric scale: 0 (none), 1 (mild), 2 (moderate), 3 (severe), 4 (life-threatening), 5 (fatal). Most definitions of DLT exclude grade 1 or 2 toxicities, and possibly some grade 3 toxicities if these are expected and manageable—for example, neutropenia or nausea/vomiting. Thus, a composite definition of DLT might be “grade 3 nonhematologic toxicity or grade 4 hematologic toxicity.” One must also specify the time frame during which toxicities will be evaluated for purposes of the trial. This is typically a relatively short time, such as 4 weeks or one treatment cycle, and, thus, captures only acute toxicities. Toxicities that occur after the specified observation period are not reflected in the outcome of the phase I trial, but may influence how

the agent is used in later phase II trials.

Phase I Design Options

Almost all phase I trials prespecify the starting dose of the agent being tested and a sequence of doses to be tested subsequently. The initial dose level is generally derived either from animal experiments, if the agent in question is completely novel, or by conservative consideration of previous human experience, if the agent in question has been used before but with a different schedule and route of administration or with other concomitant drugs. A common starting point based on the former is from one-tenth to one-third of the mouse LD_{10}, the lethal dose for 10% of mice, adjusted for size of the animal on a per-kilogram basis or by some other method. Subsequent dose levels are determined by increasing the preceding dose by decreasing fractions—for example, 100%, 67%, 50%, 40%, and 33%—thereafter. Such sequences are often referred to as modified Fibonacci. With some agents, particularly biologic agents, the dose levels may be determined by log (i.e., 10-fold) or half-log increases of the preceding dose.

Designs for phase I trials are constrained by the practical need to use relatively small numbers of patients and the ethical need to approach the MTD conservatively. By far the most common design option for phase I trials is the 3+3 design. This design, or minor variations on it, has been in use since the 1950s. Briefly, beginning at the first dose level, cohorts of three patients are entered. If all three patients receive the agent at the specified dose without DLT, then the next cohort of three patients is entered at the next higher dose level. If two of three patients experience DLT, then the toxicity associated with that dose is considered unacceptable, and the dose level below it (if any was tested) is considered the MTD. If one of three patients experiences DLT, then an additional cohort of three patients is entered at the same dose level. If no further DLT is seen, then escalation to the next dose level is permitted for the next cohort; otherwise, the toxicity is considered unacceptable, and the dose level below it is considered the MTD.

If the starting dose is too low, and/or the spacing of doses is too small relative to the steepness of the dose–response curve, then large numbers of patients may be enrolled at doses without toxicity (and likely with no therapeutic benefit). To address this problem, an accelerated titration design may use only single patients at the initial dose levels. Escalation continues until a grade 2 toxicity is seen, and then a standard 3+3 design is implemented at the next lower dose level. Because dose escalation is permitted on the basis of the experience of only one patient, such designs are usually restricted to situations in which there is some human experience with the agent, and the toxicity profile is known to be manageable.

Another design option, based on a Bayesian approach, is referred to as the continual reassessment method. Although there are many variations in the details, the basic concept is to define the probability of DLT that is acceptable (e.g., 20% or 33%), assume a simple mathematical model for a dose–response curve, and then, after each patient (or cohort of patients) has been treated, update the mathematical estimate of the dose–response curve and treat the next patient (or cohort) at the dose level at which the estimated probability of DLT would be closest to the target. Although it is well recognized in the statistical literature that model-based designs can outperform the 3+3 design in many aspects, this design is still frequently used in practice because of its simplicity and transparency.

The modified toxicity probability interval design was proposed as a design that is simple to implement yet has superior performance compared with the 3+3 design.[9] In it, toxicity

probability intervals are defined that refer to underdosing, proper dosing, and overdosing. Bayesian-model–based inference is used to determine the likelihood that a dose toxicity rate will be in each of these intervals. Dose-escalation decisions are easily made based on the three dosing intervals; they can be described using simple tables for ease of application. The modified toxicity probability interval design tends to treat fewer patients at doses greater than the MTD and is more likely to identify the true MTD than the 3+3 design.

For some treatments, toxicity is not expected to be substantial throughout the anticipated therapeutic range of doses, and the objective of dose finding is to determine the range of biologically active doses. In this setting, further escalation of the dose to an MTD is not needed to maximize the benefit of the treatment.

PHASE II

Trials falling under the umbrella of phase II can be highly variable in design. These can range from small, single-arm trials involving a dozen patients to double-blind, placebo-controlled trials involving 200 patients. Trials like the latter typically fall into the phase II category only because they use an endpoint or sample size that falls short of that required to get regulatory approval for a drug. Nevertheless, there are some typical features that characterize a phase II trial: the endpoints are related primarily to efficacy, rather than to toxicity; the sample size is moderately small, often 25 to 50 patients; the efficacy endpoint is short term and/or not definitive, such as tumor response; and the study relies on historical experience as context for judging whether the result is promising enough to carry forward to a phase III trial. This is the type of trial that will be considered phase II for purposes of this discussion.

Phase II Endpoints and Patient Population

The general objective of a phase II trial is to evaluate the potential effectiveness of a drug or regimen in a specific patient population. The patient population is usually somewhat narrowly defined (e.g., patients with stage III estrogen-receptor–negative breast cancer). Typically, patients enrolled in phase II trials have experienced treatment failure with at least one or two standard therapies; however, in diseases with no effective therapy, or when adding a new agent to the standard of care, a phase II trial may be tenable in the first-line setting. Finally, there are cases in which the treatment being evaluated in a phase II study is not novel, but is being applied to a new patient population (e.g., a different type of cancer, or a subtype of cancer defined by a genetic or another biologic marker).

As noted, the primary endpoint of a phase II trial is efficacy. The specific endpoint driving the trial design reflects a balance between the ability to assess it during a relatively short time frame (weeks or months) and its validity as a measure of true long-term benefit. For this reason, 5-year survival is almost never an endpoint for a phase II trial, although 6-month or 1-year survival might be. With cytotoxic agents, partial or complete tumor response is a common and accepted phase II endpoint; with cytostatic agents, stable disease or lack of progression might be included as a successful short-term response.

A number of schemes for defining tumor response have been established. For solid tumors, the Response Evaluation Criteria in Solid Tumors (RECIST) is standard. Most response definitions for solid tumors are based on the size and presence of measurable lesions. Other criteria must be used for hematologic malignancies. Whatever criteria are used, the trial design must specify how and when response will be assessed. The assessment criteria used to judge the outcome of the trial must be homogeneous within the trial and also reasonably comparable

to other trials or to whatever data are used as historical context.

In addition to tumor response and survival, there has been growing interest in the use of tumor biomarkers or other biochemical measures to assess the effectiveness of therapy (e.g., prostate-specific antigen in prostate cancer, CA125 in ovarian cancer, and carcinoembryonic antigen in colon cancer). A biomarker is a single trait or signature of traits that separates different populations, including genetic sequencing or mutation of cancer. The interest in biomarkers correlates especially with the use of so-called targeted therapy, which may have very specific mechanisms of action that are measured by a variety of assays, possibly from blood or tumor samples that can be obtained quickly and easily; although, the assays themselves may be neither inexpensive nor quick. Unfortunately, the appropriate use of biomarkers as surrogate endpoints requires specific criteria that may be difficult to validate. Notably, it is not sufficient to establish a correlation between the biomarker and outcome. A full discussion of these issues is beyond the scope of this chapter, but in general, one should be cautious in evaluating claims of effectiveness that are based on biomarkers or other surrogate endpoints.

Phase II Design Options

First, consider the most common phase II paradigm: a simple single-arm trial using historical outcomes as a point of reference for the design and interpretation of the trial. Such a trial is often designed from a hypothesis-testing point of view. For example, suppose that tumor response is the endpoint of choice, and that standard regimens have a response rate of approximately p_0, or otherwise that a regimen with a response rate of p_0 would be considered not worthy of further study. Conversely, suppose that p_1 is a response rate that would represent meaningful improvement compared with standard regimens or otherwise that a regimen with a response rate of p_1 would be considered of interest for further study.

The hypothesis-testing paradigm assumes that at the end of the trial, one will either (a) conclude that the true response rate for the regimen is greater than p_0 or (b) not conclude this. The design parameters must also include a specification of the false-positive (type I or α) error rate and false-negative (type II or β) error rate. The false-positive error rate is the probability of falsely concluding that the true response rate for the regimen is greater than p_0, when in fact it is equal to p_0. The false-negative error rate is the probability of falsely not concluding that the true response rate for the regimen is greater than p_0, when in fact it is greater than p_0. Often the false-negative rate is evaluated at p_1, the target of interest; these error rates typically range from 5 to 20%. The possibility of relatively high error rates is accepted, because low error rates require a larger sample size for the trial; however, the major factor driving the sample size is the difference between p_0 and p_1: the larger the difference, the smaller the sample size required for a specified set of error rates. This fact often leads to unrealistic design assumptions—i.e., setting p_0 unrealistically low or p_1 implausibly high.

Table 5-4 shows some possible trial designs under a variety of assumptions about p_0 and p_1 and allowable error rates. The value r is the minimum number of responses required in n patients required to conclude (with a specified type I error rate no greater than α) that the true response rate for the regimen is greater than p_0. A common misconception is that observing r responses allows one to conclude that the true response rate is at least p_1. That this is not the case is obvious from the fact that the observed minimum response rate required (i.e., r/n) is

less than p_1.

Table 5-4 Examples of Single-Stage Phase II Designs

Design Criteria				Resulting Design	
p_0	p_1	α	β	n	r
0.10	0.25	0.05	0.10	55	10
0.10	0.25	0.05	0.20	40	8
0.10	0.25	0.10	0.10	40	7
0.10	0.25	0.10	0.20	31	6
0.10	0.25	0.05	0.10	33	7
0.10	0.25	0.05	0.20	25	6
0.10	0.25	0.10	0.10	25	5
0.10	0.25	0.10	0.20	18	4
0.50	0.70	0.05	0.10	53	33
0.50	0.70	0.05	0.20	37	24
0.50	0.70	0.10	0.10	39	24
0.50	0.70	0.10	0.20	28	18

Abbreviations: p_0, response rate under null hypothesis; p_1, response rate under alternative hypothesis; α, type I (false-positive) error rate if $p = p_0$; β, type II (false-negative) error rate if $p = p_1$; n, smallest sample size that satisfies design criteria; r, minimum number of responses required to reject null hypothesis and conclude that $p > p_0$.

In some cases, the endpoint of interest in a phase II trial may not be tumor response but a time-to-event endpoint, such as overall survival or progression-free survival. For many cancer diagnoses, unfortunately, the median time to death or progression is measured in months or weeks. Thus, for example, if historical data suggest that the median progression-free interval with standard regimens is 3 months, this can be recast into the paradigm by noting that this is equivalent to specifying that the percentage of patients alive and progression-free at 3 months, p_0, is 50%. With some simple assumptions about the distribution of progression times, a hypothetical improvement to the median progression-free interval can be converted to a value of p_1 at 3 months.

The hypothesis-testing framework is useful for formulating a design and deciding on a sample size. In reality, however, it is rare for the hypothesis test to be formally carried out at the end of the trial. Instead, one calculates an estimate and confidence interval for the response rate associated with the agent and places this in context with a host of other factors before deciding whether further trials are warranted. The estimated response rate is relatively imprecise (Table 5-5) and actually provides only a rough indication of the response rate.

A common alternative to the simple single-stage design is a one that enrolls patients in two stages. The motivation for this alternative is simple. For example, consider the first scenario in Table 5-4, requiring 55 patients and 10 observed responses in order to reach a successful conclusion. Suppose that in a particular trial, after 25 patients have been treated, only two

responses have been observed. Thus, in order to reach the target of 10 responses, 8 must be observed in the final 30 patients, a seemingly unlikely scenario given what has been observed in the initial patients. Two-stage designs formalize the intuitive notion that the trial should be terminated early if the results are poorer than hoped for and that there is little chance of a successful outcome to the trial. This is done by dividing the enrollment into two stages and specifying the minimum number of responses that must be observed in the first stage before enrolling the second stage. Many two-stage designs may satisfy a given set of design parameters. One common criterion for selecting a two-stage design is to use the optimal Simon design, which minimizes the average number of patients that would be enrolled if the true response rate was no better than the historical reference p_0. Table 5-6 shows the optimal Simon two-stage design for the same situations as in Table 5-4. Note that the maximum sample size for these designs is often only slightly larger than for a single-stage design, with error rates satisfying the same specifications. For example, the design for the first scenario uses (at most) 57 patients compared with the 55 patients required with a single-stage design.

Table 5-5 Confidence Intervals for True Response Rates

Observed Rate = 0.10			Observed Rate = 0.50		
n	***r***	**95% CI**	***N***	***r***	**95% CI**
10	1	0.3, 44.5	10	5	18.7, 81.3
20	2	1.2, 31.7	20	10	27.2, 72.8
30	3	2.1, 31.7	30	15	31.3, 68.7
40	4	2.8, 23.7	40	20	33.8, 66.2
50	5	3.3, 21.8	50	25	35.5, 64.5
60	6	4.9, 17.6	60	30	39.8, 60.2

Abbreviations: CI, confidence interval for true response rate (Clopper-Pearson exact interval); *n*, sample size; *r*, observed number of responses.

The term “optimal” relates to a mathematical criterion, which sometimes leads to a design with an imbalance in the sizes of the stages that seems impractical; for example, by assigning 70% of the enrollment to the first stage. In such cases, there are almost always alternatives that are mathematically not quite optimal, but are more appealing in terms of the split between stages while still satisfying the other design parameters.

All of the designs considered thus far are single-arm, nonrandomized; however, some phase II trials use random assignment to allocate patients to more than one arm. Phase II trials may also randomly assign patients to a control or placebo group; this is discussed further in the next section. The reasons motivating randomized phase II designs with multiple therapeutic arms are many and sometimes somewhat controversial. Some studies assert that there is no intent to compare the arms: they are to be regarded as independent trials of different agents or regimens that happen to target the same patient population, and random assignment is simply a mechanism to ensure that the arms enroll patients with roughly similar characteristics.

Table 5-6 **Examples of Two-Stage Phase II Designs (Optimal Simon Design)**

Design Criteria				Resulting Design			
				First Stage		Overall	
p_0	p_1	α	β	n_1	r_1	N	r
0.10	0.25	0.05	0.10	28	4	57	10
0.10	0.25	0.05	0.20	18	3	43	8
0.10	0.25	0.10	0.10	21	3	50	8
0.10	0.25	0.10	0.20	13	2	34	6
0.10	0.25	0.05	0.10	18	3	35	7
0.10	0.25	0.05	0.20	10	2	29	6
0.10	0.25	0.10	0.10	12	2	35	6
0.10	0.25	0.10	0.20	7	1	18	4
0.50	0.70	0.05	0.10	23	13	57	35
0.50	0.70	0.05	0.20	15	9	43	27
0.50	0.70	0.10	0.10	21	12	45	27
0.50	0.70	0.10	0.20	12	7	32	20

Abbreviations: p_0, response rate under null hypothesis; p_1, response rate under alternative hypothesis; α, type I (false-positive) error rate if $p = p_0$; β, type II (false-negative) error rate if $p = p_1$; n_1, sample size for first stage; n, total sample size after both stages; r, total number of responses required to reject null hypothesis and conclude $p > p_0$; r_1, minimum number of responses required in first stage to enroll second stage.

The more classic randomized phase II trial is one in which two or more variations of the same experimental agent, or two or more closely related experimental agents, are compared in order to "pick the winner" for subsequent study or for comparison against standard therapy in a phase III trial. For example, two plausible doses of an agent or a gene vaccine may be carried in three possible vectors. In this case, the stated desire is to compare the arms and pick the best one, but since both arms are experimental there is no need to control the false-positive (type I) error rate. That is, if the true response rate for two experimental arms is equivalent, there is no error in picking one over the other. This is in contrast to the prototypical phase III paradigm, in which concluding that the experimental arm is different from standard, when in fact they are equivalent, is considered an error.

In a pick-the-winner design, the arm that has the highest observed response rate at the end of the trial is selected for further study. The sole design consideration is that if the response rates in the two arms differ by a specified amount *A,* then the false-negative (type II) error rate should be no higher than β. Thus, Δ is a difference in response rates that is considered clinically important. If two arms differ by this amount or more, then the sample size should be large enough that the observed response rate in the better arm will be higher than that in the other arm, with probability 1 – β. Table 5-7 provides some examples of design parameters for a randomized phase II trial and the sample size required for each. One advantage of the pick-the-

winner design is that the objective of picking the winner requires fairly modest sample sizes, which is often feasible in the phase II setting. However, because of these limited sample sizes, these studies are not powered to do formal statistical hypothesis testing between the arms, and these comparative statistical analyses should not be conducted.

Increasingly phase II trials are conducted in a biomarker driven fashion.[10,11] Biomarkers may be prognostic, whereby they affect the risk of the outcome in the absence of treatment, or predictive, whereby they change the outcome in response to a particular targeted treatment. Biomarkers that are prognostic may be used to identify high-risk patients, so that enriching the patient population for those with the biomarker can make it easier to detect a signal due to the higher event rate. If the biomarker is predictive for a particular therapy, then a biomarker subgroup would be expected to have a stronger efficacy signal. Basket trials may be used to enroll patients with similar tumor molecular characteristics across multiple tumor locations, in order to treat them with the same biomarker targeted treatment. Umbrella trials are often used to conduct multiple trials under one protocol, where patients first have their biomarker profile assessed and then are assigned to a particular randomization and biomarker targeted treatment scheme depending on their biomarker profile.

Table 5-7 Minimum Sample Size (per Arm) for Pick-the-Winner Randomized Phase II Designs

	Two Arms (p_0, p_1)		Three Arms (p_0, p_0, p_1)	
Difference ($p_1 - p_0$)	$1 - \beta = 0.80$	$1 - \beta = 0.90$	$1 - \beta = 0.80$	$1 - \beta = 0.90$
0.10	45	92	78	134
0.15	22	43	37	61
0.20	13	25	22	35

Abbreviations: $1 - \beta$, probability that arm with highest true response rate has highest observed response rate; p_0, lower response rate; p_1, higher response rate.

A final phase II design strategy that should be mentioned is an approach known as “adaptive randomization.” The trial starts out by randomly assigning patients in equal proportions to each arm. As outcome data on these patients accumulate, the randomization scheme is altered so that it favors arms in which the strength of the evidence that the response rate is greater than p_0 is greatest. Conversely, it disfavors arms in which the strength of evidence is lowest, and ultimately may drop arms altogether if the strength of evidence falls too low. Adaptive randomization has been used in biomarker-based designs, such as the I-SPY2 trial,[12] so that patients with certain biomarker profiles who respond more favorably to certain treatments will be randomly assigned more frequently to those agents. Such designs are associated often with Bayesian methods, although this is not an essential feature of the approach.

Although adaptive randomization seems like a highly rational way to select among competing experimental regimens, in practice it is often difficult to mount such a trial. The different agents likely have different sponsors and advocates, each of which naturally has a principal interest in their own agent and is reluctant to cede control of its evaluation to an external process. Others have some ethical discomfort with the notion of unequal allocation based on evidence of

efficacy, feeling that this violates the principle of clinical equipoise (that one truly is unable to say which treatment is better for the patient population to be enrolled).

Biases in Phase II Trials

Among all the phases of therapeutic development, phase II is the most fraught with the potential for bias. The major source of bias is the absence of contemporaneous randomized comparison groups. Historical outcomes vary widely, for many reasons, and past experience may reflect many factors besides the agents being tested. These can include the eligibility criteria defining the patient population; the definition, timing, and methods used to assess outcome; standards of supportive care that vary by institution and over time; the use of surrogate endpoints; and, of course, simple random variation. Even in the absence of any systematic bias—an ideal unlikely to be achieved—the random outcomes observed in relatively small numbers of patients lead to many false conclusions. The most observable of these are false-positive results—agents that look promising in phase II trials often fail to be proven effective in phase III trials. Less observable, but just as unfortunate, are agents that are in truth effective but fail to show positive results in phase II trials. Randomized control arms are sometimes used in phase II trial settings to remove potential sources of bias resulting from historical control comparisons[13]; however, they introduce additional variability in the treatment-effect estimate. As a result, they typically require larger sample sizes and may use a higher type I error rate in order to maintain sufficient power to identify promising agents in the phase II setting.

PHASE III

The randomized clinical trial is the gold standard of clinical research, and this is the trial that is most often referred to as a “phase III trial.” The classic goal for the phase III trial is to compare an experimental therapy with a standard therapy. A common analogy applied to this setting is that of a legal trial. In a clinical trial, one formulates a null hypothesis that the experimental treatment is equally as effective as the standard (the defendant is innocent), although, of course, there must be some scientific basis to believe otherwise (the prosecution has evidence). In order to establish effectiveness (guilt), a trial is conducted that will lead to the rejection of the null hypothesis in a convincing way (beyond a reasonable doubt). As in a legal trial, failure to reject the null hypothesis (finding of not guilty) is not the same as establishing equivalence of the therapies (innocence).

Of course, randomized clinical trials do not always fit the classic paradigm of an experimental therapy compared with standard therapy, but the principles underlying the design and analysis will most likely be equally applicable.

Basic Principles

The primary goal of a phase III trial is to provide a comparison of treatments that is free of the many biases that occur when trying to compare phase II trials conducted at different times, at different institutions, among different patient populations, etc. The accepted standard for ensuring freedom from bias is randomization. Randomization is not the only way to create comparable treatment groups, nor does randomization guarantee that the results of a particular trial are correct, but it does allow one to control and quantify the possibility of error.

The most common randomization strategy is equal allocation among all treatment arms.

From the standpoint of statistical power, this is the most efficient allocation, and also the one most compatible with the notion of clinical equipoise. A common variation of simple randomization is stratified randomization, which seeks to ensure even greater balance between arms by randomly assigning patients within strata defined by factors that strongly predict outcome. Additionally, the randomization may be blocked, which generally refers to a form of stratification designed to keep the number of patients allocated to each arm balanced over time. Stratification and blocking are most useful in small trials, in which random imbalances large enough to skew the composition of the treatment arms are not impossible. When the trials become larger (several hundred patients), these devices are largely superfluous, as it becomes highly unlikely that the arms will become meaningfully imbalanced by chance.

Departures from equal allocation sometimes occur—for example, a 2:1 allocation between the experimental and control arms. Most commonly, this is justified using the argument that this allocation makes the trial more attractive to potential patients and their physicians, particularly when there is no way to get access to an experimental agent except through participation in the trial. It also allows one to generate more experience with the new agent. However, this argument seems to presume that the experimental therapy is likely to be more effective than standard therapy, which contradicts the principle of equipoise.

Other common, but by no means necessary, components of a phase III design include the use of a placebo, and the implementation of blinded (to the patient) or double-blinded (to both patient and physician) treatment assignments. Although randomization can help ensure that the treatment arms are balanced with respect to patient characteristics at the start of the trial, it cannot remove bias that occurs after the trial starts, when differences arise between arms with respect to the conduct of the trial or the evaluation of trial data. This bias can be entirely unintentional and unconscious, but it reflects behavior by either patients or physicians that compromises the benefits of randomization. The susceptibility of trials to bias can vary considerably depending on the endpoint in question. For example, placebo effects and ascertainment bias are probably unlikely to affect a trial in which mortality is the primary endpoint. On the other hand, assessment of tumor response without blinding to treatment assignment could be subject to subtle bias, and studies with self-reported quality-of-life endpoints are obviously prone to placebo effects.

The use of placebo as the control arm in therapeutic oncology trials is extremely rare, since usually some form of therapy is available, even if it is ineffective. A placebo control is much more likely to be used in adjuvant trials or in trials of combination therapy in which a new agent is being added to an existing combination. Though one may question the extent to which placebo effects play a role in such settings, if a placebo is feasible it adds credibility to a trial even if the likelihood of placebo effects is small. In some cases, of course, the nature of the treatments differs so much that neither a placebo nor blinding is feasible.

The most acceptable primary analysis of a phase III trial is the intention-to-treat analysis. This analysis includes all patients enrolled in an arm of a randomized trial, no matter what happens thereafter—for example, if they are unable to receive the full course of treatment, they cross over to another treatment, etc. Since any of these contingencies can be related to the treatment itself and to the effectiveness of the treatment, an unbiased analysis must incorporate that information. For example, if a new drug is potentially effective but many patients will not take it because of its side effects, then as a practical matter it may not be as effective as a drug with fewer side effects.

Nevertheless, alternative analyses may be undertaken that deviate from the intention-to-treat principle. These may involve analyzing a subset of patients (e.g., those who received a

minimum amount of therapy) or defining the treatment groups according to the treatment actually received instead of the treatment to which they were randomly assigned. These alternative analyses can be informative, but must be interpreted cautiously and are problematic when the results differ markedly from the intention-to-treat analysis.

Other subset analyses may be undertaken to evaluate whether the treatment difference, if any, varies according to other factors, such as disease stage, age, or the presence of a biomarker. Even if specified in advance, the results of such subset analyses must be interpreted cautiously. Phase III studies are almost never large enough to have reliable power in subsets of patients; conversely, examining many subsets of patients in a trial with an overall negative result can lead to spurious findings that are caused by only random fluctuation.

Interim Analysis

Randomized phase III trials can be large, expensive, and of several years' duration. For this reason, most phase III trials have a provision for interim analysis at one or more points in time, with the possibility of terminating the trial early. The indications for early termination can be varied and are generally specified in advance. These may include strong evidence that the experimental therapy is better than the control therapy, strong evidence that it is worse, or a determination that the trial will not be conclusive (futility). Interim analyses are also ethically important, as information may be sufficient early to alter trial conduct.

A number of statistical approaches to interim analysis codify the timing and nature of the analyses and the threshold required to terminate the trial early. In the case that the trial is to be stopped early because of evidence that the experimental therapy is superior, the overall false-positive rate (type I error rate) for the trial needs to be quantified and controlled because multiple analyses of the data without adjustment can lead to inflation of the type I error rate. Because small sample sizes are subject to a large amount of random variation, the threshold for stopping a trial early generally involves a high degree of statistical significance, meaning type I error rates that are much lower than a standard 0.05 level of significance (e.g., as low as 0.001 or 0.0001). Also, if some of the type I error rate is "spent" during interim analyses, then the significance level for the final analysis will be lower than nominal. The threshold significance levels at each of the interim analyses and final analysis comprise the stopping boundaries.

In some cases, the data at an interim analysis contain little suggestion that there is a difference in outcome between arms, or indicate that the difference is much smaller than hypothesized when designing the trial. Based on the accumulated data and assumptions about the true treatment effect, it is possible to generate estimates of the probability that the trial will prove successful at demonstrating the superiority of the experimental arm. If this probability is too low, the trial may be terminated early so as to minimize unnecessary time and expense. This is referred to as "stopping for futility." On the other hand, as previously noted, the inability to demonstrate a difference is not the same as demonstrating equivalence. A trial that is terminated early for futility may be inconclusive. Therefore, in some cases, it may be desirable to complete a trial that cannot demonstrate a treatment benefit, if completing the trial might allow one to make firm conclusions regarding the lack of benefit.

Although the interim analysis plan for a phase III trial should be prespecified and an integral part of the trial design, the decision to stop a trial early involves complex and important issues that cannot be summarized in a simple statistical test. Typically, the results of an interim analysis will be reviewed by a data and safety monitoring board. The role of this board is to independently review the results of an interim analysis, consider the results in context with a

host of other factors (which may be scientific, ethical, legal, or financial), and make a recommendation as to whether to continue the trial or not.

Endpoints

Phase III clinical trials focus on identifying whether the treatment being investigated provides a direct clinical benefit to patients. In the oncology setting, an improvement in survival is often the gold standard for demonstrating such a benefit. However, other endpoints are also used to demonstrate clinical benefit, while providing efficiencies in trial design.[14] “Progression-free survival” (PFS), defined as the time until disease progression or death, or “disease-free survival” (DFS), defined as the time until disease relapse or death, provide a faster determination of the endpoint that can speed up trial completion. DFS typically uses only the patients who have a complete response, whereas PFS can be defined for all patients. “Time to progression” (TTP) is defined as the time until disease progression, but is complicated by how to handle patients who die from causes other than progression (see the section on Competing Risks and Cumulative Incidence for more detail). Event-free survival may include additional “events,” besides death and progression, but these are often defined in a study-specific way. All of these endpoints may introduce many complications in interpretation. Superiority on TTP, PFS, or DFS can occur despite a therapy causing more toxic deaths, and superiority on PFS or DFS can occur because of a more favorable safety profile, without any therapeutic effect on the cancer. Often PFS or DFS may not be established surrogate endpoints for overall survival, meaning that it is not known whether an improvement in these endpoints actually correlates with an improvement in overall survival. This makes it unclear whether an improvement in PFS or DFS really represents a direct clinical benefit to patients, especially in the presence of treatment toxicities. Endpoints may be subject to assessment bias, so additional trial design considerations are important, including patient/physician blinding, independent endpoint review committees, and regular disease evaluations. Patient-reported outcomes (PROs) use questionnaires to measure how a patient feels and functions; therefore, PROs can also be important for assessing direct clinical benefit of a treatment being evaluated in a clinical trial. These instruments need to undergo rigorous development and testing to ensure that they are measuring what is expected and that they are reliable. Several distinct aspects of PROs are important for understanding the benefits and toxicities of treatment, including the burden of disease symptoms, physical functioning and the ability to conduct activities of daily life, and symptomatic adverse events. Blinding in the trial design is important for these outcomes in order to avoid assessment bias, and completeness of data collection is crucial in order to minimize the impact of missing PRO data and the biases that this may introduce.

Adaptive Designs

"Adaptive trial designs" are defined as those that include a provision for changing the future course of the trial using accumulated data. Several features of adaptation in exploratory or early-phase clinical trials have already been described, including continual reassessment methods in phase I trials, and adaptive randomization in phase II trials. Here adaptations used in the confirmatory clinical trial setting are described.[15] The implications of adaptations are different depending on whether the changes are made blinded or unblinded to the available data on treatment differences; for example, increasing the sample size because of a lower-than-expected overall event rate has minimal impact on the final analysis because it does not actually utilize the treatment differences. In contrast, unblinded adaptation is subject to greater scrutiny,

and requires careful attention to statistical methodology and operational procedures in order to ensure that the results are free from bias. Several types of adaptations in late-stage clinical trials have been considered. Seamless phase II/III clinical trials combine the phase II trial (which may involve dose selection from among multiple doses) and the phase III trial (which uses the final selected dose for inference). This can be operationally efficient since it eliminates time between phase II and III, and it can be statistically efficient, since the data from the two stages are combined for inference. Sample size reestimation designs allow for an increase in sample size based on interim assessments of the treatment effect, particularly when the interim treatment effect is in a promising zone in which the study may be underpowered. An adaptive population-enrichment design allows for restricting enrollment to a biomarker-based subgroup at an interim analysis, if it appears that the biomarker-positive patients may benefit from treatment and the biomarker-negative patients do not.

Equivalence and Noninferiority Designs

Although most phase III trials are undertaken with an underlying goal of demonstrating a difference between treatment arms, there are circumstances in which the goal is merely to demonstrate that one therapy is equivalent, or at least not inferior, to another. For example, a therapy that is less toxic, less inconvenient, or less expensive than another would be preferred if it was nearly equally effective.

It is impossible to design a trial to demonstrate that two therapies are exactly equivalent, and highly unlikely in truth that they are. Instead, one specifies the smallest difference that would be of practical clinical significance—for example, a 5% difference in 1-year survival—and then designs a trial that has high power to reject the null hypothesis (low type II error rate) if such a difference truly existed. A successful trial from the standpoint of equivalence would then fail to reject the null hypothesis. Note that the concepts of a false-positive or a false-negative conclusion are in a way reversed from the usual design perspective, and the typical rates of type I and type II error employed in such designs might need to be reconsidered. Equivalence studies are notoriously large because the difference in outcome said to define equivalence is typically smaller than the difference hypothesized for a superiority trial, which dramatically affects the sample size. For example, as seen in Table 5-8, a trial with an equivalency threshold set at a 5% difference requires a sample size four times as large as a superiority trial powered to detect a 10% difference.

Table 5-8 **Required Sample Size (Per Arm) for Equivalence and Noninferiority Trials with a Binomial Endpoint ($p_0 = 0.50$, $\alpha = 0.05$, and $1 - \beta = 0.90$)**

Allowable Difference ($p_0 - p_1$)	Equivalence Design	Noninferiority Design
0.25	77	69
0.20	124	108
0.15	227	191
0.10	519	429
0.05	2,095	1,713

An alternative to an equivalency design that can require a somewhat smaller sample size is the noninferiority design. In this case, one specifies an acceptable upper limit to inferiority of the new therapy compared with the old—that is, how much worse it could be and still be considered acceptable. The trial is designed by formulating a null hypothesis that the new therapy has that level of inferiority, or worse, and then is powered to reject that null hypothesis for a specified alternative assumption (which might be equivalence, a lesser degree of inferiority, or even superiority). This usually results in a smaller sample size than an equivalence design, partly because it involves a one-sided hypothesis test, but often as a result of claiming a wider limit of acceptability for noninferiority than for equivalence.

KEY POINTS

- Phase I trials focus on identifying safe doses or combinations of therapies using small sample sizes to minimize exposure to therapies with unknown toxicity profiles.
- Phase II trials are difficult to interpret because so many factors can vary from trial to trial.
- The typical sample sizes used in phase II trials provide imprecise estimates of outcome.
- Promising results from phase II trials are often not confirmed in phase III trials.
- Biomarker-driven trials may improve efficiency by directly targeting patients who are most likely to respond to treatment.
- Phase III trials require careful consideration of study design parameters, including randomization, blinding, and choice of endpoint, to minimize bias in the assessment of the treatment benefit.

CORRELATIVE STUDIES

Many studies in oncology are focused on evaluating the association between measurable attributes of a patient or the patient's disease at a particular point in time and subsequent events or outcomes. These attributes may be measured before the start of treatment, possibly with a view toward predicting the therapy most likely to be effective, or after treatment has been initiated, with the intent of predicting whether the treatment is working. Although almost any clinical study is involved with evaluating association in the broad sense, the term "correlative study" most often refers to studies in which the attribute being associated is not clinically apparent but must be assessed through some kind of test procedure—imaging, immunohistochemistry, gene expression, or any of a wide range of other procedures. Also bear in mind that a correlative study may or may not involve the analysis of "correlation," which is a statistical term for a specific kind of association.

Correlative studies can be conducted during any of the phases of therapeutic development and, in fact, are often explicitly incorporated as ancillary objectives in a therapeutic trial. They can also be conducted completely independently of therapeutic trials. The potential range of correlative studies is so broad that it is impossible to summarize succinctly the statistical methods or designs for such studies; this chapter first shows some examples of a basic measure of correlation and illustrates some general pitfalls in the evaluation of correlation. This

chapter also discusses two important issues that can occur under the umbrella of correlative studies: the relationship between correlation and causation and the issue of multiple comparisons.

Examples of Correlation

As previously noted, “correlation” is a generic term that might describe almost any trial or analysis of association, but it may be helpful to consider a very basic notion of correlation that occurs when both factors being studied are measurable on a continuous scale, exemplified by the *x*–*y* scatterplot and the sample correlation coefficient.[16] The scatterplot is simply a visual representation of how one factor varies as a function of another. The Pearson correlation coefficient, *r,* is a measure of the linear correlation between the two variables: a value of +1 means perfect correlation, a value of 0 means no correlation, and a value of –1 means perfect inverse correlation. The associated value r^2 ranges from 0 to 1 and is interpreted as the fraction of the variation in one variable that is explained by variation in another. For r^2, variation is measured by the sum of squared deviations from the mean, but there are many other measures of variation. The degree of correlation is a function of three factors: (a) the magnitude of the association (i.e., whether the change in one variable is associated with a large or small change in the other); (b) the consistency of the relationship (i.e., whether the changes are consistent or highly variable); and (c) the linearity of the relationship. The first two factors pertain generally to any measure of correlation; the third is a consideration for Pearson’s correlation coefficient *r.*

Figure 5-2 provides several examples of an *x*–*y* scatterplot, along with a fitted line and the value of *r*. The top panels illustrate how both the scatter and steepness of the association affect the degree of correlation. Moving from panel A to panel B, the data are just as variable, but there is an increase in the rate of change in *y* as a function of the change in *x* (slope), resulting in higher correlation. In panel C, the slope stays the same as in panel B, but the variability increases, decreasing correlation. The bottom panels illustrate common pitfalls that occur in correlation studies. In panel D, the apparent correlation between *x* and *y* is based on a single point that is far away from the majority of data. It is debatable whether this represents a real biologic phenomenon. Conversely, in panel E, an outlying observation obscures an apparent correlation in the majority of observations. Finally, in panel F, there is a clear relationship between *x* and *y,* but it is not a linear relationship and, therefore, is not reflected in *r*.

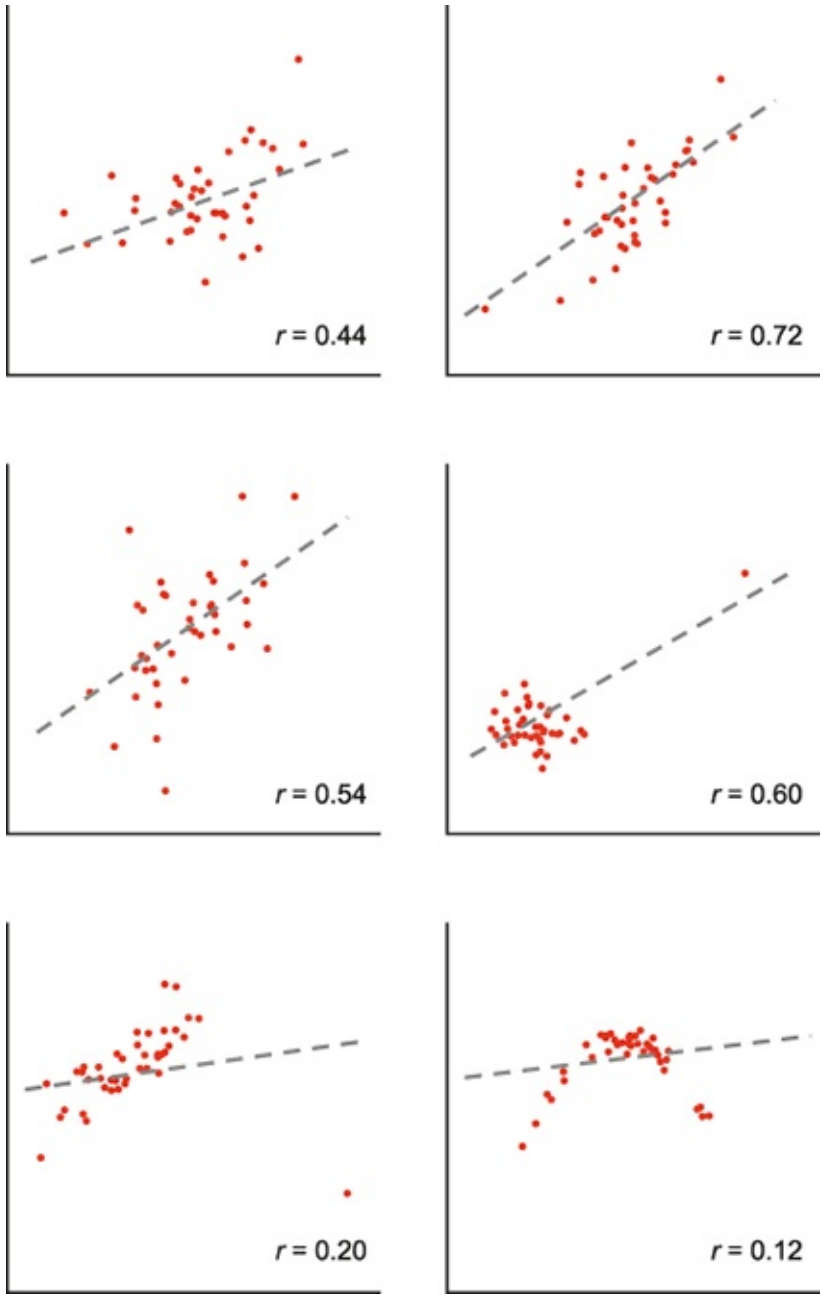

Fig. 5-2 Examples of linear correlation.

The six panels illustrate possible correlations between two variables, *x* and *y.* The dashed line indicates the least-squares line fit to the data, and *r* is the Pearson correlation coefficient.

Correlation and Causation

One setting in which correlative studies have become common is the development of so-called targeted therapies. These therapies are designed around specific attributes of tumors, which nominally can be quantified by measuring some biologic parameter. It may be possible to establish a clear correlation between this biomarker and prognosis; it may also be possible to establish that a targeted therapy has an effect on the biomarker in a direction that would imply a more favorable prognosis. Taking these two correlations together, it might appear that this is a clear indication that the therapy would be effective for that cancer, but this is not necessarily the case. Figure 5-3 indicates how this seeming contradiction can occur when the biomarker is correlated with the disease process but is not part of the causal pathway related to the ultimate outcomes of interest.

A familiar analogy would be the association of elevated blood pressure and cholesterol with various forms of cardiovascular disease. Although there are many drugs that lower blood

pressure and cholesterol, there is no guarantee that these drugs will be effective in lowering the risk for the correlated cardiovascular disease. In order for this to be true, the elevation of blood pressure or cholesterol must be part of the causal pathway to the cardiovascular event, not just a marker or symptom of the severity of the disease process. The same must hold true in order for the effect of a targeted therapy on a cancer biomarker to be considered an indicator of efficacy; that is, the biomarker must reflect at least part of the direct causal pathway by which growth or spread of the tumor has an effect on the survival of the patient.

Multiple Comparisons

Advances in technology have made it possible to assess hundreds, thousands, or even millions of potential markers within reasonable limits of expense and time. This is particularly true in the field of genomics, in which single chips have the ability to simultaneously quantify the expression of 20,000 genes or to genotype more than a million single-nucleotide polymorphisms. Although some sophisticated statistical methodology may underlie the quantification of gene expression or assigning a genotype, the basic methodology for evaluating a correlation with outcome could be based on a simple t-test or chi-square test that is repeated thousands or hundreds of thousands of times.

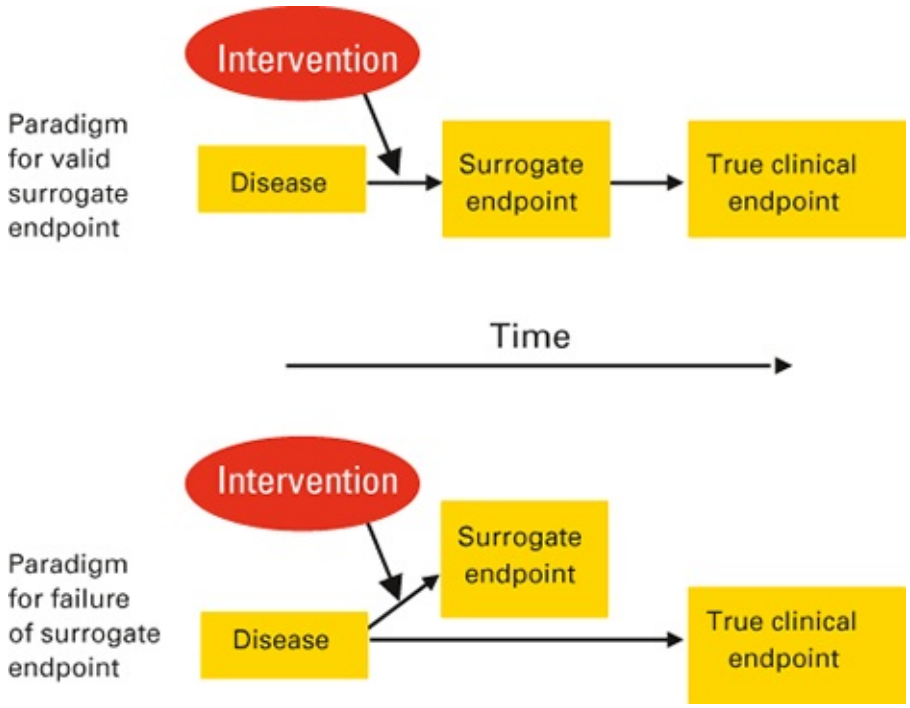

Fig. 5-3 Criteria for surrogate endpoints.

A schematic illustrating how a surrogate endpoint, or biomarker, may or may not be valid as a substitute for the true clinical endpoint. At the top, the surrogate endpoint is in the causal pathway of the disease process. An intervention that affects the surrogate endpoint should also affect the true clinical endpoint. At the bottom, the surrogate endpoint results from an independent causal pathway. It will be correlated with the clinical endpoint, but an intervention affecting the surrogate endpoint will have no effect on clinical outcome.

From the hypothesis-testing point of view, if each of these tests of association has a positive (type I) error rate set at conventional levels, such as 5%, then the number of false-positive correlations found will be enormous. For example, consider a gene expression study of 20,000 genes that is to be correlated with tumor response in hopes of determining one or more markers that signal a high likelihood of treatment failure. Even if the 20,000 genes have been

selected to represent a range of plausible causal pathways, only a small fraction of them are likely to be truly correlated with outcome. As an order-of-magnitude calculation, the number of false-positives that will result from 20,000 hypothesis tests conducted with a 5% type I error rate is 1000, which is far too many to represent practical progress.

Although it is obvious in this setting that some measure must be taken to decrease the number of false-positive correlations, it is not always clear what specific target to set. For example, if one insists that the rate of *any* false-positive correlation must be 5%, then a simple, though conservative, method is to apply the Bonferroni correction, which divides the nominal single-test error rate by the number of tests. In the example at hand, this would mean conducting each test with a type I error rate of 0.0000025. Although there are methods to make this conservative adjustment more accurate, it is not clear that this is even a reasonable goal. For example, it seems unduly conservative to demand that the rate of even a single false-positive result across 20,000 tests be only 5%. Unless the size of the study is increased, a reduction in the false-positive error rate by four orders of magnitude will increase the false-negative error rate, perhaps to the point at which correlations of a plausible magnitude cannot be detected.

Another method of controlling false-positives considers the error rate among the tests that have been declared positive, not among all tests. This is called the false discovery rate (FDR). With this approach, if there were 100 positive tests, an FDR of 5% would mean that, on average, 5 would be false-positives. Most researchers would consider such a result highly successful. In fact, 10 positive tests with an FDR of 20 to 30% could be considered an excellent result and would greatly reduce the scale of the subsequent studies required to replicate and validate the findings. The FDR method is generally less conservative than a strict Bonferroni adjustment, though as previously noted, there are ways to calibrate the Bonferroni approach (e.g., through permutation) to make it more comparable to the FDR approach.

Although examples have been described previously in which the need to account for multiple tests is obvious, the problem of false-positives remains even when dealing with 5 to 10 markers. Explicit accounting of the multiple tests is often omitted in such situations, but this does not obviate the need for independent replication and validation of any apparent correlation.

KEY POINTS

- Common measures of correlation assess the linear correlation between variables. Lack of linear correlation does not necessarily mean that the variables are not related.
- Measures of correlation may be sensitive to a few outlying observations.
- Correlation, by itself, does not imply causation. Even though a biomarker may be correlated with both treatment and outcome, this is not sufficient to establish that the biomarker is a useful surrogate endpoint.

STATISTICAL ANALYSIS METHODS

This section discusses some of the more important and advanced statistical methods that are common in oncology studies. Of course, each of these is itself the subject of entire books, and,

thus, only the most basic features of these methods can be covered here. The greater part of this section is devoted to the analysis of survival or time-to-event data, which are ubiquitous in the evaluation of clinical research. Some other advanced methods that may be encountered are also covered.

A common feature of the analytic methods discussed here is that they can be extended to incorporate the simultaneous effects of multiple variables on outcome, referred to as "regression analysis." Regression analysis involving multiple variables is frequently referred to as multivariate (or sometimes multivariable) analysis, in contrast to univariate analysis, which considers only one variable at a time. Adjustment for multiple variables is particularly important in comparative studies using retrospective or other nonrandomized data or in developing predictive models to evaluate multiple, possibly correlated factors.

SURVIVAL ANALYSIS

Because of the potentially long temporal course of the disease, a large part of the evaluation of cancer and its treatment involves extended periods of follow-up, often spanning many years. Measures of therapeutic efficacy or prognostic value are frequently defined by the percentage of patients alive at a particular time or alive and free of recurrence at a particular time. Conversely, one might be interested in the median time to death, recurrence, or some other defining event. Often it is not possible to follow all patients until the defining event occurs, or even until they have reached a specified length of follow-up.

The analysis of data related to the duration of time until an event is generically referred to as "time-to-event analysis" or "survival analysis."[17] The methods employed in such analysis must take into account the fact that some patients will not be followed until the time of the event, but provide partial information about the length of that time—that is, the length of time from the start of follow-up until the time of analysis. The discontinuation of follow-up prior to a defining event is called "censoring." The fraction of event times that are censored may range from near zero, in settings where almost all patients die or have recurrent disease, to greater than 90%, in settings with excellent survival.

The most common display of censored survival data is the survival curve. This is an estimate of the underlying survival function, $S(t)$, that defines the probability of surviving past time t or more generally that the time to a defining event exceeds t. Although this is the way that data are visualized, the statistical analysis of such data is more often based on a related quantity called the "hazard function," $\lambda(t)$, which is the underlying rate at which events occur among the population of patients at risk. This is feasible because there is a well-defined and fundamental mathematical relationship between the survival function and hazard function; intuitively, if the rate of events increases, then the probability of surviving without that event decreases.

The most common methods associated with displaying and analyzing time-to-event data are described later. There are two key assumptions underlying all of these methods. One is that the censoring of event times, if it occurs, is not related to the subsequent occurrence of the event—that is, that the reason for censoring is uninformative with respect to what happens afterward. Another fundamental principle of survival analysis, since survival is a predictive quantity, is that only past information can be used in modeling and analyzing future events. An example in which the latter principle is violated would be the division of patients into two groups, depending on whether or not they had a tumor response, and evaluating time to death from the time of initiation of therapy. Therefore, the groups are defined using future information, and unbiased predictions of survival after the start of therapy cannot use this information.

Kaplan–Meier Curves

The universal standard for providing estimates of survival curves is the Kaplan–Meier estimator (sometimes also called the “product-limit estimator”). This is typically plotted as a step function, with a step occurring at every unique death time. The calculation involved in the Kaplan–Meier estimator is actually quite simple—the height of each step is the height of the curve at the previous step multiplied by the fraction of patients at risk at the particular death time who survive beyond that time. The number of patients at risk at a particular point in time is the number of patients who have not died or been censored before that time. For example, suppose that the time until death or censoring is measured to the nearest week. If the estimated survival probability just before 14 weeks is 0.6, there are 10 patients who have not died or been censored before 14 weeks, and one patient dies at 14 weeks, then the height of the curve drops at that time from 0.6 to 0.54 [0.6 × (9/10)]. In plots of Kaplan–Meier curves, it is common to indicate points of censor with tick marks or to provide a table indicating the numbers of patients at risk at convenient benchmarks.

Because the Kaplan–Meier estimate is the product of fractions with progressively smaller denominators, the precision of the estimate decreases over time. This is readily apparent if confidence intervals are provided, as the confidence intervals will grow increasingly wide over time. In almost all cases, the confidence intervals provided with a Kaplan–Meier curve are based on pointwise estimates of the variability of the survival estimate; it is usually not correct to infer that the bands contain the entirety of the true survival curve with the stated level of confidence. The step following the last observed time of death is often extended out as far as the last censoring time, although, technically, the estimate is undefined after the last death. As previously noted, the steps in the right-hand tail of the estimated curve grow larger as the number of patients at risk decreases. If the last patient under observation dies, then the estimated survival probability drops to zero at that time point.

Figure 5-4 illustrates a Kaplan–Meier curve in a relatively small sample of 33 patients, 15 of whom died. Tick marks indicate the points at which surviving patients are last known to be alive. The gray lines indicate pointwise 95% confidence intervals for the survival probability. The green line indicates how median survival is estimated from a Kaplan–Meier curve: this is the time at which the estimated survival probability first drops below 50%.

Although in the previous discussion only deaths have been referred to, the Kaplan–Meier method readily encompasses the concept of event-free survival. For example, the estimate of disease-free survival counts both deaths and relapses as events, and the curve steps down whenever either event occurs, using the same calculation. The term “overall survival” is usually meant to refer to a survival curve that counts only deaths as events. The term “actuarial survival” is a misnomer—it refers back to a different method of estimating the survival curve (the actuarial or life-table method) that was used prior to the introduction of the Kaplan–Meier method but is now obsolete in the medical context. The Kaplan–Meier method should not be used when the intent is to estimate the probability of being free of a particular kind of event, for example a particular cause of death. This is a “competing risks” problem and requires the use of methods described as follows.

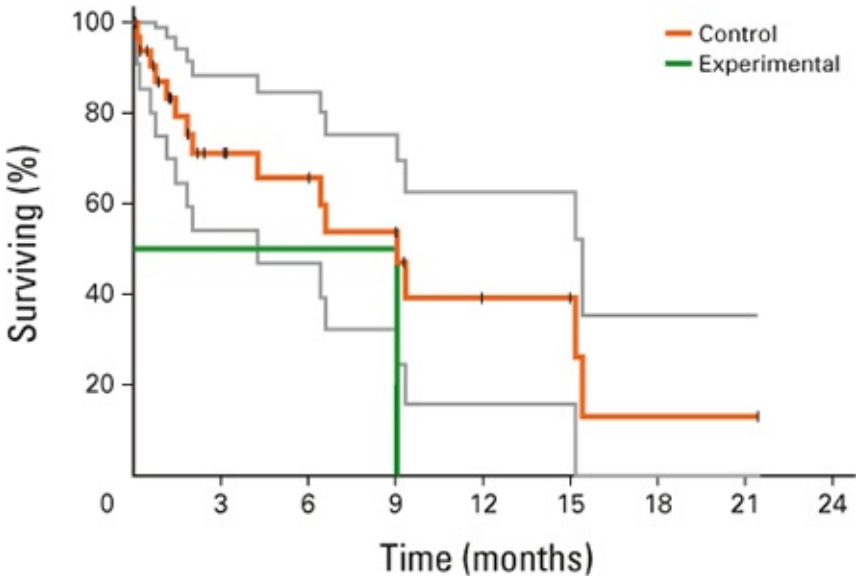

Fig. 5-4 A survival curve and related quantities.

The orange line is an example of a Kaplan–Meier curve for a group of 33 patients. At any point in time, the curve estimates the probability of surviving at least as long as that time. Gray lines indicate the 95% confidence intervals for the survival probability calculated at each point in time. Tick marks indicate times at which surviving patients are last known to be alive. The green line indicates how median survival would be calculated: in this curve, the survival probability drops to less than 50% at 9 months.

Comparing Kaplan–Meier Curves

The comparison of survival curves can be approached in several ways: (a) by comparing the estimated survival probability at a fixed point in time; (b) by comparing the time at which the estimated survival probability is a fixed value, usually the median; or (c) by comparing the survival curves across the entire period of follow-up. In general, the first two approaches should be avoided unless there is a very strong justification for focusing on a particular survival time or percentile. This is because the comparison clearly can vary depending on the point chosen.

The most common way to compare survival curves across time is with the log-rank statistic, as illustrated in Fig. 5-5, which compares disease-free survival in a hypothetical clinical trial of an experimental compared with a control treatment. Perhaps somewhat surprisingly, this statistic is not based directly on the calculated survival estimates; rather, it is based on a comparison of the number of events observed in one group to the number of events that would have been expected in that group if the deaths occurred solely in proportion to the numbers of patients at risk. If this difference is too extreme (as reflected in a p value), then it provides evidence that the underlying event rates in the groups are different. The standard log-rank test is most sensitive to situations in which the event rates in the groups differ by the same ratio across time. There are weighted versions of this test that are appropriate if the differences are expected to occur primarily during the early or later periods of follow-up; however, the intent to use a weighted log-rank test should be specified prior to observing where the differences in event rates occur.

The comparison of survival curves is a special case of HR analysis, performed through Cox regression, which is discussed later. In fact, the log-rank test is also a test of the equality of hazard rates in the two groups. The result of the HR analysis is also provided in Fig. 5-5, illustrating the notion that better survival is associated with a lower event rate for mortality.

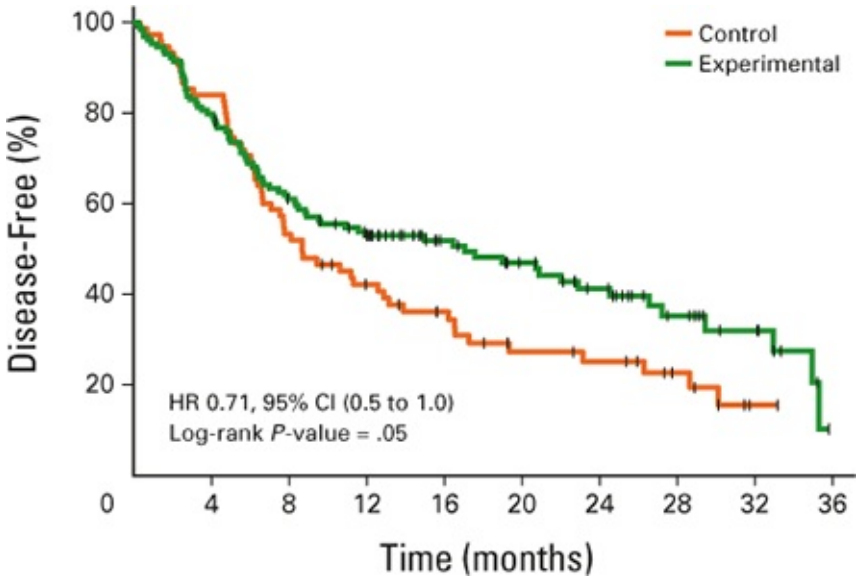

Fig. 5-5 Comparing survival curves.

The two curves represent a hypothetical comparison of disease-free survival for two treatments. The curves drop when a patient experiences relapse or dies without relapse (treatment-related mortality).

Competing Risks and Cumulative Incidence

As noted previously, when there are multiple types of events that define event-free survival, or multiple causes of death, then probabilities associated with a specific type of event or a specific cause of death should not be estimated by Kaplan–Meier methods. For example, suppose that one is interested in comparing breast cancer mortality as opposed to all-cause mortality (the complement of overall survival) between two treatment groups. The relevance of this comparison might be debated, since cause-of-death classification can be fairly subjective. A common but incorrect approach to this problem is to censor patients at the time of a non–breast-cancer death, and to plot the complement of the resulting Kaplan–Meier curve as a representation of cumulative breast cancer mortality over time. The problem with this approach is that patients who die of other causes are not even hypothetically at risk for future death from breast cancer—the implicit assumption that they are, which is appropriate for the standard types of censoring, results in an overestimation of the probability of breast cancer death.

The correct calculation of cumulative incidence in the competing risks setting must take into account the probability of remaining at risk (or event-free). When this is done, the sum of the cumulative incidence probabilities for each of the types of events is exactly the complement of the event-free survival probability. For example, at any point in time, (a) the overall survival probability, (b) the probability of breast cancer death, and (c) the probability of non−breast-cancer death will sum to 100%.

Although Kaplan–Meier methods are generally inappropriate for generating estimates of cumulative incidence in the presence of competing risks, the comparison of cumulative incidence curves is properly handled using the same previously discussed log-rank statistic, with events other than the type of interest being censored at the time of their occurrence. This seeming contradiction relates to the fact that in neither case is the log-rank statistic based directly on the estimates of the event probabilities themselves. Rather, it is based on the relative numbers of events that occur in each patient group, given the numbers of patients remaining at risk in each group over time. Thus, it is appropriate, for this purpose, to censor patients who experience competing events at the time of the event, since they are no longer at risk for the event of interest.

Figure 5-6 illustrates competing risks analysis derived from the same data shown in Fig. 5-5. Disease-free survival reflects two competing risks: relapse and death without relapse, which perhaps reflects toxic complications of treatment. Panel A shows the cumulative incidence of relapse and Panel B the cumulative incidence of treatment-related mortality. The sum of these two incidences, plus the event-free survival probability from Fig. 5-5, will equal 100% at any point in time. The curves and the log-rank analysis clearly suggest that the improvement in disease-free survival associated with the experimental arm is based largely on a reduction in treatment-related mortality, with little apparent effect on relapse.

At the risk of making the issue seem overly complicated, it should be noted that in the competing risks setting, the results of statistical analysis may not always appear concordant with the visual interpretation of cumulative incidence curves. This is because incidence is a composite result of (a) the rate at which events occur among those at risk (the hazard rate), and (b) the size of the population at risk. For example, consider a setting in which toxic regimens with potentially fatal complications are employed in a setting with high rates of relapse. The events of relapse and nonrelapse death constitute competing risks. Suppose that one regimen is much more effective than the other in preventing relapse but has the same underlying toxicity, based on a HR analysis showing equivalent hazard rates for nonrelapse death in the two groups. In this case, the cumulative incidence of nonrelapse death will appear higher in the group receiving the more effective therapy. This is because the effectiveness of the therapy in preventing relapse places more patients at risk for nonrelapse death.

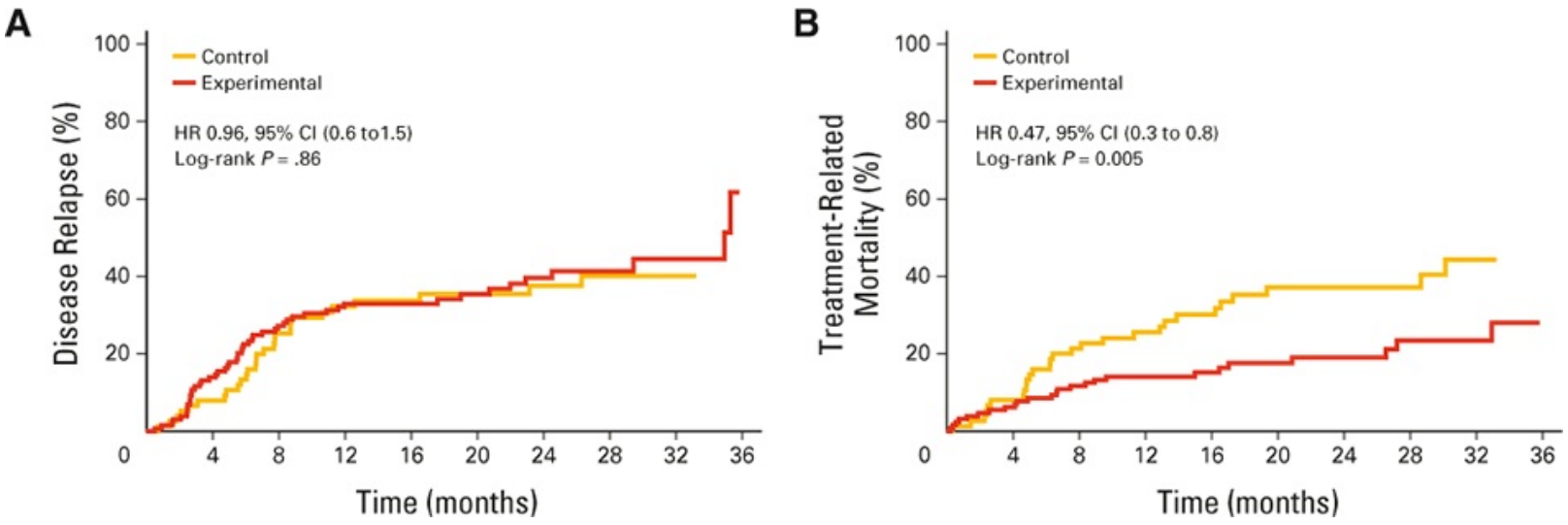

Fig. 5-6 Cumulative incidence curves and competing risks.

The data from Fig. 5-5 are decomposed into the two competing risks of relapse (A) and treatment-related mortality (B). Most of the improvement in disease-free survival in the experimental arm is attributable to a decrease in treatment-related mortality; there is no observed difference in the rate of relapse between arms among those at risk for relapse.

The intent of the previous example is not to imply that the HR analysis is correct or that the cumulative incidence analysis is misleading. The important point is that competing risks should not be evaluated in isolation. Factors that influence one type of event may or may not influence another type, and an informed interpretation of data from a competing-risks setting should consider each type of event. Further, a complete analysis should evaluate not only the underlying rates of the event types, which may be biologically more meaningful, but also the net outcome reflected in their cumulative incidence, which may bear on clinical interpretation.

Cox Regression

Although many clinical trials can be analyzed using only the previous methods, there are many settings in which one wishes to incorporate more information about patient characteristics than just the treatment arm to which they were assigned. This is particularly true in nonrandomized comparisons, where patient groups may not be homogeneous with respect to factors known to affect outcome. Although accounting for these imbalances is in no way a substitute for randomization, it is, nevertheless, helpful to evaluate the extent to which patient characteristics influence the difference, or lack of difference, among treatment groups. In other cases, the interest is not in comparing arms of a clinical trial, but in determining factors that are predictive of better or worse survival. This information is useful in designing trials, counseling patients about their likely prognosis, or gaining increased biologic understanding.

Like other regression models, the Cox regression model relates patient characteristics, called "covariates," to outcome. It is not the only model or method for doing this with time-to-event endpoints, but it is by far the most common regression model used in the context of medical research. As previously noted, one of the fundamental quantities defining survival is the hazard function, $\lambda(t)$, which is the rate at which events occur among patients at risk for the event. The Cox model, or proportional-hazards model, assumes that covariates multiplicatively influence a baseline hazard function, $\lambda_0(t)$, which applies when the covariates have a specified baseline or reference value. One reason for the popularity of the Cox model is that it makes no assumptions about the form of this baseline hazard. For example, suppose that the reference value for patient sex is female. The hazard rate for females is thus $\lambda_0(t)$, and that for males would be specified as $\lambda_0(t)e^{\beta male}$, so that the effect of being male is to multiply the hazard function by the quantity $e^{\beta male}$. The quantity β_{male} is a regression coefficient that captures the magnitude and direction of the effect. If β_{male} is greater than zero, then $e^{\beta male}$ is greater than one and the effect of being male (relative to being female) is an increased hazard rate. Assuming that the hazard rate is for an untoward event like mortality, this means a higher mortality hazard rate and poorer survival. If the coefficient is less than zero, then the hazard multiplier is less than one, and this would yield a lower mortality hazard and better survival. Note that $e^{\beta male}$ is also the ratio of the hazard function for males to the hazard function for females at any point in time, and it is called the HR. The basic Cox model implicitly assumes that this HR for males compared with females is the same at any time point (the proportional-hazards assumption); however, techniques are available for relaxing this assumption. Covariates need not relate to discrete groups but can be defined quantitatively. For example, suppose that the reference value for patient age is 50. Then the multiplicative effect of age on the hazard function could be expressed as $e^{\beta age}$; for every year of age older than 50 the hazard rate is multiplied by the quantity $e^{\beta age}$. When multiple covariates are included in the Cox model, the interpretations of the HRs are considered to be adjusted for the other factors in the model. For example, if a Cox model includes both sex and age, then $e^{\beta male}$ would represent the HR for males compared with females of a similar age.

The basic regression model assumes that the covariates affect the hazard independently—that is, that the effect of age is the same for males and females, but more complicated models can be constructed allowing interaction among covariates. Covariates for prognostic models are defined at the start of the survival period, but one can also allow the covariates to change over time, in which case they are called "time-dependent covariates." The Cox regression model also extends directly to the analysis of cause-specific hazard rates found in the

competing-risks setting, by incorporating censoring for events of other types.

BINARY DATA ANALYSIS

In contrast to time-to-event analysis, there are occasions when the outcome of a clinical trial or other exercise may be summarized by the presence or absence of an event, an outcome, or a characteristic. This dichotomization of outcome is said to be “binary data.” Such data do not necessarily exclude aspects of time: for example, if outcome can be ascertained on all patients, then the occurrence of an event during a defined period of time can be a binary outcome. This is referred to as “risk,” but binary outcomes can refer to things other than risk. For instance, two groups of patients with breast cancer might be compared with respect to the percentage of patients with estrogen receptor–positive disease. The same or similar statistical methods may be applied to both scenarios.

Chi-Square Analysis

For basic statistical analysis of binary endpoints, such as comparing one or more groups in terms of the risk of an event or the percentage with a certain characteristic, the most common methodology is based on the chi-square test (also mentioned in Table 5-1). For very small sample sizes, the accuracy of p values from the chi-square analysis may be in doubt, and the Fisher exact test is the most common alternative, although it is generally quite conservative.

Like the log-rank test for survival analysis, the basic methods associated with binary data provide a test of equality, but not necessarily a measure of effect. The most straightforward measure of effect is the simple difference in proportions. Other common measures of effect associated with binary outcomes[18] must be used with some caution in typical applications involving clinical data. For example, if p is the risk of an event, then the odds of the event are $p/(1 - p)$. Conversely, if ψ is the odds of an event, then the risk of the event is $\psi/(1 + \psi)$. In certain epidemiologic settings, where p is small, the ratio of the odds of an event between groups (odds ratio [OR]) will be approximately equal to the ratio of the risks (relative risk) and is a standard measure of association or effect. In clinical settings, however, the values of p associated with risk are not necessarily small. Although the same underlying statistical methods may be applicable, the OR in such settings may be nonintuitive or even misleading. For example, consider a patient group with a risk for recurrence of 90% compared with another group with a risk for recurrence of 80%. The OR for risk for recurrence is 2.25, but clearly the risk for recurrence is not nearly doubled. Similar considerations apply when interpreting an HR in survival analysis. If the risk for an event is not too large, then an HR will approximate a risk ratio; however, the divergence between a risk ratio and an HR is not as dramatic as that between a risk ratio and an OR. For example, a risk ratio of 2.0 (0.4/0.2) corresponds to an OR of 2.67 and to an HR of 2.25 (under an exponential assumption).

Logistic Regression

The most common method for incorporating covariate effects into binary data analysis is logistic regression. The formulation of the underlying statistical model is not that dissimilar from Cox regression. If $\psi_0 = p_0/(1 - p_0)$ is the odds of the event of interest for a specified baseline or reference value of the covariates (such as female sex), then the odds of the event for a male are specified as $\psi_0 e^{\beta male}$ so that the quantity $e^{\beta male}$ is the multiplicative effect on the baseline odds. It is also the OR for the risk for the event for males compared with females, although, as

noted, one must be cautious in interpreting that as a risk ratio. Similarly, the multiplicative effect of a continuous covariate like age on the baseline odds (odds at age 50) would be expressed as $e^{(\text{age} - 50)\beta\text{age}}$; for every year of age older than 50, the odds of the event are multiplied by the quantity $e^{\beta age}$.

ANALYSIS OF RECURRENT EVENTS

In the discussion of survival analysis, the time to an event that occurs only once, such as death, or that is generally only of interest the first time it occurs, such as relapse was considered. Of course, patients whose disease relapses may be re-treated, go into remission, and then relapse again, but this is usually a question for a different study. Other events may occur repeatedly over time, and the rate of occurrence of such events is of interest. Examples of this relate commonly to the study of treatment complications, such as infection, seizure, or any sequelae that occur in distinct, well-defined episodes.

One technique for analyzing data of this kind involves what is called Poisson regression. This is related to the Poisson process, the classic example of which is the emission of particles in the process of radioactive decay. This stochastic event is characterized by the fact that after one particle is emitted, the distribution of the time to the next particle is the same, regardless of how long the process has been going on. The rate of events over time is denoted λ, and during a period of the time *t,* the number of events that occurs follows a Poisson distribution, which is characterized by its mean, equal to $\lambda \cdot t$. Poisson regression allows one to model the effect of covariates on λ in a manner analogous to that for Cox regression and logistic regression. For example, if λ_0 is the rate of events for a specified baseline or reference value of the covariates (such as female sex), then the rate of events for a male are specified as $\psi_0 e^{\beta male}$ so that the quantity $e^{\beta male}$ is the multiplicative effect on the baseline rate, or the rate ratio for males relative to females. The same considerations apply to continuous covariates, such as age.

There are more complicated analytic strategies that can be applied when one is unwilling to assume that the event rate λ is constant over time; for example, by partitioning the time axis into intervals and modeling the counts in each interval separately. Cox regression also can be used to separately model the time to first event, time from first event to second event, time from second event to third event, etc.

LONGITUDINAL DATA ANALYSIS

In many studies, patients may be assessed repeatedly over extended periods of time. Data that arise from repeated measurement of the same patient over time are called “longitudinal data” or sometimes “clustered data.” The distinction from the previous section is that the quantity being studied is inherently measurable at any point in time. Common examples of such data would be quality-of-life assessments or the evaluation of biomarker levels over time. Pharmacokinetic data are a specialized case of longitudinal data, which have specific methods for analysis that are beyond the scope of this chapter.

It is possible to do useful analysis of longitudinal data using very basic statistical methods—for example, by comparing groups at a fixed point in time, or by comparing one time to another. However, such methods may not allow one to evaluate the trajectory of the quantity being studied as a whole and do not fully accommodate common features of longitudinal data, such as missing data, variable times of assessment, and risk factors that also change over time. In order to analyze all of the data simultaneously, one must take into account the fact that

repeated observations from the same patient are likely correlated. For example, one patient may report relatively high quality of life during the entire period of study and another low quality of life, although both patients may experience a similar change over time.

Appropriately accounting for this within-patient correlation is not necessarily straightforward, and the methods involved may be quite complex and are beyond what can be presented in detail here. There are two fairly common approaches to handling longitudinal data analysis. Although the nomenclature may vary, one is generally referred to as a "linear mixed models approach" and the other as a "generalized estimating equation approach." The term *mixed* in the former case refers to the simultaneous estimation of parameters that model the mean effects (the effects of clinical interest) and parameters that model the within-patient correlation structure of the data. One must make explicit assumptions about the latter, and the results may be sensitive to that assumption. The generalized estimating equation approach makes less explicit assumptions about the correlation structure. This is an advantage, particularly if one has no particular interest in the correlation structure itself, which is often the case when the interest is in comparing outcomes between groups or evaluating the effects of other factors on outcome.

KEY POINTS

- Survival analysis techniques are used to analyze outcomes describing the time until an event occurs, which may be subject to censoring or competing risks.
- Although Kaplan–Meier curves are the universal standard for graphically representing time-to-event endpoints, the statistical analysis of such curves is usually not based on a direct comparison of the curves themselves. Rather, the comparison is based on the underlying hazard rate—the rate of events among patients remaining at risk—using the log-rank test.
- Similar considerations apply to the comparison of cumulative incidence curves.
- Cox regression is used to model the hazard rate in survival analysis, where the effect of a covariate can be summarized through a hazard ratio or relative risk.
- Binary data analysis is used for outcomes with yes/no or binary responses. Chi-square or Fisher exact tests are used to compare proportions between groups. Logistic regression is used to model the odds of a response, where the effect of a covariate is summarized through an odds ratio.
- Analysis of recurrent events is done when patients can experience an event repeatedly over time. Poisson regression is often used to model the event rate, where the effect of a covariate is summarized through a relative risk.
- Longitudinal data analysis is used to model outcomes that are assessed repeatedly over time. These methods must account for missing data commonly occurring in this setting, as well as correlation between measurements on the same individual.

SUMMARY

Statistical considerations are a key component in both the design and the analysis of clinical

research studies. Proper study design allows one to control the systematic and random factors that affect patient outcomes in clinical studies, and proper analysis allows one to make the best possible judgment as to which is more important. Few oncologists engaged in clinical research have sufficient statistical training or knowledge to do this on their own, which is why statisticians are in high demand in medical research and are considered a vital part of the research endeavor. Statisticians are also frequently engaged in evaluating research proposals for funding purposes and in reviewing research papers for publication in medical journals.

Although most clinical studies published in major medical journals have likely involved a statistician in both the conduct of the study and in the review of the article, it is still essential for the practicing oncologist to have some rudimentary familiarity with common statistical concepts and terminology, which has been the goal of this chapter. Such knowledge will enhance his or her ability to evaluate the medical literature, explain treatment options to patients, and make informed decisions about joining research studies available to the community.

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GENETIC TESTING FOR HEREDITARY CANCER SYNDROMES

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OVERVIEW

During the past two decades, the availability of clinical genetic counseling and testing for hereditary cancer predisposition syndromes has had a major impact on the practice of medical and preventive oncology. The identification and treatment of patients with an inherited predisposition to cancer is now one of the core elements of oncologic care, with statements and guidelines on genetic testing and management provided by the American Society of Clinical Oncology (ASCO) and other organizations.[1-6] Importantly, the taking of a family history by medical oncologists, and the continued updating of this dynamic information on a regular basis, allows for the identification of patients and families who may benefit from genetic counseling and testing and opportunities for precision prevention oncology, a strategy wherein cancer prevention recommendations are specifically tailored to the individual patient.

In this chapter, we review the major principles that guide genetic counseling and testing, highlight the differences between testing and counseling for high-penetrance versus moderate-penetrance cancer susceptibility genes, and discuss ways of integrating genetic test results into the care of oncology patients. The advent of next-generation sequencing (NGS) technologies has added further complexity to the assessment of the genetic risk of cancer, including implications for tumor and germline analysis, the widespread use of multigene (panel) testing for inherited cancer susceptibility, and the increased identification of incidental or uncertain genetic findings. Oncologists are encouraged to recognize the importance of both pretest and posttest genetic counseling and to build relationships with local genetic counselors and other genetic specialists and to see them as allies in the challenge of helping patients and their families through a diagnosis of cancer. Notably, genetic counseling is not just for patients who have already undergone testing and were found to have genetic alterations; rather, it is for patients and families who are considering the option of genetic testing in the future or for individuals who may simply benefit from a risk assessment discussion.[7] Resources for finding genetic specialists include the National Society of Genetic Counselors (NSGC), the American Board of Genetic Counseling, the National Cancer Institute Cancer Genetics Services Directory, and the GeneTests Clinic Directory .[8] Resources for learning more about cancer genetics and risk assessment include the ASCO University Cancer Genetics Program, NSGC, and the National Human Genome Research Institute.[9,10]

Although a detailed description for each of the cancer susceptibility genes and syndromes is outside the scope of this chapter, Table 6-1 is a concise reference for noteworthy high- and moderate-penetrance genes and their associated cancer risks. Table 6-2 includes a detailed

summary of noteworthy cancer susceptibility genes, including cancer risks, recommended interventions, and syndromic features. Additionally, because many of the more common cancer predisposition syndromes are discussed elsewhere, when appropriate, please refer to the specific chapters for additional information on breast cancer, gastrointestinal cancers, gynecologic cancers, and leukemias (Chapters 7, 10, 12, and 16, respectively).

Table 6-1 Overview of High- and Moderate-Penetrance Genes by Associated Cancers[11-13]*

	Breast	Ovary	Endometrium	Colorectum	Polyposis	Gastric and/or Small Bowel	Pancreas	Melanoma	Prostate	Renal	Thyroid	Other
APC				X	X (adenomatous)	X	(X)				X	X (desmoid tumors, hepatoblastoma, medulloblastoma)
*APC** I1307K				X†								
ATM	X	(X)					X					Autosomal recessive Ataxia telangiectasia
BAP1								X (uveal and cutaneous)		X		X (malignant mesothelioma)
BARD1	(X)	(X)										
BMPR1A				X	X (juvenile)	X						
BRCA1, BRCA2	X	X					X	(X)	X			
BRIP1		X										Autosomal recessive Fanconi anemia
CDH1	X (lobular)					X (diffuse gastric)						
CDKN2A							X	X				
CDK4							X	X				
CHEK2	X	(X)		X					(X)			
GREM1				X	X (mixed)							
FH										X (type 2 papillary, tubule-papillary, collecting-duct carcinoma)		
FLCN										X (oncocytoma, chromophobe, oncocytic hybrid tumor)		
MAX												X (pheochromocytoma, paraganglioma)
MEN1							X (gastro-entero-pancreatic tract, well-differentiated endocrine tumors)					X (pituitary tumors, parathyroid tumors, carcinoid tumors, adrenocortical tumors)
MET										X (type 1 papillary)		
MITF								X		(X)		
MLH1, MSH2, MSH6, PMS2, EPCAM		X	X	X		X	X			X (ureter and renal pelvis)		X (sebaceous gland neoplasms, brain)

	Breast	Ovary	Endo-metrium	Colorectum	Polyposis	Gastric and/or Small Bowel	Pancreas	Melanoma	Pros-tate	Renal	Thyroid	Other
MRE11A	(X)	(X)										
MUTYH (monoallelic)				X								
MUTYH (biallelic)				X	X	X						
NBN	(X)											Autosomal recessive Nijmegen breakage syndrome
NF1	(X)											High-penetrance neurofibromatosis type 1
PALB2	X	(X)					X					
POLD1, POLE				X	X							
PTEN	X		X	X	X (hamartomatous)					X	X (often follicular)	
RAD50	(X)	(X)										
RAD51C, RAD51D		X										*RAD51C*: Autosomal recessive Fanconi anemia
RET											X (medullary, C cell hyperplasia)	X (pheochromocytoma, parathyroid adenoma)
SDHB, SDHC, SDHD, SDHA, SDHAF2										X	(X)	X (pheochromocytoma, paraganglioma, GIST)
SMAD4				X	X (juvenile)	X						
STK11	X	X (SCTAT)	X	X	X (Peutz-Jeghers)	X	X					X (adenoma malignum of the cervix; testes Sertoli cell; lung)
TMEM127												X (pheochromocytoma)
TP53	X			X		X	X			X		X (sarcoma, leukemia, adrenocortical, brain, others)
TSC1, TSC2										X (renal cell carcinoma, angiomyolipomas, oncocytoma)		(X) (possible neuroendocrine tumors; subependymal giant cell astrocytomas)
VHL							X (neuroendocrine tumors)			X		X (pheochromocytoma, paraganglioma)

*Blue rows reflect high-penetrance genes; white rows reflect moderate-penetrance genes. X denotes that evidence supports the association; and (X), that to date, there is limited or insufficient data regarding the extent of the association.

†Risk estimate for *APC*I1307K* is based on Ashkenazi Jewish population.

Abbreviations: GIST, gastrointestinal stromal tumor; SCTAT, sex cord tumors with annular tubules

Table 6-2 Noteworthy Genes, Syndromes, and Management Considerations

Genes and Details	Syndrome	Penetrance	Associated Neoplasms	Management Considerations	Other Notes	Key References
APC Tumor suppressor Dominant inheritance	Familial adenomatous polyposis (FAP) Attenuated FAP (AFAP) Variant: Turcot syndrome	High	Colorectal lesions (adenomatous polyposis and cancer) Gastric and duodenal/ small bowel lesions (adenomatous polyps and cancer) Desmoid tumors Thyroid (typically papillary) Hepatoblastoma (usually ≤ 5 years old) Pancreatic Medulloblastoma (Turcot syndrome)	Colonoscopy and total colectomy based on polyp burden Upper endoscopy Consideration of small-bowel visualization Thyroid exam and consideration of ultrasonography Consideration of childhood liver palpation, abdominal ultrasound, AFP measurement (investigational)	Genotype-phenotype correlations between classic FAP and AFAP: mutations on the 5′ and 3′ ends of the gene correlate with AFAP High de novo mutation rate (~20-25%) Extracolonic features: congenital hypertrophy of the retinal pigment epithelium (CHRPE); osteomas, supernumerary teeth; desmoid tumors, epidermoid cysts; gastric fundic gland polyps Particularly cribriform-morula variant of papillary thyroid carcinoma Chemoprevention not a replacement for colonoscopy and colectomy	Lynch et al.[14]; Nieuwenhuis et al.[15]; Bisgaard et al.[16]
*APC**I1307K (c.3920T→A)		Moderate	Colorectal	Colonoscopy based on family history or similar to risk for first-degree relative	Ashkenazi Jewish founder mutation Not associated with polyposis	Ma et al.[11]; Laken et al.[17]; Locker et al.[18]
ATM	Ataxia telangiectasia	Moderate (monoallelic/ heterozygous carriers) Rare: High (biallelic)	Monoallelic carriers: Breast Possibly pancreas Biallelic carriers: Leukemia Lymphoma	Monoallelic carriers: Breast screening with annual mammogram and breast MRI starting at age 40 years or as per family history* Biallelic carriers: AT specialist for multidisciplinary management	Monoallelic carriers: limited evidence for pancreas or prostate cancer Risk of autosomal recessive AT condition in biallelic offspring of heterozygous carriers AT: Childhood cerebellar ataxia, telangiectasias of the conjunctivae, immunodeficiency, sensitivity to radiation	Tung et al.[10]; Gatti et al.[19]; Suarez et al.[20]; Renwick et al.[21]; Grant et al.[22]; Pritchard et al.[23]; Walsh et al.[24]
BAP1 Possible Tumor suppressor Dominant inheritance	*BAP1* Tumor Predisposition syndrome	Undetermined	Atypical Spitz tumors Uveal melanoma Malignant mesothelioma Cutaneous melanoma Clear cell renal cell carcinoma Basal cell carcinoma	Eye examinations Dermatologic examinations Consideration of abdominal ultrasonography and/or MRI of the kidneys	Limited evidence for possible other associated tumors: non-small cell lung adenocarcinoma, breast cancer, cholangiocarcinoma, meningioma, neuroendocrine carcinoma	Pilarski et al.[25]; Testa et al.[26]; Wiesner et al.[27]; Abdel-Rahman et al.[28]
BLM	Bloom's syndrome	Low/ undetermined (monoallelic/ heterozygous carriers) Rare: high (biallelic)	Biallelic: Myelodysplasia Variety of epithelial carcinomas (gastrointestinal, genitourinary), lymphoid, hematopoietic, sarcomas, central nervous system, etc.	Biallelic carriers: Bloom's syndrome specialist for management	Monoallelic carriers: Limited evidence for risk of colorectal and breast cancer Bloom's syndrome: chromosome breakage syndrome with growth deficiency, erythematous facial skin lesion, immunodeficiency, frequent infections Founder mutation in Ashkenazi Jewish population	Sanz et al.[29]; Bloom et al.[30]; German et al.[31]; Cunniff et al.[32]; de Voer et al.[33]; Prokofyeva et al.[34]
BMPR1A and *SMAD4*: Tumor suppressor Dominant inheritance	Juvenile polyposis syndrome	High	Gastrointestinal lesions (juvenile/ hamartomatous polyps and cancer [colorectal, stomach, small bowel])	Colonoscopy based on polyp burden Upper endoscopy Surgical management based on polyp burden HHT screening	*Juvenile* refers to polyp histology, not age at onset *SMAD4* mutations associated with HHT *SMAD4* mutations associated with massive gastric polyposis Limited evidence for association with pancreas	Larsen Haidle et al.[35]; Syngal et al.[36]; Brosens et al.[37]; Jass[38]; Chow and Macrae[39]; Iyer et al.[40]; Friedl et al.[41]

Genes and Details	Syndrome	Penetrance	Associated Neoplasms	Management Considerations	Other Notes	Key References
BRCA1 or *BRCA2* Tumor suppressor Dominant inheritance	Hereditary breast and ovarian cancer syndrome	High	Breast (*BRCA1*: often triple-negative tumor) Male breast Ovarian (epithelial; high-grade serous), fallopian tube, primary peritoneal Prostate (high Gleason score) Pancreatic (exocrine)	Breast screening with annual mammogam and breast MRI starting at age 25–30 Male self-exam and clinical breast exam Optional risk-reducing mastectomy Risk-reducing BSO PSA measurement and digital rectal exam Consideration of eligibility and pros/cons of chemoprevention with tamoxifen Consideration of eligibility for treatment with PARP inhibitors Investigational pancreas screening	Founder mutations in certain populations—Ashkenazi Jewish, Icelandic, etc. Autosomal recessive Fanconi anemia with biallelic germline mutations	Chen and Parmigiani[42]; Gonzalez-Angulo et al.[43]; Kauff et al.[44]; Gallagher et al.[45]; Fong et al.[46]; Levy-Lahad et al.[47]; SaloMullen et al.[48]; Meyer et al.[49]; King et al.[50]; see Chapters 7 and 12 for HBOC and PARP inhibitors
BRIP1 Possible tumor suppressor		Moderate (monoallelic/ heterozygous carriers) Rare: high (biallelic)	Ovarian (heterozygous carriers)	Consider risk-reducing BSO at age 50–55 or as per family history†	Risk of autosomal recessive Fanconi anemia in biallelic offspring of heterozygous carriers	Tung et al.[10]; Ramus et al.[51]; Pennington et al.[52]
CDH1 Tumor suppressor Dominant inheritance	Hereditary diffuse gastric cancer syndrome	High	Diffuse gastric cancer Lobular breast cancer	Prophylactic total gastrectomy Breast screening with annual mammography and breast MRI Optional risk-reducing mastectomy	Upper endoscopy not proven to be an effective method of screening for or detecting diffuse gastric cancer Insufficient evidence for colorectal cancer	Guilford et al.[53]; Kaurah et al.[54]; van der Post et al.[55]
CDKN2A Tumor suppressor *CDK4* Oncogene Dominant inheritance	Familial atypical multiple mole melanoma (FAMMM) syndrome	High	Melanoma and dysplastic nevi Pancreas	Dermatologic exam Investigational pancreas screening	Risk of melanoma may be independent of genetic test result *CDKN2a* (p16) founder mutation in the Netherlands	Vasen et al.[56]; Goldstein et al.[57]; Vasen et al.[58]
CHEK2 Tumor suppressor Dominant inheritance		Moderate	Breast Colon	Breast screening with annual mammography and breast MRI starting at age 40 or as per family history* Colonoscopy based on family history or similar to risk for first-degree relative	Genotype-phenotype: different risks for truncating mutations vs. missense mutations Limited evidence for association with prostate cancer	Tung et al.[10]; Ma et al.[11]; CHEK2[59]; Han et al.[60]; Weischer et al.[61]
DICER1 Dominant inheritance	*DICER1* syndrome	High	Pleuropulmonary blastoma (PPB) Ovarian sex cord stromal tumors (Sertoli-Leydig cell tumor, juvenile granulosa cell tumor, gynandroblastoma) Cystic nephroma Thyroid gland neoplasia (cancer, multinodular goiter, adenomas)	No guidelines have been established Consideration of annual physical exam with targeted systems review and possible imaging	Other features: ciliary body medulloepithelioma; botryoid-type embryonal rhabdomyosarcoma of the cervix or other sites; nasal chondromesenchymal hamartoma; renal sarcoma; pituitary blastoma; pineoblastoma Early-onset disease (before age 40) Maternal-fetal medicine care when lung cysts are identified prenatally Papillary or follicular thyroid cancer	Doros et al.[62]; Foulkes et al.[63]; Schultz et al.[64]; Slade et al.[65]; Faure et al.[66]

Genes and Details	Syndrome	Penetrance	Associated Neoplasms	Management Considerations	Other Notes	Key References
GREM1 (SCG5-GREM1) Dominant inheritance	Hereditary mixed polyposis syndrome	High	Colorectal lesions (polyps of mixed histologies and cancer)	Colonoscopy and surgical management based on polyp burden	Only a 40-kb duplication upstream of *GREM1* (spanning 3′ end of *SCG5* and region upstream of *GREM1*) implicated in disease; identified in Ashkenazi Jewish population	Whitelaw et al.[67]; Jaeger et al.[68]; Plesec et al.[69]
Fanconi anemia (multiple genes [at least 20]) Recessive inheritance (most genes) Dominant inheritance (*RAD51* gene) X-linked inheritance (*FANCB* gene)	Fanconi anemia	High: biallelic for the recessive genes and monoallelic for *RAD51*, *FANCB*, *BRCA2*, *PALB2*, *BRCA1* Moderate: monoallelic for *BRIP1*, *RAD51C*	Myelodysplastic syndrome Acute myeloid leukemia Squamous cell carcinoma of head and neck, esophagus, vulva Genitourinary (cervix, Wilms tumor, neuroblastoma) Other solid tumors: liver, brain, skin, breast, gastrointestinal Associated cancers for *BRCA2*, *PALB2*, *BRIP1*, and *RAD51C* carriers	Fanconi anemia specialist for management Hematopoietic stem cell transplantation (HSCT) Early detection and surgical management of solid tumors: oral/otolaryngology/ear-nose-throat examination; gynecologic examination. Human papilloma virus prevention Management for *BRCA2*, *PALB2*, *BRIP1*, and *RAD51C* carriers (discussed elsewhere)	Increased chromosome breakage in lymphocytes tested with diepoxybutane and mitomycin C (does not identify carriers) Physical abnormalities (not in all patients): short stature, abnormal skin pigmentation (café-au-lait or hypo- or hyperpigmentation), skeletal malformations of the upper and lower limbs (thumbs, radii, hands, ulnae), microcephaly, developmental delay, and ophthalmic, genitourinary, cardiac, gastrointestinal, central nervous system anomalies Progressive bone marrow failure (not in all patients): pancytopenia, thrombocytopenia, leukopenia Extreme toxic effects from chemotherapy or radiation Genes and complementation groups: *BRCA2* FA-D1, *BRIP1* FA-J, *PALB2* FA-N, *RAD51* FA-R, *RAD51C* FA-O, *BRCA1* FANCES, and *XRCC2* FANCU	Mehta and Tolar[70]; Kutler et al.[71]; Rosenberg et al.[72]; Auerbach et al.[73]; Kutler et al.[74]; Faivre et al.[75]; Brosh et al.[76]
FH Tumor suppressor Dominant inheritance	Hereditary leiomyomatosis and renal cell cancer (HLRCC)	High	Cutaneous leiomyomata Uterine leiomyomata Renal tumors (type 2 papillary, tubule-papillary, collecting-duct carcinomas; unilateral, solitary lesions)	Dermatologic and gynecologic examination; evaluate for changes suggestive of leiomyosarcoma Medication or resection of leiomyomata Imaging for and surgical management of renal tumors	Fumarate hydratase enzyme assay might be helpful in some situations Risk for uterine leiomyosarcoma is unclear Biallelic *FH* mutations cause a recessive disorder known as fumarate hydratase deficiency—metabolic disorder, profound developmental delay, seizures, fumaric aciduria	Pithukpakorn et al.[77]; Launonen et al.[78]; Tomlinson et al.[79]; Stewart et al.[80]; Sanz-Ortega et al.[81]; Schmidt and Linehan[82]; Barrisford et al.[83]
FLCN Tumor suppressor Dominant inheritance	Birt-Hogg-Dube syndrome	High	Cutaneous (fibrofolliculomas, trichodiscomas/angiofibromas, perifollicular fibromas, acrochordons) Pulmonary cysts Renal tumors (oncocytoma, chromophobe, oncocytic hybrid tumors)	No consensus at this time Dermatologic care Imaging for and surgical management (nephron-sparing) of renal tumors	Fibrofolliculomas are specific to BHD Lung cysts are multiple and bilateral Spontaneous pneumothorax Renal tumors are multifocal, bilateral, and slow-growing Other features: parotid lesions, oral papules, thyroid lesions Unclear data regarding colon cancer Possible genotype-phenotype correlations	Kutler et al.[71]; Toro et al.[84]; Hasumi et al.[85]; Kuroda et al.[86]; Furuya et al.[87]

Genes and Details	Syndrome	Penetrance	Associated Neoplasms	Management Considerations	Other Notes	Key References
KIT (c-Kit) Oncogene Dominant inheritance		High	GISTs	No consensus at this time Imaging and endoscopy might be considered	Diffuse interstitial cell of Cajal hyperplasia (ICCH) Skin hyper- or hypo-pigmentation Mast-cell disorders Related gene: *PDGFRA*	Nishida et al.[88]; Forde et al.[89]; Ricci[90]; Lasota et al.[91]; Ricci et al.[92]
MEN1 Tumor suppressor Dominant inheritance	Multiple endocrine neoplasia type 1 (MEN1)	High	Gastroenteropancreatic (GEP) tract well-differentiated endocrine tumors Pituitary tumors (prolactinoma) Parathyroid tumors Carcinoid tumors Adrenocortical tumors	Biochemical testing Imaging Surgical management Various medications	Primary hyperparathyroidism, hypercalcemia, oligomenorrhea/amenorrhea, galactorrhea, Zollinger-Ellison syndrome (gastrinoma), insulinoma, glucagonoma, VIP-secreting tumor (VIPomas) Other features: skin (angiofibromas, collagenomas), lipomas, central nervous system lesions (meningioma, ependymoma), leiomyomas	Giusti et al.[93]; Machens et al.[94]; Lemos et al.[95]; Thakker et al.[96]
MET (c-Met) Oncogene Dominant inheritance	Hereditary papillary renal carcinoma (HPRC)	High	Papillary renal cancer (multifocal, bilateral, type 1 papillary)	Imaging Surgical management		Kutler et al.[71]; Coleman et al.[97]; Rini et al.[98]
MLH1, MSH2, MSH6, PMS2, and *EPCAM* Tumor suppressor Dominant inheritance	Lynch syndrome (formerly, hereditary nonpolyposis colorectal cancer [HNPCC]) Variant: Muir-Torre syndrome Variant: Turcot syndrome Variant: Constitutional mismatch repair deficiency syndrome (biallelic mutations; recessive inheritance)	High	Colorectal Endometrial Ovarian (epithelial) Stomach Small bowel Upper urinary tract (renal pelvis, ureter) Pancreas Hepatobiliary tract Sebaceous neoplasms (Muir-Torre syndrome) Glioblastoma (Turcot syndrome)	Colonoscopy every 1-2 years starting at age 20-25 Consideration of prophylactic colectomy Hysterectomy and risk-reducing BSO Consideration of upper endoscopy Consideration of urinalysis or urine cytology Consideration of eligibility for treatment with cancer immunotherapy with checkpoint blockade Consideration of aspirin for chemoprevention	Tumor analyses with immunohistochemical (IHC) staining, microsatellite instability (MSI) analysis, somatic tumor genetic analysis, *BRAF* V600E somatic analysis, *MLH1* promoter hypermethylation analysis Amsterdam criteria I and II; revised Bethesda guidelines Recent recommendations for universal screening of colorectal and endometrial cancers Genotype-phenotype correlations emerging but not significant enough to alter management Limited evidence for moderate risk of breast and prostate cancer Autosomal recessive inheritance (biallelic [homozygote or compound heterozygote]) with childhood onset of severe CMMR-D syndrome (café-au-lait macules, solid tumors, hematologic cancers)	Aarnio et al.[99]; Lynch et al.[100]; de Vos tot Nederveen Cappel[101]; Hampel et al.[102]; Bupathi et al.[103]; Castro et al.[104]; Bum et al.[105]; Shia[106]; Zhang[107]; Bouzourene et al.[108]; Vasen et al.[109,110]; Umar et al.[111]; Pérez-Carbonell et al.[112]; Lu[113]; South et al.[114]; Hamilton et al.[115]; Bakry et al.[116]; Raymond et al.[117]; Walsh et al.[118]; see Chapter 10: Gastrointestinal Cancers
MUTYH Recessive inheritance	*MUTYH*-associated polyposis (MAP)	High	Colorectal lesions (adenomatous polyposis and cancer; serrated and hyperplastic polyps also described) Stomach Duodenal lesions (adenomatous polyps, cancer)	Colonoscopy and total colectomy based on polyp burden Upper endoscopy	Phenotypically similar to *AFAP* Two Northern European founder mutations Controversy regarding risk in heterozygous carriers (see *MUTYH* monoallelic/heterozygous carrier)	Al-Tassan et al.[119]; Sieber et al.[120]; Cleary et al.[121]; Lubbe et al.[122]; Aretz et al.[123]; Nielsen et al.[124]

Genes and Details	Syndrome	Penetrance	Associated Neoplasms	Management Considerations	Other Notes	Key References
MUTYH monoallelic/ heterozygous carrier		Moderate	Colorectal	Colonoscopy based on family history or similar to risk for first-degree relative	Controversy regarding risk	Ma et al.[11]; Lubbe et al.[122]; Win et al.[125]; Jenkins et al.[126]
NBN	Nijmegen breakage syndrome (NBS)	Moderate (monoallelic/ heterozygous carriers) Rare: High (biallelic)	Monoallelic carrier: breast Biallelic carrier: lymphoma	Monoallelic carriers: breast screening with annual mammography and breast MRI starting age at age 40 or as per family history* Biallelic carriers: NBS specialist for multidisciplinary management	Heterozygous carrier breast cancer risk; limited evidence for prostate cancer Slavic founder mutation Risk of autosomal recessive condition in offspring of heterozygous carriers (NBS) NBS: chromosomal breakage, microcephaly, dysmorphic features, immunodeficiency, lymphomas	Tung et al.[10]; Pritchard et al.[23]; Walsh et al.[24]; Zhange et al.[127]; Dembrowska-Bagińska[128]
NF1 Tumor suppressor Dominant inheritance	Neurofibroma-tosis type 1	High (moderate risk for breast cancer)	Cutaneous neurofibromas Plexiform neurofibromas Optic nerve and other CNS gliomas Malignant peripheral nerve sheath tumors Breast (moderate risk) Others: GIST, leukemia	NF1 specialist for management Physical exam; ophthalmologic exam; imaging; surgical management Breast screening with annual mammography and breast MRI as per family history*	Café-au-lait macules, axillary and inguinal freckling, iris Lisch nodules, learning disabilities, scoliosis, tibial dysplasia, vasculopathy	Ricci[90]; Friedman[129]; Madanikia et al.[130]; Seminog et al.[131]; Walker et al.[132]
PALB2 Tumor suppressor Dominant inheritance		High	Breast Limited evidence for pancreatic cancer	Breast screening with annual mammogram and breast MRI starting at age 30 or as per family history* Optional risk-reducing mastectomy based on family history Investigational pancreas screening	Insufficient evidence for ovarian cancer Risk of autosomal recessive Fanconi anemia in biallelic offspring of heterozygous carriers	Salo-Mullen et al.[45]; Antoniu et al.[133]; Easton et al.[134]; Jones et al.[135]; Slater et al.[136]; Stadler et al.[137]
POLD1 *POLE* Dominant inheritance	Polymerase proofreading-associated polyposis (PPAP)	High	Colorectal lesions (polyps and cancer)	Colonoscopy and surgical management based on polyp burden	Disease-causing mutations occur in the exonuclease domain Limited data regarding extracolonic cancer risk	Palles et al.[138]; Valle et al.[139]; Church et al.[140]; El Sayed et al.[141]; Spier et al.[142]; Bellido et al.[143]
PRSS1 *SPINK1* *CFTR* *CTRC* Various modes of inheritance	Hereditary pancreatitis	High (*PRSS1*) Variable (*SPINK1*, *CFTR*, *CTRC*)	Pancreas	Pancreatitis management	Pancreatitis (recurrent, acute, chronic throughout lifetime) More severe disease if biallelic mutations are present Biallelic (homozygote or compound heterozygote) *CFTR* mutations associated with cystic fibrosis	LaRusch et al.[144]; Solomon et al.[145]; Solomon and Whitcomb[146]; Rosendahl et al.[147]
PTCH Tumor suppressor Dominant inheritance	Gorlin syndrome/ nevoid basal cell carcinoma syndrome	High	Jaw (odontogenic) keratocysts Basal cell carcinomas Medulloblastoma (primitive neuroectodermal tumor [PNET]–desmoplastic)	Referral to a specialist for management Physical examination Avoidance of sun exposure and at least annual dermatologic examination Surgical management	Other features: congenital skeletal anomalies, cleft lip/ palate, cerebral/falx calcifications, macrocephaly with frontal bossing, polydactyly, intellectual disability, lymphomesenteric or pleural cysts, palmar/plantar pits, cardiac fibromas, ovarian fibromas, ocular abnormalities Related gene: *SUFU*	Evans and Farndon[148]; Soufir et al.[149]; Athar et al.[150]; Smith et al.[151]

Genes and Details	Syndrome	Penetrance	Associated Neoplasms	Management Considerations	Other Notes	Key References
PTEN Tumor suppressor Dominant inheritance	Cowden syndrome/ *PTEN* hamartoma tumor syndrome	High	Breast Thyroid (most often follicular) Endometrial Colorectal lesions (hamartomas, ganglioneuromas, cancer) Genitourinary tumors (renal cell carcinoma)	Breast screening with annual mammography and breast MRI Optional risk-reducing mastectomy Thyroid exam and ultrasound Endometrial screening with random biopsy and ultrasonography Optional hysterectomy Colonoscopy Renal imaging	Major and minor criteria (tumors, physical and dermatologic/ mucocutaneous findings, developmental disability) Macrocephaly Bannanyan-Riley-Ruvalcaba syndrome *PTEN*-related Proteus syndrome Autism spectrum disorder Lhermitte-Duclos disease	Eng[152]; Nelen et al.[153]; Tan et al.[154]; Heald et al.[155]; Eng[156]; Tan et al.[157]; Pilarski et al.[158]; McBride et al.[159]; Haiback et al.[160]; Schrager et al.[161]; Pilarski[162]
RAD51C and *RAD51D* Tumor suppressor		Moderate Rare: high (biallelic *RAD51C*)	Ovarian	Consider risk-reducing BSO at age 50-55 or as per family history†	Risk of autosomal recessive Fanconi anemia in biallelic *RAD51C* offspring of heterozygous carriers	Tung et al.[30]; Meindl et al.[163]; Loveday et al.[164]; Song et al.[165]; Loveday et al.[166]
RB1 Tumor suppressor Dominant inheritance	Retinoblastoma	High	Retinoblastoma (trilateral disease = cooccurrence of pinealoblastoma) Bone or soft-tissue sarcomas Melanoma Others	Ophthalmologic examination and imaging; care by a multidisciplinary team Avoidance of radiation	Knudson's two-hit hypothesis Usually bilateral or multifocal disease Mosaic forms, therefore, analysis of both tumor tissue and blood important RNA studies may also be recommended Low-penetrance mutations identified Parent-of-origin effect in some families	Lohmann et al.[167]; Knudson[168]; Abramson et al.[169]; Abramson et al.[170]; Dimaras et al.[171]; Kleinerman et al.[172]; Klutz et al.[173]; Price et al.[174]
RET Oncogene Dominant inheritance	Multiple endocrine neoplasia type 2 Three subtypes: MEN2A (aka Sipple syndrome) Familial medullary thyroid carcinoma MEN2B	High	Medullary thyroid carcinoma (multifocal, bilateral) and primary C-cell hyperplasia Pheochromocytoma (bilateral) (MEN2A and 2B) Parathyroid adenoma/ hyperplasia (hyperparathyroidism, hypercalcemia, renal stones) (MEN2A)	Prophylactic thyroidectomy (varies from infancy to age 5 or older depending on specific *RET* pathogenic mutation; genotype-phenotype correlations) Surgical management of identified disease Serum calcitonin concentration Consideration of eligibility for treatment with kinase inhibitors Biochemical screening and imaging for pheochromocytoma and parathyroid abnormalities	Genotype-phenotype correlations MEN2A: MTC in early adulthood FMTC: MTC in middle age MEN2B: MTC in early-childhood mucosal neuromas (lips, tongue), dysmorphic features (large lips, "marfanoid" body habitus), gastrointestinal ganglioneuromatosis *RET* gene also associated with Hirschsprung disease	Marquart and Eng[175]; American Thyroid Association et al.[176]; Eng[177]; Wells et al.[178]
SDHB, *SDHC*, *SDHD*, *SDHA*, and *SDHAF2* Tumor suppressors Dominant inheritance	Hereditary paraganglioma-pheochromocytoma syndrome	High (particularly *SDHB* and *SDHD*)	PGL–sympathetic and parasympathetic PCCGISTs Renal clear cell carcinoma Papillary thyroid carcinoma (unclear data)	Biochemical screening, physical exam, and imaging Screening may begin as early as age 10 Pharmacologic treatment Surgical management	Secretory and non-secretory PGL High blood pressure, headache, anxiety, profuse sweating, palpitations, pallor *SDHB*: high risk of malignant transformation *SDHD*: parent-of-origin effect–disease-causing when paternally inherited *SDHAF2*: possible parent-of-origin effect (paternal inheritance)	Ricci[90]; Kirmani et al.[179]; Lenders et al.[180]; Gottlieb and Tomlinson[181]; Pai et al.[182]; Neumann et al.[183]

Genes and Details	Syndrome	Penetrance	Associated Neoplasms	Management Considerations	Other Notes	Key References
STK11 (LKB1) Tumor suppressor Dominant inheritance	Peutz-Jeghers syndrome	High	Gastrointestinal lesions (PJS-type hamartomatous polyps; colorectal, stomach, small bowel cancer) Breast Pancreas Gynecologic (ovarian, cervix, uterus) Testes (Sertoli cell) Lung	Colonoscopy Upper endoscopy with small-bowel visualization Breast screening with annual mammography and breast MRI Investigational pancreas screening Gynecologic exam Testicular exam	Mucocutaneous hyperpigmentation of mouth, lips, nose, eyes, genitalia, fingers; may fade after puberty Females: Sex cord tumors with annular tubules (SCTAT); adenoma malignum of the cervix	Syngal et al.[36]; McGarrity et al.[184]; Beggs et al.[185]; Tomas et al.[186]; Giardiello and Trimbath[187]; Jasperson and Burt[188]; Stoffel et al.[189]
TP53 Tumor suppressor Dominant inheritance	Li-Fraumeni syndrome	High	Soft-tissue and bone sarcomas Breast Brain Adrenocortical carcinoma Leukemia Others: gastrointestinal, genitourinary, lung, lymphomas, thyroid, neuroblastoma, skin	Breast screening with annual breast MRI and mammography beginning in the 20s and 30s, respectively Optional risk-reducing mastectomy Physical exam, including dermatologic and neurologic exams Colonoscopy Investigational whole-body MRI Consideration of radiation avoidance, if clinically appropriate	Classic LFS criteria Chompret criteria Consider genetic testing in *BRCA*-negative isolated early-onset breast cancer (age < 30) Breast cancers more likely to be estrogen-, progesterone-, HER2/neu-receptor positive	Schneider et al.[190]; Li and Fraumeni[191]; Li et al.[192]; Srivastava et al.[193]; Chompret et al.[194]; Gonzalez et al.[195]; Bougeard et al.[196]; Villani et al.[197]
TSC1 and *TSC2* Tumor suppressor Dominant inheritance	Tuberous sclerosis complex	High	Kidney: renal cell carcinomas, angiomyolipomas (benign and malignant), epithelial cysts, oncocytoma (benign adenomatous hamartoma)	TSC specialist for management: imaging; dermatologic, dental, ophthalmologic examinations; Echocardiography, electrocardiography Consideration of eligibility for treatment with mechanistic target of rapamycin (mTOR) inhibitors Surgical management	Skin (hypomelanotic macules, facial angiofibromas, shagreen patches, cephalic plaques, ungual fibromas); brain (cortical dysplasias, subependymal nodules and subependymal giant cell astrocytomas, seizures, intellectual disability/developmental delay, autism spectrum disorder, psychiatric illness); heart (rhabdomyomas, arrhythmias); Lungs (lymphangioleiomyomatosis) Genotype-phenotype correlations: higher risk of renal cell carcinoma in *TSC2* Possible association with neuroendocrine tumors	Northrup et al.[198]; Northrup et al.[199]; Patel et al.[200]; Crino et al.[201]; Borkowska et al.[202]; Al-Salem et al.[203]; Au et al.[204]; Qin et al.[205]; Spurling Jeste et al.[206]; Dworakowska et al.[207]
VHL Tumor suppressor Dominant inheritance	von Hippel-Lindau syndrome	High	Clear cell renal cell carcinoma Pheochromocytoma, paragangliomas Pancreatic neuroendocrine tumors	Neurologic, ophthalmologic, audiologic examinations Biochemical screening Imaging Surgical management	Hemangioblastomas of the brain, spinal cord, and retina; renal cysts; pancreatic cysts; endolymphatic sac tumors; epididymal and broad ligament cysts Genotype-phenotype correlations: VHL type 1, type 2A, type 2B, type 2C with different risks of pheochromocytoma or renal cell carcinoma	Frantzen et al.[208]; Lonser et al.[209]; Maher et al.[210]; Binderup et al.[211]; Kwon et al.[212]; Grubb et al.[213]; Corcos et al.[214]; Blansfield et al.[215]

*Earlier initiation of breast cancer surveillance may be warranted in the presence of a significant family history of breast cancer.
†Earlier consideration of risk-reducing BSO may be warranted in the presence of a clear family history of ovarian cancer (>1 case).
Note: Leukemia/lymphoma predisposition syndromes are not listed; refer to Chapters 16 and 17. The majority of childhood onset conditions are not listed; refer to Lindor et al.[216]
Abbreviations: *AFAP*, attenuated familial adenomatous polyposis; AFP, alpha-fetoprotein; AT, ataxia telangiectasia; BHD, Birt-Hogg-Dube; BSO, bilateral salpingo-oophorectomy; CMMR-D, constitutional mismatch repair deficiency; CNS, central nervous system; FAP, familial adenomatous polyposis; FMTC, familial medullary thyroid carcinoma; GIST, gastrointestinal stromal tumor; HBOC, hereditary breast and ovarian cancer; HHT, hereditary hemorrhagic telangiectasia; LFS, Li-Fraumeni syndrome; MEN, multiple endocrine neoplasia; MRI, magnetic resonance imaging; NBS, Nijmegen breakage syndrome; NF1, neurofibromatosis type 1; PCC, pheochromocytoma; PGL, paraganglioma; PJS, Peutz-Jeghers syndrome; PSA, prostate-specific antigen; TSC, tuberous sclerosis complex; VIP, vasoactive intestinal peptide.

THE HEREDITARY NATURE OF CANCER

Although the heritability of cancer has long been recognized and described by astute physicians, the past four decades have witnessed significant strides in our understanding of the genetic basis of cancer susceptibility. By studying cancer-prone families who demonstrate Mendelian modes of inheritance, over 100 rare, high-penetrance cancer predisposition genes have now been identified; these include *BRCA1* and *BRCA2* in hereditary breast and ovarian cancer (HBOC) syndrome, the DNA mismatch repair genes in Lynch syndrome, *TP53* in Li–Fraumeni syndrome, and *APC* in familial adenomatous polyposis (FAP).[217] Identification of such cancer predisposition syndromes has resulted in the incorporation of genetic testing into the treatment of oncology patients, marking one of the first applications of personalized medicine and allowing for tailored cancer screening, prevention, and more recently, even therapeutic measures. Only a fraction of the familial risks of cancer are explained by the known high-

penetrance cancer predisposition syndromes. For example, in the case of breast cancer, 10% of diagnoses are related to high-penetrance pathogenic genetic variants (e.g., *BRCA1* and *BRCA2* pathogenic genetic variants), whereas the remainder are due to familial factors (e.g., additional shared hereditable factors and/or shared environmental factors) or other endogenous or exogenous factors (e.g., age and hormone exposure).[218] Estimates of the extent to which familial cancer risk contributes to cancer incidence have come from the Nordic twin studies, which evaluated the risk of cancer in monozygotic and same-sex dizygotic individuals.[219,220] In the largest familial study of cancer to date, including more than three decades of follow-up, the heritability (the proportion of disease risk variability in a population due to genetic factors) was estimated to be 33%, with significant heritability observed for cancers of the prostate, ovary, kidney, breast, and uterus as well as melanoma and nonmelanoma skin cancer.[220]

Over the past decade, the emergence of new genomic technologies, along with prior candidate gene studies, has started to redefine the genetic architecture of cancer beyond the classic Mendelian single-gene syndrome model (Fig. 6-1). In fact, we are now aware of dozens of moderate-penetrance genes that generally confer a modest degree of cancer risk, with a relative risk (RR) of 2 to 5. Although screening for such moderate-penetrance genes was not routinely undertaken in the past, with the availability of next-generation sequencing, screening for mutations in many genes simultaneously, often in multigene panels, has become readily available. The value of screening for moderate-penetrance genes remains controversial, as neither the clinical validity (the accuracy with which a genetic test predicts the development of cancer) nor the clinical utility (the degree to which the use of the genetic test informs clinical decision-making and leads to improved health outcomes) has been clearly proven.[222]

In addition to the high- and moderate-penetrance cancer genes, hundreds of additional genetic loci have been identified for nearly all the common malignancies; this has been possible largely with the use of genomewide association studies, with each genetic variant, usually in the form of single-nucleotide polymorphisms (SNPs), being associated with only a slightly increased risk of cancer (RR, ~1.1–1.5) (Fig. 6-1).[223] Given the limited clinical validity and utility of SNPs with such small effect sizes, clinical testing for individual risk loci is not performed, although research efforts to incorporate low-penetrance risk alleles into models for risk stratification for public health programs and cancer screening may eventually be feasible.

Finally, as our genetic understanding of cancer susceptibility has evolved, we have come to appreciate that, like other common human diseases, including heart disease, diabetes, and obesity, the vast majority of cancer diagnoses do not have a single genetic cause but are likely associated with the effects of multiple genes in combination with lifestyle and environmental factors. These polygenic and gene-environment interactions make cancer a multifactorial disease whose complexity we are just beginning to unfold.

KEY POINTS

- The high-penetrance cancer susceptibility genes account for only a small proportion of all cancer diagnoses, most notably in breast, ovarian, and colorectal cancers. Based on evidence from twin studies, familial risks for cancer exist outside of the high-penetrance cancer susceptibility syndromes, particularly prostate, ovary, breast, uterus, and melanoma skin cancer.
- Clinical validity (the accuracy with which a genetic test predicts the development of

disease) and clinical utility (the degree to which the use of the genetic test informs clinical decision-making and leads to improved health outcomes) should be taken into account when genetic testing is being considered.

- Genetic testing for moderate-penetrance cancer susceptibility genes associated with a 2- to 5-fold increased risk of specific cancers has become more commonplace, although the clinical validity and utility of testing for many of these genes is not yet fully defined.

GENETIC COUNSELING

Genetic counseling and genetic testing are considered an integral part of the management of individuals with cancer and have been incorporated into practice guidelines of several medical authorities including ASCO, American Gastroenterological Association (AGA), American College of Obstetricians and Gynecologists (ACOG), Society of Gynecologic Oncology (SGO), and the National Comprehensive Cancer Network (NCCN).[1-6] The National Society of Genetic Counselors (NSGC) has defined genetic counseling as the "process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease."[224] Genetic counseling with or without genetic testing provides an opportunity for discussion of concerns regarding one's family cancer history and possible implementation of cancer screening and prevention efforts based on family history alone.

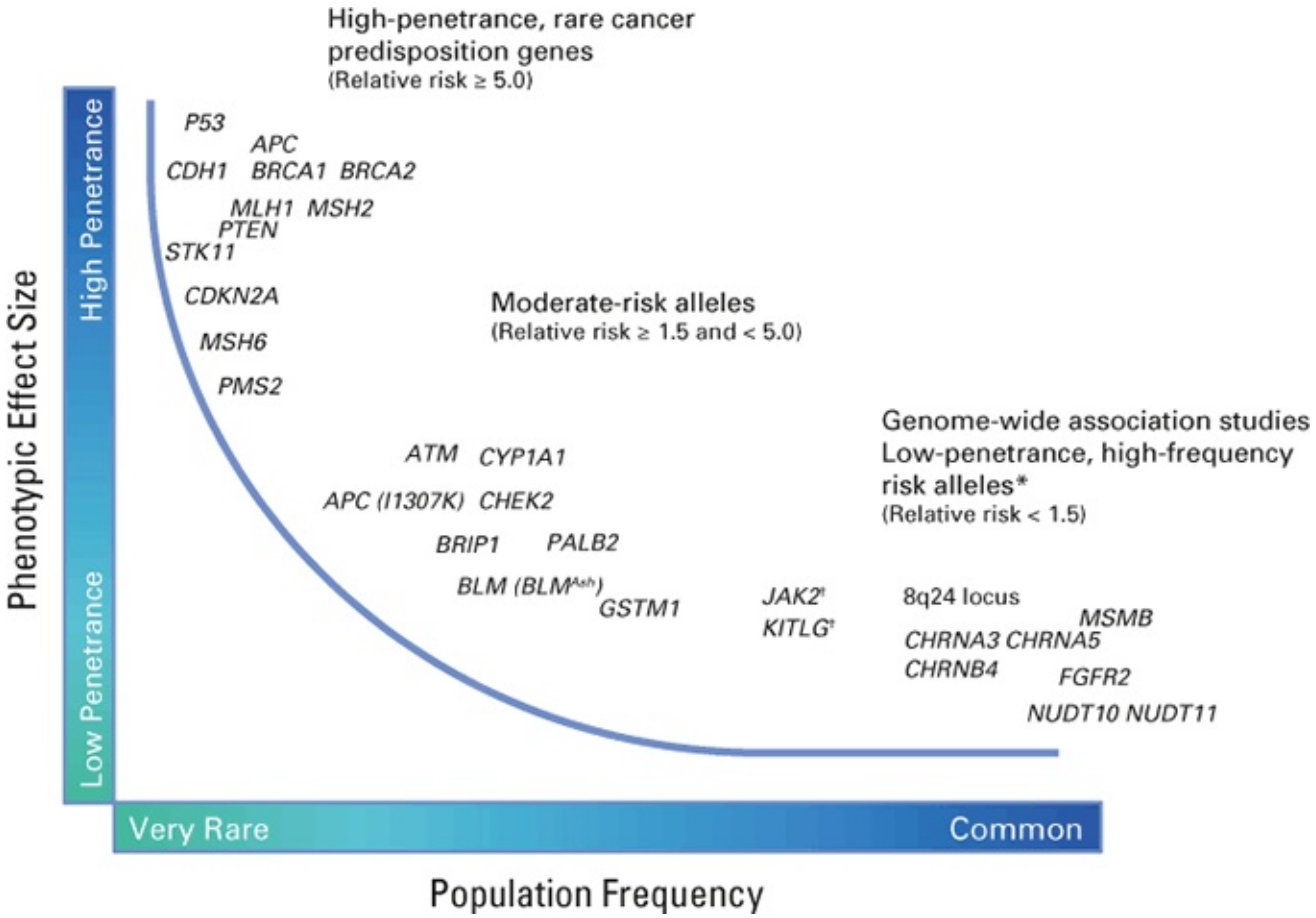

Fig. 6-1 Phenotypic effect size and frequency of occurrence.

*Named genes reflect only the most likely candidate genes to be implicated by the marker single nucleotide polymorphisms (SNPs) identified from the genomewide association studies.

†The marker SNPs mapping to *JAK2* in myeloproliferative neoplasms and *KITLG* in testicular germ cell tumors have odds ratios of approximately 3.0, with allele frequencies ranging from 20 to 40%.

Source: Stadler ZK, Thom P, Robson ME, et al. Genome-wide association studies of cancer. J Clin Oncol. 2010;28:4255–4267. Epub 2010 Jun 28. PMID: 20585100.

The traditional model of genetic counseling for hereditary cancer syndromes includes both pre- and post-test consultations with a genetic counselor and often a geneticist. While the number of board-certified genetic counselors has grown by 85% since 2006,[224] a workforce shortage does exist. Given this, expanded models of service delivery are now being used, including tele-medicine, telephone-based methods, and genetic counseling provided by other practitioners in the context of coordinated patient care.[1,225] Many oncology patients are now offered genetic testing through next-generation sequencing analyses of tumor and sometimes nontumor specimens for the purpose of clinical trial eligibility. Expanding the role of medical oncologists and nurses to include genetic counseling to and testing of oncology patients when appropriate is one model to meet patients' needs. Importantly though, no matter which clinician provides genetic risk assessment, the principles of genetic counseling should be at the foundation of the patient interaction.

PRETEST GENETIC COUNSELING

Pretest genetic counseling is often considered to be analogous to the informed consent process and is therefore a vital step in helping patients and families determine whether genetic testing (and to what extent) is appropriate[226] (Table 6-3). Some states require informed consent prior to genetic testing (e.g., New York),[227,228] and genetic counseling is one of the ways to fulfill this requirement. Elements of pretest genetic counseling include data collection (medical and family histories, pertinent physical examination), data analysis and risk assessment, education regarding differential diagnoses/genes, evaluation of testing options and various results, selection of appropriate analyses and laboratories, and exploration of the medical, psychosocial, familial, and possible financial consequences of testing.[8] In the context of genetic counseling, psychosocial assessment of a patient may overlap with psychosocial considerations in oncologic care and include investigation of familial communication, the need for additional forms of support, and a patient's understanding of and ability to respond to the various possible ramifications of genetic testing.

The collection and construction (using standardized nomenclature) of family pedigrees is a highly important part of genetic cancer risk assessments. It is standard to evaluate at least three generations of a patient's maternal and paternal lineages, along with the family's ancestral background.[229] Individuals of certain ancestries may have higher risks for specific hereditary syndromes because of the presence of founder mutations;[230] therefore, the knowledge of ancestral background is often critical. In addition to ancestry, the number of relatives, sexes, ages at disease onset, ages at death, multiple primary tumors versus metastatic disease, endogenous and exogenous risk factors, past interventions such as oophorectomies or colorectal polypectomies, and the presence of unusual features or preneoplastic lesions (such as colon polyps, dysplastic moles) are all important pieces in the collection of a family history.[7,9] Pathology reports and medical records from family members' cancer diagnoses are often reviewed by genetic counselors, as inaccuracies in patient-reporting may occur.[231] Family structures may be truncated for a variety of reasons, including number of births and miscarriages, sexes (a paucity of females may explain a lack of gynecologic cancers), adoption, divorce, early death, or estrangement.[232]

Table 6-3 **Components of Informed Consent and Pretest Education in Clinical Cancer Genetics**[227]

Traditional Pretest Counseling for Susceptibility Testing (Purpose of Testing)	Pretest Counseling for Multigene Panel Testing*	Pretest Education for Somatic Mutation Profiling with Potential for Incidental Germline Findings (Purpose of Testing)
Information on specific genetic mutation(s) or genomic variant(s) being tested, including whether range of risk associated with variant will affect medical care	Discussions of specific genes may need to be batched, because it may not be feasible to review each gene individually; high-penetrance syndromes being evaluated should be described (e.g., hereditary breast and ovary, Lynch, hereditary diffuse gastric, Li-Fraumeni); patients should be made aware of possible detection of high-penetrance mutations not suggested by personal or family history; genes of uncertain clinical utility may need to be described more generally.	Discussion of possibility of discovering information relevant to inherited risk and range of possible germline risks that may be identified (differs for targeted sequencing vs. whole-exome or whole-genome sequencing); if there will be a mandatory search for secondary findings, this should be explained, and the option to decline to learn results should be provided.
Implications of positive (mutation confirmed to be deleterious), negative (no identified change in genetic sequence), or uncertain (genetic variant of unknown clinical significance) result	Particular attention should be paid to implications of positive results in less well-understood or lesser-penetrance genes and findings of mutations in genes associated with syndromes not suggested by personal or family history.	Criteria that will be used to identify germline variants that would be returned to patient or family should be described.
Possibility test will not be informative	Attention should be paid to current high rate of variants of uncertain significance.	Emphasis that purpose of test is not to identify germline risk and that dedicated testing directed by personal or family history is available
Risk that children and/or family members have inherited genetic condition	Highlight potential reproductive implications to family of mutations in genes linked to recessive disorders (e.g., *ATM*, Fanconi [*BRCA2*, *PALB2*], *NBN*, *BLM*)	Discussion about how incidental findings may be relevant to other family members
Fees involved in testing and counseling; for DTC testing, whether counselor is employed by testing company		
Psychological implications of test results (benefits and risks)		
Risks and protections against genetic discrimination by employers or insurers		
Confidentiality issues, including DTC testing companies and policies related to privacy and data security		
Possible use of DNA samples for future research		
Options and limitations of medical surveillance and strategies for prevention after genetic or genomic testing		
Importance of sharing genetic and genomic test results with at-risk relatives so they may benefit from this information		Consider identifying surrogate who could receive incidental results on behalf of patient in event patient has died or is otherwise unable to receive results.
Plans for disclosing test results and providing follow-up		

*Same general components as traditional counseling, with special considerations as listed.
Abbreviations: DTC, direct-to-consumer.
Source: Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. J Clin Oncol. 2015;33:3660-3668. Epub 2015 Aug 31. PMID: 26324357.

While such an extensive assessment is not expected from an oncologist, it is important to note that oncologists are uniquely positioned to identify individuals who may have an inherited predisposition to cancer or are at a higher risk for additional primary cancers. In fact, obtaining a family history of cancer at an initial patient consultation, as well as periodic reassessment of the dynamic family history during long-term follow-up, is an integral part of oncologic care. The recommended key elements for a minimum adequate cancer family history are highlighted in an ASCO expert statement and should help oncologists identify patients who would benefit from referral to clinical cancer genetics specialists (Table 6-4).[233]

POSTTEST GENETIC COUNSELING

Posttest genetic counseling includes disclosure and interpretation of test results; education about medical implications, management options (screening, risk reduction, therapeutic implications), and appropriate referrals and resources; investigation of the psychological reaction and familial repercussions related to the test results; and the opportunity to provide emotional support.[8] Even for patients who have negative or inconclusive results on genetic testing, posttest genetic counseling is still critically important, as patients and families may still be considered at increased risk for disease and for negative psychological reactions. Importantly, most family histories of cancer are not explained by pathogenic mutations in the known high-penetrance cancer predisposition genes. As such, many cases of familial breast cancer or familial colorectal cancer remain unexplained, but individuals in these families may still be at increased risk for cancer. In the absence of an identified familial mutation, genetic counselors may use various models to help predict risk for family members; this may in turn help inform the use of certain screening methods (see Chapter 7: Breast Cancer). For example, even in the absence of a *BRCA1* or *BRCA2* pathogenic mutation, sisters and daughters of a woman with breast cancer may still be at high enough risk to warrant breast MRI screening.[234] Failure to understand the uninformative nature of a negative or inconclusive genetic test result may lead to nonadherence to medical recommendations.[7] Lastly, posttest genetic counseling should include planning for communication of the genetic test results, disease risks, and medical recommendations to at-risk family members.

Table 6-4 Recommended Key Elements for Minimum Adequate Cancer Family History[233]

First-degree relatives: siblings, parents, children
Second-degree relatives: grandparents, aunts, uncles, grandchildren, nieces, nephews, half siblings
Both maternal and paternal sides
Ethnicity
For each cancer case in the family, establish: Age at cancer diagnosis Type of primary cancer
Results of any cancer predisposition testing in any relative

NOTE. Family history should be taken at diagnosis and updated periodically.

INCORPORATING GENETIC COUNSELING AND TESTING INTO THE CARE OF THE ONCOLOGY PATIENT

Genetic counseling can occur at multiple points in the oncology setting, and it is important for an oncologist to determine, in conjunction with the patient, when genetic counseling and testing is most appropriate (Fig. 6-2).

Genetic counseling and testing at the time of cancer diagnosis (i.e., peridiagnosis, pretreatment) has multiple benefits. Identification of an inherited cancer predisposition syndrome may impact treatment decisions including extent of surgery, chemotherapy and targeted therapeutic options, eligibility for clinical trials, and the risks of radiation. For example, women with *BRCA1*- and/or *BRCA2*-associated breast cancer may decide to pursue risk-

reducing bilateral mastectomy as opposed to breast-conserving surgery, and women interested in mastectomy with reconstruction, if clinically reasonable, may opt to avoid radiation in order to achieve a better aesthetic outcome.[235] Additionally, individuals with Lynch syndrome–associated colon cancer may consider extensive colectomy instead of segmental colon resection to reduce the risk of metachronous colon cancer.[236] For patients with advanced cancers, genetic testing may help to tailor treatment plans and could have implications for clinical trial eligibility. For example, targeted therapies with PARP inhibitors may be an option for patients with *BRCA*-associated ovarian or metastatic breast cancer[237] and programmed cell death 1/programmed cell death ligand 1 (PD-1/PD-L1) checkpoint blockade may be an effective treatment in a patient with a mismatch repair–deficient colorectal cancer.[238] Because the peridiagnostic period may be emotional and overwhelming for patients, genetic counseling and testing may be deferred to a later time. Also, obtaining genetic test results within the desired time frame may not be logistically possible if the disease is extensive and there is a need for immediate intervention.

Genetic counseling and testing may also occur during the treatment period or shortly thereafter (i.e., posttreatment). Genetic testing at this time allows patients to make informed decisions about future cancer surveillance and prevention to help manage the risk for new primary cancers. For example, a woman treated for *BRCA*-associated breast cancer may pursue risk-reducing bilateral salpingo-oophorectomy to reduce her risk of a future ovarian cancer.[44] A woman treated for Lynch syndrome–associated endometrial cancer may consider the use of daily aspirin (chemoprevention) to help reduce the risk of a future colorectal cancer.[105]

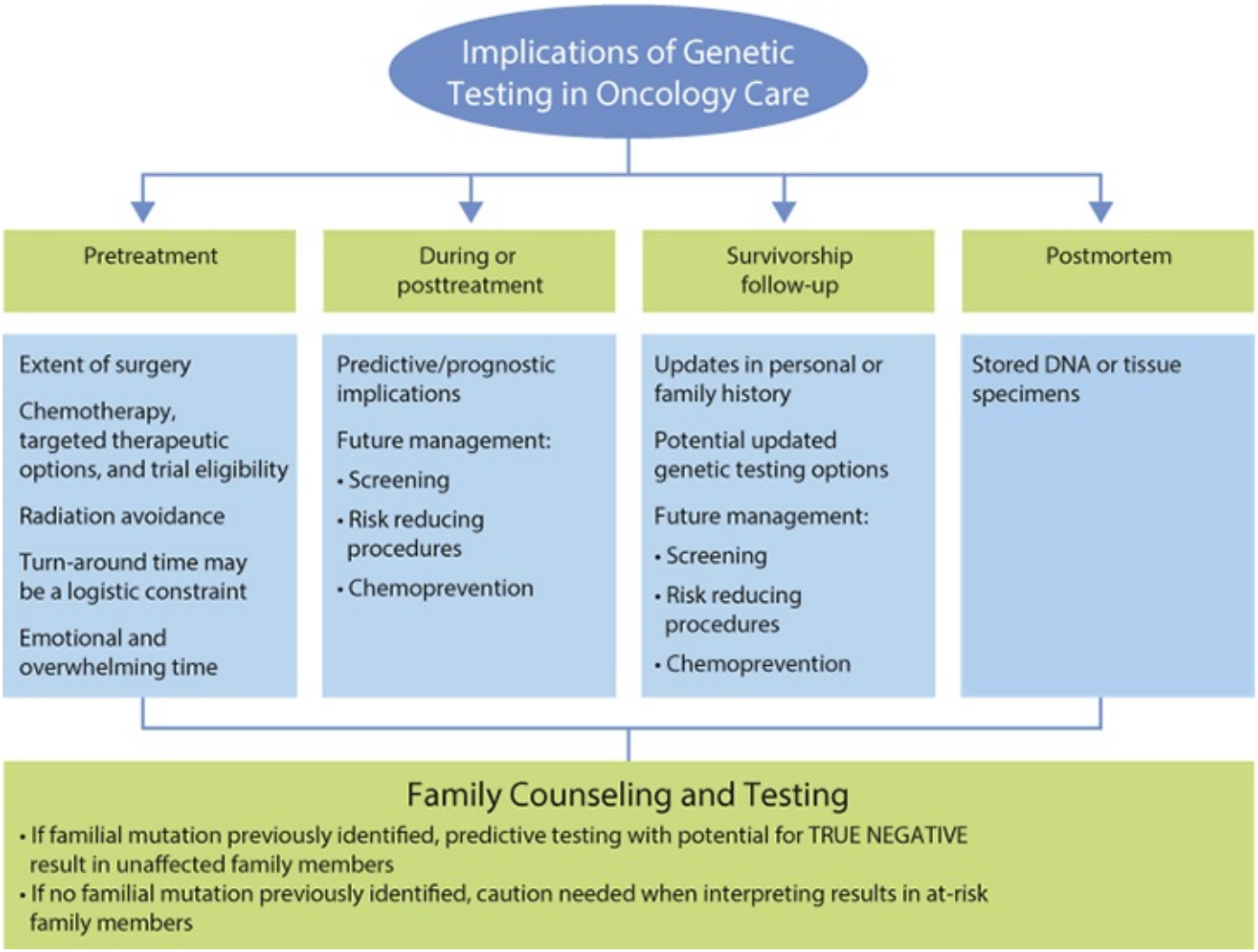

Fig. 6-2 Incorporating genetic counseling and testing into the management of patients with cancer.

IDENTIFYING APPROPRIATE PATIENTS FOR REFERRAL TO GENETIC COUNSELING AND TESTING

Although most cancers are not due to high-penetrance cancer predisposition syndromes, it is crucial for oncologists to be familiar with common “red flag” indications for referral to genetic specialists. Early or unusual age at cancer onset is a key indicator often associated with hereditary cancers. Cancer type and its natural history need to be taken into account when determining if a particular age at onset is unusual. For example, breast cancer in a woman in her 30s warrants referral to genetic counseling and testing, whereas a papillary thyroid cancer diagnosis in a woman of the same age is not particularly unusual and does not necessarily warrant referral. Multiple primary cancers, including bilateral, synchronous, and/or metachronous diagnoses may indicate a genetic susceptibility and warrant genetic risk assessment. A family history of the same type of cancer or multiple related cancers (i.e., colorectal and endometrial cancers; sarcomas and adrenocortical tumors) seen in successive generations should also be a red flag for referral. Additional unique features, such as certain types of gastrointestinal polyps, dermatologic features, ancestries (i.e., those known to have founder mutations), and neoplastic pathologies may also indicate a need for a cancer genetics consultation.[239] In Table 6-5 information on select cancer syndromes and commonly associated neoplastic or preneoplastic pathologies is provided for helping to recognize key features for particular syndromes. NCCN has published criteria for when referrals for genetic counseling and testing should be considered.[240] Also, some third-party payers have established their own criteria for when genetic testing is deemed medically indicated and may not necessarily be congruent with the aforementioned NCCN guidelines. Not all patients and families who undergo genetic counseling proceed with genetic testing, for various reasons (e.g., a lack of medical necessity/indication, not meeting one’s insurance provider’s testing criteria, or declination by the patient/family); however, genetic consultation may provide the opportunity to discuss concerns about a family’s cancer history and, in certain cases, cancer screening and prevention efforts may be implemented based on family history alone.

While taking a thorough medical and family history is important and will aid in the process of identifying possible red flags, it is important for clinicians to realize that not all individuals or families found to have a mutation actually fit into the classic syndrome phenotype descriptions. With next-generation sequencing being performed on patients’ tumor and sometimes germline specimens, a significant number of patients are found to carry germline mutations in genes that would have not been suspected on the basis of their personal or family histories. For example, targeted next-generation sequencing of matched tumor and germline specimens for 76 known cancer predisposition genes identified that 17.5% (182 of 1040) of patients with advanced cancer had an actionable germline mutation; 55.5% of these would not have been detected using clinical genetic testing guidelines alone.[241] Given this finding, it is important that genetic counseling models evolve and that clinicians who provide cancer-focused genetic counseling be skilled in discussing the implications of identified germline mutations with patients and families in the absence of a significant history of cancer.

Table 6-5 **Genetic Cancer Predisposition Syndromes and Selected Associated Pathologies**	
Neoplastic or Preneoplastic Pathologies	**Associated Genetic Syndromes and Genes**
High-grade or poorly differentiated ductal breast cancer with estrogen-receptor, progesterone-receptor, and HER2-neu negativity	*BRCA1*, hereditary breast and ovarian cancer syndrome
Lobular breast cancer	Hereditary diffuse gastric cancer syndrome (*CDH1*)
High-grade serous (papillary serous) ovarian cancer	Hereditary breast and ovarian cancer syndrome (*BRCA1*, *BRCA2*)
Clear cell or endometrioid ovarian cancers	Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*)
Ovarian sex cord tumors with annular tubules (SCTATs)	Peutz-Jeghers syndrome (*STK11*)
Clear cell or endometrioid endometrial cancers	Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*)
Uterine leiomyomas	Hereditary leiomyoma renal cell carcinoma syndrome (*FH*)
Adenoma malignum of the cervix	Peutz-Jeghers syndrome (*STK11*)
Colorectal cancer with tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring cells, medullary growth pattern	Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*)
Lauren's diffuse type/signet ring cell/linitus plastica gastric cancer	Hereditary diffuse gastric cancer syndrome (*CDH1*)
Hamartomatous gastrointestinal polyps	Peutz-Jeghers syndrome (*STK11*); juvenile polyposis syndrome (*BMPR1A*, *SMAD4*); Cowden syndrome (*PTEN*)
Pancreatic neuroendrocine tumors	Multiple endocrine neoplasia type 1 (*MEN1*); von Hippel-Lindau (*VHL*)
Renal papillary type I carcinoma	Hereditary papillary renal cancer syndrome (*MET*)
Renal papillary type II, collecting duct, tubulopapillary carcinomas	Hereditary leiomyoma renal cell carcinoma syndrome (*FH*)
Renal clear cell carcinoma	von Hippel-Lindau (*VHL*)
Renal oncocytoma	Birt-Hogg-Dube syndrome (*FLCN*); tuberous sclerosis complex (*TSC1*, *TSC2*)
Renal angiomyolipoma	Tuberous sclerosis complex (*TSC1*, *TSC2*)
Renal chromophobe	Birt-Hogg-Dube syndrome (*FLCN*)
Sertoli cell tumors of the testes	Peutz-Jeghers syndrome (*STK11*)
Medullary thyroid cancer	Multiple Endocrine Neoplasia type 2 (*RET*)
Cribriform-morula variant of papillary thyroid carcinoma	Familial adenomatous polyposis (*APC*)
Follicular thyroid cancer	Cowden syndrome (*PTEN*)
Medulloblastoma	Turcot syndrome variant of familial adenomatous polyposis (*APC*); Gorlin syndrome (*PTCH*)
Glioblastoma	Turcot syndrome variant of Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*)
Basal cell carcinoma	Xeroderma pigmentosum (multiple XP-associated genes); Gorlin syndrome (*PTCH*)
Sebaceous adenoma, sebaceous carcinoma, keratoacanthoma	Muir-Torre syndrome variant of Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*)
Fibrofolliculomas	Birt-Hogg-Dube syndrome (*FLCN*)
Facial tricholemmomas	Cowden syndrome (*PTEN*)

CONSIDERATIONS IN GENETIC COUNSELING AND TESTING FOR FAMILY MEMBERS

For families identified as harboring a pathogenic cancer–predisposing genetic mutation, unaffected family members can pursue predictive genetic testing with single amplicon (i.e., site-specific) mutation analysis to determine whether they also inherited the familial mutation. For individuals in the family who are found to be carriers of the mutation, increased and early cancer surveillance and preventive and/or risk-reducing measures can be implemented. Oncologists may be involved in the care of a deceased patient's unaffected relatives. If DNA from affected patients can be stored prior to death, these specimens may be used by family members for appropriate genetic evaluations in the future. In circumstances in which affected patients are deceased or not available for genetic testing and no DNA specimens are available, unaffected family members may proceed with individualized genetic evaluation. However, such

results should be interpreted with caution. For example, if a patient dies from breast cancer without undergoing genetic testing and her surviving daughter later tests negative for pathogenic mutations in the *BRCA1* and *BRCA2* genes, how are these results to be interpreted? The daughter's result is considered an "uninformative negative" result. Explanations for this situation include the possibility that the patient/mother actually did harbor a *BRCA1* or *BRCA2* pathogenic mutation, which the daughter did not inherit, consistent with a "true negative" test result. Alternatively, the patient/mother carried an unidentifiable *BRCA1* or *BRCA2* gene mutation or a pathogenic mutation in a different breast cancer predisposition gene that the daughter may or may not also carry. Lastly, the patient/mother's cancer may have been due to sporadic/nonhereditary factors.

ETHICAL PRINCIPLES AND CHALLENGES IN GENETIC COUNSELING

The field of genetic counseling is guided by multiple ethical principles. Four key concepts include autonomy, nonmaleficence, equity, and duty to warn. In the genetic counseling and testing process, an individual has autonomy, or the right to decide whether or not to learn what is coded in his or her DNA. Respect for individual autonomy applies to the testing of minors. If medical treatment of the child would not be altered by the knowledge of an inherited cancer predisposition syndrome, the future autonomy of the child is often taken into consideration.[242] A guiding criterion for when genetic testing should be considered is when the test result may impact medical management.[1,243] For syndromes that involve disease onset or preventive measures in childhood, such as classic FAP or Li–Fraumeni syndrome, genetic testing in the context of genetic counseling and with assent from the child (often ages ~7–17) is accepted.[7] Nonmaleficence is translated into "do no harm," and this concept is particularly relevant to the process of genetic test result interpretation.[244] There are several different possible types of genetic test results (detailed later in this chapter) and each may come with distinct implications for a patient and his or her family members. Therefore, it is critical for clinicians who provide genetic counseling and testing services to understand the various possible results and to translate this information into appropriate treatment recommendations for the patient and family in order to avoid unnecessary medical intervention and psychosocial ramifications. Another emerging issue within the field of hereditary cancer is the determination of risk estimates and clinical management recommendations for moderate-penetrance genes. Many of the moderate-penetrance genes are now routinely incorporated into genetic evaluations in the setting of multigene panels. However, cancer risks associated with these mutations often remain uncertain and result in medical management recommendations that are not evidence-based and potentially pose a risk of harm to patients and family members. With regard to equity, it is noted that access to genetic counseling services and testing is not uniform, as a variety of social and economic barriers, such as physical access (rural vs. urban settings), cost, insurance coverage, fear of discrimination and/or social stigma, and mistrust of the medical system, often come into play.[242] Investigation of these barriers and finding ways to mitigate them will continue to become increasingly important for the responsible translation and use of genetic technologies in our society.[242] Knowledge of a cancer predisposition syndrome requires familial communication, which, not uncommonly, in many families is less than ideal. The concept of a "duty to warn" and the extent of a clinician's responsibility to a patient's family remain controversial in the field of genetics. Previous court rulings have taken different stances on clinicians' duty to warn patients' at-risk family members of inherited risks for cancer.[242,245-247] It is vital for clinicians to understand that there is clearly a direct responsibility to discuss a

patient's genetic test results, to inform the patient that family members may be at risk for an inherited cancer syndrome and that there is a strong recommendation that family members be made aware of and warned of this risk, and to clearly document this communication with the patient.[243,247]

KEY POINTS

- Genetic counseling is a communication process that helps patients understand and adapt to the various implications of having a genetic condition.
- Genetic counseling should include both pre- and posttest discussions and can be performed at various times during the management of oncology patients.
- Thorough medical and family histories are vital for accurate genetic risk assessments.
- The field of genetic counseling is guided by multiple ethical principles, including autonomy, nonmaleficence, equity, and duty to warn.

TUMOR ANALYSES

Although many patients may be identified for genetic counseling and testing on the basis of their personal and/or family history of cancer, for medical oncologists, review of a patient's tumor pathology could also provide the initial clue that a particular tumor may be occurring in the setting of a cancer predisposition syndrome. For example, triple-negative (estrogen-, progesterone-, and HER2/neu-negative) breast cancers are associated with an increased incidence of *BRCA1* germline pathogenic variants, and genetic testing is considered medically indicated for all women at or under age 60 who have this type of cancer according to NCCN and many third-party payers. Patients with medullary thyroid cancer should be referred for genetic testing of the *RET* gene. Table 6-5 reviews additional important cancer predisposition syndromes and tumor pathology associations. For some cancer predisposition syndromes, like Lynch syndrome, analysis of tumor tissue is an integral step in helping to identify at-risk patients. As tumor sequencing technologies rapidly advance and become more commonplace in medical oncology, the importance of tumor tissue analysis as it applies to informing germline genetics must be emphasized.

TUMOR ANALYSIS INFORMS GERMLINE SUSCEPTIBILITY: THE CASE OF LYNCH SYNDROME

The hallmark feature of Lynch syndrome (previously known as HNPCC [hereditary nonpolyposis colorectal cancer)–associated tumors is the presence of microsatellite instability (MSI) resulting from the accumulation of mismatch mutations in the genome, especially at regions of repetitive DNA known as microsatellites, driven by an underlying defect in the mismatch repair pathway (MMR-D). Identification of MMR-D may either be pursued through a polymerase chain reaction–based technique that assesses MSI at a designated set of markers[107,111,248] or through immunohistochemical (IHC) staining of the four DNA mismatch-repair proteins (MLH1, MSH2, MSH6, PMS2) to assess for protein loss in one or more of the MMR proteins.[106] Whereas MSI and MMR-IHC analyses are highly concordant, MMR-IHC has surpassed MSI testing as the

initial screening test for Lynch syndrome because the pattern of protein loss can help direct germline genetic testing.

In the most common Lynch syndrome–associated cancers, including colorectal and endometrial cancers, the need for tumor screening for Lynch syndrome has traditionally been based on the age at cancer diagnosis or on the strength of the personal and family history, as outlined in the revised Bethesda guidelines.[111] However, as per the most recent guidelines from EGAPP (Evaluation of Genomic Applications in Practice and Prevention Working Group) and NCCN, screening of all colorectal tumors (or at least all colorectal tumors in patients less than age 70 at diagnosis or those over age 70 meeting revised Bethesda guidelines) and endometrial tumors via MSI or MMR-IHC analysis is now recommended.[249,250] For patients with abnormal screening test results (MSI-high or MMR-D tumor), various algorithms have been developed to help guide subsequent evaluations; these may include germline genetic testing or further tumor analyses, such as *MLH1* promoter hypermethylation and/or *BRAF* V600E somatic mutation.[249,250]

NEXT-GENERATION TUMOR SEQUENCING: IMPLICATIONS FOR GERMLINE-SUSCEPTIBILITY

Next-generation sequencing of tumors (i.e., somatic mutation profiling) for helping to define therapeutic targets has become increasingly common in the field of medical oncology. Somatic mutation profiling is available via a number of commercial laboratories and academic institutions and generally consists of a multigene panel that incorporates numerous genes previously implicated in carcinogenesis, many of which are also associated with germline cancer predisposition syndromes.

If tumor-only sequencing is undertaken, the majority of sequence variants identified in the patient's tumor will represent acquired/somatic mutations resulting from tumor development, but importantly, mutations in the germline DNA will also be unmasked. For example, tumor-only sequencing of a 25-year-old woman with breast cancer may identify a missense *TP53* mutation. Given the patient's very early age at breast cancer diagnosis, this mutation may represent a germline mutation consistent with Li–Fraumeni syndrome, as opposed to an acquired mutation, with implications for future cancer risk for the patient and her family members. If more extensive tumor analysis, such as exome or whole-genome sequencing is performed, predispositions to nononcologic diseases may also be revealed. Although these are considered to be incidental results, the identification of such genetic changes may be clinically significant, and the medical oncologist who requests the tumor-only sequencing, along with the patient, should be aware that somatic mutation profiling may result in germline findings for which referral to genetics specialists and confirmatory germline testing is recommended.

Somatic mutation profiling may also be undertaken through the analysis of both tumor and normal DNA. Laboratories using this method analyze the tumor and normal DNA simultaneously and apply informatic analyses to subtract the inherited (germline) variants from the tumor sequence. This results in the reporting of only tumor-specific or tumor-acquired variants. Importantly, in this tumor/normal sequencing approach, since the germline genetic information is not reported, pathogenic germline mutations in known cancer susceptibility genes would remain masked, requiring the medical oncologist to refer the patient for clinical genetic counseling and testing based on traditional criteria, including personal and family cancer histories.

Lastly, somatic mutation profiling may also reveal mutational patterns that predict the presence of a cancer susceptibility syndrome. For example, mutational load on somatic profiling

may identify hypermutated tumors, which may result from MMR-D/MSI-H, a marker of Lynch syndrome.[251] As such, somatic mutation profiling that reveals the presence of a hypermutated endometrial tumor should prompt MMR-IHC or MSI testing and, if appropriate, genetic referral. Bioinformatic tools that predict MSI from somatic mutation profiling have been developed and are being incorporated into the somatic mutation profiling pipelines to help clinicians correctly identify tumors with MMR-D/MSI.[252,253]

KEY POINTS

- Evaluation for Lynch syndrome typically starts with tumor screening for microsatellite instability or DNA mismatch–repair deficiency. In the case of an abnormal screening test, subsequent tumor and/or germline evaluation is warranted to make the diagnosis of Lynch syndrome.
- Next-generation sequencing of tumors (i.e., somatic mutation profiling) for the identification of therapeutic targets can be performed with or without the inclusion of parallel normal (nontumor) DNA sequencing. In order to appropriately interpret the results and determine potential hereditary risks for the patient, a clinician ordering tumor somatic mutation profiling must be aware of the testing approach used.
- Genetic evaluation of somatic (tumor) tissue can potentially reveal germline pathogenic variants that may be of significance for a patient and/or family members.

GERMLINE ANALYSES

SPECIMENS AND LABORATORY STANDARDS

For germline genetic testing, the most commonly used specimen is blood because of its high DNA yield. Some commercial laboratories now offer germline genetic analyses on sputum specimens; however; not all analyses may be validated for such use. For patients who have undergone allogeneic bone marrow or stem cell transplantation, tissue, rather than blood, is necessary for germline analysis, and frequently a skin punch biopsy is obtained for fibroblast culture, which can then be used for germline analysis. Lastly, when single amplicon analysis or targeted mutation analysis is needed, some laboratories may perform the analysis on paraffin-fixed tissue (tumor or normal). For example, a deceased individual's paraffin-fixed tissue could be used for analysis of the three common Ashkenazi Jewish founder mutations in the *BRCA1* and/or *BRCA2* genes, thus helping to inform a family member's risk assessment.[254]

Laboratories performing molecular genetic testing are subject to the general Clinical Laboratory Improvement Amendments (CLIA) regulations and must meet standards for quality, accuracy, and reliability.[255] In addition, the Centers for Disease Control and Prevention (CDC) and the Centers for Medicare and Medicaid Services (CMS) have taken additional steps to ensure quality management with regard to molecular genetic testing for heritable disease and conditions.[256] Variations in state regulations of genetic and genomic tests also exist, with some states requiring laboratory certificates and licensure exceeding CLIA standards (i.e., New York, Washington).[257] Notably, CLIA requires that tests not regulated by the U.S. Food and Drug Administration (FDA) meet criteria for analytic validity, but demonstration of clinical utility and clinical validity are not required components. As a result, multigene panels for cancer

susceptibility testing may include genes with limited scientific evidence with regard to cancer risk.[1,258] At the federal level, the FDA serves as an additional regulatory pathway for certain genetic tests. The FDA has promoted draft guidance for the future regulation of such laboratory-developed tests.[259]

GERMLINE GENETIC TEST RESULTS

On germline analysis, patients must be prepared for several different types of test results (Fig. 6-3):

- Pathogenic/deleterious mutation (variant)
  - In high-penetrance genes, pathogenic mutations are presumed to be responsible for the patient's personal or family history of cancer. (This may not always be the case, though, when multigene panel testing with moderate-penetrance genes is performed; see subsequent section entitled Genetic Testing Using Multigene Panels for further discussion.)
- Suspected pathogenic/ deleterious mutation (variant)
  - With this result, there is high suspicion, but not complete certainty regarding the pathogenicity of the genetic alteration. Caution must be taken when counseling a patient and family members regarding this result.
  - If presymptomatic/predictive testing for the alteration is performed for a family member, increased cancer surveillance recommendations may still be indicated even in the absence of a positive result.
- Genetic variant of uncertain clinical significance (VUS)
  - An alteration is detected, but the laboratory does not have enough data to allow for clinical classification/interpretation of the alteration's effect on the gene's function or protein product or clinical relevance. Patients and family members should be counseled about the ambiguous nature of the result and the continued need for all family members to consider themselves at risk.
  - Communication with the testing laboratory regarding what is known about the genetic variant is a reasonable first step for any clinician. Various resources, tools, and research analyses may be used by genetic counselors and geneticists to help provide further clarification. With time and access to additional data, many labs reclassify these variants; and many, perhaps most, are reclassified as being benign.[260]
- Likely benign variant
  - An alteration is detected, but the laboratory has a low suspicion of it being associated with disease.
- Negative/normal result
  - No alterations of clinical significance or uncertain significance identified. Negative results may not be informative and a patient and family members may still harbor a pathogenic mutation in a different cancer predisposition gene.
  - *True negative:* In the case that an individual is being tested for a previously identified familial pathogenic mutation, a negative result is considered a "true negative result," and for the associated cancers, the individual is presumed to be at the same risk as the general

population.

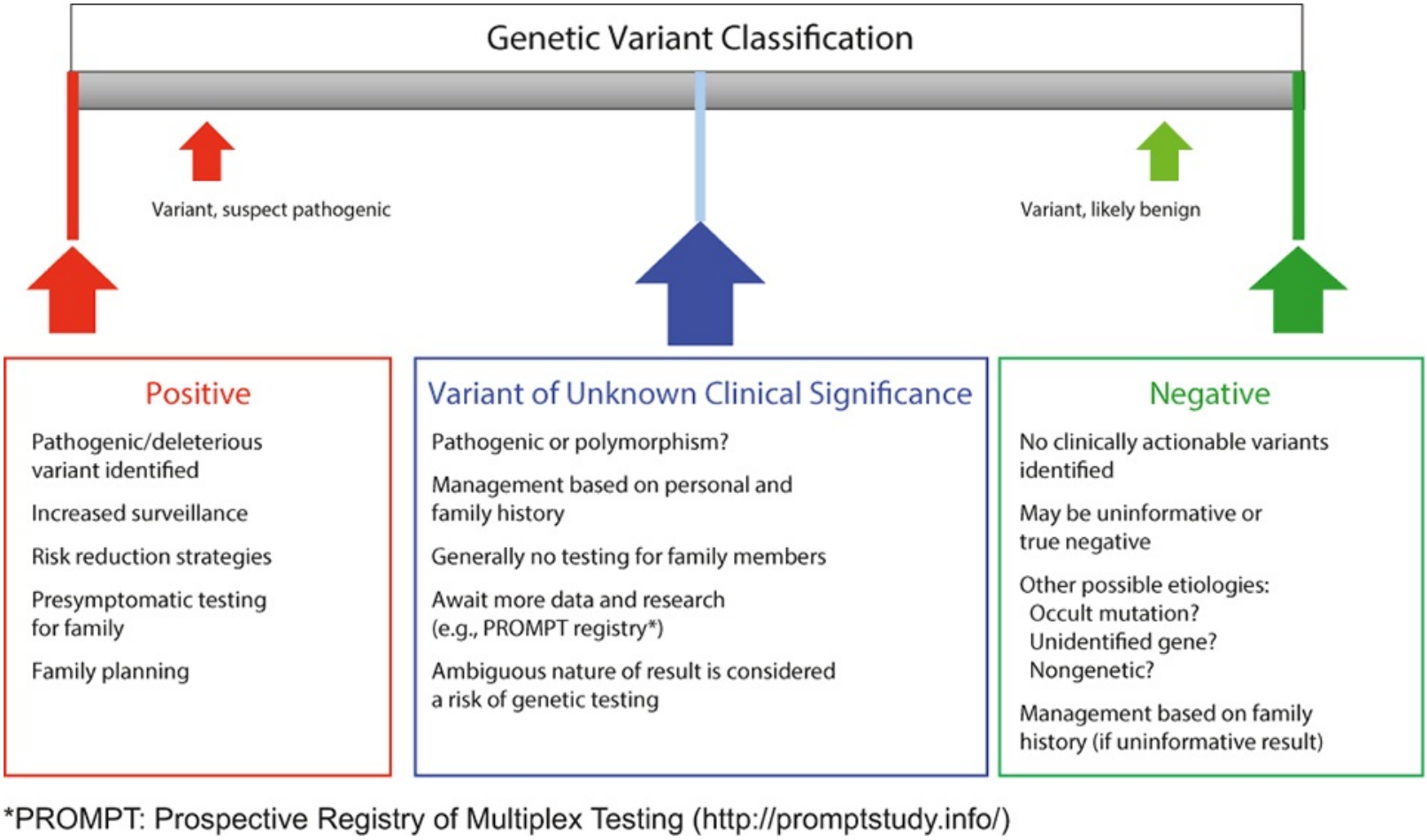

Fig. 6-3 Spectrum of genetic test results.

APPROACHES TO GERMLINE GENETIC TESTING

Phenotype-Directed Genetic Testing

The field of cancer genetic testing and counseling has traditionally followed a phenotype-based approach for genetic testing wherein the selection of genes to be analyzed is based on the patient's personal or family cancer history and would include only genes associated with the demonstrated phenotype. A related, second approach is to focus on ancestry-specific founder mutations. Founder mutations are genetic alterations observed with high frequency in a distinct group that is or was geographically or culturally isolated and in which one or more of the ancestors was a carrier of an altered gene. With reexpansion of the population, the founder mutation is perpetuated, usually at a higher prevalence. Founder mutations have been identified in several populations.[230,261-266] A common example pertains to individuals of Ashkenazi Jewish descent, in whom the prevalence of the three founder mutations in *BRCA1* and *BRCA2* is 2.5%, leading to a lower threshold for genetic testing of Ashkenazi Jewish patients affected with HBOC-related cancers compared to individuals from nonfounder populations; this is supported by NCCN and third-party payers.[230] A third approach pertains to families with a previously identified familial mutation; in these cases, predictive/presymptomatic testing for the site-specific mutation can be undertaken for accurate cancer risk assessment.

Genetic Testing Using Multigene Panels

In contrast to sequential single-gene and phenotype-driven testing, next-generation sequencing technologies have enabled the use of multigene panels for germline analysis, wherein multiple cancer susceptibility genes are assessed simultaneously. Disease-specific multigene panels for nearly all of the common cancers (breast, ovary, uterine, colon, kidney, advanced prostate) as well as pan-cancer panels are now widely available through commercial laboratories.[222] The ease of use, cost, and time efficiency associated with multigene panel testing for cancer susceptibility has resulted in a dramatic increase in the application of this testing approach over the past 5 years. It is an especially useful approach when significant genetic heterogeneity exists or multiple genes/syndromes may be implicated on the basis of phenotype or family history.[222] For example, in individuals with early-onset or hereditary pheochromocytoma/paraganglioma, simultaneous as opposed to sequential testing for 10 genes has proven to be an efficient testing method for this genetically heterogeneous syndrome.

On the other hand, multigene panels also have several limitations. This approach to genetic testing poses a significant challenge for the traditional pretest counseling model discussed previously, as the in-depth counseling that is provided for single-gene testing is not possible for a panel that may include as many as 20 to 30 genes (Table 6-1). If the panel contains high-penetrance genes, especially those with implications for multiple tumors or childhood cancers (e.g., *TP53*), or drastic risk-reducing measures like gastrectomy (e.g., *CDH1*), an unexpected positive result without pretest discussion and preparation may result in distress and anxiety. This is particularly the case when a patient's personal or family history is not in line with the hereditary syndrome identified using the multigene panel. For example, if a *CDH1* pathogenic mutation is unexpectedly identified in a patient who has no personal or family history of diffuse gastric cancer or lobular breast cancer, the patient and physician are left in a clinical conundrum as to whether historical cancer risk estimates based on ascertainments of familial hereditary diffuse gastric cancer kindreds are applicable and whether to pursue risk-reducing gastrectomy, which is associated with significant morbidity. Additionally, multigene panels also generally include genes associated with moderate-penetrance cancer risk (Table 6-4), where the associated cancer spectrum, lifetime risks, age-associated penetrance, and appropriate management recommendations have not yet been fully defined. Importantly, the presence or absence of a mutation in a moderate-penetrance gene may not provide clarity with respect to cancer risk. In fact, a patient with a positive test result may not require additional surveillance, while a patient with a negative result, especially in the context of a significant family history, may still be recommended to undergo increased cancer surveillance. Multigene testing also results in a higher incidence of an uncertain/ambiguous genetic test results (as previously described) leading to further difficulties with the interpretation of results. A genetic registry called PROMPT (Prospective Registry of Multiplex Testing) has been created to help clarify some of the questions raised by multigene panel testing.[267] Interestingly, an initial finding from PROMPT highlighted the conflicting classifications of a number of genetic alterations across different commercial laboratories resulting in varying clinical interpretations of genetic variants with implications for medical management recommendations. [268]

A final point on multigene panel analyses that is important for provider and patient to understand is that some of the genes included on the panel may have reproductive implications. For example, the *NBN* gene is associated with a rare, but severe autosomal recessive condition (Nijmegen breakage syndrome). Although the presence of a monoallelic mutation may have limited implications, it may point to a risk for offspring to have a more severe condition, and preconception/prenatal genetic counseling for the family may be indicated.

GENOME AND EXOME ANALYSES

The aforementioned approaches to genetic testing have in common a distinct focus on cancer-related genes. However, with the advent of clinical exome and whole-genome sequencing, pathogenic or suspected pathogenic mutations may be uncovered in genes unrelated to the primary medical reason for testing; these findings have been termed "secondary findings."[269] Considerable debate and discussion has been prompted with regard to the extent to which primary data should be analyzed for secondary findings and which, if any, pathogenic variants discovered should be disclosed to patients. In an effort to standardize the reporting of actionable information from clinical genomic sequencing, in 2013, the American College of Medical Genetics and Genomics (ACMG) published a list of 56 medically actionable genes,[270] updated to 59 genes in 2016,[271] in which pathogenic mutations are recommended to be reported because of the high likelihood of severe disease that may be preventable if identified before symptoms occur. The ACMG's initial 2013 recommendation for a "mandatory" return of clinical genomic sequencing results for these genes was met with considerable debate, and the recommendations were later updated to provide patients the opportunity to "opt out" of the analyses of genes unrelated to the indication for testing, with the decision to be made during the process of informed consent before testing (Table 6-1). Notably, 24 of the current 59 ACMG reportable genes are associated with cancer predisposition syndromes, highlighting the relevance of these recommendations to the field of medical oncology.

Genomic sequencing is a powerful tool; however, significant further challenges include standardization of variant classification, filtering, and curation of variant pathogenicities. Inconsistencies among clinical molecular laboratories and clinical genomic sequencing analyses have been highlighted,[272] and integration of multiple lines of support using standardized methods is necessary for classifying genetic alterations into one of five categories: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign.

To meet this challenge, the National Institute of Health has supported the formation of ClinGen, an authoritative central resource aimed at defining the clinical relevance of genomic variants for use in precision medicine and research.[273] ClinGen is often used by genetic counselors and geneticists; this resource aims to answer critical questions regarding clinical validity, pathogenicity, and clinical usefulness or medical actionability of a particular genomic finding. The cornerstone of ClinGen is ClinVar, a freely available web-based archive that is maintained by the National Center for Biotechnology Information (NCBI) and reports on interpretations of clinical significance of variants and allows for both deposition and retrieval of variant data and annotations.[274,275]

The BRCA Challenge is an international project that aims to further knowledge regarding the genetic underpinnings of breast and other cancers through worldwide data sharing.[276] Integrated efforts, such as ClinGen/ClinVar and the BRCA Challenge, are crucial to ensuring appropriate interpretation of genomic variants before incorporation into patient care.

DIRECT-TO-CONSUMER GERMLINE GENETIC ANALYSES

Direct-to–consumer (DTC) genetic testing has challenged the traditional practical and ethical frameworks established in the field of clinical genetics. DTC genetic tests are advertised and sold directly to individuals, generally without supervision by a healthcare professional. Saliva-collection kits allow consumers to send their specimens directly to commercial laboratories with results generally returned by mail, e-mail, or phone. DTC testing is available for both disease- and non–disease-related phenotypes, including "recreational genomic" testing for genetic traits

such as detecting asparagus odor in urine. The FDA, the CDC, and the Federal Trade Commission have issued consumer warnings about the claims of certain genetic tests and their use for medical management. Nonetheless, many DTC tests are currently available and patients undergoing such analysis for cancer or medical risk assessment should be directed to genetics specialists for assistance with interpretation of the results.

OTHER CONSIDERATIONS RELATED TO GERMLINE GENETIC ANALYSES

For oncology patients unable or unwilling to undergo genetic testing during their lifetime, and in those with uninformative results, commercial DNA banking may be a reasonable consideration. Many commercial laboratories now work with patients, families, physicians, and hospice-care providers to have a sample of blood (or other tissue) collected before death and stored for future use by a designated individual/family member. The affected individual's DNA can be used when the family is ready to have testing performed or if science advances with regard to the availability of additional clinical genetic tests.

Some individuals may consider using genetic test results to help inform reproductive decisions. For example, instead of conceiving naturally, some individuals may consider the use of assisted reproductive technologies such as in vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD) or the use of donor gametes (eggs or sperm). IVF with PGD has been used for multiple inherited cancer syndromes.[277] Other reproductive options that may be considered include adoption or prenatal diagnosis via chorionic villus sampling (CVS) or amniocentesis, with consideration of pregnancy termination.

Many individuals may express concerns over insurance coverage and insurance-related repercussions of genetic counseling and testing. Most third-party payers include some level of coverage for genetic counseling and testing services. Some payers have established personal and family history criteria that must be met in order for medical necessity to be established; others may follow suggested testing guidelines that have been published by groups such as the NCCN.[278,279] Some payers require the involvement of a genetic counselor in the pretesting counseling and testing process. Many commercial laboratories offer insurance coverage determination before performing genetic testing. Federal legislation through the Genetic Information Nondiscrimination Act (2008), and in some cases additional state legislation, provides protection against genetic discrimination by one's employer and health insurance provider.[280] Unfortunately, protection against discrimination by life, disability, and long-term care insurance providers is not universal in the United States at this time. The potential risks for out-of-pocket costs related to genetic counseling and testing services and genetic discrimination are a necessary part of the pretest counseling and informed consent process.[7]

KEY POINTS

- Clinical molecular genetic testing must be performed according to Clinical Laboratory Improvement Amendments (CLIA) regulations and must meet standards for quality, accuracy, and reliability. Additional state-specific regulations for genetic testing laboratories may also apply.
- Germline genetic test results typically fall into one of five categories of genetic variants: pathogenic, likely pathogenic, uncertain clinical significance, likely benign, and benign. Recommendations for management of cancer risk and predictive testing for family

members differ significantly based on the classification of the variant and should be assessed carefully.

- Multigene panel cancer susceptibility testing is challenging the traditional phenotype-directed and often serial approach to genetic testing. When appropriate, multigene panel testing may be both a cost and time efficient method for genetic testing.
- Multigene panel testing poses challenges for pretest counseling and may result in unexpected pathogenic variants and a higher incidence of variants of unknown clinical significance.
- Genome and exome analyses may identify pathogenic or suspected pathogenic genetic variants in genes unrelated to the primary medical reason for testing, termed “secondary findings.”
- The Genetic Information Nondiscrimination Act, enacted in 2008, provides protection against genetic discrimination by an individual’s employer and health insurance provider.

GENETICS IN MEDICAL ONCOLOGY PRACTICE

The collection of family history data, and the continued updating of this dynamic information on a regular basis, is an important task for medical oncologists and allows for the identification of patients and families who may benefit from genetic counseling and testing. Genetic counseling is not just for patients who have already undergone testing and were found to have genetic alterations; rather, it is for patients and families who are considering the option of genetic testing in the future or for individuals who may simply benefit from a risk-assessment discussion.[7] Oncologists are encouraged to recognize the importance of both pretest and posttest genetic counseling and to build relationships with local genetic counselors and other genetic specialists and see them as allies in the challenge of helping patients and their families through a diagnosis of cancer. Resources to find genetic specialists include the National Society of Genetic Counselors (NSGC), the American Board of Genetic Counseling, Inc., the National Cancer Institute Cancer Genetics Services Directory, and the GeneTests Clinic Directory.[8] Resources to learn more about cancer genetics and risk assessment include the ASCO University Cancer Genetics Program, NSGC, and the National Human Genome Research Institute.[9,227]

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BREAST CANCER

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Recent Updates

Breast Cancer Staging

- Because the specific prognosis for an individual cannot be determined solely by anatomic staging, revisions to breast cancer staging in the AJCC 8th edition (to be implemented January 1, 2018) notably incorporate prognostic molecular markers including histologic grade, hormone receptor and HER2 status, and 21-gene assay results, with classic TNM anatomic criteria. (*AJCC Cancer Staging Manual.* 8th ed. New York: Springer; 2017)

Molecular Prognostic and Predictive Markers

- Results from independent prospective evaluation of the 21-gene recurrence score assay (Oncotype DX) and the 70-gene signature (MammaPrint) provide early but still incomplete validation of these tools as prognostic indices that may furthermore be predictive of adjuvant chemotherapy benefit. (Sparano JA, *N Engl J Med* 2015; Cardoso F, *N Engl J Med* 2016)
- In 2016, ASCO published clinical practice guidelines on the use of biomarkers to guide adjuvant systemic therapy for early-stage invasive breast cancer. (Harris LN, *J Clin Oncol* 2016)

Adjuvant Systemic Therapy

- The MA.17R trial evaluated extended therapy with an aromatase inhibitor (AI) in postmenopausal women with ER-positive operable breast cancer. Continuing the AI for a total of 10 years improved 5-year disease-free survival (DFS) (defined by recurrence and contralateral breast cancer events), by a couple of percentage points, compared with those who discontinued their AI after the initial 5 years. There was no difference in 5-year OS or quality-of-life measures; however, bone-related toxicities (bone pain, fractures, and new-onset osteoporosis) were more frequent among those taking letrozole. (Goss PE, *N Engl J Med* 2016)
- In NSABP B-42, however, after an initial 5 years of adjuvant endocrine therapy in postmenopausal women, there was no significant difference in 5-year DFS (defined by recurrence, contralateral breast cancer, nonbreast cancer, and death) for those who discontinued therapy compared with those who received an AI for an additional 5 years. Extended endocrine therapy did significantly reduce the risk of distant relapse and improve the breast cancer–free interval. Two additional phase III studies did not demonstrate a DFS benefit from extended therapy with an AI beyond an initial 5 years of adjuvant endocrine treatment. (Mamounas EP, San Antonio Breast Cancer Symposium 2016)
- The APHINITY trial randomly assigned 4805 patients with HER2-positive, node-positive or high-risk node-negative breast cancer to adjuvant chemotherapy with trastuzumab and placebo/pertuzumab. Pertuzumab reduced the risk of an invasive DFS event by 19% compared with placebo (hazard ratio [HR], 0.81; 95% CI; 0.66, 1.00; p = 0.045) at a median follow-up of 45.4 months. Treatment was effective in all subgroups; however, those with node-positive and/or hormone receptor–negative disease appeared to derive the most benefit. Diarrhea was increased in the pertuzumab arm, predominantly during chemotherapy and with the TCH regimen. Cardiac toxicity was low and not different between the two arms. (vonMinckwitz G, *J Clin Oncol* 2017)
- In the phase III ExteNET trial, 2840 patients with early-stage HER2-positive breast cancer were randomly assigned in a double-blind, placebo-controlled study of neratinib following completion of adjuvant trastuzumab treatment. One year of adjuvant neratinib was associated with a 2-year invasive DFS rate of 94.2% compared with a rate of 91.9% in those receiving placebo (HR, 0.66; 95% CI; 0.49, 0.90; p = 0.008). These results led to the FDA approval of neratinib in 2017. (Chan A, *Lancet Oncol* 2016)

- A joint Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline on the use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer recommended that zoledronic acid or clodronate be considered as adjuvant therapy for postmenopausal patients with breast cancer who are deemed candidates for adjuvant systemic therapy. Postmenopause includes natural menopause or that induced by ovarian suppression or ablation. (Dhesy-Thind S, *J Clin Oncol* 2017)

Neoadjuvant Systemic Therapy

- While the addition of carboplatin to neoadjuvant anthracycline- and taxane-based chemotherapy in patients with stage II and III triple-negative breast cancer significantly increased pathologic complete response rates in two large prospective trials, the 3-year DFS and overall survival (OS) results were conflicting, with only one trial demonstrating improved clinical outcomes. Its use remains investigational. (Sikov WM, San Antonio Breast Cancer Symposium 2015; von Minckwitz G, San Antonio Breast Cancer Symposium 2015)

Locoregional Therapy

- The 2016 ASCO/ASTRO/SSO guidelines recommend postmastectomy radiotherapy (PMRT) to those with T1–2 breast cancer with one to three positive lymph nodes and to those with positive lymph nodes following neoadjuvant systemic therapy. There is currently insufficient evidence to recommend whether PMRT should be administered or can be routinely omitted in those with clinically negative nodes who receive neoadjuvant systemic therapy or in those with a complete response in the lymph nodes with neoadjuvant systemic therapy. (Recht A, *J Clin Oncol* 2016)

Recurrent or Metastatic Disease

- The OlympiAD trial evaluated the PARP inhibitor olaparib as monotherapy compared with single-agent chemotherapy of physician choice in patients with germline *BRCA*-mutant, HER2-negative advanced breast cancer. Olaparib was associated with an objective response rate of 60% and a superior median progression-free survival (PFS) of 7.0 months, compared with 4.2 months for patients receiving conventional chemotherapy (HR, 0.58; p = 0.0009). (Robson ME, *J Clin Oncol* 2017)
- The PALOMA-2 trial evaluated letrozole alone and combined with the CDK4/6 inhibitor palbociclib as first-line therapy for hormone receptor–positive, HER2-negative advanced breast cancer. This trial demonstrated an improvement in median PFS from 14.5 months with letrozole alone to 24.8 months for the combination therapy (p < 0.001). Objective response rates were also higher. OS data remain immature. (Finn RS, *N Engl J Med* 2016)
- The PALOMA-3 trial evaluated fulvestrant alone and combined with palbociclib after progression on prior endocrine therapy for hormone receptor–positive, HER2-negative advanced breast cancer. This trial demonstrated an improvement in median PFS from 4.6 months with fulvestrant alone to 9.5 months for the combination therapy (HR, 0.46; p < 0.0001). (Cristofanilli M, *Lancet Oncol* 2016)
- The MONALEESA-2 trial evaluated letrozole alone and combined with the CDK4/6 inhibitor ribociclib as first-line therapy for postmenopausal, hormone receptor–positive, HER2-negative advanced breast cancer. A preplanned interim efficacy analysis demonstrated an improvement in PFS (HR, 0.556; 95% CI; 0.429, 0.720; p < 0.0001). The results of this study led to FDA approval of ribociclib in combination with an AI as first-line therapy in this patient population. (Hortobagyi G, *N Engl J Med* 2016)
- The FALCON trial evaluated fulvestrant compared with letrozole as first-line therapy for hormone receptor–positive, HER2-negative advanced breast cancer. This trial demonstrated an improvement in PFS from 13.8 months with letrozole to 16.6 months with fulvestrant (p = 0.0488). (Robertson JFR, *Lancet* 2016)

Supportive Care

- A randomized trial that compared up-front zoledronate at monthly or every-3-month intervals for 2 years demonstrated equivalent skeletal-related outcomes in patients with bone metastases. (Himelstein AL, *JAMA* 2017)
- In 2016, ASCO and the American Cancer Society developed a comprehensive set of guidelines that extend beyond cancer surveillance recommendations to further address symptom management, surveillance and management of late toxicities of cancer therapy, and general wellness (weight management, nutrition, activity, etc.) recommendations. (Runowicz CD, *J Clin Oncol* 2016)

OVERVIEW

The incidence of breast cancer, the most common cancer in U.S. women, has remained steady over the past decade; mortality from breast cancer has consistently declined annually since

approximately 1990, primarily as a result of advances in systemic therapy. For early-stage breast cancer, advances in surgery and radiation oncology have led to the deescalation of locoregional therapy. In select patients, axillary lymph node dissection may be avoided, and partial-breast irradiation or hypofractionated whole-breast irradiation may be alternatives to traditional whole-breast irradiation. Improvements in the efficiency of drug development have led to the rapid study of several new targeted, investigational agents. As a result, in the past 5 to 10 years, several new treatment options for patients with metastatic hormone receptor–positive or HER2-positive breast cancer have appeared. Better therapeutic options are still needed for patients with estrogen-receptor–negative, progesterone-receptor–negative, HER2-negative ("triple-negative") disease. Advances in supportive care have reduced serious complications of breast cancer treatment and improved symptom management and patient quality of life.

EPIDEMIOLOGY

Breast cancer remains the most common malignancy diagnosed among women in the world, with about 1.7 million women worldwide diagnosed in 2012, accounting for 25% of all new cancer cases.[1] The incidence rates are higher in economically developed regions such as North America, Western Europe, and Australia/New Zealand and lower in economically developing areas such as sub-Saharan Africa and Asia. The incidence rates of breast cancer in developed countries increased between 1980 and 1990 because of the increased use of breast cancer screening and changes in reproductive factors. Since 2000, the postmenopausal breast cancer incidence has decreased in these countries, attributed to the decline in the use of menopausal hormone therapy.[2]

Worldwide, breast cancer was the most common cause of cancer death in women, and it accounted for 521,817 of the total estimated 8.2 million cancer-related deaths in 2012.[3] Since 1990, the United States, the United Kingdom, and France have experienced a reduction in breast cancer–related deaths, primarily thought to be due to more effective systemic therapies and improvements in early detection. In contrast, changes in reproductive patterns, increased obesity, and decreased physical activity are thought to have contributed to a 2- to 3-fold increase in the incidence of breast cancer in African and Asian countries, with a corresponding increase in breast cancer deaths.[4] In the United States, an estimated 249,260 new cases of invasive breast cancer were expected to be diagnosed in 2016, involving 2600 men and 246,660 women.[5] It was also estimated that there were 61,000 new cases of in situ breast cancer diagnosed in 2016. There are more than 2.8 million breast cancer survivors in the United States. Breast cancer continues to be the most common malignancy among women in the United States, and it remains the second most common cause of cancer-related death among women (behind lung cancer), with an estimated 40,450 deaths in women attributed to breast cancer in 2016.

In the United States, following an initial increase in the incidence of localized (node-negative) and regional disease in the 1980s to 1990s, the incidence of each category has decreased by 2.3% and 2.8% per year, respectively. Between 1998 and 2007, the overall incidence of breast cancer decreased by 0.5% per year. Following a striking 7% decrease in incidence between 2002 and 2003, the rate remained relatively stable from 2003 to 2011.[6] There has been no noticeable annual change in the 6% incidence of metastatic disease diagnosed at the time of presentation.[5] The mortality from breast cancer decreased by 36% from 1989 to 2012, and the rate has been level among women younger than age 50.[7]

Race and ethnicity are important considerations in the evaluation of breast cancer incidence and mortality in the United States. The incidence of breast cancer is higher among white women than among black women (e.g., 128 non-Hispanic white women vs. 124 non-Hispanic black women per 100,000 were diagnosed with breast cancer from 2008 to 2012). Some factors that contribute to the higher incidence seen among white women include more frequent use of menopausal hormone therapy and more widespread use of screening mammography. When mortality data are evaluated the incidence is reversed (e.g., 22 white women vs. 31 black women per 100,000 died of breast cancer from 2008 to 2012).[8] Multiple factors play a role in this observation. Breast cancer is more likely to develop before the age of 40 in black women than in white women; black women are also more likely to be diagnosed at a more advanced stage of breast cancer and to have high-grade, triple-negative tumors. In addition, it may be that more nonsignificant breast cancers—those that would never have caused clinically apparent or life-threatening disease—are diagnosed in white women because of higher rates of screening. Breast cancer–related incidence and death are lower among Asian, Native American, and Hispanic women living in the United States compared with non-Hispanic white women.[9]

KEY POINTS

- The incidence of breast cancer is increasing in nonindustrialized countries because of lifestyle changes (i.e., obesity and decreased physical activity).
- The incidence of breast cancer has decreased in the United States since 2002, likely as a result of a reduction in the use menopausal hormone therapy.
- Compared with non-Hispanic white women, black women have a lower overall incidence of breast cancer but a higher rate of breast cancer–related mortality, attributed to more advanced stage at diagnosis and higher prevalence of the triple-negative subtype of breast cancer.

RISK FACTORS

AGE AND GENDER

In the United States, older age and female sex are the most important risk factors for the development of breast cancer. The lifetime risk for breast cancer among women in the United States is estimated at 1:8 (12%), with multiple risk factors identified (Table 7-1).

Table 7-1 **Established Risk Factors for Breast Cancer: Fixed Factors**	
Factor	**Relative Risk**
Gender (female vs. male)	100
Age (≤ 50 vs. > 50)	6.7
Endocrine factors	
Age at menarche (< 10)	1.4–1.9
Age at first birth (> 35)	1.7
Nulliparity	1.4
Age at menopause (> 55)	1.3
Benign breast disease	
ADH, LCIS	4.0–5.0
Family history	
First-degree relatives	2.0–7.0
BRCA1 or BRCA2 mutation	10–30
PALB2 mutation	5.0–9.0
p53 (Li-Fraumeni)	1.5–6.0
Cowden syndrome	2.0–4.0
Ashkenazi Jewish ethnicity	1.4
Therapeutic radiation	35

Abbreviations: ADH, atypical ductal hyperplasia; LCIS, lobular carcinoma in situ.

Male breast cancer is uncommon, accounting for approximately 1% of all breast cancers.[3] Men are usually diagnosed after age 60; the specific risk factors for this disease among men include genetic predisposition associated with *BRCA2* or *PALB2* mutations, Klinefelter syndrome, testicular alterations that result in testosterone deficiency (such as undescended testes or testicular injury), and syndromes that increase the estrogen-to-testosterone ratio (such as obesity or cirrhosis).[10-12]

FAMILIAL

A family history of breast and/or ovarian cancer, particularly if onset occurred at younger than age 50, is associated with a higher risk of breast cancer. Approximately 5 to 10% of all breast cancers are associated with highly penetrant gene mutations, such as *BRCA1* and *BRCA2.* An additional 15 to 20% of women diagnosed with breast cancer have a positive family history, which may be the result of inheritance of several low-penetrance genes that increase risk, or alternatively, to shared environmental exposures. In some families, both the inheritance of low-penetrance genes and shared environmental factors may operate synergistically. Having first-degree relatives with breast cancer portends a 2-fold higher risk of developing breast cancer.[13] This risk can increase 3- to 4-fold if a first-degree relative was diagnosed at an age younger

than 50 or when two first-degree relatives are affected.[13,14] Having a previous diagnosis of breast cancer is also associated with a higher risk of developing contralateral disease, which can be compounded when a family history of breast cancer is present.

GENETIC

Hereditary breast cancer is characterized by the presence of high-penetrance genotypes, inheritance through maternal and/or paternal ancestry, and associations with other malignancies and/or familial situations (as indicated in Fig. 7-1).[15] Optimally, the individual to undergo genetic testing within a family would be the youngest woman who carries the diagnosis of either ovarian or breast cancer. If a genetic linkage is not found in that individual, further testing among family members is usually not beneficial, unless there is a suspicion that the tested individual has a spontaneous breast cancer (phenocopy). In that setting, a second affected individual within the family should be tested.

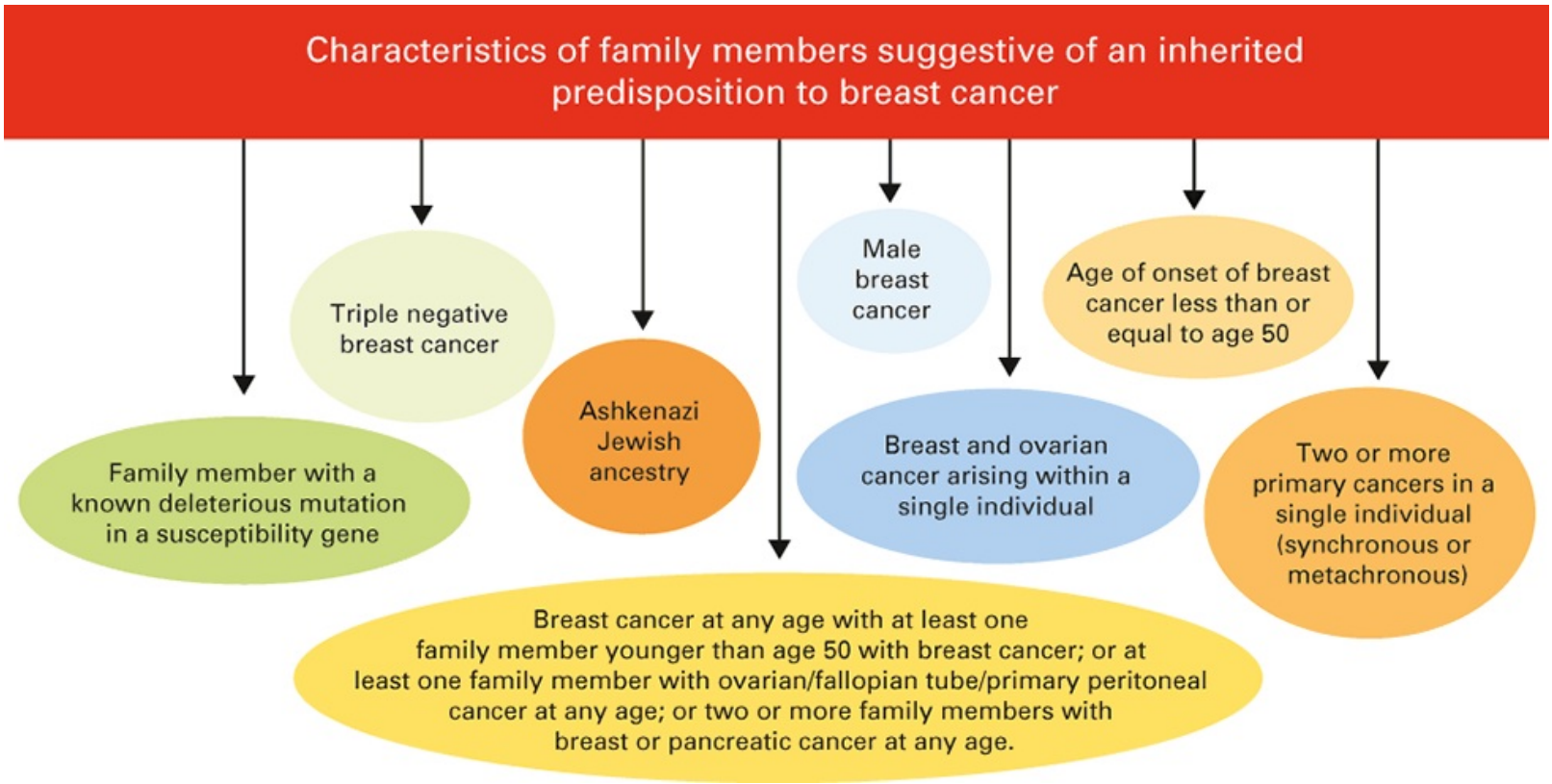

Fig. 7-1 Factors associated with higher risks of an index patient carrying a genetic predisposition for breast cancer.

Germline mutations in several genes have been identified as being associated with a high probability of breast and/or ovarian cancer developing. The most common genes are *BRCA1* and *BRCA2,* which are transmitted in an autosomal-dominant pattern. The protein products of *BRCA1* and *BRCA2* function as tumor suppressors that protect chromosomal stability by enabling homologous recombination following double-stranded DNA breaks. *BRCA2* binds directly to RAD51, an enzyme that is essential for homologous recombination. *BRCA2* is also the gene related to Fanconi anemia, and it works in concert not only with RAD51 and *BRCA1,* but also with *PALB2,* to facilitate recruitment of these enzymes to sites of DNA damage, resulting in repair.[16]

Mutations in *BRCA1* appear to be associated primarily with breast and ovarian cancer risk, whereas *BRCA2* mutations are associated with other malignancies, such as prostate cancer

(relative risk [RR] with age younger than 65, 7.33), pancreatic cancer (RR, 3.51), malignant melanoma (RR, 2.58), gallbladder and bile duct cancer (RR, 4.97), and stomach cancer (RR, 2.59).[17,18] The risk of male breast cancer before age 80 is approximately 7% among *BRCA2* mutation carriers.[19] Among women with *BRCA1* or *BRCA2* mutations, the risk of breast cancer over a lifetime is estimated to be 50 to 75%. The risk of developing ovarian cancer is higher with a *BRCA1* mutation (30 to 40%) than with a *BRCA2* mutation (10 to 20%).[20] The development of contralateral breast cancer is also increased (RR for *BRCA2*, 3.4; RR for *BRCA1*, 4.5), although this risk is less pronounced among women older than age 50 (10.8%) than among patients who were diagnosed at younger than age 30 (28.2%).[21] In addition, the use of more effective systemic therapies contributes to a reduction in the development of contralateral breast cancer.[17]

Approximately 2.5% of individuals of Ashkenazi Jewish ancestry carry one of three "founder" mutations—5382insC or 185delAG for *BRCA1* or 617delT for *BRCA2*. These account for 12% of breast cancers and 35% of ovarian cancers in this population. An additional 2 to 4% have nonfounder mutations.[22]

Certain subtypes of breast cancer occur more commonly with specific genetic mutations. For example, *BRCA1* mutations are associated with triple-negative breast cancer (TNBC); invasive lobular carcinoma seen in conjunction with a family history of diffuse gastric carcinoma can occur with mutations in the E-cadherin gene *CDH1;* and HER2-positive breast cancer is more prevalent in *TP53* mutations (Li–Fraumeni syndrome).[23-25]

PALB2 (partner and localizer of *BRCA2*) has emerged as a relevant gene associated with predisposition to breast cancer.[26,27] Loss-of-function mutations in *PALB2* are observed in 0.6 to 3.9% of families with a history of breast cancer. As compared to the general population, women who harbor a *PALB2* mutation have a 5- to 9-fold risk of breast cancer, with the magnitude of risk inversely correlated with age. The cumulative risk of breast cancer by age 70 is about 35% for *PALB2* mutation carriers, and this is further influenced by birth cohort and other familial factors.[28]

The Li–Fraumeni syndrome is related to germline mutations in *TP53.* These highly penetrant mutations are very rare (1 in 5000 people) and are associated with a 90% lifetime risk of a malignancy developing, which includes breast cancer in very young women (younger than age 30), sarcoma, leukemia, adrenocortical carcinomas, and brain tumors. Cowden syndrome is also a rare, autosomal-dominant syndrome; 80% of cases are caused by mutations in the *PTEN* tumor suppressor gene (10q23). In this syndrome, breast cancer can occur in conjunction with thyroid, kidney, and endometrial cancer in addition to specific physical findings such as macrocephaly, hamartomas, autism, and trichilemmomas of the face, hands, and feet.[29]

There are now a number of multiplex test panels that assess both high- and moderate-penetrance genes for use in families who test negative for a known familial cancer syndrome, yet have characteristics suggestive of an inherited risk. The challenges of using these panels include a limited understanding of risk associated with moderately penetrant genes and high prevalence of detecting variants of uncertain significance.[30]

REPRODUCTIVE/ENDOGENOUS HORMONES

Estrogens clearly play a role in breast cancer risk and development. Increased levels of premenopausal endogenous hormones are associated with an increased risk of disease among postmenopausal women.[31] Terminal differentiation of breast epithelium occurs following a full-

term pregnancy. This histologic change in breast parenchyma appears to be protective and associated with a reduction in breast cancer risk when first full-term pregnancy occurs at a younger age (younger than 30). Lactation may also convey protection; however, the duration of lactation required for this benefit is not well defined. A greater understanding of molecular subtypes of breast cancer (i.e., hormone receptor–positive vs. triple-negative) has led to greater specificity in defining the role of reproductive risk factors. An early onset of menarche, late age of menopause, and nulliparity are all related to extended estrogen exposure and elevated risk of hormone receptor-positive disease (estrogen receptor [ER]–positive and/or progesterone receptor [PR]–positive).[32] In contrast, triple-negative disease is associated with an increasing number of births and is not associated with nulliparity or age at first full-term delivery.[33]

EXOGENOUS HORMONES

Menopausal hormone therapy in the form of combination estrogen and progesterone is associated with an increased risk of developing invasive breast cancer (hazard ratio [HR], 1.26); however, the risk returns to normal within 2 years after discontinuation of menopausal hormone therapy (Table 7-2).[34] Women taking combination menopausal hormone therapy have also been found to have a more advanced stage of breast cancer at the time of diagnosis. The global cessation of combination menopausal hormone therapy in 2002 was associated with an 8.6% reduction in the annual incidence of invasive breast cancer, primarily observed in HR-positive disease and in women older than age 50.[2] Breast cancer risk does not appear to be related to a limited duration of unopposed estrogen use (< 10 years) or oral contraceptive use; however, oral contraceptive use may be associated with an increased risk in the setting of a *BRCA* mutation.[35,36]

Table 7-2 Established Risk Factors for Breast Cancer: Modifiable Factors

Factor	Relative Risk
Exogenous hormones	
Oral contraceptive pills	0.9–1.0
Estrogen replacement (> 10 years)	1.1
Estrogen and progesterone	1.4–3.0
Postmenopausal obesity (BMI > 30)	2.5
Exercise (> 3 hours/week)	0.6
Alcohol use	1.1–2.2
Diet	1.0
Extremely dense mammographic tissue	4.0–6.0

Abbreviation: BMI, body mass index.

RADIATION EXPOSURE

Low-level radiation exposure is associated with an increased risk of breast cancer, as high as 3.6-fold, and can occur with multiple fluoroscopic examinations, frequent diagnostic radiographs for scoliosis, and historically, as treatment for thymic enlargement, skin hemangiomas, and benign breast disease. Survivors of Hodgkin lymphoma and other hematologic malignancies who received therapeutic mediastinal or mantle-field radiation have a higher risk of breast cancer, which is dependent on dose of radiation and the radiation field volume. The relative risk can range from 37 to 57, accompanied by a greater propensity for bilateral breast cancer to develop. The risk is greatest when treatment occurred during active proliferation of breast tissue (i.e., between ages 15 and 25). The median time to the development of breast cancer after treatment is approximately 18 years; however, increased risk can start as early as 8 years after treatment. The risk continues to increase over time, wherein the estimated cumulative incidence of breast cancer after 25 to 30 years of follow-up ranges from 12 to 26%. Use of lower doses of therapeutic radiation involving smaller volumes has resulted in lower risks of breast cancer.[37-39]

MAMMOGRAPHIC DENSITY

Mammographic density is classified according to the proportion of radiopaque areas on a mammogram, representing epithelial and stromal tissue, relative to radiolucent areas, representing fat. While quantitative measures of mammographic density exist, they are not routinely used in clinical practice. The Breast Imaging Reporting and Data System (BI-RADS) Atlas issued by the American College of Radiology categorizes breast density composition into four lettered categories based on a visual assessment of the mammogram.[40]

a. The breasts are almost entirely fatty.
b. The breasts have scattered areas of fibroglandular density.
c. The breasts are heterogeneously dense, which may obscure small masses.
d. The breasts are extremely dense, which lowers the sensitivity of mammography.

Mammograms classified as heterogeneously or extremely dense are considered dense, whereas as mammograms in the other two categories are not. There is a linear trend associated with increasing mammographic density and risk of breast cancer, wherein women with greater than 75% breast density have a 4- to 6-fold higher risk of disease.[41] Exogenous hormone use, such as menopausal hormone therapy or oral contraceptives, results in increased mammographic density, whereas endogenous estrogen levels have not shown a consistent association with mammographic density. Lower mammographic density may be a reflection of involution of the terminal ductal lobular units, a natural aging process of the breast that is associated with a lower breast cancer incidence.[42,43] Mammographic density and mammographic sensitivity are inversely related, primarily because of the masking of cancer by superimposition of overlapping radiopaque dense breast tissue. Mammographic density has been found in some studies to be a principle factor in the failure of mammography to detect cancer as well as in the presentation of interval cancers.[44,45] Addition of tomosynthesis to digital mammography for screening is associated with an increased cancer detection rate for women with both dense and nondense breast tissue; in one study, the benefit was largest for the group of women with heterogeneously dense breasts, but there was no benefit in women with extremely dense breasts.[46]

Twenty-eight states have legislation requiring that women be notified about breast density after screening mammography, although there is currently no consensus on whether women

with dense breasts should be advised to pursue supplemental screening. Supplemental screening modalities, including whole-breast screening ultrasound, molecular breast imaging, and screening breast magnetic resonance imaging (MRI), have been shown to increase cancer detection as compared with mammography alone in women with dense breasts, but the impact on breast cancer outcomes is unknown. Insurance coverage for supplemental screening is variable.

BENIGN PROLIFERATIVE BREAST DISEASE

Pathologic changes within the breast have been shown to be independent risk factors for breast cancer. Benign proliferative lesions without atypia do not necessarily fall into this category, whereas benign proliferative breast disease with atypia, such as atypical ductal hyperplasia, atypical lobular hyperplasia, and lobular carcinoma in situ (LCIS), is associated with a 4-fold increased risk of breast cancer developing in either breast.[47] Lobular neoplasia (atypical lobular hyperplasia and LCIS) is associated with about a 30% risk of breast cancer developing over 25 years. The risk is increased in patients with multiple foci of disease and in women who do not have any evidence of breast involution.[48] Thus, following a diagnosis using core needle biopsy, it is recommend that most individuals undergo an excisional procedure to determine whether ductal carcinoma in situ (DCIS) or invasive disease is present. The histologic type of atypical hyperplasia (i.e., ductal vs. lobular) does not affect risk, although the number of foci of atypia is associated with a higher incidence of risk.[49] Women younger than age 45 with atypical hyperplasia have a higher RR (6.76) for the development of breast cancer. Interestingly, some data suggest that a family history of breast cancer does not appear to be additive to risk in the setting of benign proliferative disease.[48]

BEHAVIORAL FACTORS

Consumption of one alcoholic beverage per day is associated with a 12% increased risk of breast cancer and has a linear correlation such that a 10% increase in risk is associated with every additional 10 g/day of alcohol (or 0.75 to 1 alcoholic beverage per day) consumed. The risk is independent of type of alcohol consumed and may be related to an increase in serum hormone levels.[50-52]

Obesity (body mass index [the weight in kilograms divided by the square of the height in meters], > 30) increases the risk of breast cancer in postmenopausal women by more than 63%, but is inversely correlated with risk in premenopausal women.[53] However, when used as an indicator of body fat distribution, a larger waist circumference is associated with a greater incidence of premenopausal ER-negative breast cancer.[54] Waist circumference and body mass index are markers of visceral adiposity associated with the metabolic syndrome—a condition of hyperglycemia, hyperinsulinemia, and insulin resistance. The association of obesity with both increased breast cancer risk and mortality from breast cancer appears to be due to the effects of obesity on the increased production of estrogen and insulin activation of tyrosine kinase growth receptor pathways.[55,56]

Physical activity appears to be inversely related to breast cancer risk, in that 4 to 7 hours per week of recreational exercise is associated with a 12 to 60% reduction in risk among both premenopausal and postmenopausal women. A number of epidemiologic observations suggest that the beneficial effects of exercise may be due to weight control, hormonal effects, and/or changes in immune function.[57]

Isoflavones (i.e., phytoestrogens most commonly found in soy), vitamin D, dairy products,

and high-fat diets have unclear relationships to the incidence of breast cancer.[58]

RISK-DETERMINATION MODELS

Several models are available to predict the risk of breast cancer based on family history and/or to determine the probability of carrying a *BRCA* mutation (Table 7-3). The Claus model includes first- and second-degree relatives with breast and/or ovarian cancer and incorporates the age at diagnosis.[59] BRCAPRO,[60] the Tyrer–Cuzick model (the IBIS),[61] and the BOADICEA model[62] all calculate risk based on the probability of carrying a genetic mutation.[63]

Table 7-3 Risk Factors Used in Risk Assessment Models

Modified Gail model	Age, age at menarche, age at first live birth, number of breast biopsies, history of atypical hyperplasia, number of first-degree relatives with breast cancer, race
Claus model	Age, first- and second-degree relatives with breast cancer, age at onset of breast cancer, ovarian cancer in a relative, paternal family history
BRCAPRO model	Age, first- and second-degree relatives with breast cancer, age at onset of breast cancer in a relative, bilateral breast cancer in a relative, ovarian cancer in a relative, breast cancer in a male relative
International Breast Cancer Intervention Study (IBIS) model (Tyrer-Cuzick model)	Age, body mass index, age at menarche, age at first live birth, age at menopause, HR therapy, number of prior breast biopsies, presence of atypical hyperplasia, lobular carcinoma in situ, number of first- and second-degree relatives with breast cancer, age at onset of breast cancer in a relative, bilateral breast cancer in a relative, ovarian cancer in a relative
Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)	Age, first-, second-, and third-degree relatives with breast cancer, age at onset of breast cancer in a relative, bilateral breast cancer in a relative, ovarian cancer in a relative, breast cancer in a male relative

The modified Gail model is the most widely used risk-assessment tool; it incorporates nongenetic factors such as current age, age at menarche and first full-term pregnancy or nulliparity, number of breast biopsies and presence of atypical hyperplasia, number of first-degree relatives with breast cancer, and race (www.cancer.gov/bcrisktool). The original Gail model was modified and validated to incorporate race as a risk factor, specifically assessing breast cancer risk in black women (Contraceptive and Reproductive Experience [CARE] model).[64] The modified Gail model is an excellent tool to determine risk on a population basis; however, the 5-year or lifetime risk of disease calculated for an individual woman is not robust.[65] This model will also underestimate risk if there is a significant genetic predisposition. Prevention strategies are often considered when the modified Gail model calculates a 5-year risk exceeding 1.67%; however, this calculation does not take into account factors such as breast density or presence of LCIS, and it may also underestimate the risk associated with atypia.[66]

KEY POINTS

- Atypical hyperplasia and lobular carcinoma in situ are associated with a 30% risk of breast cancer over 25 years.
- *BRCA1* and *BRCA2* mutations are associated with a 50 to 75% lifetime risk of the development of breast cancer and a 30 to 40% risk *(BRCA1)* or 10 to 20% risk *(BRCA2)*

of the development of ovarian/fallopian tube–type cancer.

- Postmenopausal obesity and alcohol use are associated with a higher risk of breast cancer.
- Increased breast density is associated with higher risk of breast cancer.
- Increased physical activity is associated with a lower risk of breast cancer.

PREVENTION

The current goal of breast cancer prevention is to reduce the risk of the development of disease with minimal toxicity. Women with the following characteristics may consider risk-reducing surgery: a positive test for a high-penetrance genetic mutation, a strong family history of breast cancer that is not associated with a pathogenic mutation in a breast cancer susceptibility gene, or a strong family history of breast cancer and have not been tested for a hereditary breast cancer syndrome. Both lifestyle and medical risk-reducing strategies can be discussed with women at any degree of breast cancer risk. Additionally, surgical approaches are available for women with higher risks.

RISK-REDUCING SURGERY

Because of the difficulty in detecting ovarian or fallopian tube cancer at an early stage, it is recommended that women with *BRCA* mutations (hereditary breast and ovarian cancer syndrome) undergo risk-reducing bilateral salpingo-oophorectomy (RRSO), typically between age 35 and 40 and upon completion of childbearing. The National Comprehensive Cancer Network (NCCN) guidelines specifically note that it is reasonable to delay until age 40 to 45 in patients with a *BRCA2* mutation, since the median age at onset of ovarian cancer tends to occur 8 to 10 years later than in patients with a *BRCA1* mutation. RRSO has been shown to decrease the risk of ovarian cancer (which includes primary peritoneal and fallopian tube cancers) by approximately 85% (HR, 0.14), and reduce the risk of a first diagnosis of breast cancer among both *BRCA1* and *BRCA2* mutation carriers (HR, 0.63, and HR, 0.36, respectively). It is furthermore associated with a lower breast cancer–specific mortality (HR, 0.44), lower all-cause mortality (HR, 0.40), and lower ovarian cancer–specific mortality (HR, 0.21).[67] Subsequent to RRSO, there remains a small risk of primary peritoneal carcinoma among *BRCA* mutation carriers. In one study of 509 *BRCA* mutation carriers who underwent RRSO, at median follow-up of 38 months, peritoneal cancer had developed in only 3 (0.6% of patients, all with the *BRCA1* mutation).[68] There appears to be an age effect of RRSO on breast cancer risk, wherein women who undergo RRSO after age 50 do not obtain a significant reduction in the risk of breast cancer. RRSO does not seem to affect the risk of contralateral breast cancer after a prior diagnosis of breast cancer;[69] however, RRSO is associated with a significant reduction in mortality in women with ER-negative breast cancer who have a *BRCA1* mutation (HR, 0.38; $p = 0.007$).[70] The concern about the adverse effect on mortality from inducing early menopause may be safely ameliorated with short-term menopausal hormone therapy given until age 50 without an apparent compromise in the overall benefit of RRSO on breast cancer risk.[71]

Bilateral risk-reduction mastectomy (RRM) has been shown to reduce the risk of breast cancer by more than 90% in women with hereditary breast and ovarian cancer syndromes.[72] Women at high or moderate risk of breast cancer (i.e., known genetic linkage or a significant

family history without a known genetic predisposition) should have a discussion with their doctors concerning prevention. Skin-sparing mastectomy appears to be as effective as total mastectomy, and early data indicate that nipple-sparing mastectomy may be reasonable in this patient population.[73] Reconstructive surgery following mastectomies does not appear to increase breast cancer risk. In the absence of a *BRCA* mutation, contralateral prophylactic mastectomy performed following the diagnosis of invasive breast cancer has not been associated with an improvement in overall survival (OS).

MEDICAL RISK REDUCTION (CHEMOPREVENTION)

When used for the treatment of invasive breast cancer, endocrine therapy has resulted in a significant reduction in the risk of contralateral breast cancer. The 15-year follow-up of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview analysis demonstrated a 39% reduction in the development of a primary contralateral breast cancer with 5 years of adjuvant tamoxifen use.[74] This observation prompted several randomized trials examining the efficacy of selective estrogen-receptor modulators (SERMs), such as tamoxifen, in reducing the risk of breast cancer among high-risk women. The National Surgical Adjuvant Breast and Bowel Project BCPT P-1 trial defined a high-risk cohort as pre- or postmenopausal women older than age 60, women age 35 or older with a 5-year predicted disease risk of 1.66% or higher as predicted by the Gail model (see the Risk-Determination Models section), or women with a diagnosis of LCIS. A 7-year follow-up report of 13,388 women enrolled in the BCPT who were randomly assigned to receive 20 mg of tamoxifen or placebo daily for 5 years[75] demonstrated that tamoxifen reduced the risk of invasive breast cancer by 43%. The incidence of ER-positive invasive breast cancer was reduced by 62%, but there was no effect on the risk of ER-negative breast cancer. The risk of noninvasive breast cancer (DCIS) was also reduced by 37%.

These results were supported by several other randomized trials involving tamoxifen, including the IBIS-1 trial (34% risk reduction), the Royal Marsden Tamoxifen Prevention trial (39% risk reduction), and the Italian Randomized Tamoxifen Prevention trial (76% risk reduction).[76-78] The eligibility requirements of these studies varied, as did the acceptance of concurrent menopausal hormone therapy or bilateral oophorectomy among participants, making cross-study conclusions more difficult. None of the studies demonstrated an effect on all-cause mortality.[79]

Both the prevention studies and the studies using tamoxifen for the treatment of breast cancer demonstrated an association between tamoxifen use and an increased incidence of endometrial cancer, thromboembolic phenomena, cataracts, and gynecologic and vasomotor symptoms (vaginal discharge and hot flashes). In the P-1 trial, tamoxifen also has been shown to reduce the incidence of osteoporotic bone fractures (of the hips, spine, or radius) by 29% among women age 50 or older (RR, 0.71; 95% CI; 0.52, 0.97).[75] The risk of endometrial cancer was increased with tamoxifen use (RR, 3.28; 95% CI; 1.87, 6.03), which translated to a 1.6% risk with tamoxifen compared with a baseline 0.7% risk over 7 years.[75] The majority of tamoxifen-associated endometrial cancers present with postmenopausal bleeding, are typically adenocarcinomas, are early stage, and affect women older than age 50. There are no data to support routine screening for endometrial cancer using transvaginal ultrasound or biopsy, unless abnormal vaginal bleeding is present.[80] The risk of venous thromboembolic events was also significantly increased with tamoxifen use (deep venous thrombosis RR, 1.44; pulmonary embolism RR, 2.15). The risk of stroke is not consistently increased among the tamoxifen studies, and this association is not supported by large population studies.

A second-generation SERM, raloxifene, was shown to reduce the incidence of invasive breast cancer by 69 to 72% when investigated as a treatment for osteoporosis in two clinical trials, the MORE and CORE trials.[80] The use of raloxifene was not associated with an increased risk of endometrial cancer, which made it a promising SERM to use for breast cancer prevention among postmenopausal women. The NSABP P-2 STAR trial compared the efficacy of 5 years of tamoxifen to raloxifene among postmenopausal women who met the same high-risk criteria defined in the BCPT.[81] The initial evaluation, after a median follow-up of 4 years, demonstrated no difference between the effects of the two SERMs in the development of invasive breast cancer among the 19,747 women enrolled in the STAR trial. However, after an extended follow-up of nearly 8 years, raloxifene retained only 76% of the effectiveness of tamoxifen in reducing the risk of invasive cancer. Whereas the initial evaluation of the STAR trial showed no statistical effect of raloxifene on DCIS risk, the 9.7-year follow-up revealed raloxifene to be only about 18% as effective as tamoxifen in reducing the risk of DCIS.[82,83] There was no difference in mortality outcome between the two SERMs. Raloxifene use was associated with significantly less toxicity than tamoxifen—specifically, fewer endometrial cancers and thromboembolic events. Thus, while raloxifene did not appear to decrease breast cancer risk as well as tamoxifen did, its better safety profile makes it a reasonable chemoprevention alternative to tamoxifen in postmenopausal women.

A recent meta-analysis of the individual participant data from all randomized prevention trials involving SERMs, including arzoxifene and lasofoxifene (nine trials, 83,399 participants), demonstrated a 10-year cumulative incidence of breast cancer that equaled 6.3%, versus 4.2% among patients who received placebo or the SERM.[84] The reduction in breast cancer was evident both during years 0 to 5 (42%), and during years 5 to 10 (25%). The increased risk of endometrial cancer was confined to tamoxifen use during years 0 to 5 (HR, 1.64), and although the number of venous thromboembolic events was increased overall, there was no effect on incidence of myocardial infarction, stroke, or transient ischemic attacks. SERM use had no effect on the risk of ER-negative breast cancer or on overall mortality.

Clinical trials exploring the efficacy of adjuvant aromatase inhibitors (AIs), compared with tamoxifen, for the treatment of early-stage breast cancer have shown a 48% relative reduction in risk of contralateral breast cancer with the use of an AI.[80] In addition, the AIs lacked an association with the risk of endometrial cancer and thromboembolic phenomena. These data prompted the investigation of exemestane, a steroidal third-generation AI, in the prevention of invasive breast cancer among postmenopausal women at high risk. The general eligibility criteria for enrollment in the placebo-controlled National Cancer Institute of Canada CTC MAP.3 trials were essentially the same as those used for the BCPT and the STAR trial.[85] Ethical justification for this placebo-controlled trial stemmed from the lack of benefit in mortality seen with the use of U.S. Food and Drug Administration (FDA)–approved SERMs for prevention. The results of the MAP.3 prevention trial, at 35-month follow-up, demonstrated a 65% reduction in the incidence of invasive breast cancer and a 73% reduction in the incidence of ER-positive invasive breast cancer among women taking exemestane for 5 years as compared with those taking placebo. Although adverse events were more common in the exemestane group (88% vs. 85%; $p = 0.003$), arthritis and menopausal symptoms were statistically more frequent. The international, randomized placebo-controlled trial known as IBIS-II, supports the finding that AIs, in this case, 5 years of anastrozole, reduce the risk of hormone receptor–positive invasive breast cancer and DCIS by more than 50% (HR, 0.47; $p < 0.0001$) among postmenopausal women at high risk for the development of breast cancer.[86] As was seen in the prevention studies using SERMs, anastrozole neither conveyed a risk reduction for ER-negative breast

cancer nor improved survival.

SUMMARY OF RECOMMENDATIONS FOR MEDICAL PREVENTION

Both tamoxifen and raloxifene have been approved by the FDA for use in the prevention of breast cancer; however, raloxifene is approved for use only in postmenopausal women.[87] Tamoxifen (20 mg daily for 5 years) can be offered to women who are at high risk of breast cancer. Raloxifene (60 mg daily for 5 years) can also be offered to postmenopausal women who are at high risk of breast cancer. Women can use raloxifene for longer than 5 years if the medication is used to treat osteoporosis; however, the studies examining its effect on breast cancer risk used a treatment duration of only 5 years.[80] Very few women with *BRCA* mutations have been specifically evaluated in prevention trials; therefore, the role of primary medical prevention in this population is not well known. However, data suggest that tamoxifen can reduce the development of contralateral breast cancers in *BRCA1* (42% risk reduction) or *BRCA2* (52% risk reduction) mutation carriers following the diagnosis of breast cancer.[88] Extrapolating from these data, tamoxifen can be offered as a medical prevention strategy among *BRCA*-positive patients who have not been diagnosed with breast cancer, similar to the strategy for high-risk women who are not mutation carriers. Exemestane and anastrozole have been shown to reduce the risk of invasive breast cancer among high-risk postmenopausal women, and they are supported by ASCO and NCCN guidelines for breast cancer prevention; however, they have not yet been FDA-approved for this indication (Table 7-4). The use of other medications for breast cancer prevention (e.g., metformin, aspirin) remains investigational.

Table 7-4 Breast Cancer Medical Prevention Trials

Trial	Patients	Comparison	RR (95% CI)	RR for HR+ (95% CI)
STAR[81]	19,747	Raloxifene vs. tamoxifen	1.24 (1.065, 1.47)	NA
MAR3[85]	4,560	Exemestane vs. placebo	0.35 (0.18, 0.70)	0.27 (0.12, 0.60)
IBIS-II[86]	1,920	Anastrozole vs. placebo	0.50 (0.32, 0.76)	0.42 (0.25, 0.71)
Italian[78]	5,408	Tamoxifen vs. placebo	0.84 (0.60, 1.17)	0.61 (0.38, 0.99)
Royal Marsden[77]	2,471	Tamoxifen vs. placebo	0.78 (0.58, 1.04)	0.48 (0.29, 0.79)
IBIS-I[76]	7,145	Tamoxifen vs. placebo	0.73 (0.58, 0.91)	0.66 (0.50, 0.87)
BCPT P-1[75]	13,338	Tamoxifen vs. placebo	0.57 (0.46, 0.70)	0.38 (0.28, 0.50)

Abbreviations: RR, relative risk for invasive breast cancer; RR for HR+, relative risk for hormone receptor-positive invasive breast cancer; NA, data not available for most recent evaluation.

LIFESTYLE MODIFICATIONS

Physical Activity

A substantial amount of data associating lifestyle modification with a reduction in risk of breast cancer stems from extrapolation of studies that link lifestyle factors and risk of a second primary contralateral breast cancer or a systemic breast cancer recurrence. Moderate exercise (2 to 3 hours per week) has been reported to reduce breast cancer recurrence and all-cause mortality by approximately 40 to 67%.[89] Three prospective cohort studies demonstrated that current total or recreational exercise can reduce the incidence of breast cancer by 20 to 30%, primarily among premenopausal women.[90] All types of activity appear to be beneficial and associated with risk reduction when performed at any point in life. Some data endorse a greater benefit with activity if it is performed later in life (after age 50), is more vigorous, occurs

more frequently and for a longer duration, and occurs among postmenopausal women.[91] The biologic mechanism behind physical activity and risk reduction is unknown, although some studies support an interaction among estrogen, fasting insulin levels, insulin resistance, and lipid metabolism.[89] Although it can be argued that the true effect of physical activity on breast cancer recurrence has not yet been conclusively proven, exercise has far-reaching benefits for improvement in overall quality of life, fatigue scores, and sleep quality.

Diet and Weight Change

The correlation among alcohol consumption, obesity, and the risk of breast cancer is well established. However, the current data that support risk reduction as it applies to alcohol and obesity focus on avoidance of the exposure or attribute, rather than the introduction of specific interventions. Although moderate alcohol intake may increase breast cancer risk, it decreases heart disease mortality. Good data are lacking as to whether moderate alcohol use after a diagnosis of breast cancer influences mortality.[92,93] The majority of studies have not conclusively supported a reduction in risk from an increased consumption of fruits and vegetables. Although a study from the Women's Health Initiative suggested a 9% reduction in risk when women consumed a low-fat diet, prospective studies evaluating dietary changes and their effect on breast cancer risk have not been conclusive.[90,94] Vitamin supplements, specifically vitamin D and calcium, have not been shown to affect the development of breast cancer to date.[95] Ongoing studies are addressing this question.

KEY POINTS

- RRSO, if performed before age 50, reduces the risk of ovarian cancer by 85% and reduces the risk of breast cancer by 40 to 60% for women who are *BRCA* mutation carriers.
- Bilateral risk-reducing mastectomy reduces the risk of breast cancer by more than 90%.
- Five years of tamoxifen or raloxifene reduces the risk of primarily ER-positive invasive breast cancer by approximately 40% but does not affect overall mortality.
- The AIs, exemestane and anastrozole, are other options for breast cancer risk reduction in postmenopausal women.

SCREENING

AVERAGE RISK

Effective screening for breast cancer detects disease during the preclinical phase (i.e., prior to the development of symptoms) and, therefore, has a favorable effect on breast cancer–related mortality based on the premise that earlier-stage disease is associated with a more favorable prognosis. Decades of controversy have surrounded standard screening recommendations for breast cancer because the published randomized trials are plagued by inconsistent quality of imaging, flawed study design or execution, insufficient duration of follow-up, and problems regarding lead-time bias. Mammographic screening has been available for more than 30 years. During this time there has been progressive improvement in image quality, causing screening

trial results to be outdated before adequate follow-up is completed. Results have been further complicated by highly variable rates of acquisition and implementation of these technologic advances at different medical facilities and in different locations. Unfortunately, as additional randomized trials will never be performed, we are limited to the data at hand.

Data from a 2002 evaluation of the randomized trials suggested a 22% reduction in breast cancer mortality among women older than age 50 who are undergoing mammographic screening. An updated evaluation of these randomized trials in 2009 demonstrated a 14% reduction in breast cancer mortality among women ages 50 to 59 and a 32% reduction in breast cancer mortality among women ages 60 to 69.[96] The effect of mammographic screening on breast cancer mortality among women ages 40 to 49 or older than age 70 is less robust. An evaluation of eight randomized trials demonstrated a 15% reduction in breast cancer mortality with screening among women ages 39 to 49; however, no strong data exist that show a statistical benefit of screening women older than age 70.

The optimal interval for mammographic screening is not known. The advantage of shorter intervals is an increased chance of detecting faster-growing cancer at an earlier stage, but this comes with the disadvantage of a higher false positive rate. Based on six modeling groups that estimated benefits, risks, and use of resources, a biennial screening interval was preferred to annual screening, as it achieved 81% of the benefit with nearly half of the false-positive results.[97] The optimal age at which to begin screening remains unclear and is based upon personal risk. The U.S. Preventive Services Task Force (USPSTF) recommends initiating biennial screening at age 50 and continuing until age 74.[98] The American Cancer Society (ACS) updated their recommendations in 2015 and supports annual imaging beginning at age 40 and strongly recommends annual screening from ages 45 to 54 followed by a transition to biennial screening, which continues as long as a woman's overall health is good and she has a life expectancy of 10 years or longer.[99]

The DMIST trial conducted by the American College of Radiology Imaging Network (ACRIN) compared digital images with film-screen mammographic images among 49,528 women.[100] The overall diagnostic accuracy for digital and film-screen images was similar; however, digital mammography was superior in the accuracy of malignancy detection among pre- or perimenopausal women, women younger than age 50, and women with dense breast tissue. This translated into an improved sensitivity of digital mammography over film-screen mammography by 3 to 24%. There has been a gradual and now nearly complete conversion to digital from film screen technology in the United States. Although digital imaging provides only a small increase in sensitivity compared with optimally performed film imaging, the move to digital imaging has greatly improved and standardized image quality across all sites.

Digital breast tomosynthesis (DBT) mammography is a newer technology that enables three-dimensional imaging of the breast, similar to computed tomography (CT).[101] Investigators have found that DBT results in slightly greater sensitivity, but more importantly, they have also seen a significant reduction in recall rates. Interpretation times are longer with DBT than with digital imaging, but the amount of radiation exposure is now equivalent to standard mammography when synthesized 2D technology is utilized.

There has been increasing interest in using additional screening tests for women with dense breast tissue, given that they are at increased risk of breast cancer and have decreased mammographic sensitivity. Some advocate whole-breast ultrasound, molecular breast imaging, or MR exams as supplemental screening for these patients. All of these techniques increase detection at the expense of higher cost and higher rates of false-positive results. It is still to be determined which, if any, may become the procedure of choice. None of these techniques has

been considered as an alternative to mammography.

Breast self-examination has not been found to improve the detection of early-stage breast cancer on a population basis. Two population studies from Leningrad and Shanghai showed no difference in the rate of cancer detection, tumor characteristics, or breast cancer–related mortality when breast self-examination was performed after instruction, compared with no breast self-examination.[102,103] Clinical breast examinations also do not appear to have affected breast cancer detection or mortality from a population perspective.[104] However, numerous health organizations, including the ACS and the USPSTF, recommend clinical breast examination in conjunction with mammographic screening among women older than age 40.[105] Beginning at age 20, health care providers should encourage women to become familiar with their breasts and report any changes to a health care professional.

HIGH RISK

The routine use of MRI screening for the general population of asymptomatic women is not recommended by the ACS because of its high cost, limited access, and high false-positive rates. Given its substantial sensitivity, the optimal use for this method is in screening a high-risk population. Among patients with *BRCA* mutations, screening mammography can miss more than 50% of all breast cancers. Supplementing mammography with MRI has been shown to improve the sensitivity from 25% to 59% and to 80% to 100% when MRI is added.[106] The specificity of combined mammography and MRI is lower (73 to 93%) than the specificity of mammography alone. Annual MRI screening among *BRCA* carriers has been shown to detect more interval cancers and earlier-stage cancers (DCIS and stage I, 13.8% with MRI, vs. 7.2% without MRI) compared with women not screened with MRI.[107] Adding annual MRI screening to mammography is associated with a 70% reduction in the incidence of lymph node–positive or large invasive breast cancers.

This impressive improvement in detection of earlier-stage disease in high-risk women prompted the ACS to review and present recommendations for annual MRI screening in conjunction with mammography for specific high-risk groups.[99,108] Clear evidence exists to support the recommendation for annual MRI screening with mammography for *BRCA* carriers. First-degree relatives of a *BRCA* carrier who are untested are considered high-risk and should be offered annual MRI screening. Women with other inherited risk factors, such as Li–Fraumeni or Cowden syndrome, are also recommended to have MRI screening, as are women who received mantle radiation for the treatment of lymphoma prior to age 30. Caution must be used in recommending annual MRI screening for women whose estimated lifetime risk of breast cancer is greater than 20%, since ACS guidelines specifically state that this risk should be determined by calculations obtained using risk models that are dependent on family history, such as BRCAPRO. The Gail model does not meet these criteria (see the Risk-Determination Models section). To date not enough evidence supports annual MRI screening for women with dense breast tissue or the diagnosis of LCIS, atypical ductal hyperplasia, or DCIS. In addition, data are insufficient to support routine MRI screening for all women whose only risk factor is a history of invasive cancer.

Nuances of Breast Cancer Screening in High-Risk Women

The majority of the data supporting recommendations for breast cancer screening among women at high risk because of hereditary factors stems from studies among *BRCA* carriers. However, the recommendations for screening apply to all of the hereditary breast cancer

syndromes. In general, screening for hereditary breast cancer begins at age 25 and includes annual mammography and annual breast MRI with biannual clinical breast exams. Since an estimated 29% of *BRCA*-associated cancers present as "interval" cancers (i.e., cancers presenting during the interval following a normal mammogram), women will often have their breast imaging (mammogram and MRI) alternate every 6 months coincidently with their clinical breast examination, although no data support that this screening schedule is superior to that of concurrent breast imaging.[109] Women who have received chest radiation treatment for lymphoma are screened in a similar fashion, beginning approximately 10 years after completing radiation therapy.[110] For women at high risk because of familial (nonhereditary) reasons, initiation of screening should begin approximately 10 years earlier than the age of the youngest woman in the family diagnosed with breast cancer, but not later than age 40.

DIAGNOSIS

Neither physical examination nor imaging can correctly identify whether a breast mass is malignant. Only 60% of the diagnoses of palpable breast masses by physical examination are correct. This reinforces the necessity of tissue biopsy for pathologic evaluation in order to confirm malignancy. Ultrasonography is usually the first diagnostic procedure performed to evaluate palpable breast masses in women younger than age 30. Diagnostic mammography is used for this purpose in women older than age 30. Diagnostic mammography differs from screening mammography in that it adds images to the standard two-view imaging used with screening (i.e., craniocaudal and mediolateral oblique). If a suspicious finding is seen on a diagnostic mammogram or if the palpable breast mass is mammographically occult, a targeted ultrasound is used to obtain specific characteristics that will differentiate a suspicious solid mass from a benign cyst.

Although a fine-needle aspiration (FNA) biopsy of a palpable breast mass is less invasive than a core-needle biopsy, FNA specimens often yield insufficient tissue for analysis and cannot differentiate invasive from noninvasive carcinoma.[111] FNA of suspicious palpable axillary lymph nodes is acceptable given the limited variability of tissue present within a lymph node. It is also appropriate to use FNA in the evaluation of a simple cyst detected by ultrasound, since drainage of the cystic fluid without reaccumulation can imply a benign etiology and eliminate the need for further evaluation.

Core needle biopsies can be obtained via ultrasound guidance or stereotactically when suspicious calcifications are seen on mammography and do not have an associated density. The amount of tissue obtained by core needle biopsy is usually sufficient to characterize the lesion and, when cancer is identified, to perform quantitative immunohistochemical (IHC) analysis of hormone receptors (ER/PR) and HER2 protein status. This provides sufficient information about the cancer to allow the initiation of neoadjuvant systemic therapy, if needed, without compromising future treatment. Core biopsies also provide enough detail about the pathology to permit decisions concerning surgical options, such as the need for sentinel lymph node biopsy and breast conservation. The need to identify the site of biopsy is crucial, so a radiolucent clip is commonly placed in the lesion as a locator. The specific aspects of the procedure of core needle biopsy depend on location of the abnormality within the breast, size of the abnormality, including extent of calcifications, and breast size. Some high-risk benign lesions may require additional tissue excision in order to avoid missing an area within the breast that has more potential to be malignant.

MRI can also be used to evaluate the extent of disease within the breast following the

detection of invasive breast cancer. A meta-analysis of 19 studies assessing the role of MRI in revealing multifocal or multicentric disease found a 16% incidence of additional disease within the affected breast.[112] This was associated with an 8.1% conversion from breast conservation to mastectomy and an 11.3% need for additional surgery following wide excision. MRI is also able to detect multicentric DCIS, but it is not very accurate in assessing noninvasive tumor size. Caution must be used when assessing the contralateral breast with MRI after the diagnosis of breast cancer because it has been shown to detect an occult contralateral malignancy in approximately 3% of patients. This results in a high rate of biopsies and contralateral mastectomies, despite a lack of evidence that these findings will result in a survival advantage.[27]

KEY POINTS

- Mammographic screening has been shown to result in a 23% reduction in breast cancer–related mortality among women ages 50 to 70 and a 15% reduction in breast cancer mortality among women ages 40 to 50.
- Annual mammography and annual magnetic resonance imaging of the breasts should be performed among women with known inherited predispositions to breast cancer (e.g., *BRCA* mutations) beginning at age 25 and in women who have received mantle radiation for the treatment of lymphoma, beginning 10 years after the completion of radiation.
- A core biopsy of a suspicious breast finding is preferable to a fine-needle aspiration in order to accurately assess the histology of the tissue and the status of estrogen receptor, progesterone receptor, and HER2.

PROGNOSTIC INDICATORS

TUMOR/NODE/METASTASIS (TNM) STAGING

The TNM system, under the direction of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), is the standard staging system used for cancer.[113] With reference to breast cancer, as of 2017, the AJCC 7th edition staging is applicable (Table 7-5). This and previous editions have focused entirely on anatomic criteria, a measurement of disease extent, which aids in grouping patients with generally similar prognoses who may need similar therapy. To some degree, the TNM system enables clinical trial activity and the assessment of outcomes. In some situations, the TNM stage can provide a great deal of information in and of itself. For example, the prognosis for stage 0 disease, or DCIS, can be applied from TNM staging, since biologic characteristics of DCIS have little impact on survival. Another application of the TNM staging system in breast cancer is in differentiating stage IV (metastatic) disease (which is incurable in the vast majority of patients) from all other stages of disease that are associated with curative-intent treatment.

Table 7-5 **TNM Classifications and Staging System of the American Joint Committee on Cancer, Version 7 (AJCC)[113]**

a. The stage of a multifocal cancer is based upon the size of the largest foci.

b. The pathologic staging after neoadjuvant therapy has a "y" preceding the TNM stage.

c. The nodal staging after surgical dissection is preceded by "p"

Classification	
Primary Tumor (T)	
TX	Cannot be assessed
T0	Tumor is not present
Tis	Carcinoma in situ
T1	≤ 2.0 cm
T1mi	≤ 0.1 cm
T1a	> 0.1 cm but ≤ 0.5 cm
T1b	> 0.5 cm but ≤ 1.0 cm
T1c	> 1.0 cm but ≤ 2.0 cm
T2	> 2.0 cm but ≤ 5.0 cm
T3	> 5.0 cm
T4	Any size tumor with extension through the chest wall (T4a) or skin ulceration/nodules (T4b) or both (T4c)
T4d	Inflammatory breast cancer
Regional Lymph Nodes (N)	
NX	Cannot be assessed
N0	Nodal involvement absent
N0(i+)	Isolated tumor cells: size ≤ 0.2 mm or fewer than 200 cells
N1	Clinical: movable ipsilateral axillary lymph nodes
pN1mi	Micrometastasis: > 0.2 mm (or > 200 cells) but ≤ 2.0 mm
pN1a	One to three positive axillary lymph nodes; at least one > 2.0 mm
pN1b	Pathologically positive internal mammary lymph nodes
pN1c	Criteria of both N1a and N1b
N2	Clinical: ipsilateral axillary lymph nodes that are fixed or matted; or clinically apparent internal mammary lymph nodes in the absence of clinically positive axillary lymph nodes

pN2a		Four to nine positive axillary lymph nodes; at least one > 2.0 mm	
pN2b		Clinically apparent internal mammary lymph nodes in the absence of axillary lymph node involvement	
N3		Clinical: ipsilateral infraclavicular lymph node involvement with or without axillary lymph node involvement; or clinically apparent internal mammary lymph nodes with axillary lymph node involvement; or involvement of ipsilateral supraclavicular lymph nodes	
pN3a		> 10 positive axillary lymph nodes, or infraclavicular lymph node involvement	
pN3b		Positive axillary lymph nodes with clinical or pathologic involvement of internal mammary lymph nodes	
pN3c		Ipsilateral supraclavicular lymph node involvement	
Metastases (M)			
M0		No clinical or radiographic evidence of distant metastasis	
MI		Distant detectable metastasis as determined by classic clinical and radiographic means and/or histologically proven to be larger than 0.2 mm	
Staging			
Stage	Tumor (T)	Node (N)	Metastasis (M)
0	Tis	N0	M0
IA	T1*	N0	M0
IB	T0–1*	Nlmic	M0
IIA	T0–T1*	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0–2*	N2	M0
	T3	N1–2	M0
IIIB	T4	N0-2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

*T1 includes T1mi.
The original source for this material is the *AJCC Cancer Staging Manual*, 7th ed. (2010) published by Springer Science and Business Media LLC, www.springerlink.com.

Because the specific prognosis for an individual cannot be determined solely by the TNM staging system and also requires an analysis of the tumor biology, revisions to breast cancer staging in the AJCC 8th edition (to be implemented January 1, 2018) notably incorporate prognostic molecular markers with classic TNM anatomic criteria.[114] The 8th edition has resulted in significant changes for breast cancer staging. While there remains an anatomically staged group (which is essentially the same as in the 7th edition, with minor updates and clarifications), it is only to be utilized in countries where biomarkers are not available. The prognostic staged group is noted to be preferred and required in the United States. It uses a combination of traditional TNM staging and data from biomarkers, including histologic grade, hormone receptor and HER2 status, and Oncotype DX results (see the Molecular Prognostic and Predictive Markers section).

With this new prognostic stage grouping and inclusion of the biomarker data, the staging of

41% of breast cancer stages has changed as compared with the 7th edition. For example, T1-2 ER-positive cancers with one to three involved lymph nodes and an Oncotype DX recurrence score less than 11 is now stage IB (previously stage IIB). Additionally, T1b TNBC with negative lymph nodes is now stage IIA (previously stage IA).

It will take some time for the breast cancer community to discuss and adapt their thinking to this new tumor staging system. With regard to this ASCO-SEP chapter, unless specifically stated, the designated stages will be per the AJCC 7th edition.

ANATOMIC PROGNOSTIC INDICATORS

Prognostic features of breast cancer can be divided into two categories: anatomic and biologic. Data suggest that the biologic characteristics of this disease offer considerable information to aid in the decision-making process about systemic therapies.

Lymph Node Involvement

The most important anatomic prognostic indicator for localized breast cancer is tumor involvement within axillary lymph nodes. Intramammary lymph nodes are found within the breast parenchyma and are included in the axillary lymph node category when they contain breast cancer metastasis. The clinical detection of ipsilateral internal mammary or supraclavicular lymph node involvement is associated with a greater risk of local disease recurrence as well as a risk of distant metastasis. Regardless of other characteristics of the breast cancer, the number of axillary lymph nodes involved with disease is linearly related to the risk of systemic recurrence and disease-specific survival.

In the past, the number of lymph nodes involved with metastasis has been grouped into three categories: 1 to 3 positive lymph nodes (N1), 4 to 9 positive lymph nodes (N2), and 10 or more positive lymph nodes (N3). The size of the tumor contributes to prognosis for N0 and N1 disease, whereas prognosis is predominantly governed by the nodal involvement once four or more nodes are positive. Without adjuvant systemic therapy, systemic metastasis will develop in more than 70% of patients with N3 disease; approximately 60% of patients with N2 disease and 25 to 55% with N1 disease will experience relapse, whereas only 20 to 35% of patients without lymph node involvement will experience relapse within 20 years.[115] These data are based on routine level I and level II axillary lymph node dissections (ALNDs) in which at least 6 to 10 lymph nodes were evaluated.

For well over a decade, the evaluation of the clinically negative ipsilateral axilla has been performed by sentinel lymph node (SLN) surgery, this procedure usually identifies one or more lymph nodes draining the primary tumor and is used for intense histopathologic assessment. In the past, patients with a positive SLN routinely underwent a completion ALND. The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial demonstrated the equivalence in OS between a completion ALND and observation for women with one or two positive axillary lymph nodes after SLN surgery.[116,117] Eligible women in Z0011 had clinical T1-2N0 disease and were all treated with breast-conserving surgery and tangential whole-breast irradiation (WBI). The acceptance of these results is related largely to an understanding that breast cancer treatment decisions can be made on the basis of biologic characteristics of the tumor and do not require the quantification of the specific number of lymph nodes.

The size of the metastatic component within the axillary lymph node is also prognostically important. Macrometastasis (> 2 mm) and micrometastasis (> 0.2 mm or > 200 cells, but none > 2 mm) are classified as positive nodal involvement. There is a greater risk for disease

recurrence and death with macrometastatic disease as compared with micrometastatic involvement.[118] Isolated tumor cell clusters (clusters of cells not > 0.2 mm, or < 200 cells) found within a sampled axillary lymph node are believed to represent cells in transit, and they are associated with a prognosis comparable to that of lymph node-negative disease.

Tumor Size

Tumor size, referring to the invasive component only, is measured microscopically and is one of the most important prognostic indicators for breast cancer. The size of associated DCIS does not influence the risk of systemic disease, but may contribute to the risk of ipsilateral cancer recurrence following breast conservation. Larger sizes of invasive cancer are associated with a shorter recurrence-free survival and higher breast cancer–specific mortality. Multifocal (two or more foci of disease within one quadrant of the breast) or multicentric (two or more foci of disease in separate quadrants) disease occurs in 10 to 30% of cases and is associated with a higher frequency of positive lymph nodes and risk of ipsilateral breast recurrence following breast conservation therapy. Tumor staging is based on the size of the largest tumor, and does not take into account other smaller foci.

BIOLOGIC PROGNOSTIC INDICATORS

Histology

The majority of invasive mammary carcinomas are either infiltrating ductal carcinomas (IDCs; 75%), infiltrating lobular carcinomas (ILCs; 10%), or a combination of the two. Compared to IDC, ILC is characterized by more difficult mammographic detection, increased frequency of multifocality and indistinct borders, older age at onset, larger tumor size, lower grade, and a higher incidence of bilateral breast involvement at the time of diagnosis.[119] There is a significant early advantage in disease-free and overall survival for patients with ILC; however, this is followed by a significant late advantage for patients with IDC 10 years after diagnosis.[120] Rarer subtypes of IDC include pure tubular (1 to 4%), mucinous, medullary, papillary, and adenocystic. These subtypes have distinct pathologic criteria for classification, and are often associated with a more favorable prognosis; whereas the rare subtype of metaplastic carcinoma has an extremely unfavorable prognosis.[121,122]

The histologic grading system for breast cancer is a semiquantitative evaluation of morphologic features consisting of the percentage of tubular formation, degree of nuclear pleomorphism, and mitotic count within a predefined area.[123] Based on the scoring of these characteristics, three grades reflect breast cancer differentiation: low, intermediate, and high. Several grading systems have been accepted for breast cancer, namely the modified Bloom–Richardson system and the Nottingham system. These grading systems have acceptable reproducibility and they have been validated in multiple studies demonstrating a correlation between disease-free survival (DFS) and breast cancer–specific survival with the tumor grade.[119,124] The histologic grade is an independent prognostic indicator that has been closely linked to the molecular biology of breast cancer.

Lymphovascular Invasion

The presence of tumor emboli within lymphatic or vascular channels is associated with a less favorable prognosis, and all the more so with ipsilateral breast recurrence than with systemic recurrence; however, their presence does not preclude breast conservation. Dermal lymphatic

involvement is present in 75% of patients with inflammatory breast cancer, which is associated with a poor prognosis and requires mastectomy and ALND for locoregional treatment. An incidental finding of dermal lymphatic involvement, even in the absence of other clinical criteria defining inflammatory breast cancer, may be associated with a higher risk of local disease recurrence.

Proliferation Rate

In the past, S-phase fraction and DNA flow cytometry were used to assess the proliferation rate of breast cancer. The complexity of the technology required to perform these analyses resulted in difficulties with quality control, and the clinical value of these indicators declined. Ki67 is a nuclear antigen specific for proliferating cells. IHC staining of the antigen is used as a marker of proliferation, with increased proliferation correlating with adverse prognostic indicators such as tumor size, nodal involvement, and histologic grade. The interpretation of the proliferation rate by Ki67 is somewhat subtle, and there is a lack of reproducibility of results among pathologists. Furthermore, there is a lack of standardization of testing between pathology labs. Thus, more data are required before it is widely accepted as an independent prognostic indicator. ASCO Biomarker guidelines specifically advise that the Ki67 labeling index by IHC should not be used to guide the choice of adjuvant chemotherapy,[125] although some institutions do use it.

MOLECULAR PROGNOSTIC AND PREDICTIVE MARKERS

We are gaining a greater understanding of the biology of breast cancer. The advantage of this greater understanding is that it provides basic prognostic information, but more importantly, these features are valuable in predicting response to targeted therapeutic interventions. The following sections provide more detail regarding molecular prognostic and predictive factors.

Hormone Receptors: Estrogen and Progesterone Receptors

The ER and PR are weak prognostic indicators, but they are highly predictive of response to endocrine therapy. The ER functions as a ligand-dependent transcriptional factor that regulates gene expression through interaction with hormone response elements.[126] The two isoforms of ER are ER-alpha and ER-beta. The IHC method of detecting functional ER measures ER-alpha levels. The PR also has two isoforms and regulates gene expression. The IHC analysis of PR is essentially a functional assay, with a positive PR representing an active ER pathway, even if ER expression is negative.

The majority of hormone receptor–positive breast cancers have functional ER and PR, whereas cancers that are ER-positive/PR-negative are less frequent but still respond to endocrine therapy. ER-negative/PR-positive cancers are uncommon, occurring in 1 to 5% of cases, and recently updated data suggest that they may not derive significant benefit from endocrine therapy.[127] Among all breast cancers, 55% are ER-positive/PR-positive, 16% are ER-positive/PR-negative, and 4% are ER-negative/PR-positive.[124] Approximately 25% are hormone receptor–negative. There is a proportional response to endocrine therapy with respect to the amount of hormone positivity observed with IHC. The definition for positive hormone receptor status remains controversial; however, data support efficacy with endocrine therapy in the setting of any percentage of ER-positive disease.[128]

The prognostic utility of hormone receptors is generally overshadowed by their frequent

association with older patient age and lower tumor grade with negative lymph nodes. However, ER-positive/PR-positive disease is associated with a modestly superior disease-free interval, local recurrence rate, and OS compared with ER-negative/PR-negative disease, particularly within the first 5 to 10 years following diagnosis. The single hormone receptor–positive subtypes (ER-positive/PR-negative and ER-negative/PR-positive) have outcomes that lie between those of the ER/PR-positive and ER/PR-negative subgroups. The risk of disease recurrence is greatest within the first 5 years for patients with hormone receptor–negative disease and then it dramatically declines.[129] Hormone receptor–positive breast cancer has a tendency toward a slower rise in risk of recurrence and a more gradual decline, with only half of all relapses occurring within the first 5 years after diagnosis. Late distant recurrences (more than 10 years after diagnosis) can occur in patients with hormone receptor–positive disease despite optimal therapy.[130]

The androgen receptor has more recently been a focus of interest; however, its utility remains investigational. The methods to analyze androgen receptor expression by IHC vary between pathology laboratories, and there is no universally accepted cutpoint for androgen receptor–positivity. In TNBC, despite lower pathologic complete response (pCR) rates with neoadjuvant chemotherapy,[131] patients with luminal androgen receptor molecular subtype (by gene expression analysis) were found to have a better prognosis than those who did not.[132] Early-phase clinical trials with androgen receptor antagonists have yielded encouraging results for this molecular subtype of TNBC. [133]

HER2

HER2 is a member of the epidermal growth factor receptor (EGFR) tyrosine kinase family, which includes four transmembrane receptor proteins: EGFR-1, HER2, HER3, and HER4. Receptor activation, either through ligand binding or ligand-independent effects, results in homo- or heterodimerization of the receptor proteins, which stimulates cellular growth, cell survival, migration, and angiogenesis. Overexpression of the HER2 185-kd protein is a consequence of gene amplification, which occurs in approximately 20% of all breast cancers. HER2 status is defined by ASCO/CAP guidelines, which were updated in 2013.[134] Protein expression can be determined by IHC analysis using anti-HER2 antibody staining with 0 or 1+ categorized as negative, 2+ as equivocal, and 3+ as positive. Fluorescence in situ hybridization (FISH) evaluates for *HER2* gene expression and classifies tumors as HER2-positive (gene amplification) when the ratio of *HER2* gene copies to the centromeric portion of chromosome 17 (HER2:CEP17 ratio) is greater than or equal to 2.0 or when the single probe average *HER2* copy number is greater than or equal to 6.0 signals per cell. Up to 24% of breast cancers that are HER2 2+ by IHC have gene amplification and benefit from HER2-directed therapy; therefore, FISH analysis should be performed on all specimens that are equivocal (2+) on IHC analysis. The impact of soluble levels of the HER2 extracellular domain, detected in the serum, remains controversial.

HER2 overexpression or amplification is a strong predictive factor for response to HER2-directed therapy, including trastuzumab, a humanized monoclonal antibody directed at the extracellular domain of the 185-kd protein; pertuzumab, another humanized monoclonal antibody directed at the extracellular dimerization domain of HER2; ado-trastuzumab emtansine, an antibody-drug conjugate of trastuzumab and the microtubule inhibitor DM1; and lapatinib, an oral dual tyrosine kinase inhibitor of both HER2 and EGFR-1.

HER2 status is a modest prognostic indicator if a patient does not receive HER2-directed

therapy. It is correlated with a highly proliferative subtype of breast cancer, demonstrated by high-grade histology and lymph node involvement.[135] Independent of other prognostic indicators, including size, lymph node involvement, and hormone receptor status, HER2-positive disease that is not treated with anti-HER2 therapy is associated with a shorter DFS and breast cancer–specific survival. However, the degree of HER2 positivity is not associated with prognosis, and higher levels of HER2 do not predict increased efficacy from HER2-directed therapy.

Intrinsic Molecular Subtypes

The use of whole-genome analysis has transformed the understanding of breast cancer by identifying molecular ("intrinsic") subtypes, each with specific gene expression signatures and clinical characteristics. In addition to being prognostic for systemic disease recurrence, the intrinsic subtypes are now being established as prognostic indicators in terms of local disease recurrence following breast conservation or mastectomy.[136,137]

In general, the luminal subtypes includes the hormone receptor–positive breast cancers. It is the most common subtype, with an incidence of approximately 67%.[138] The luminal A subtype expresses more ER-related genes, is often low-grade, has a low incidence of *TP53* mutations, and is associated with the best overall prognosis in terms of DFS, OS, and locoregional disease relapse. Luminal B cancers express more proliferation and HER2-related genes and fewer ER-related genes, when compared with luminal A cancers. Luminal B cancers are often higher-grade and have a less favorable overall prognosis than luminal A cancers.

The HER2 intrinsic subtype does not express hormone receptors, but overexpresses genes within the *ERBB2* amplicon. These cancers are frequently HER2-positive, more often high-grade, and associated with more frequent *TP53* mutations (40 to 80%).

The basal-like subtype has a gene expression profile that mimics basal epithelial cells by not expressing hormone-related or HER2-related genes. This subtype expresses proliferation-related genes and basal cytokeratins 5, 6, and 17, and has a greater propensity to be high-grade and contain *TP53* mutations. Basal-like cancers are associated with the least favorable prognosis, with a high risk of systemic and local disease relapse and breast cancer-related death.[139] They are often classified as triple-negative because they are commonly negative for ER and PR expression, as well as HER2 overexpression. *BRCA1*-associated cancers are often basal-like, whereas *BRCA2* breast cancers include the entire spectrum of intrinsic subtypes, very much like sporadic cancers. The existence of a true fifth intrinsic subtype, "normal breast," is controversial.

Not only are the individual molecular subtypes associated with prognosis, but they also provide predictive information about the efficacy of specific therapies. Basal-like cancers are often more sensitive to DNA-damaging chemotherapy agents, such as cisplatin, whereas luminal A cancers are often treated effectively with endocrine therapy alone. Luminal B cancers often benefit from the addition of chemotherapy to endocrine treatment. The basal-like subtype is also associated with a greater probability of achieving a pCR following neoadjuvant chemotherapy, whereas the luminal A and B subtypes are less likely to do so.[140] Routine use of molecular subtyping for clinical purposes is not yet feasible; however, with the extensive development of targeted therapy in a field increasingly focused on personalized medicine, molecular subtyping may play a larger role in the treatment of breast cancer in the future.

MULTIFACTOR PROGNOSTIC INDICES

There are a number of indices that incorporate the multiple prognostic indicators into a cohesive

assessment. These models focus primarily on anatomic characteristics and include only the traditional molecular variables such as hormone receptor and HER2 status. The Nottingham Prognostic Index identifies three prognostic groups based on tumor size, lymph node status, and histologic grade.[141] Adjuvant! Online (www.adjuvantonline.com) has been a web-based prognostic calculator that utilizes the same indicators as the Nottingham Prognostic Index, plus patient age, comorbid conditions, lymph node status, and hormone receptor status. In addition to prognosis, Adjuvant! Online provided an estimate of the benefit of treatment with endocrine therapy and/or chemotherapy; however, it did not include HER2 status or information about the effects of trastuzumab therapy on HER2-positive disease.[142] Adjuvant! Online was deactivated in late 2015 for modification, and as of February 2017 it remains unavailable. It refers clients to another website, called “Predict” (http://www.predict.nhs.uk/predict.html), a tool that provides prognostic information based on patient and tumor characteristics.

These multifactor prognostic indices provide much better prognostic and predictive information than was available prior to their existence,[143] but additional prognostic and predictive information is provided by gene expression information.

Gene Expression Signatures

Differential gene expression profiling for breast cancer (a way of putting into practice some molecular prognostic and predictive factors discussed in the previous sections) has produced several validated tests to assess the risk of both local and systemic disease recurrence among breast cancers with a more favorable prognosis. They have not yet added substantial information about prognosis for the higher-risk subtypes, such as the HER2-positive or hormone receptor–negative breast cancers. The 70-gene signature MammaPrint (Agendia BV, Amsterdam, the Netherlands) was developed while studying a group of women younger than age 55 with node-negative disease and tumor sizes smaller than 5 cm. The signature was subsequently validated in a group of women (younger than age 53) with lymph node–positive or –negative disease.[144] Among the group with the poor prognostic signature, there was a 5-fold increase in the risk of systemic recurrence at 10 years compared with the group with the good prognostic signature. MammaPrint has been independently validated by the TRANSBIG consortium, which included women younger than age 60 with lymph node–negative disease.[145] Prospective validation of the 70-gene signature is ongoing in the MINDACT trial.[146] In this phase III study 6693 women with early-stage breast cancer were enrolled and their genomic risk (by 70-gene signature) and clinical risk (by a modified version of Adjuvant! Online) were determined. Women at low clinical and genomic risk (2745 [41.0%]) did not receive adjuvant chemotherapy, and those at high clinical and genomic risk (1806 [27.0%]) did receive chemotherapy. Patients with discordant clinical and genomic risk results were randomly assigned to either their genomic or clinical risk profile for determination of the use of chemotherapy. A total of 1550 patients (23.2%) were found to have high clinical and low genomic risk. At 5 years, the distant DFS rate among those who did not receive adjuvant chemotherapy was 94.7% (95% CI; 92.5, 96.2). The primary endpoint was met in that the lower boundary of the 95% CI for the 5-year distant DFS rate was ≥ 92% (i.e., the noninferiority boundary), supporting that chemotherapy was not very beneficial for patients with low genomic risk, despite higher clinical risk. In terms of absolute numbers, in a planned secondary analysis, the difference in the distant DFS rate between these patients and those who received chemotherapy was 1.5% in favor of the latter group.

The 21-gene expression assay known as Oncotype DX (Genomic Health, Redwood City,

California) was developed and validated through analysis of tumor biospecimens from patients enrolled in the NSABP B-14 clinical trial, which randomly assigned patients with ER-positive, node-negative disease to tamoxifen adjuvant therapy or placebo.[147] This is the most widely used prognostic test in the United States. The recurrence score is used as a continuous function and assesses residual risk of systemic recurrence among women with ER-positive breast cancer treated with tamoxifen. The risk of recurrence is classified as low, intermediate, and high. The prognostic value of this model has also been validated among patients treated with AIs and combination chemotherapy for node-negative and node-positive disease. The ongoing validation RxPONDER trial will better illustrate whether women with low recurrence scores can safely avoid chemotherapy in the setting of node-positive disease.[148]

The 21-gene expression assay has established utility in predicting the benefit of chemotherapy when added to tamoxifen as adjuvant treatment. Patients with low-risk disease (i.e., low recurrence score) do not appear to benefit from chemotherapy when given in addition to tamoxifen in the setting of lymph node–negative disease, regardless of menopausal status; similar findings are observed in the setting of postmenopausal lymph node–positive disease.[149,150] The 21-gene expression assay has also been shown to predict risk of local disease recurrence (ipsilateral breast, chest wall, and regional nodal), regardless of the administration of tamoxifen or chemotherapy.[151]

The prospective TAILORx trial was designed to clinically validate the prognostic and predictive value of the 21-gene expression assay in hormone receptor–positive, HER2-negative, lymph node–negative breast cancer. Initial results indeed confirm that patients with a low risk recurrence score of 0 to 10 (1626 [15.9%]) have a very favorable prognosis when treated with adjuvant endocrine therapy alone (no chemotherapy). Their 5-year rate of invasive disease–free survival was 93.8% (95% CI; 92.4, 94.9), freedom from recurrence of breast cancer at a distant site 99.3% (95% CI; 98.7, 99.6), and OS 98.0% (95% CI; 97.1, 98.6).[152] In this trial, patients with an intermediate recurrence score (defined as scores of 11 to 25) were randomly assigned to either receive or not receive adjuvant chemotherapy; those patients remain in follow-up and outcomes are eagerly anticipated.[153]

In 2016, ASCO published clinical practice guidelines on the use of biomarkers to guide adjuvant systemic therapy for early-stage invasive breast cancer.[126] Consistent with NCCN guidelines, the ASCO panel supported the use of the 21-gene assay (Oncotype DX) for adjuvant systemic therapy clinical decision-making in patients with lymph node–negative disease. The panel also provided recommendations on the clinical utility of biomarker and multifactor indices, including MammaPrint, EndoPredict, PAM50, Breast Cancer Index, Mammostrat, IHC4, urokinase plasminogen activator, and plasminogen activator inhibitor type 1.

INITIAL EVALUATION FOR OPERABLE BREAST CANCER

The initial evaluation of patients diagnosed with operable breast cancer includes a physical examination and breast imaging with diagnostic mammography with or without ultrasound. Additional diagnostic testing should be individualized, especially the use of breast MRI (see the Diagnosis section above). Baseline laboratory tests such as a complete blood count, hepatic transaminases, and alkaline phosphatase can be obtained for women who will need chemotherapy and/or for those in whom clinical symptoms or signs are suggestive of metastatic disease. Positron-emission tomography (PET)/CT has not been shown to be beneficial in evaluating local disease (i.e., the primary breast cancer or axilla); however, it can be a useful

tool for problem solving, such as determining the extent of locoregional disease when stage III disease is present.[154] In the absence of symptoms, systemic imaging studies to evaluate for metastases are not recommended for patients with stage 0, I, or II disease. Patients with stage III disease, however, should be considered for systemic staging by a CT of the chest and abdomen (with or without a CT of the pelvis) and a bone scan. PET/CT is another option, but this has not been shown to be superior to CT and bone scan for staging purposes.

There are several consultative services to be considered for patients with a new diagnosis of breast cancer. Genetic counseling should be provided for patients with a positive family history of cancer or other characteristics that may suggest an inherited predisposition, as outlined in the Risk Factor section of this chapter. Premenopausal women who use a hormonal method of contraception should be maintained on this form of contraception until an effective nonhormonal alternative can be implemented to replace it. In such cases, referral to a gynecologist or a women's health specialist is indicated. Per ASCO guidelines,[155] all patients of reproductive age should be counseled regarding the risks of infertility (due to chemotherapy) and/or delayed child-bearing (due to adjuvant endocrine therapy). Consultation with a reproductive specialist should be obtained for those interested in fertility preservation. Oocyte, sperm, and embryo cryopreservation are established methods for fertility preservation. Several trials have evaluated suppression of ovarian function with gonadotropin-releasing hormone (GnRH) agonists administered concurrently with chemotherapy as a method of fertility preservation. These trials yielded mixed results, and the primary outcome was commonly the recovery of ovarian function (menses) as opposed to a true measure of fertility, a successful pregnancy. A recent meta-analysis of 7 trials with 856 randomly assigned and evaluable patients demonstrated that the use of GnRH agonists was associated with a higher rate of recovery of regular menses after 6 months (odds ratio [OR], 2.41; 95% CI; 1.40, 4.15) and at least 12 months (OR, 1.85; 95% CI; 1.33, 2.59) after the last chemotherapy cycle. The use of GnRH agonists was also associated with a higher number of pregnancies (OR, 1.85; 95% CI; 1.02, 3.36).[156]

KEY POINTS

- Pathologic features associated with favorable prognosis include small tumor size, negative lymph node status, low tumor grade, absence of lymphovascular invasion, and positive hormone receptor status.
- The degree of estrogen receptor expression is positively correlated with response to endocrine therapy.
- HER2-positive status is predictive of benefit from HER2-directed therapy; it also is a modest negative prognostic indicator for patients who do not receive HER2-directed therapy.
- Several molecular biomarkers and gene expression signatures provide prognostic information; however, only the 21-gene recurrence score and 70-gene signature have done so with prospective data.
- The 21-gene expression assay was the first to be validated to predict the benefit of adjuvant chemotherapy, and early data support that the 70-gene signature provides similar information.

TREATMENT OF EARLY-STAGE DISEASE: STAGES 0, I, II, AND III

STAGE 0: DUCTAL CARCINOMA IN SITU (TisN0M0)

An appropriate definition of DCIS was accepted by the U.S. National Cancer Institute (NCI) during a State-of-the-Science conference and can be described as a “complete replacement of normal ductal cells with a spectrum of abnormal cells confined to the ducts without invasion.”[157] With the acceptance of mammographic screening in 1980, the incidence of DCIS has increased more than 7-fold, most commonly among women older than age 50, accounting for about 20% of all breast cancers in the United States. Important features of DCIS include size, histologic subtype (comedo, micropapillary or papillary, cribriform, and solid), cytologic or nuclear grade (low, intermediate, or high), presence of central necrosis, and ER status. A multigene assay, the Oncotype DX DCIS, has been validated as a prediction tool for recurrence risk among patients with DCIS treated with breast-conserving surgery without whole-breast radiotherapy; however, its utility in clinical practice has yet to be defined.[158]

An estimated 15 to 50% of DCIS will ultimately progress to invasive disease if left intact, either by direct transformation or by developing in parallel from a single progenitor cell.[159] The exact biologic mechanism is not known, nor can we distinguish which subset of DCIS will progress to invasive breast cancer. Therefore, by definition, we generally overtreat a proportion of women with DCIS in order to achieve the goal of decreasing subsequent development of ipsilateral invasive breast cancer. The risk of local recurrence of DCIS or development of invasive cancer following simple mastectomy without ALND is approximately 1%; however, breast-conserving therapy and mastectomy provide equivalent long-term disease-specific survival. In an analysis of individual patient data from 3729 patients treated during four randomized controlled trials that began before 1995 demonstrated that radiotherapy reduced the 10-year risk of recurrent DCIS or invasive breast cancer following breast-conserving surgery from 28% to 12% ($p < 0.00001$).[160] Local recurrence rates with breast-conserving therapy for a significant proportion of favorable DCIS diagnosed in modern practice with screening mammography is lower. In the Radiation Therapy Oncology Group (RTOG) 9804 study, patients with mammographically detected low- or intermediate-grade DCIS measuring less than 2.5 cm and a final margin width of 3 mm or more were randomly assigned to observation or whole-breast radiotherapy. The 7-year local failure rate was 0.9% in the radiotherapy arm, versus 7% with observation.[161] Both conventional (5 to 6 weeks) and hypofractionated (3 to 4 weeks) whole-breast radiotherapy are appropriate adjuvant radiotherapy options for DCIS. Accelerated partial-breast irradiation, commonly administered over 5 days, is under investigation for patients with DCIS and early-stage breast cancer. For example, a large randomized trial supported by the NCI (NSABP B-39) comparing this therapy with conventional WBI following breast-conserving surgery has completed accrual and long-term follow-up is awaited.The American Society for Therapeutic Radiation Oncology (ASTRO),[162] practice guidelines endorse accelerated partial-breast irradiation as a suitable option for patients with favorable DCIS who meet eligibility criteria for the RTOG 9804 study. Sentinel lymph node surgery is not necessary when breast conservation is performed for DCIS; however, this procedure may be considered with mastectomy because of the possibility of finding occult invasive disease within the breast, since a sentinel biopsy is not possible after the mastectomy has been performed.[163]

Approximately 50% of local recurrences following a diagnosis of DCIS are invasive. Overall, there is no difference in mortality between the local therapies, with 10-year breast cancer

survival following a diagnosis of DCIS being about 96 to 98%. Although ipsilateral development of invasive cancer is associated with a 2-fold greater mortality risk, this risk is not associated with a recurrence of DCIS alone.[164] The addition of tamoxifen (20 mg daily for 5 years) to breast conservation plus whole-breast radiotherapy (breast-conservation therapy [BCT]), contributes an additional 32% relative reduction in the risk of local recurrence and a 53% relative reduction in the risk of contralateral disease over the course of 15 years after diagnosis; however, the benefit of tamoxifen is seen only with ER-positive DCIS and has not yet been associated with improved OS.[165] The NSABP B-35 trial was designed to compare the efficacy of adjuvant tamoxifen with anastrozole in postmenopausal women who undergo BCT for ER-positive DCIS. These data demonstrated that anastrozole substantially decreased recurrences, especially in women ages 50 to 60, and in women older than age 60, recurrence rates were similar.[166] OS did not differ significantly according to hormonal therapy received. Tamoxifen and anastrozole are good options, and considerations regarding toxicities should influence drug choices for individual women. Further evaluation to define the role of systemic therapy in addition to BCT is pending the analysis of NSABP B-43, which compared two cycles of trastuzumab with placebo in HER2-positive DCIS.

KEY POINTS

- Diagnostic mammography with or without breast ultrasound is recommended for all women with a new diagnosis of operable (stages 0 through III) breast cancer.
- Additional diagnostics (e.g., laboratory tests, breast MRI, axillary ultrasound, chest x-ray, CT, PET/CT, or bone scan) should be individualized based on symptoms, exam findings, and clinical staging.
- DCIS (stage 0) accounts for approximately 20% of breast cancers in the United States.
- DCIS treated by mastectomy or BCT results in equivalent breast cancer–related 5-year survival rates, which, on average, approach 98%.
- For women with ER-positive DCIS who elect to undergo BCT, adjuvant tamoxifen reduces the risk of ipsilateral and contralateral recurrence with no established survival benefit.
- Adjuvant tamoxifen and anastrozole are appropriate options for decreasing subsequent invasive breast cancers in postmenopausal women with ER-positive DCIS treated with BCT.

STAGES I AND II DISEASE

For operable breast cancer, the treatment approach focuses both on local (breast and regional lymph nodes) and systemic disease control. These therapies complement each other and are not mutually exclusive—systemic treatment adds benefit to local disease control and local therapies will reduce the risk of systemic recurrence.[167] A meta-analysis from the EBCTCG reviewed 15-year survival data from 25,000 women and found that the addition of WBI following breast-conservation surgery also resulted in an approximate 5% reduction in breast cancer mortality.[168] Systemic therapy with tamoxifen reduces the relative incidence of ipsilateral breast recurrences by 50% in ER-positive disease, whereas chemotherapy reduces the relative

local recurrence rate by 33%, regardless of hormone receptor status. Both endocrine therapy and trastuzumab can safely be given concurrently with radiotherapy; however, chemotherapy is usually completed prior to starting radiation therapy. The choices for both local and systemic therapies are based on the prognostic indicators described previously, and treatment options have been outlined by several organizations to help guide decision-making.[169-171]

Local Disease Control

Breast-Conservation Therapy. The Fisher hypothesis of breast cancer describes invasive breast cancer as a systemic disease at its inception. This theory differed from the Halstedian philosophy of direct nodal extension of disease beginning in the breast. To test the Fisher hypothesis, pivotal trials were designed to limit the extent of surgery for the treatment of early-stage breast cancer. The NSABP B-04 found that, after 25 years, there was no difference in OS between radical mastectomy and simple mastectomy. These results were extended to NSABP B-06, which also demonstrated no significant difference in OS between total mastectomy and BCT.[172] A comparable survival outcome between mastectomy and BCT is also supported by several larger randomized trials. In general, radiation to the conserved breast reduces the relative risk of any first recurrence (locoregional or distant) by approximately 50%.[173] A meta-analysis of individual patient data for 10,801 women in 17 randomized trials demonstrated that 16% absolute reduction in any first recurrence and a 4% reduction in 15-year risk of breast cancer death with the addition of radiotherapy following breast-conserving surgery. Although the individual risk of ipsilateral breast cancer recurrence appears to be intrinsically subtype-specific,[137] modern systemic therapy has contributed to improved local control following BCT across all tumor types. Randomized controlled trials have demonstrated 10-year local recurrence risks of just 2 to 7% in patients with early-stage breast cancer.[174-176] Based on these results, options for local disease control in patients with operable (stages I and II) disease include total mastectomy or breast-conserving surgery (lumpectomy) and WBI, with BCT being the preferred procedure. Sentinel lymph node surgery is performed in both settings in clinically node-negative disease.

Optimal characteristics for breast conservation include the ability to resect the entire tumor with adequate negative surgical margins. Acceptable cosmetic outcome is important, and therefore the ability to adequately remove the cancer depends on the size of the cancer and the size of the breast (see the Neoadjuvant Systemic Therapy section). The definition of *adequate negative surgical margins* is no ink on tumor for invasive breast cancer and a 2 mm margin is recommended for DCIS.[177] The presence of an extensive intraductal component (defined as DCIS occupying at least 25% of an invasive carcinoma or a lesion that is predominantly DCIS with one or more foci of invasive disease) is not a contraindication to BCT, as long as negative margins are obtained. There are a few relative contraindications to breast conservation for operable disease, such as multicentric disease, prior radiation therapy, and some connective-tissue diseases involving the skin (e.g., scleroderma), which restrict the ability to safely give radiation.

For many years, patients with stage I or II invasive disease undergoing BCT have commonly been treated with tangential WBI over a course of 5 to 6 weeks (25 fractions).[178] Often, an additional 10- to 16-Gy boost to the tumor bed is given over 1 week, so that the breast receives 45 to 50 Gy of radiation and the tumor bed receives a total of 60 Gy. The boost has been shown to reduce the risk of local recurrence, specifically among women younger than age 50 and among those with high-grade invasive cancer.[179] Hypofractionated whole breast

radiotherapy in which the breast receives 40 to 42.5 Gy over 3 weeks (15 to 16 fractions) is now an established option for the majority of women with early stage breast cancer based on randomized trials demonstrating equivalent local control and comparably favorable toxicity compared with the more traditional 25 fraction approach.[174,176] In the UK Standardisation of Breast Radiotherpapy B (START-B) randomized controlled trial, the locoregional relapse rate was 4.3% at 10 years with hypofractionated (40 Gy in 15 fractions with or without a 10-Gy boost), compared with 5.5% in the conventionally fractionated arm (50 Gy in 25 fractions with or without a 10-Gy boost). Late effects such as breast shrinkage, telangiectasia, and breast edema all favored the 40 Gy arm. In patients who undergo breast-conserving surgery without adjuvant radiotherapy, the majority of ipsilateral recurrences develop in or near the tumor bed. Recurrences in other parts of the affected breast are rare (3 to 4%) and are believed to be new cancers rather than recurrences of the original cancer. This phenomenon has led to the concept of limiting radiation to the breast by using accelerated partial-breast irradiation, which, as discussed in the section on Stage 0, is emerging as a standard treatment option for carefully selected women with favorable invasive and noninvasive breast cancer.[180]

The potential morbidity associated with complete levels I and II ALND is substantial, translating into a risk of upper-extremity lymphedema of 20 to 30%. SLN surgery is associated with fewer complications and a lower lymphedema rate (6 to 7%) and is the procedure of choice for the surgical evaluation of the clinically negative axilla. The SLNs are the first lymph nodes to receive lymphatic drainage from the breast tumor and are the most likely site to contain metastatic involvement. SLNs are identified by lymphatic mapping using vital blue dye and/or radiolabeled colloid. The average number of SLNs is two to three nodes per patient. The *sentinel* lymph nodes are then dissected and intensively examined at two step-section levels of paraffin-embedded tissue that are stained with hematoxylin and eosin. Routine IHC staining for cytokeratins is not recommended, and most therapeutic decisions should be based on assessment with hematoxylin and eosin.[181,182] Based on a review of 69 studies involving 8059 patients comparing ALND with SLN surgery, the false-negative rate of SLN surgery is approximately 8%, and is comparable when used during breast conservation or mastectomy.[183]

If an SLN cannot be identified or if the axilla is clinically positive, a complete level I and II ALND is usually performed. Up to 48% of patients with a positive SLN have further axillary lymph node involvement, which supported the ASCO recommendation for completing an ALND when the SLN is positive.[183] The ACOSOG trial Z0011, however, found that patients with one to two positive axillary lymph nodes who are treated with breast conservation and tangential whole-breast radiotherapy may achieve adequate disease control of the axilla without undergoing an ALND or receiving more extensive axillary radiotherapy.[117] In this study, 891 eligible patients with clinical T1 or T2 tumors, a clinically negative axilla (N0), and only one or two positive sentinel lymph nodes following SLN biopsy were randomly assigned to receive or not to receive ALND. There was no difference in axillary recurrence rate, DFS, or OS between the two groups; therefore, consideration can be made to avoid a complete ALND in the setting of one or two positive SLNs, when these criteria are present.[184] This approach has not been evaluated among patients having a mastectomy, receiving neoadjuvant therapy, or opting for breast conservation but not receiving whole-breast radiotherapy. In these individuals, completion ALND is still often recommended after finding a positive SLN. However, recent data provide more support for using SLN surgery following neoadjuvant chemotherapy (see the section on Locoregional Therapy under Stage III Disease).

The ipsilateral axillary apex, infraclavicular and supraclavicular areas, along with the internal mammary lymph nodes should be irradiated (i.e., regional nodal irradiation) when four or more

axillary lymph nodes are positive. In addition, regional nodal irradiation should be considered when one to three axillary lymph nodes are involved.[185,186] The NCIC-CTG MA.20 clinical trial randomly assigned 1832 women to either WBI or WBI with regional lymph nodal irradiation.[185] Patients who received WBI and regional lymph nodal irradiation attained a significant improvement in locoregional and distant DFS with a nonsignificant trend toward an improved OS. This improvement in disease control was obtained at a cost of increased toxicity due to pneumonitis and lymphedema. The ultimate decision to add radiation fields to WBI should be based on individual risks and benefits.

There are special circumstances in which the addition of radiation therapy following breast conservation may be avoided. Older women with favorable tumor characteristics may undergo breast conservation surgery alone, as long as they receive adequate endocrine therapy. This determination is based on findings from a randomized trial of 636 women older than age 70 with ER-positive, pathologic T1 (≤ 2 cm), clinically N0 disease, who received breast conservation surgery and tamoxifen with or without whole-breast radiation therapy.[175] At 10 years, the locoregional recurrence rate was 2% with radiation and 10% without radiation; however, only 6% of the overall deaths were related to breast cancer, and there was no difference in DFS or OS. Partial breast irradiation is another reasonable option in patients with favorable disease.

Although mastectomy is the preferred approach for the majority of women with *BRCA*-associated breast cancer in order to reduce the risk of second cancers, BCT remains an acceptable means of local therapy if the patient prefers this approach. A multi-institutional study of 655 women with *BRCA1* and *BRCA2* mutations treated with either BCT or mastectomy demonstrated a higher local recurrence rate with BCT; however, the majority of the ipsilateral breast recurrences were second cancers.[187] Systemic therapy reduced the incidence of local recurrences among those treated with BCT. There was no difference in breast cancer–specific survival or OS between patients treated with BCT and those treated with mastectomy.

Total Mastectomy and Postmastectomy Radiotherapy (PMRT). Patients with a clinically negative axilla who are not candidates for BCT should undergo a total mastectomy and SLN biopsy, with completion ALND if the SLN biopsy is positive. An EBCTCG analysis of 1314 women who had axillary dissection and one to three positive nodes demonstrated that postmastectomy radiotherapy reduced the 10-year absolute risk of any first recurrence (both locoregional and distant) by 11.5% and reduced the 20-year absolute risk of breast cancer mortality by 7.9%. For the 1772 women with four or more positive nodes, postmastectomy radiotherapy reduced the 10-year absolute risk of any first recurrence by 8.8% and 20-year breast cancer mortality by 9.3%.[188] For this reason, PMRT should be considered following the completion of adjuvant chemotherapy when one or more axillary lymph nodes are involved; when there is clinical evidence of infraclavicular, supraclavicular, or internal mammary lymph node involvement; or when surgical margins are positive. There remains some controversy about the absolute benefits of PMRT in some subsets of patients with one to three axillary lymph nodes. Because of stage migration and improvements in systemic therapy and other aspects of multidisciplinary breast cancer care, recurrence rates may be low enough for some patients with favorable disease features that the risks of PMRT outweigh the potential benefits. Recommendations for treatment should be individualized and based on other adverse characteristics, such as lymphovascular involvement, triple-negative tumor status, young age, or close surgical margins (< 1 mm), as well as the potential risks of radiotherapy in a particular patient.[189] Radiation can safely be given concurrently with endocrine therapy or trastuzumab. Radiation concurrent with chemotherapy is not recommended. PMRT is also beneficial in the

treatment of locally advanced disease (e.g., tumor invading the chest wall or skin involvement). The optimal sequence of treatment in this setting is usually systemic therapy followed by surgery then radiation (see the section on Neoadjuvant Systemic Therapy under Stage III Disease). The use of modern treatment planning has improved targeting of areas at risk and resulted in less toxicity to the heart, great vessels, and lungs.

Adjuvant Systemic Therapy. The decision to add systemic therapy to the local treatment of breast cancer is based on the risk of distant metastasis and the benefit of therapies to reduce that risk. The features described in the section on Prognostic Indicators are utilized to determine risk of distant recurrence. In addition, age is an independent prognostic feature in that women younger than 35 years of age have a worse 5-year OS compared with women ages 35 to 69 (74.7% vs. 83.8–88.3%).[190] The threshold for offering adjuvant therapy is often reduced in this setting. Increased breast cancer mortality has also been observed in elderly patients (> age 65) based on results of several population-based studies and randomized trials. This finding is attributed to a later stage at diagnosis, higher comorbidity, and treatment discrepancies.[191] Relatively few clinical trials have included a substantial number of women older than age 70. In this patient population, the decision to administer adjuvant therapy is highly dependent on treatment-associated toxicity and the presence of comorbid conditions.

In general, breast cancer with a tumor larger than 0.5 cm and N0 has a high enough risk of systemic recurrence to warrant consideration of adjuvant treatment (Fig. 7-2). Tumors that are 0.5 cm or smaller and N0 may not necessarily gain a clinically significant benefit from systemic chemotherapy or HER2-directed therapy from the standpoint of reducing the risk of distant disease; however, if the cancer is hormone receptor–positive, adjuvant endocrine therapy is often considered, to reduce the risk of both systemic and local disease recurrence, given its favorable safety profile. Aside from these generalizations as to who would benefit from adjuvant therapy, the specific choice of treatment is based on the molecular profile of the cancer, namely the hormone receptor (ER/PR) and HER2 status. Collaborative meta-analyses of adjuvant therapy in early-stage breast cancer have been performed every 5 years by the EBCTCG since 1985.[74,127] These overview analyses lend support to current adjuvant therapy recommendations; however, the specific treatments should be based on individual clinical trial outcomes.

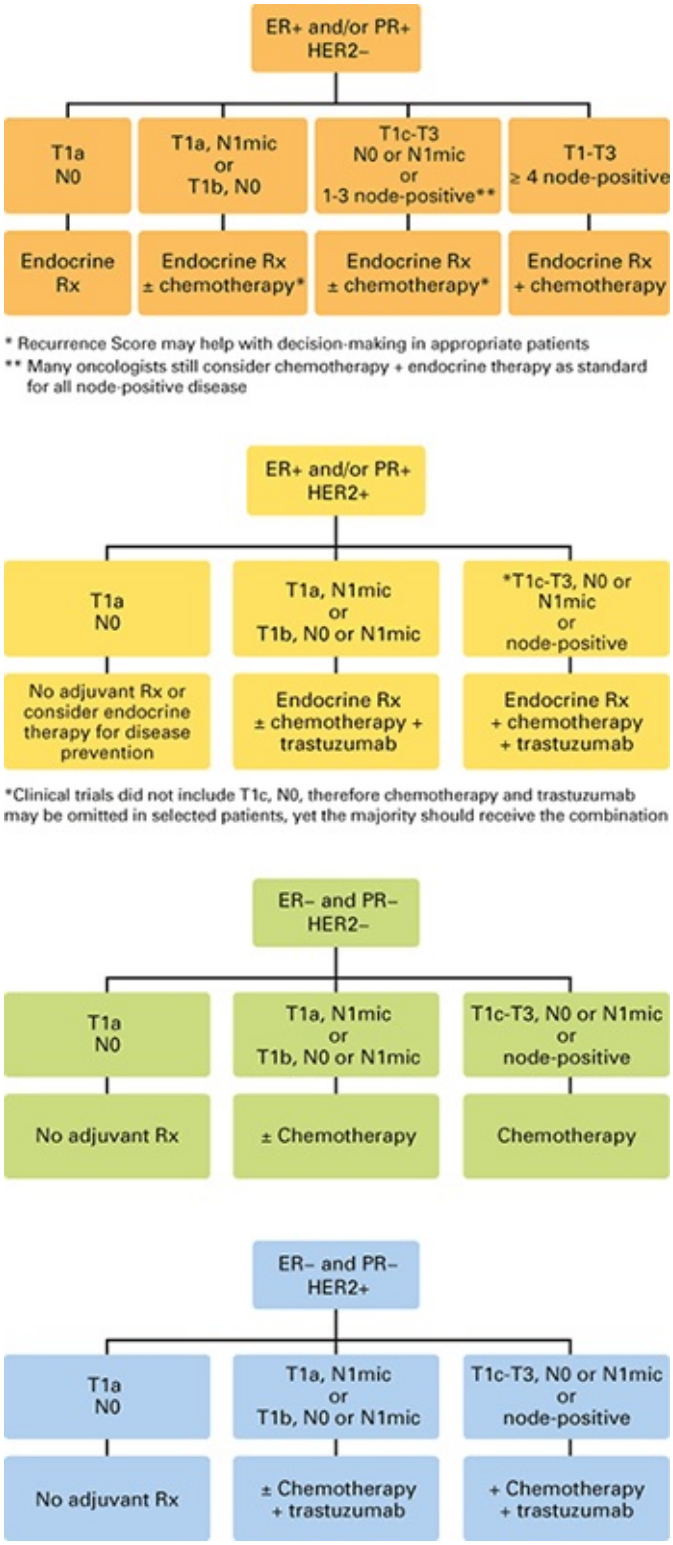

Fig.7-2 Guidelines for adjuvant systemic therapy.

Guidelines for adjuvant systemic therapy for (A) hormone receptor-positive, HER2-negative disease, (B) hormone receptor-positive, HER2-positive disease, (C) hormone receptor–negative, HER2-negative, and (D) hormone receptor–negative, HER2-positive disease. Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

HORMONE RECEPTOR–POSITIVE DISEASE

Endocrine Therapy

Endocrine therapy reduces the risk of systemic recurrence and increases OS among women with hormone receptor–positive (ER and/or PR) breast cancer, regardless of age, menopausal status, nodal involvement, tumor size, HER2 status, or use of chemotherapy. For this reason, endocrine therapy should be considered as adjuvant therapy for almost all women with

hormone receptor–positive disease.[192,193] An exception to this involves older women with favorable breast cancer prognoses, especially with comorbid medical conditions. A commonly used adjuvant endocrine therapy is tamoxifen, which is effective in both pre- and postmenopausal women when given for 5 years. The EBCTCG meta-analysis showed that 5 years of tamoxifen reduced the relative risk of distant recurrence by approximately 41% and of dying by 34% (Table 7-6).[74]

Table 7-6 Benefit of Adjuvant Endocrine Therapy in Hormone Receptor–Positive Disease

Study	Endocrine Therapy/Duration	RR Recurrence (95% CI)	RR Mortality (95% CI)
Primary therapy			
EBCTCG[74]	Tamoxifen (5 yr)	0.61 (0.57, 0.65)	0.70 (0.64, 0.75)
ATAC[201]	Anastrozole vs. tamoxifen (5 yr)	0.90 (0.82, 0.99)	1.00 (0.89, 1.12)
BIG 1-98[202]	Letrozole vs. tamoxifen (5 yr)	0.88 (0.78, 0.99)	0.81 (0.69, 0.94)
Sequential therapy			
BIG 1-98[202]	Tamoxifen/letrozole vs. letrozole	1.05 (0.84, 1.32)	1.13 (0.83, 1.53)
	Letrozole/tamoxifen vs.letrozole	0.96 (0.76, 1.21)	0.90 (0.65, 1.24)
Extended therapy			
NCIC CTG MA.17[218]	Tamoxifen (5 yr) followed by letrozole (5 yr)	0.68 (0.55, 0.83)	0.98 (0.78, 1.22)
ATLAS[194]	Tamoxifen (10 yr)	0.84 (0.76, 0.94)*	0.93 (0.86, 1.00)*

Abbreviations: RR, relative risk.
*Comparing 5 years with 10 years of tamoxifen use.

Some studies support longer duration of tamoxifen for adjuvant treatment. The ATLAS trial randomly assigned 12,894 women with ER-positive disease to continued tamoxifen use for an additional 5 years (10 years total) or to discontinue tamoxifen after 5 years of treatment.[194] Continued tamoxifen use reduced the rate of recurrence and improved OS, with the benefits being more robust during the later years. The absolute mortality reduction was 2.8% at 15 years following diagnosis, which was 10 years after starting the second 5-year period of treatment. These results are supported by the aTTom trial, which randomly assigned 6953 women with ER-positive early-stage breast cancer to an additional 5 years of tamoxifen or discontinuation of tamoxifen after 5 years of treatment.[195] This trial also demonstrated an improved breast cancer recurrence rate and OS, specifically seen after 10 years of treatment. Prolonged tamoxifen use was associated with an increased incidence in pulmonary embolism (HR, 1.87) and endometrial cancer (HR, 1.74), with a 3.1% cumulative risk of endometrial cancer after 5 years of tamoxifen therapy, translating into an absolute increase in endometrial cancer mortality equaling 0.2%.[194] Though these data support increased efficacy of prolonged tamoxifen use, the decision must be weighed against potential adverse outcomes on an individual basis. For patients with early-stage disease (e.g., stage I) who are at low risk of disease recurrence, the potential toxicities may outweigh the benefits.

Substantial efforts have been made to determine the mechanisms of tamoxifen resistance in hormone receptor–positive disease. Tamoxifen undergoes extensive hepatic metabolism to metabolites (4-hydroxy-tamoxifen and endoxifen) that are known to be pharmacologically more active than tamoxifen, in terms of ER binding affinity and ability to suppress estradiol-stimulated cell proliferation.[196] Although serum concentrations of 4-hydroxy-tamoxifen are consistently low,

endoxifen concentrations are highly variable.[197,198] Cytochrome P450 2D6 (CYP2D6) is the primary hepatic enzyme responsible for tamoxifen metabolism.[199] Secondary analyses of prospective adjuvant tamoxifen studies (NCCTG 89-30-52,[200] ATAC,[201] BIG 1-98,[202] and ABCSG 8[203]), have reached discrepant conclusions on the importance of *CYP2D6* genetic variation and its association with DFS. In separate secondary analyses of NCCTG 89-30-52 and ABCSG 8, as compared with CYP2D6 extensive metabolizers, CYP2D6 poor metabolizers had a significantly higher rate of recurrence and death in patients treated with tamoxifen monotherapy. This was not observed in those treated with anastrozole, a drug not metabolized by CYP2D6.[203] Although the ATAC trial reported no association between *CYP2D6* genotype and clinical outcomes, less than 19% of the patients receiving tamoxifen were analyzed for this and conclusions could not be generated. Methods to analyze this association in the BIG 1-98 trial have been controversial.[204,205] Additional studies have demonstrated that endoxifen concentrations (but not 4-hydroxy-tamoxifen or tamoxifen) were associated with the risk of recurrence.[206,207] Although results of prospective studies are awaited, the development of endoxifen as a therapy is ongoing; early results demonstrate promising antitumor activity in patients with prior progression while taking tamoxifen.[208] Currently, ASCO guidelines do not recommend the use of CYP2D6 polymorphisms to guide selection of adjuvant endocrine therapy.[125]

Data from the EBCTCG meta-analysis that evaluated women younger than age 50 found that ovarian ablation alone improved DFS by 11% and improved OS by approximately 5%; however, this benefit was not significant when chemotherapy was administered, likely because of chemotherapy-induced amenorrhea. There did appear to be a greater effect among women younger than age 40.[74] A meta-analysis of 16 trials involving 11,906 premenopausal women using luteinizing hormone–releasing hormone (LHRH) agonists to induce ovarian suppression did not demonstrate a significant benefit when used alone; however, the addition of an LHRH agonist to chemotherapy, with or without tamoxifen, resulted in a 13% (95% CI; 2.4, 21.9; p = 0.02) reduction in risk of recurrence and a 15% (95% CI; 1.8, 26.7; p = 0.03) reduction in risk of dying—both of borderline significance.[209] Because of the variability in study design and consequent outcomes, tamoxifen became the standard endocrine therapy for premenopausal women.[210]

In 2014, the long-awaited results of the SOFT and the TEXT have challenged the paradigm for adjuvant endocrine therapy in premenopausal women.[211,212] In TEXT, women were randomly assigned to receive 5 years of tamoxifen or exemestane with concurrent ovarian function suppression (OFS). In SOFT, women were randomly assigned to receive 5 years of tamoxifen, tamoxifen plus OFS, or exemestane plus OFS. As a result of a low number of DFS events, the statistical analysis was amended to allow for a joint analysis of the exemestane plus OFS and tamoxifen plus OFS groups from both trials (total of 4690 patients). After a median follow-up of 68 months, the DFS was 91% for exemestane plus OFS and 87% for tamoxifen plus OFS (HR, 0.72; 95% CI; 0.60, 0.85). There was no significant difference in OS.

These results are contradictory to those from ABCSG-12, a trial in which premenopausal women were randomly assigned to receive tamoxifen plus OFS (alone or combined with zoledronate) or anastrozole plus OFS (alone or combined with zoledronate).[213] In this trial, women overall had a more favorable prognosis (no adjuvant chemotherapy was allowed) and absolute differences in clinical outcomes were small; however, after a median follow-up of 94 months, there was no difference in DFS between arms, and anastrozole plus OFS was associated with a 63% increase in the risk of death, compared with tamoxifen plus OFS (HR, 1.63; 95% CI; 1.05, 1.45; p = 0.03).

For the primary analysis in SOFT comparing tamoxifen and tamoxifen plus OFS after a median follow-up of 67 months, the addition of OFS to tamoxifen did not significantly improve DFS in the primary analysis; however, exemestane plus OFS did result in significant gains in DFS compared with tamoxifen (HR, 0.70; 95% CI; 0.53, 0.92). There was no significant change in any of the clinical endpoints among patients who did not receive chemotherapy. In those who did receive adjuvant chemotherapy (53% of 1084 patients) and retained premenopausal status after chemotherapy (typically younger women with higher grade and larger tumors), the DFS was 77% with tamoxifen, 81% with tamoxifen plus OFS, and 84% with exemestane plus OFS. The data from these trials support the consideration of OFS with exemestane for adjuvant endocrine therapy in premenopausal patients at high risk of breast cancer recurrence (e.g., age 35 or younger, or for whom adjuvant chemotherapy is recommended). Tamoxifen monotherapy appears to be sufficient for lower-risk women who do not require adjuvant chemotherapy.

Although tamoxifen retains its efficacy in postmenopausal women, AIs (i.e., inhibitors of the enzyme that converts androgens to estrogens) should be considered for the treatment of postmenopausal women, either following 5 years of tamoxifen, following 2 to 3 years of tamoxifen, or as initial therapy for 5 years. Tamoxifen remains an option for women who are not candidates for, or who cannot tolerate, AIs. When administered as monotherapy, AIs are not effective in pre- or perimenopausal women, and thus should not be used for adjuvant therapy in this group of patients in the absence of concurrent OFS. It is important to remember that chemotherapy-induced amenorrhea can be transient, and therefore endocrine therapy should, generally, be based on the menopausal status prior to treatment. There are three third-generation AIs: anastrozole and letrozole (nonsteroidal inhibitors) and exemestane (a steroidal inhibitor). Despite the fact that letrozole suppresses estradiol levels the most, they all appear to be comparable in efficacy[214,215] and to have similar side effects, including arthralgias, myalgias, and a reduction in bone density. Osteorporosis/osteopenia, hypertriglyceridemia, and hypercholesterolemia were less frequent with exemestane as compared with anastrozole.

An analysis of 12 trials that evaluated the efficacy of AIs used as adjuvant therapy can be divided into three cohorts: 5 years of primary therapy, switching to an AI after 2 to 3 years of tamoxifen, and extended therapy with an AI following 5 years of tamoxifen.[192] Compared with 5 years of tamoxifen, the use of an AI as primary therapy was associated with a 29% proportional reduction in risk of recurrence, whereas switching from 2 to 3 years of tamoxifen to an AI resulted in a 40% proportional reduction in risk of recurrence.[216] This translated into a 5% absolute reduction in disease recurrence with the use of an AI compared with tamoxifen alone.

Three studies demonstrated a modest benefit in risk of disease relapse, all utilizing a switch to an AI following tamoxifen; two studies switched to an AI after 2 to 3 years of tamoxifen, and one study switched following 5 years of tamoxifen. In longer follow-up, one trial, the Intergroup Exemestane Study, demonstrated a small improvement in OS.[217] Three trials of extended endocrine therapy (i.e., an AI for 3 to 5 years following 5 years of tamoxifen) also demonstrated additional reduction in disease recurrence; however, only one (NCIC CTG MA.17[218]) demonstrated a modest improvement in OS. It has been stated by some breast cancer experts that postmenopausal women should receive treatment with an AI during their first 5 years of adjuvant therapy, with the optimal strategy being either initially using an AI as primary endocrine therapy or switching from tamoxifen after 2 years to an AI for an additional 3 years. However, when the survival benefit from antiestrogen therapy is low to modest, some women will reasonably choose tamoxifien over an AI, given the different side-effect profiles.[219] Women who are intolerant of an AI after 2 years of treatment may switch to tamoxifen for the

remaining 3 years without compromising their outcomes.

Data are now available from several clinical trials evaluating extended duration of AI treatment beyond 5 years. In the MA.17R trial, 1918 postmenopausal patients completing 5 years of adjuvant AI were randomly assigned to continue their AI for an additional 5 years or to switch to placebo.[220] The majority of these patients had also received tamoxifen for some duration prior to initiation of their AI, with the median time from breast cancer diagnosis to registration being 10.6 years. The 5-year DFS rate was 95% with letrozole and 91% with placebo (HR, 0.66; p = 0.01). There was no difference in 5-year OS (93% with letrozole and 94% with placebo). There was a significant reduction in the annual incidence rate of contralateral breast cancer (0.21% with letrozole and 0.49% with placebo; HR, 0.42; p = 0.007). While there were no differences in quality-of-life measures, bone-related toxicities (bone pain, fractures, and new-onset osteoporosis) were more frequent among those taking letrozole.

In the DATA trial, 1912 postmenopausal patients were randomly assigned to 3 or 6 years of adjuvant AI after an initial 2 to 3 years of tamoxifen.[221] The study was negative for its primary endpoint of DFS. Adapted 3-year DFS was 83.1% and 79.4%, respectively, for those receiving an AI for 6 years or 3 years (HR, 0.79; p = 0.07). The difference was significant in the subgroup of patients with ER- and PR-positive, lymph node–positive disease who received adjuvant chemotherapy.

In NSABP B-42, 3966 postmenopausal patients completing 5 years of adjuvant endocrine therapy (either 5 years of AI or 2 to 3 years of tamoxifen followed by AI) were randomly assigned to receive either an AI for an additional 5 years or a placebo. At a median follow-up of 6.9 years, the DFS rate was 84.7% for those receiving 5 additional years of AI compared with 81.3% in those receiving placebo (HR, 0.85; p = 0.048); however, these results were not statistically significant, because the level for statistical significance was set at p = 0.0418 (after adjustments from interim analyses). Additionally, there was not a significant difference in OS.[222] Differences in the cumulative incidence of a breast cancer–free interval (6.7% with letrozole and 10.0% with placebo; HR, 0.71; p = 0.003) and distant recurrence (3.9% with letrozole and 5.8% with placebo; HR, 0.72; p = 0.03) were significant. When comparing the discordant DFS outcomes for the MA 17.R and B-42 trials, it is important to note that different definitions for qualifying DFS events were used in the two trials. In fact, when DFS in MA.17R was defined by adding deaths from any cause to recurrence and contralateral breast cancer, its hazard ratio was 0.80 (p = 0.06), similar to the 0.85 in B-42 (P = 0.048).

These studies suggest that an extended duration of adjuvant AI therapy may be associated with a small reduction in breast cancer recurrence and second primary breast cancer events, but these gains did not translate into a significant OS benefit. Many breast cancer experts suggest that extended AI use should not be recommended for all patients. Rather, this approach should be considered in patients at higher risk of recurrence (e.g., multiple positive lymph nodes) who have tolerated their previous adjuvant AI therapy.

Chemotherapy

Adjuvant chemotherapy reduces the risk of relapse early in the disease course (within the first 5 years) and can benefit[223] HR-positive disease in many cases. Over the past several years there has been a decrease in the use of chemotherapy for hormone receptor–positive/HER2-negative disease, stemming from recognition that, on average, chemotherapy is less beneficial in this large patient subgroup than in those with HER2-positive or triple-negative disease.

Nevertheless, there certainly are patients with HR-positive disease who obtain a sizable benefit from the administration of chemotherapy in addition to endocrine therapy. Chemotherapy can be considered when the tumor size is larger than 0.5 cm regardless of nodal status or when there is lymph node involvement regardless of tumor size. Factors that prompt the use of chemotherapy are a high histologic grade, a moderate to large disease burden, and a high 21-gene expression assay determined by Oncotype DX.[150] When both chemotherapy and endocrine therapy are recommended, chemotherapy is given first, then endocrine therapy.

While the role of the Oncotype DX 21-gene expression assay in assessing the benefit of adding chemotherapy to endocrine therapy in lymph node-positive disease is not as well established, a single retrospective analysis of a prospective trial and other indirect evidence in postmenopausal patients support that it may be helpful in determining chemotherapy benefit for patients with positive lymph nodes.[151] The ongoing RxPONDER trial is further exploring the value of the 21-gene expression assay in this clinical scenario. Despite the pending results of this trial, recent data support that Oncotype DX testing is done relatively frequently in patients with node-positive disease, and results of this testing influences clinical decision-making.[224]

There are several appropriate chemotherapy regimens used for adjuvant treatment in HER2-negative disease; the regimens used in adjuvant therapy for HER2-positive disease are discussed in the section on HER2-Positive Disease. Some principles for administering adjuvant chemotherapy are as follows[74]:

- Administer full-dose chemotherapy based on actual height and weight;
- Base chemotherapy administration in elderly patients on individual risk:benefit ratios, as most studies involved patients younger than age 70;
- Dose escalation adds no benefit to standard-dose chemotherapy in adjuvant treatment; and
- Combination chemotherapy is preferred and has greater benefits in women with node-positive and/or hormone receptor–negative disease.

In general, multidrug regimens containing anthracyclines and taxanes are appropriate for higher-risk disease, whereas shorter and less complex regimens can be used for node-negative tumors and selected node-positive tumors with more favorable disease biology (Table 7-7). The choice of regimen is dependent on the overall risk of disease recurrence and the relative reduction of risk with the administration of chemotherapy, balanced by the toxicity of the drugs, patient comorbidities, and patient preference. In hormone receptor–positive disease, anthracycline-containing chemotherapy reduces the relative risk of recurrence by 36% and reduces the relative risk of death by 35% when administered sequentially with tamoxifen.[75] In hormone receptor–positive breast cancer, the addition of taxanes to anthracycline-based regimens reduces the relative recurrence risk by an additional 12% and reduces the relative mortality risk by an additional 11%.[233] Chemotherapy regimens that are appropriate for use as adjuvant therapy in both hormone receptor–positive and hormone receptor–negative disease are outlined as follows.

Table 7-7 Adjuvant or Neoadjuvant Chemotherapy Options	
HER2-Negative Disease	Doxorubicin/cyclophosphamide × 4 cycles[225]
	Docetaxel/cyclophosphamide × 4 cycles*[226]
	Cyclophosphamide/methotrexate/5-fluorouracil × 6 cycles[225]
	Dose-dense doxorubicin/cyclophosphamide × 4 cycles followed by dose-dense paclitaxel × 4 cycles*[244]
	Doxorubicin/cyclophosphamide × 4 cycles followed by 12 weeks of paclitaxel*[228]
	Docetaxel/doxorubicin/cyclophosphamide × 6 cycles[244]
HER2-Positive Disease	Doxorubicin/cyclophosphamide × 4 cycles followed by 12 weeks of paclitaxel and trastuzumab with or without pertuzumab followed by trastuzumab with or without pertuzumab (over a 40-week duration)*[248]
	Docetaxel/carboplatin/trastuzumab +/- pertuzumab × 6 cycles followed by trastuzumab +/- pertuzumab (over a 34-week duration)*[255]
	Paclitaxel and trastuzumab weekly × 12 weeks followed by trastuzumab × 40-week duration[260]
	Pertuzumab, trastuzumab, and taxane (either paclitaxel or docetaxel) × 12 weeks total followed by doxorubicin/cyclophosphamide × 4 followed by trastuzumab with or without pertuzumab (over a 40-week duration)[291]

*Preferred regimen, per 2017 NCCN guidelines.

TRIPLE-NEGATIVE DISEASE

Adjuvant endocrine therapies are not effective, without the presence of their target, in hormone receptor–negative disease. In addition, trastuzumab, the humanized monoclonal antibody against the HER2 protein, has not been shown to be effective in HER2-negative disease. For this reason, chemotherapy is the mainstay of adjuvant treatment for TNBC, a subtype of breast cancer that lacks a positively identified therapeutic target. TNBC accounts for only approximately 10 to 15% of all breast cancers, is more common among young and/or black women, and is classically associated with high-grade cancers. Unlike other subtypes of breast cancer, the biology of TNBC is such that its prognosis does not correlate as closely with tumor size or nodal involvement.[234] For example, one study suggested that once one axillary lymph node is involved, additional axillary nodal involvement does not affect the poor prognosis already associated with node-positive TNBC. In addition, node-negative TNBC with a tumor size greater than 0.5 cm (T1b or higher) has a high enough risk of disease recurrence and death to warrant a discussion of adjuvant chemotherapy.[235]

As stated previously, the efficacy of chemotherapy is greater in TNBC, in which the risk of systemic recurrence is greatest within the first 2 to 3 years, and unlike hormone receptor–positive disease, the risk of recurrence is negligible after 5 to 10 years.

The comparison of anthracycline-containing to methotrexate-containing regimens in adjuvant therapy improved the proportional reduction in risk of recurrence by 12% and death by 15%.[74] These data support the use of anthracyclines for adjuvant treatment—the most commonly used combination regimen being doxorubicin and cyclophosphamide (AC) for four cycles. A relatively small randomized trial compared four cycles of AC with four cycles of another two-drug regimen, docetaxel and cyclophosphamide (TC), among women with stages I to III breast cancer.[226] After a 7-year follow-up, there was a 6% improvement in DFS and a 5% improvement in OS with the TC regimen. Although the trial was relatively small, these data suggest that the two regimens are comparable. TC was associated with less cardiotoxicity and

a lower risk of treatment-induced leukemia compared with AC, but both of these toxicities are relatively rare.

The question of duration of therapy was addressed by CALGB 40101, which evaluated 3171 patients with primarily lymph node–negative disease (94% node negative) and randomly assigned them to either four or six cycles of AC or single-agent paclitaxel.[236] Both regimens were administered every 2 weeks, with no difference in outcome (relapse-free survival or OS) between four or six cycles of treatment.

Based on a meta-analysis of 13 randomized trials involving 22,453 women, the addition of taxanes to anthracycline-containing regimens resulted in a 17% reduction in the relative risk of relapse and a 18% reduction in the relative risk of death at 5 years. This translates into a 5% absolute improvement in DFS and a 3% improvement in OS.[237] This relative benefit is constant, regardless of the type of taxane used (paclitaxel or docetaxel), patient age, or number of lymph nodes involved. It has been suggested that the addition of a taxane in sequence may offer a greater advantage compared with regimens in which the taxane is combined with the anthracycline; however, only a small number of trials provide evidence for this suggestion.

Initial adjuvant taxane studies demonstrated superior DFS and OS when four cycles of paclitaxel were administered following four cycles of AC, compared with four cycles of AC alone (CALGB 9344).[238] Similar results were seen when three cycles of docetaxel were given following three cycles of 5-fluorouracil, epirubicin, cytoxan (FEC), compared with six cycles of FEC (FNCLCC PACS 01 trial).[239] Two concurrent studies compared six cycles of 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) with six cycles of docetaxel, doxorubicin, cyclophosphamide (TAC) in both node-positive breast cancer (BCIRG 001) and high-risk node-negative disease (GEICAM 9805).[240] Both studies demonstrated the superiority of TAC in reducing the relative risk of recurrence by 30%, but only the node-positive study found a relative reduction in risk of death, by about 30%.

Comparing the two strategies of adding taxanes to anthracycline-containing regimens, BCIRG 005 did not demonstrate a difference between six cycles of TAC and four cycles of AC followed by four cycles of docetaxel. NSABP B30, however, showed a superior DFS and OS with four cycles of AC followed by four cycles of docetaxel compared with four cycles of TAC or four cycles of docetaxel, doxorubicin.[241,242] Neutropenia is associated with the combination regimens more frequently, whereas neuropathy and nail changes are more common with the sequential therapies that include docetaxel. NSABP B-38 expanded this concept by comparing six cycles of TAC with two regimens: either four cycles of AC followed by four cycles of paclitaxel given every 2 weeks, or with this regimen with gemcitabine added to the paclitaxel arm.[243] The additional chemotherapy (gemcitabine) did not add benefit; however, six cycles of TAC was comparable in DFS and OS with four cycles of AC followed by four cycles of paclitaxel. Again, the toxicity profile differed between the two regimens, with neutropenic fever and diarrhea being more prevalent with TAC chemotherapy.

In an attempt to determine the optimal taxane and the best schedule for adjuvant therapy use, the ECOG 1199 study compared docetaxel with paclitaxel, both given either weekly for 12 weeks or every 3 weeks for four cycles, after completing four cycles of AC (given every 3 weeks) in node-positive and high-risk node-negative disease.[228] Data from this trial and other trials support that paclitaxel, administered weekly for 12 weeks, is better than the three other options of taxane administration. In an exploratory subset analysis of the ECOG 1199 trial, weekly paclitaxel increased 10-year DFS to 69% for TNBC, compared with about 59% in the other three arms. Overall 10-year survivals were 75%, compared with about 66%.

A dose-dense, every-2-week, chemotherapy schedule with growth factor support has been

associated with improved clinical outcomes compared with chemotherapy administration on a conventional every-3-week schedule. This was supported by CALGB 9741, in which 2005 women with lymph node–positive disease were randomly assigned to receive similar doses of AC for four cycles followed by paclitaxel for four cycles, given by dose-dense or conventional schedule.[244] The dose-dense regimen (every-2-week administration with filgrastim support) resulted in a 26% reduction in relative risk of recurrence and a 31% reduction in relative risk of death. As expected, within the group receiving the superior dose-dense regimen, patients with TNBC fared better as compared with patients with hormone receptor–positive disease in terms of improved reduction in risk of recurrence (32% vs. 19%); however, this was not significant. A meta-analysis of randomized trials that evaluated dose-dense adjuvant therapy confirmed the CALGB 9741 findings of a 15% relative reduction in risk of recurrence and a 10% relative reduction in risk of dying.[245] Patients with TNBC again obtained greater benefit compared with those with hormone receptor–positive disease.

HER2-POSITIVE DISEASE

HER2 is an important therapeutic target for the 15 to 20% of breast cancers that are classified as HER2-positive either by overexpressing the HER2 protein (3+ by immunohistochemistry) or by *HER2* gene amplification (FISH dual probe ratio ≥ 2.0 or single-probe average copy number ≥ 6 signals per cell). HER2 is an adverse independent prognostic indicator and predicts benefit with trastuzumab, the humanized monoclonal antibody against the extracellular domain of HER2. Trastuzumab has limited efficacy as a single agent in metastatic disease and has been studied in combination with chemotherapy only in the adjuvant setting. Patients with HER2-positive cancer that is node-positive regardless of tumor size or node-negative with tumor size greater than or equal to 1.0 cm (T1c or higher) should be offered a combination of chemotherapy and trastuzumab for adjuvant treatment. There have been several attempts at delineating the smallest tumor size in lymph node–negative, HER2-positive disease that will benefit from chemotherapy and trastuzumab. Several studies have demonstrated that T1a and T1b, HER2-positive, node-negative breast cancer has a substantial risk of recurrence and death.[246,247] Several other studies support the recommendation that HER2-positive, node-negative, T1b tumors be considered for trastuzumab-based therapy if other adverse characteristics are present (e.g., high grade, young age). The role of trastuzumab-based therapy in patients with T1aN0 disease remains unknown.

When added to chemotherapy, trastuzumab substantially improves DFS and OS compared with chemotherapy alone in HER2-positive disease. A meta-analysis of five adjuvant therapy studies that involved 9748 patients demonstrated a 38% reduction in the relative risk of recurrence and a 34% reduction in the relative risk of dying from any cause.[248] The largest individual analysis combined two U.S. studies: the three-arm NCCTG N9831 and the NSABP B-31. The NCCTG N9831 randomly assigned 1944 patients to chemotherapy alone (AC every 3 weeks for four cycles followed by weekly paclitaxel for 12 weeks), chemotherapy followed by 1 year of trastuzumab (sequential arm), or chemotherapy with 1 year of trastuzumab beginning with the paclitaxel (concurrent arm). The NSABP B-31 randomly assigned 2101 patients to chemotherapy (AC every 3 weeks for four cycles followed by paclitaxel every 3 weeks for four cycles) or chemotherapy and trastuzumab beginning with the paclitaxel.[229] Regardless of other patient or tumor characteristics, the addition of trastuzumab to chemotherapy resulted in a 48% relative improvement in DFS and a 39% relative improvement in OS.

The HERA trial evaluated combination chemotherapy followed by observation or 1 or 2 years

of adjuvant trastuzumab.[249-251] At an 11-year median follow-up, the HERA trial demonstrated that 1 year of trastuzumab significantly reduced the risk of a DFS event (HR, 0.76; 95% CI; 0.68, 0.86) and death (HR, 0.74; 95% CI; 0.64, 0.86), compared with observation. Two years of adjuvant trastuzumab did not improve DFS outcomes compared with 1 year of this drug. Estimates of 10-year DFS were 63% for observation, 69% for 1 year of trastuzumab, and 69% for 2 years of trastuzumab.[251] The results of the aforementioned studies suggest an interaction between chemotherapy and trastuzumab wherein concurrent administration may be of greater benefit as compared with sequential treatment. This concept was supported by an analysis of the NCCTG N9831 study that compared chemotherapy (AC every 3 weeks for four cycles followed by weekly paclitaxel for 12 weeks) followed by 1 year of trastuzumab (sequential arm) or chemotherapy with 1 year of trastuzumab beginning with the paclitaxel (concurrent arm).[252] The concurrent administration of trastuzumab with paclitaxel was associated with a 23% reduction in risk of an event as compared with sequential trastuzumab administration, suggesting that combined chemotherapy and trastuzumab is more beneficial than chemotherapy followed by trastuzumab.

The currently accepted duration of adjuvant trastuzumab is 1 year. The HERA trial randomly assigned patients receiving trastuzumab to 1 or 2 years of treatment, and showed no difference in progression-free survival (PFS) or OS after an 11-year follow-up.[253] Cardiac toxicity was greater with the 2-year duration. In contrast, the Finnish Breast Cancer Group's FinHer trial evaluated the benefit of 9 weeks of trastuzumab added to three cycles of docetaxel or vinorelbine followed by three cycles of FEC (without trastuzumab).[254] Patients who received trastuzumab experienced a 35% improvement in distant DFS; however, this was not significant. A large phase III trial that involved 3380 women (PHARE) failed to demonstrate noninferiority with a 6-month as compared with 12-month duration of trastuzumab.[230] The recommended duration of adjuvant trastuzumab is 1 year, given concurrently with a taxane; it should be given concurrently with endocrine therapy for hormone receptor–positive disease.

In the adult heart, HER2 functions to modify cardiac muscle response to stress. In theory, trastuzumab can interfere with the ability of the heart to adjust to stress, resulting in cardiac damage. The addition of trastuzumab in the adjuvant studies resulted in less than a 4% difference in congestive heart failure or death between the treatment arms, which was less than the early stopping rules required. However, 5% of patients experienced asymptomatic decreases in ejection fraction that required discontinuation of trastuzumab. Risk of cardiac compromise was associated with advanced age, hypertension, and initial ventricular function.

Concern about cardiac toxicity prompted investigation into a non–anthracycline-containing trastuzumab regimen: Taxotere (docetaxel), carboplatin, Herceptin (trastuzumab) (TCH), administered every 3 weeks for six cycles. BCIRG 006 compared this regimen with four cycles of AC every 3 weeks followed by four cycles of docetaxel alone or with 1 year of trastuzumab beginning with docetaxel.[242,255] BCIRG 006 confirmed a benefit with the addition of trastuzumab to chemotherapy; there was a 3% absolute difference in DFS and a 1% difference in OS at 5 years favoring the AC plus docetaxel and trastuzumab arm over the TCH arm. It should be noted, however, that the study was not designed to compare the two trastuzumab-containing arms and any conclusions about the benefits of one regimen over another should be considered exploratory. TCH was associated with less cardiac toxicity and risk of secondary leukemia compared with the AC plus docetaxel and trastuzumab regimen, making it an acceptable treatment alternative.

Thus, AC for four cycles followed by 12 weekly doses of paclitaxel with concurrent trastuzumab (TH), and then trastuzumab to complete a year, is commonly chosen as treatment

for a patient who is at substantial risk of disease recurrence and does not have significant risk factors for cardiac toxicity.[223] For patients at lower risk of disease recurrence or with significant cardiac risk factors, TCH represents a reasonable alternative. Although the standard doxorubicin, cyclophosphamide, paclitaxel, trastuzumab regimen prescribes AC administered every 3 weeks, there are safety data to support administering AC every 2 weeks for four cycles (dose-dense) rather than every 3 weeks prior to 12 weeks of TH.[256] When trastuzumab is used as a single agent following chemotherapy, it is commonly given every 3 weeks.[257] Cardiac monitoring with echocardiography or nuclear ventriculography is recommended every 3 months during adjuvant trastuzumab treatment.

ALTTO trial data failed to demonstrate any significant benefit for the addition of adjuvant lapatinib to trastuzumab compared with trastuzumab alone.[258] This was seen despite that, in the neoadjuvant setting (NeoALTTO), the addition of lapatinib to trastuzumab substantially increased pCR rates.[231] This finding raises concern regarding the value of new drug development in the neoadjuvant setting; however, the patient populations and drug regimens in NeoALTTO and ALTTO differed, potentially explaining the discordant trial results.

Results of another phase III study that evaluated dual HER2-directed therapy, the APHINITY trial, were presented at ASCO 2017.[259] The APHINITY trial randomly assigned 4805 patients with HER2-positive node-positive or high-risk node-negative breast cancer to adjuvant chemotherapy with trastuzumab and placebo/pertuzumab. With a median follow-up of 45.4 months, the addition of pertuzumab to chemotherapy and trastuzumab was associated with a 3-year invasive DFS rate of 94.1% as compared with the placebo arm rate of 93.2%. Pertuzumab reduced the relative risk of an invasive DFS event by 19% compared with placebo (HR, 0.81; 95% CI; 0.66, 1.00; p = 0.045). Treatment was effective in all subgroups; however, those with node-positive and/or hormone receptor–negative disease appeared to derive the most benefit. Diarrhea was increased in the pertuzumab arm, predominantly during chemotherapy and with the TCH regimen. Cardiac toxicity was low and not different between the two arms. The role of adjuvant pertuzumab in guidelines and clinical practice remains to be defined.

Retrospective data suggest that small, node-negative, HER2-positive breast cancers have a small but real risk of distant recurrence. Most patients with these cancers were not eligible for enrollment in the pivotal adjuvant trastuzumab clinical trials, and the use of any of the standard adjuvant regimens seemed excessive to many clinicians. Given this setting, investigators at the Dana–Farber Cancer Institute and a number of other major cancer centers sought to explore the efficacy of a trastuzumab-containing adjuvant therapy regimen that included a minimal amount of chemotherapy. The phase II Adjuvant Paclitaxel Trastuzumab (APT) trial involved 406 patients with node-negative, HER2-positive breast cancers that measured less than 3 cm; more than 90% had tumors less than 2 cm.[260] In this single-arm, multi-institutional study, patients received 12 weeks of paclitaxel (80 mg/m^2) and concurrent trastuzumab, followed by 9 months of single-agent trastuzumab therapy. The 7-year DFS was 93.3% and the 7-year recurrence-free interval was 97.5% at a median follow-up of 6.5 years, with only 4 (1%) of DFS events being distant metastasis. The regimen was well tolerated, with minimal neuropathy and cardiac compromise, and it is included as a regimen option in NCCN guidelines. These results are being further explored in the ATEMPT trial, which involves patients with stage I HER2-positive breast cancer, randomly assigned to 12 weeks of TH followed by trastuzumab for 9 months or 12 months of the antibody-drug conjugate, trastuzumab emtansine (TDM-1).

Neratinib is an oral tyrosine kinase inhibitor (TKI) that targets HER2 and HER1, and it differs from lapatinib in that it is an irreversible TKI and further targets HER4. While 2 years of

adjuvant trastuzumab did not improve clinical outcomes in the HERA trial, it was thought that extended HER2-directed therapy with a different mechanism of action could result in better disease control, especially for those with high-risk disease. This served as the rationale for the ExteNET trial, a phase III randomized, double-blind, placebo-controlled study of neratinib following adjuvant trastuzumab treatment.[261] Participants included 2840 patients with early-stage HER2-positive breast cancer who were within 2 years of completing adjuvant trastuzumab therapy. While the sponsor changed twice over the course of the study, the primary endpoint of invasive DFS remained constant for the intention-to-treat analysis. Two amendments were made over the course of the study, related to eligibility criteria to (1) mandate node-positive disease, and (2) reduce the interval of time from trastuzumab completion to registration from 2 years to 1 year. One year of adjuvant neratinib was associated with a 2-year invasive DFS rate of 94.2%, compared with a rate of 91.9% in those receiving placebo (HR, 0.66; 95% CI; 0.49, 0.90, p = 0.008). The most common adverse events were diarrhea, other gastrointestinal toxicities, fatigue, rash, and stomatitis. Treatment discontinuation due to diarrhea was 16.8%. These results led to the FDA approval of neratinib in 2017. Concurrent administration of antidiarrheal prophylaxis is recommended with initiation of neratinib per the FDA label. The role of adjuvant neratinib in guidelines and clinical practice remains to be defined.

KEY POINTS

- Stages I and II breast cancer treated by mastectomy or breast-conservation therapy (BCT) results in equivalent survival.
- Both WBI after BCT and postmastectomy radiation therapy are associated with a reduction in locoregional recurrence. Meta-analyses have also shown a small benefit in breast cancer mortality from adjuvant radiation therapy.
- Adjuvant tamoxifen remains standard adjuvant endocrine treatment for premenopausal women with hormone receptor–positive disease. Ovarian function suppression adds benefit to DFS (but not OS) when combined with 5 years of adjuvant tamoxifen or exemestane in premenopausal women with high risk disease.
- As compared with 5 years, 10 years of adjuvant tamoxifen has demonstrated a small improvement in DFS, and extended-duration tamoxifen can be considered an option in high risk pre- or postmenopausal patients.
- The AIs should be considered for the treatment of hormone receptor–positive disease in postmenopausal women. Administering AIs for 5 years was shown to have similar outcomes as initial AI for 2 to 3 years, followed by tamoxifen for 2 to 3 years. Extended-duration AIs have not consistently shown benefit beyond 5 years.
- Anthracycline- and/or taxane-based adjuvant chemotherapy is standard care for women with triple-negative breast cancer. Similar regimens can be used for patients with high-risk, hormone receptor–positive disease and in combination with HER2-directed therapy for HER2-positive disease.
- One year of adjuvant trastuzumab is recommended for HER2-positive breast cancer, given concurrently for 12 weeks with taxane-based chemotherapy followed by

monotherapy to complete 1 year.

- The addition of 1 year of adjuvant pertuzumab to trastuzumab provided a small absolute reduction in the risk of an invasive DFS event, and its use can be considered for high-risk patients.

STAGE III DISEASE

Stage III disease is often classified as locally advanced disease and can be grouped into two general categories: patients with large tumors or multiple positive lymph nodes but who clearly have operable disease that can be primarily resected, and patients with inoperable disease by virtue of skin involvement, disease attachment to the chest wall, or extensive nodal involvement that precludes initial surgical resection (e.g., matted axillary lymph nodes or supraclavicular lymph node involvement). The initial diagnostic evaluation and treatment of patients with operable stage III disease can be conducted in the same manner as for patients with stage II disease; however, often the preferred method is to administer systemic therapy first (primary systemic therapy, preoperative, neoadjuvant) followed by surgery and radiation. Often this sequence is performed to improve surgical options by allowing the possibility of breast conservation or sentinel node biopsy without ALND. The sequence of treatment using neoadjuvant systemic therapy is required for the treatment of inoperable stage III disease in order to allow definitive local therapy, determine disease response to systemic therapy, and improve survival.

Locoregional Therapy

A meta-analysis of nine randomized trials that involved 3946 patients (including patients with stage II cancer) evaluated outcomes when the same systemic therapy was administered to patients with operable breast cancer, preoperatively (neoadjuvant) versus postoperatively (adjuvant), revealing no difference in mortality or distant disease recurrence.[262] Neoadjuvant systemic therapy is associated with considerable tumor shrinkage, thus allowing for a greater proportion of patients to achieve breast conservation.[263]

A greater risk of locoregional disease recurrence was found among patients who received radiation alone as local therapy, following neoadjuvant systemic therapy, excluding surgery. Even in the setting of a complete clinical disease response to neoadjuvant systemic therapy, resecting the region of the primary tumor site with appropriate breast surgery is currently recommended for optimal local disease control, although this is being evaluated in ongoing clinical trials.[263,264]

Breast-conservation surgery after neoadjuvant systemic therapy has classically been followed by radiation therapy; however, the criteria for PMRT in this setting have been less well defined, until recently. In 2016, the ASCO/ASTRO/SSO guidelines recommended PMRT for patients with positive lymph nodes following neoadjuvant systemic therapy.[265] There is currently insufficient evidence to recommend whether PMRT should be administered or can be routinely omitted in those with clinically negative nodes who receive neoadjuvant systemic therapy or in those with a complete response in the lymph nodes with neoadjuvant systemic therapy. The recommendation of the panel is to enter eligible patients into clinical trials designed to address these clinical scenarios (NSABP B-51 and A11202).

The optimal surgical management of the axilla in the setting of neoadjuvant chemotherapy remains complex and is an area under investigation. Patients with a clinically negative axilla (by

physical examination and axillary ultrasound) at the time of presentation can undergo SLN surgery after completion of chemotherapy. SLN surgery post–neoadjuvant systemic therapy is acceptable and has a similar SLN identification and false-negative rate as seen prior to systemic therapy.[266] If the SLNs are negative, then no further axillary surgery is indicated. If any of the SLNs is positive, then completion ALND is recommended.

Patients with a positive axillary lymph node confirmed by FNA biopsy or core needle biopsy at the time of diagnosis usually undergo complete axillary lymph node dissection following neoadjuvant chemotherapy; however, SLN surgery is increasingly used to evaluate for residual nodal disease. Neoadjuvant systemic therapy has been shown to convert 40 to 75% of positive lymph nodes to negative lymph nodes. Several recent multicenter clinical trials[267-269] show false-negative rates with SLN surgery in this setting that are similar to rates in patients with clinically node-negative breast cancer treated with neoadjuvant chemotherapy.

Current clinical trials are further exploring the optimal locoregional management of the axillae. Alliance A011202 is randomly assigning patients with a positive SLN after neoadjuvant chemotherapy to axillary dissection or axillary radiation to evaluate which modality provides the best local control and survival. NSABP B-51 is asking whether adjuvant nodal radiation is required in women who convert from biopsy-proven node-positive disease to pathologically node-negative disease (by SLN surgery or ALND) after neoadjuvant chemotherapy, by randomly assigning these women to nodal radiation or no radiation.

Neoadjuvant Systemic Therapy

Chemotherapy. A pCR has variable definitions in the literature; however, the consensus definition is absence of invasive carcinoma in the breast and axillary lymph nodes.[263] A pCR with neoadjuvant systemic therapy is associated with a more favorable outcome, compared with patients who have residual disease in the breast and/or axilla.[270] NSABP B-18 and NSABP B-27 compared neoadjuvant chemotherapy to adjuvant chemotherapy using chemotherapy regimens of AC alone or AC followed by docetaxel.[271] Both studies demonstrated superior DFS and OS among the patients who achieved pCR compared with those who did not, although the pCR rate was only 13 to 26%. In the final analysis, however, there remained no difference in overall DFS or OS when the chemotherapy was administered in the neoadjuvant versus the adjuvant setting.

Although TNBC is associated with a less favorable overall prognosis, this subtype of breast cancer is more chemosensitive and has a greater propensity of achieving a pCR to neoadjuvant chemotherapy, compared with hormone receptor–positive disease.[272] Patients with TNBC who achieve a pCR have a favorable OS, that is similar to patients with non-TNBC who achieve a pCR.[273] Residual disease following neoadjuvant chemotherapy in TNBC and HER2-positive disease is associated with a worse DFS compared with other subtypes of breast cancer treated similarly.[274] In this way, neoadjuvant chemotherapy can be used as a mechanism of evaluating tumor biology, disease resistance, and, ultimately, prognosis.[2754] When neoadjuvant chemotherapy is used, the regimen selected should be the same as what would be administered in the adjuvant setting, typically consisting of an anthracycline and a taxane.[263,276]

Given the relationship between pCR and OS, several neoadjuvant clinical trials have been designed to evaluate novel chemotherapy regimens, some including targeted agents, with an overarching goal of improving on existing pCR rates associated with standard therapy. In CALGB 40603, the addition of neoadjuvant carboplatin to anthracycline- and taxane-based chemotherapy was evaluated in patients with clinical stages II and III TNBC. Rates of pCR in

the breast and axilla were 41% for standard chemotherapy and 54% when carboplatin was added to the regimen (p = 0.0029).[277] This significant improvement in pCR was also achieved when carboplatin was added to a more complex neoadjuvant anthracycline- and taxane-based regimen that included bevacizumab in patients with TNBC (absolute increase of 16.3%) participating in the GeparSixto trial.[278] Despite encouraging results in a population in need of better therapies, the 3-year event free survival (EFS) results for these trials yielded different conclusions. In CALGB 40603, there was an absolute gain in EFS of 4.9%; however, this was not statistically significant.[279] In GeparSixto, there was an absolute gain in EFS of 9.7% that was statistically significant.[280] Notably, patients in GeparSixto had a better overall prognosis (more T1 and N0 disease), a larger incremental benefit from carboplatin, as well as a larger cumulative dose and longer overall duration of anthracycline and taxane chemotherapy, as compared with patients in CALGB 40603. Thus, recognizing that the platinum agents can be toxic and that these trials lack long-term safety data, as well as the discrepant EFS outcomes between these trials, many experts still consider the use of carboplatin in TNBC to be investigational. Biomarkers predictive of carboplatin benefit are needed to help guide patient selection. Optimal dosing and schedule for carboplatin, which also varied in these two trials, remains to be determined.

There is no clearly established role for adjuvant chemotherapy once neoadjuvant chemotherapy is completed, even if pCR is not attained, assuming a complete course of therapy was administered as neoadjuvant systemic therapy. There has been a single report of a pre-planned interim analysis of a phase III trial that a 24-week course of capecitabine may improve clinical outcomes for those without pCR after contemporary neoadjuvant anthracycline and taxane-based chemotherapy, leading some oncologists to utilize this approach in clinical practice.[281]

Endocrine Therapy. Neoadjuvant endocrine therapy is an acceptable treatment for postmenopausal women with hormone receptor-positive disease, although the pCR rate of 1 to 8% is lower than with chemotherapy.[264] At least five randomized trials (including patients with stage II disease) have demonstrated superiority with neoadjuvant AI treatment compared with tamoxifen.[282] The IMPACT trial compared neoadjuvant anastrozole, tamoxifen, and the combination of anastrozole and tamoxifen, and found a greater ability to achieve BCT with anastrozole compared with tamoxifen (46% vs. 22%).[283] A comparison of neoadjuvant letrozole with tamoxifen, performed by the Letrozole Neoadjuvant Breast Cancer Study Group, demonstrated a superior clinical response with letrozole (55% vs. 36%, respectively) and superior frequency of BCT (45% vs. 35%, respectively), but no difference in the low pCR rates.[284]

For post-menopausal women, all three third-generation AIs (anastrozole, letrozole, and exemestane) appear to be equally effective when administered in the neoadjuvant setting in terms of clinical response and surgical outcomes.[285] Despite low pCR rates associated with neoadjuvant endocrine therapy, surrogate markers of response can offer prognostic information about long-term clinical outcomes, including the hormone receptor status of residual disease (ER-negative is less favorable) and the Ki67 expression in residual tumor (low value is more favorable).[286] Prospective validation of these biomarkers is ongoing. Patients who have a clinical response to neoadjuvant endocrine therapy should continue on endocrine therapy postsurgery, as per adjuvant treatment recommendations (see the Stage I and II Disease, Hormone Receptor Positive Disease, and Endocrine Therapy sections). Those who do not have a clinical response should be considered for adjuvant chemotherapy to be followed by adjuvant endocrine therapy. Neoadjuvant endocrine therapy in pre-menopausal women and men remains

investigational.

HER2-Directed Therapy. Like TNBC, HER2-positive breast cancer is associated with a high probability of tumor response to neoadjuvant chemotherapy, and this response rate is increased substantially with the addition of HER2-directed treatment. Two studies evaluated neoadjuvant trastuzumab-containing regimens administering the trastuzumab with an anthracycline. A meta-analysis of these two randomized trials compared neoadjuvant chemotherapy with and without trastuzumab for HER2-positive disease.[287] Both studies demonstrated a significant benefit with added trastuzumab in the pCR rate (20 to 40% actual improvement), and a 33% relative reduction in risk of recurrence and death. The cardiac event rate was 11%. Two additional studies, using epirubicin plus cyclophosphamide (EC) every 3 weeks followed by a taxane with or without capecitabine, also initiated trastuzumab with the anthracycline and observed favorable pCR rates of 32 to 39%, with a less than 4% incidence of cardiac toxicity.[288,289] These studies provide short-term safety data for the combination of anthracycline chemotherapy and neoadjuvant trastuzumab. A recent randomized study failed to demonstrate an improvement in pCR rate with the concurrent administration of trastuzumab with anthracycline and taxane-based chemotherapy over the previously established standard to administer anthracycline-based chemotherapy alone followed by taxane-based chemotherapy with trastuzumab. Given this result and the lack of long-term safety and efficacy data, it appears best to administer trastuzumab sequentially with anthracycline-based chemotherapy, as opposed to concurrently.[290]

In an attempt to add to the efficacy of trastuzumab administered pre-operatively, two phase III trials evaluated the role of lapatinib in this setting. GeparQuinto compared four cycles of EC followed by four cycles of docetaxel concurrent with either lapatinib or trastuzumab. Among the 620 randomly assigned patients, the pCR rate was significantly higher with trastuzumab compared with lapatinib (30.3% vs. 22.7%, respectively, $p = 0.04$).[232] No difference in pCR rate was demonstrated between the lapatinib alone and trastuzumab alone arms (24.7% vs. 29.5%) in a second complex trial involving 455 patients randomly assigned to receive 6 weeks of lapatinib alone, trastuzumab alone, or lapatinib combined with trastuzumab prior to continuing HER2-directed therapy with 12 weeks of paclitaxel (NeoALTTO).[231] Combination lapatinib and trastuzumab with paclitaxel resulted in a superior pCR rate, 51.3%.

The benefit seen with dual HER2-directed therapy prompted an evaluation of pertuzumab in the neoadjuvant setting. The NeoSphere trial was an open-label, phase II study that randomly assigned 417 patients to receive four cycles of docetaxel combined with either trastuzumab, pertuzumab, or both agents versus combination pertuzumab and trastuzumab without docetaxel (a nonchemotherapy arm).[291] The combination pertuzumab and trastuzumab with docetaxel achieved the highest pCR rate of 39.3%, compared with the other groups. This trial, as well as the TRYPHAENA study,[292] combined with the survival advantage seen with pertuzumab in the metastatic setting, led the FDA to provide accelerated approval of this combination for neoadjuvant treatment of HER2-positive breast cancer. All patients in the NeoSphere trial also received adjuvant treatment with three cycles of FEC chemotherapy concomitant with trastuzumab followed by completion of 1 year of trastuzumab therapy.

Based on these results, a promising option for neoadjuvant systemic therapy of HER2-positive disease is a combination of trastuzumab and pertuzumab with a taxane-based chemotherapy. This is either preceded by or followed with an anthracycline-based regimen. Trastuzumab should be administered for a total of 1 year. The optimal chemotherapy regimen used in neoadjuvant systemic therapy with trastuzumab and pertuzumab is still unknown. Notation in the most recent NCCN guidelines allows for the use of pertuzumab in the adjuvant

setting if it was not received in the neoadjuvant setting; results of the APHINITY trial support this.

INFLAMMATORY BREAST CANCER

Inflammatory breast cancer (IBC) is an uncommon virulent subset of disease that now accounts for up to 2% of all breast cancers in the United States. IBC (T4d) is a clinical diagnosis in the setting of documented invasive breast cancer and is characterized by a rapid onset of clinical changes in the breast—skin erythema, warmth, edema (peau d'orange), breast enlargement, and pain—usually occurring within a 3-month time frame, but not present for longer than 6 months. This type of breast cancer is designated as inflammatory because the clinical signs mimic mastitis; an empiric treatment with antibiotics often delays the diagnosis of cancer. These clinical criteria differentiate IBC from a neglected locally advanced breast cancer with secondary inflammatory characteristics, which is associated with a more favorable prognosis. A discrete mass may be absent in patients with IBC, and pathologically, tumor emboli are seen within dermal lymphatics in 75% of cases.[293] The classic physical findings of the breast are due to damage of the dermal lymphatics caused by tumor emboli, and the corresponding palpable finding is known as "ridging." Patients with IBC are often younger at the age at diagnosis, are more often black, and by definition, present with inoperable disease.[294] Breast imaging with mammography usually finds asymmetrical increased density throughout the affected breast, associated with skin thickening and axillary adenopathy. MRI is more sensitive and specific in finding breast masses and confirming disease response to neoadjuvant chemotherapy, compared with mammography.[295]

Although the complete spectrum of intrinsic subtypes is seen in IBC, there is a propensity for the disease to segregate into the more proliferative HER2-positive and triple-negative molecular subtypes. Patients with IBC have as high as a 2-fold increased risk of dying of disease as patients diagnosed with noninflammatory locally advanced breast cancer, with OS rates being consistently less than 50%. Approximately 20 to 40% of patients with IBC have evident metastatic disease at the time of presentation.[296] Given the high risk of developing metastatic disease, a trimodality approach to treatment is appropriate: neoadjuvant chemotherapy followed by mastectomy with ALND and PMRT with comprehensive regional nodal irradiation. Hormone receptor–positive IBC is treated similarly to noninflammatory breast cancer, with endocrine therapy given following chemotherapy. The primary goal of this treatment sequence is to optimize conditions for a surgical intervention; the secondary goal is that it allows for real-time assessment of the primary systemic therapy's antitumor efficacy through evaluation of the pathologic disease response at the time of mastectomy.

Although the optimal neoadjuvant chemotherapy regimen for IBC has not been defined, the type of neoadjuvant systemic therapy should be selected from those regimens outlined previously for noninflammatory breast cancer. Both prospective and retrospective studies support the use of combination anthracycline- and taxane-based regimens. The addition of taxanes to anthracycline regimens has resulted in an improved pCR rate and improved OS.[297] The prognosis of HER2-positive IBC has greatly improved in the era of HER2-directed therapy. HER2-positive IBC should be treated with a dual HER2-targeted neoadjuvant regimen with trastuzumab and pertuzumab, as previously described.

IBC appears to have a unique molecular profile characterized by overexpression of the epithelial adhesion protein E-cadherin, overexpression of the *RhoC* oncogene, and a high frequency of *TP53* gene mutations, in addition to a loss of expression of *WISP3,* which has

growth and angiogenesis inhibitory functions.[298] A greater understanding of the molecular biology of IBC may help to decipher the pathophysiology of the disease and to develop rationally designed and more effective therapies.

There is a direct correlation between systemic disease control and local disease control with IBC. The goal of neoadjuvant chemotherapy is to render the breast operable. Breast conservation is contraindicated, as is SLN biopsy. A total mastectomy with levels I and II ALND improves surgical control, compared to lesser surgeries. Radiation therapy follows, although the optimal radiation dose and sequence is not well established. The chest wall and regional lymph nodes (supraclavicular, infraclavicular, internal mammary) are included in the treatment field, and the cumulative radiation dose is 50 to 66 cGy. Reconstruction of the breast is best deferred, in order to avoid delays in delivering optimal local therapy for IBC. If neoadjuvant chemotherapy results in an inadequate response in the breast, radiation can be administered prior to mastectomy.[299]

KEY POINTS

- For patients with stage II or III breast cancer, neoadjuvant chemotherapy is associated with a reduction in the need for mastectomy and/or ALND.
- For stage II or III breast cancer, survival is equivalent whether the same chemotherapy regimen is administered in the neoadjuvant or the adjuvant setting.
- Neoadjuvant endocrine therapy is an acceptable treatment approach for postmenopausal women with stage II or III hormone receptor–positive breast cancer. It can result in higher breast-conservation rates, but it infrequently results in pCR.
- Residual disease following neoadjuvant chemotherapy for TNBC and HER2-positive disease is associated with worse DFS, compared to those who achieve a pCR.
- Pertuzumab, when administered with trastuzumab and taxane-based chemotherapy, is associated with a significantly increased pCR rate; this led to its accelerated FDA approval for management of stages II and III HER2-positive breast cancer.
- Inflammatory breast cancer (IBC) is managed by neoadjuvant chemotherapy followed by mastectomy with ALND, postmastectomy radiation therapy, and adjuvant endocrine therapy, when indicated. Despite optimal multimodality care, DFS is worse compared with noninflammatory breast cancer, even for patients who achieve a pCR.

RECURRENT OR METASTATIC DISEASE

LOCOREGIONAL RELAPSE

Locoregional disease relapse can be defined as cancer recurrence in the ipsilateral breast, chest wall, or regional lymph nodes. Isolated locoregional recurrences are treated with curative intent. Those that occur within the first 5 years after diagnosis are associated with a poorer prognosis than later recurrences. Recurrences that develop after 5 years usually represent de novo second primary tumors and have a more favorable outcome compared with earlier recurrences within the proximity of the original tumor, which usually represent disease that has been resistant to prior radiation and systemic therapy. The treatment of locoregional

recurrences requires a multidisciplinary approach.

Ipsilateral breast tumor recurrence (IBTR) following BCT has been associated with a 3- to 4-fold increase in the risk of systemic metastasis. The NSABP reviewed five of its more recent adjuvant studies that involved 2669 women treated with breast-conserving surgery, radiation therapy, and systemic treatment and found that patients who experienced an IBTR had a 2.72-fold greater risk of distant disease developing at 5 years and a 2.58-fold greater risk of death, compared with those who did not have disease recurrence.[300] Patients who experienced a chest wall recurrence following mastectomy fared worse, with a 6.68-fold greater risk of distant recurrence at 5 years and a 5.85-fold greater risk of death. IBTRs are usually treated with total mastectomy, since repeat radiation treatment is contraindicated. In cases without prior radiation, BCT can be considered. Small series have evaluated repeat lumpectomy and accelerated partial-breast irradiation in the setting of prior lumpectomy and radiation and have shown low toxicity, although long-term outcome data is awaited. Regarding management of the axilla, the axilla should be evaluated with physical examination and ultrasound. If clinically negative, SLN surgery can be attempted, however it has a lower SLN identification rate.[301] ALND should be considered in cases in which SLNs have not been identified. In cases with clinically positive nodes or positive SLN(s), an ALND should be performed.

As in IBTR, chest wall recurrences after mastectomy occur most frequently within the first 5 years posttreatment and rarely occur after 10 years. The majority of chest wall recurrences develop in the proximity of the mastectomy incision, whereas fewer recurrences develop in the regional lymph node areas (in order of decreasing frequency: supraclavicular, axillary, internal mammary). A review of 11,452 women treated with standard locoregional therapy for early-stage breast cancer at the European Institute of Oncology demonstrated a shorter subsequent DFS and OS among patients in whom regional lymph node recurrences developed, compared with the DFS and OS associated with an IBTR or a nonnodal chest wall recurrence.[302] The risk of subsequent distant disease and consequent adverse effects on OS decreased with time after the initial nonnodal chest wall recurrence, whereas patients with regional lymph node recurrences remain at high risk for the development of distant disease and a shortened OS for a long time. The treatment of an isolated chest wall recurrence requires a surgical excision, if feasible, with the goal of obtaining negative margins. The chest wall and supraclavicular lymph nodes should then receive standard radiation therapy, if not given previously.

Because of the high rate of distant disease in patients who have a locoregional breast cancer recurrence, staging studies are usually performed at the time of the recurrence to evaluate for the presence of metastatic disease. On the basis of data supporting its efficacy, systemic therapy is often administered after completion of local treatment for a locoregional recurrence. The international CALOR (BIG 1-02/IBCSG 27-02/NSABP B-37) trial enrolled 162 out of a planned 977 patients with invasive breast cancer in whom an isolated local and/or regional ipsilateral recurrence developed after mastectomy or BCT.[303] Patients received radiation therapy, endocrine therapy, or trastuzumab as appropriate, and were also randomly assigned to receive chemotherapy or not. The chemotherapy regimen selection and duration of treatment was per physician choice. The 5-year DFS was improved with chemotherapy (69%) compared with no chemotherapy (57%). The benefit was primarily seen in TNBC (67% with chemotherapy vs. 35% without chemotherapy). The 5-year OS was comparable between the two groups—numerically, but not significantly, higher in the chemotherapy group (88% with chemotherapy vs. 76% without chemotherapy). Although this is a highly underpowered study, it does support consideration of chemotherapy following local or regional disease recurrence in select circumstances.

KEY POINTS

- Disease recurrence in a previously irradiated breast commonly requires a mastectomy for local disease control.
- The addition of chemotherapy after a locoregional recurrence may benefit some patients, especially those with triple-negative disease.

STAGE IV (METASTATIC) DISEASE

Metastatic breast cancer is an extremely heterogeneous entity. Treatment options depend on location of metastasis and number of sites involved, presence or absence of hormone receptor expression and HER2 overexpression, an assessment of disease responsiveness to systemic therapy based on characteristics such as disease-free interval, and an estimation of the need for rapid disease response to therapy. Given the diverse presentation of metastatic disease and the wide range of therapeutic possibilities, the goal of this section is to provide a guide for approaching treatment options rather than providing specific treatment recommendations. As with adjuvant therapy of early-stage disease, there are options for treatment outlined by different organizations to help guide decision-making.[169,304,305]

The overall goals of treating metastatic breast cancer are to slow the progression of disease, improve quality of life, and prolong survival while minimizing treatment-associated toxicity. Metastatic breast cancer is a chronic disease; sequential, single-agent therapy is a mainstay of treatment. The incorporation of new therapies over recent decades has resulted in a gradual improvement in OS by 1 to 2% per year.[306] The benefits of individual regimens are often comparable in first-line or subsequent treatment; therefore, the optimal sequence of therapies has not yet been determined.[307]

Once metastatic disease is diagnosed, its extent should be determined by radiographic imaging. The most common initial sites of metastasis include bone, liver, and lung, which can be imaged by conventional CT and bone scan. PET imaging can complement these studies, especially in the setting of lytic bone metastases, which may be underestimated on bone scanning. Central nervous system disease is less likely to be present at the initial presentation of metastatic disease; MRI of the brain can be deferred until symptoms arise. The molecular subtypes of breast cancer have a predilection for metastasizing to specific sites, which may affect the decision to image these areas. HER2-positive disease and TNBC are associated with a higher frequency of brain metastasis (in about a quarter to a third of patients in some reports) compared with the HR-positive subtype (10%).[308] Bone metastases are more common among the hormone receptor–positive subtype (68%), whereas TNBC is associated with a high frequency of metastasis to the lungs (40%). Discordance of hormone receptor and HER2 status between the primary tumor and the metastatic disease can occur in approximately 10 to 15% of cases. A biopsy of the initial metastatic site is often warranted to determine receptor status and to confirm the presence of metastatic breast cancer rather than another malignancy, either primary or metastatic. Additionally, serial biopsies along the metastatic course at the time of progression may be useful, as acquired resistance to therapies can be the result of changes in gene and protein function.

The measurement of the circulating extracellular domain of HER2 as a surrogate marker for HER2 status of the tumor has not yet been established and should be relegated to clinical

trials.[309] Other serum markers, such as the MUC-1 assays, CA 27.29 or CA 15-3, and the carcinoembryonic antigen levels, have not been shown to impact survival in nonmetastatic settings, but can complement the interpretation of imaging studies in metastatic disease. Changes in these assays, by themselves, usually should not dictate changes in therapy. The application of circulating tumor cells in the interpretation of disease response and management of therapy for metastatic disease remains investigational.

Endocrine Therapy

In the setting of hormone receptor–positive metastases that are not associated with rapidly progressing disease or visceral crisis, endocrine therapy should generally be the initial treatment approach. Objective response rates to endocrine therapy are comparable to those of single-agent chemotherapy for first-line treatment; however, the onset of action is slower for endocrine therapy, given the differing antitumor mechanisms of action. Sequential treatment with endocrine therapy regimens is appropriate; however, the likelihood of disease response and duration of response generally becomes smaller/shorter with each change in regimen. At the time of cancer progression, a switch to chemotherapy is always an option. Virtually all patients with metastatic hormone receptor–positive breast cancer ultimately receive chemotherapy. The decision to switch to chemotherapy is based on a low likelihood of a response to additional endocrine therapy, as well as on the other considerations outlined above. Chemotherapy and consideration for combination therapy should be given if the disease is rapidly progressing or in the setting of visceral crisis.

The choice of initial endocrine therapy is dependent on the menopausal status of the patient, the type of prior endocrine therapy used for adjuvant treatment, and the duration between adjuvant endocrine therapy and disease recurrence. There is an association between response to endocrine therapy and the strength of ER and PR expression. In the setting of hormone receptor–positive metastatic disease, disease response is important, but clinical benefit (defined as the percentage of complete and partial disease responses plus stable disease exceeding 6 months) may supersede disease response.

Historically, OFS has been effective in premenopausal women with hormone receptor–positive metastatic disease. The use of a GnRH agonist in the metastatic setting has resulted in outcomes similar to those for surgical ovarian ablation. Tamoxifen has also been found to be equally as effective as ovarian ablation, regardless of the degree of circulating estrogen levels. A meta-analysis of four randomized trials that involved 506 premenopausal women compared a GnRH agonist alone or combined with tamoxifen and found a 22% reduction in the risk of death and a 30% reduction in the risk of disease progression/death with the combination.[310] Patients whose disease initially responds to combination OFS and tamoxifen can subsequently be treated similarly to postmenopausal women. In this scenario, medical OFS should continue throughout the duration of such endocrine therapy; a bilateral oophorectomy may be pursued as an alternative.

In postmenopausal women, third-generation AIs (letrozole, anastrozole, and exemestane) have been shown to be superior to tamoxifen as first-line therapy for hormone-responsive metastatic disease in a meta-analysis and are associated with an 11% reduction in the risk of death.[311,312] On an individual basis, selective AIs were found to be superior to tamoxifen in terms of overall disease response rate, time to treatment failure, and clinical benefit. Unless disease progression occurred on or soon after the completion of adjuvant AI therapy, the AIs historically (before 2015) were the recommended choice for first-line endocrine therapy for

postmenopausal women.[312-314] For patients who experienced progression while taking an AI, tamoxifen or fulvestrant were often used as first-line therapy. Data also demonstrate that switching from a nonsteroidal AI (letrozole or anastrozole) to a steroidal AI (exemestane) could result in a modest disease response, suggesting a component of non–cross-reactivity.[315] Studies presented/published in 2015–2016, however, challenged the role of single-agent AI as recommended first-line therapy.

An important pathway for facilitating disease responses with endocrine therapy involves cyclin-dependent kinases (CDKs) 4 and 6. In February 2015, the FDA granted accelerated approval for palbociclib, a CDK4/6 inhibitor that blocks progression of the cell cycle from G1 to S phase. This approval was based on the results of a randomized phase II trial (PALOMA-1) of palbociclib plus letrozole versus letrozole alone as first-line therapy in 165 postmenopausal patients with ER-positive metastatic breast cancer.[316] Investigator-assessed PFS essentially doubled for patients who received palbociclib (HR, 0.49; 95% CI; 0.31, 0.74). Response rates were also increased. The final OS results were presented at ASCO 2017.[317] Median OS was 37.5 months (95% CI; 31.4, 47.8) for combination therapy, compared with 34.5 months (95% CI; 27.4, 42.6) for letrozole alone (HR, 0.897; 95% CI; 0.623, 1.294; p = 0.281). The phase III PALOMA-2 trial confirmed these findings with an improvement in median PFS from 14.5 months with letrozole alone to 24.8 months for the combination therapy (HR for disease progression or death, 0.58; 95% CI; 0.46, 0.72; p < 0.001).[318] Confirmed ORRs were also higher for the combination therapy (55%) as compared with letrozole alone (35%). OS data were immature at the time of the initial publication. As compared to letrozole alone, the combination therapy was associated with higher levels of neutropenia (rate of grade 3 or 4 events, 65%), febrile neutropenia (1.8%), thrombocytopenia, anemia, and alopecia. Dose reductions for palbociclib occurred in 36% of patients. The PALOMA-2 results led to full FDA approval of palbociclib in combination with an AI as first-line therapy. Given the outcomes of the PALOMA-1 and PALOMA-2 trials, the combination of letrozole and palbociclib has been recognized as an option for first-line endocrine therapy.[319]

The phase III MONALEESA-2 trial evaluated letrozole with placebo or in combination with a different CDK4/6 inhibitor, ribociclib, as first-line therapy in postmenopausal, hormone receptor–positive, HER2-negative advanced breast cancer.[320] A preplanned interim efficacy analysis demonstrated an improvement in PFS, with a HR of 0.556 (95% CI; 0.429, 0.720; p < 0.0001). The estimated median PFS had not been reached in the ribociclib-containing arm and was 14.7 months in the placebo-containing arm. The ORR in patients with measurable disease was 52.7% (95% CI; 46.6, 58.9) in the ribociclib plus letrozole arm versus 37.1% (95% CI; 31.1, 43.2) in the placebo plus letrozole arm. OS data are immature. These findings supported the 2017 FDA approval of ribociclib in combination with an AI as first-line therapy in this patient population. A third CDK4/6 inhibitor, abemaciclib, has been granted Breakthrough Therapy designation by the FDA by demonstrating significant clinical activity as a single agent and in combination with fulvestrant in early-phase clinical trials among patients with prior progression on endocrine therapy.[321] The results of a phase III registration trial, MONARCH 3, evaluating abemaciclib or placebo in combination with letrozole or anastrozole, are anticipated soon.

Also challenging AI monotherapy for consideration in first-line management is fulvestrant, an analog of 17-beta estradiol, which causes ER disruption and degradation when it binds to the ER, leading to inhibition of estrogen signaling and consequent cellular growth. Unlike other endocrine therapies, fulvestrant is given by monthly intramuscular injection. The CONFIRM trial demonstrated the need to use a loading dose in order to obtain steady-state drug concentrations within the first month of administration; a dose relationship was illustrated with

fulvestrant on PFS as well as OS.[322,323] The phase II FIRST study, which utilized the current standard fulvestrant dose (500 mg), demonstrated a superior time to tumor progression and OS compared with anastrozole in the first-line setting, although the clinical benefit and overall response were comparable.[324] A subsequent phase III FALCON trial confirmed an improvement in PFS with fulvestrant (16.6 months) as first-line treatment compared with anastrozole (13.8 months; p = 0.0488).[324] As a result of these studies, NCCN lists fulvestrant as one of the first-line options.

Fulvestrant has been studied in the PALOMA-3 trial, alone and in combination with palbociclib, after prior progression on endocrine therapy.[325] Notably, premenopausal patients were eligible to participate in this trial and comprised 21% of the overall study population. These patients received OFS concurrently with their assigned therapy. Median PFS was 9.5 months for the combination therapy and 4.6 months for fulvestrant alone (HR, 0.46; p < 0.0001). The safety profile was comparable to that observed in the first-line therapy trials. Hormone receptor expression levels, as well as *PIK3CA* and *ESR1* mutation status, were not associated with treatment response with palbociclib. Current ASCO guidelines support fulvestrant alone or in combination with palbociclib in the second-line clinical setting.[319]

Three studies in postmenopausal women investigated the combination of an AI with fulvestrant as endocrine therapy for recurrent hormone receptor–positive breast cancer. As these trials were initiated prior to the findings from CONFIRM, all studies used the lower dosing regimen for fulvestrant (250 mg per dose). SWOG 0226 randomly assigned patients to first-line therapy with anastrozole alone or combined with fulvestrant.[326] Approximately 60% of the patients enrolled had not been exposed to prior adjuvant endocrine therapy. With a 35-month median follow-up, PFS was longer in those receiving combination endocrine therapy compared with those receiving AI alone (15 months vs. 13.5 months; p = 0.007), as was OS (47.7 months vs. 41.3 months; p = 0.049). These data contrast with the FACT trial, which also randomly assigned patients to first-line therapy with anastrozole alone or combined with fulvestrant.[327] In SWOG 0226, two-thirds of the enrolled patients had received adjuvant tamoxifen. No difference was seen in the primary endpoint of time to progression or with median OS. The phase III SoFEA trial examined patients with disease progression while taking a nonsteroidal AI and randomly assigned them to fulvestrant plus placebo, fulvestrant plus anastrozole, or exemestane.[328] There were no differences in PFS or OS among the three groups. In total, the role of combined AI and fulvestrant is not well established because of the discrepancies previously noted and the availability of newer targeted agents.

A major signaling pathway involved in the development of endocrine resistance is the phosphoinositide-3 kinase (PI3 kinase)–Akt–mTOR pathway.[329] Inhibition of this pathway can occur by targeting mTOR with the rapamycin analogues, everolimus and temsirolimus. The efficacy of adding mTOR inhibitors to endocrine therapy is thought to be due to reversal of endocrine resistance, as evidenced by two trials in metastatic breast cancer, TAMRAD and BOLERO-2. TAMRAD was a phase II trial that involved 111 postmenopausal women whose disease was previously treated with an AI in the adjuvant (41%) and/or metastatic (67%) setting.[330] The primary endpoint of clinical benefit rate—defined as all patients with either a complete (CR), partial disease response (PR), or stable disease at 6 months—was achieved in 61% of patients who received combination everolimus and tamoxifen, compared with 42% who were treated with tamoxifen alone (exploratory p = 0.045). A greater difference in benefit from combination therapy was seen among patients with secondary (acquired) endocrine resistance (74% with combination therapy vs. 48% with tamoxifen alone), which was defined as disease relapse after 6 months of completing adjuvant AI or responding to AI treatment for metastatic

disease for 6 months or longer, compared with patients with primary (de novo) resistance (46% with combination vs. 36% with tamoxifen alone), which was defined as disease relapse during or within 6 months after completing adjuvant or metastatic AI therapy.

The results of the phase III BOLERO-2 trial further supported the hypothesis that everolimus is effective in overcoming endocrine resistance. In this trial, 724 postmenopausal women whose disease progressed or recurred while receiving a nonsteroidal AI were randomly assigned 2:1 to receive either combination everolimus and exemestane or exemestane alone.[331] The median PFS was improved with combination therapy from 4.1 to 10.6 months (HR, 0.36; $p < 0.001$). The added toxicity from everolimus includes a relatively common risk of stomatitis and a low, but potentially serious, risk of pneumonitis. This study led to the 2012 FDA approval of everolimus in combination with exemestane for the treatment of ER-positive, HER2-negative metastatic breast cancer following disease progression during treatment with a nonsteroidal AI.

Other endocrine therapy options for later lines of treatment include megestrol acetate (progestins), fluoxymesterone (androgens), or relatively high doses of estrogen.

Chemotherapy

Chemotherapy is the mainstay of treatment for metastatic hormone receptor–negative breast cancer. It is also indicated in hormone receptor–positive breast cancer in the setting of rapidly progressing or symptomatic disease, disease associated with visceral crisis, and endocrine resistance despite targeted therapeutic drugs (Table 7-8). Sequential use of single-agent chemotherapy is recommended instead of combination chemotherapy regimens, given that the latter are associated with more toxicity without a clear survival benefit. The exception to this rule is in the setting of visceral crisis or rapidly progressive disease that requires prompt cytoreduction[332]; in this setting, the increase in tumor response rates associated with combination chemotherapy may outweigh the added toxicity associated with these regimens.

Table 7-8 **Metastatic Chemotherapy Options**[170,171]		
HER2-Negative Disease	Single Agent	Paclitaxel weekly
		Doxorubicin or pegylated liposomal doxorubicin
		Docetaxel every 21 days
		Nab-paclitaxel (weekly or every 21 days)
		Capecitabine
		Gemcitabine
		Vinorelbine
		Eribulin
		Ixabepilone
		Carboplatin
		Cisplatin
	Combination	Ixabepilone/ capecitabine
		Gemcitabine/ paclitaxel
		Docetaxel/ capecitabine
		Metronomic low-dose cyclophosphamide and methotrexate
HER2-Positive Disease	Pertuzumab, trastuzumab, and taxane	
	T-DM1	
	Paclitaxel weekly and trastuzumab	
	Vinorelbine and trastuzumab	
	Gemcitabine and trastuzumab	
	Capecitabine and lapatinib	

Anthracyclines and taxanes are considered the most active chemotherapies for metastatic breast cancer, although the increased use of both drugs in adjuvant treatment has prompted the development of other non–cross-reacting agents. Single-agent anthracyclines such as doxorubicin and pegylated liposomal doxorubicin are associated with about a 35 to 40% response rate for first-line therapy, the latter being associated with a safer cardiac profile.[333]

Among the taxanes, the most commonly used single-agent drugs include paclitaxel, docetaxel, and nab-paclitaxel, which are associated with an approximately 40% response rate for anthracycline-resistant disease treated in the first-line setting. The optimal schedule varies by taxane, with preference for paclitaxel to be administered weekly and docetaxel every 3 weeks, whereas nab-paclitaxel appears equally effective either weekly or every 3 weeks.[334] A randomized trial that involved 799 patients compared the PFS of first-line therapy with weekly

paclitaxel, nab-paclitaxel, or ixabepilone.[335] The PFS for ixabepilone (7.4 months) was inferior to that for paclitaxel (11.0 months), while the PFS for nab-paclitaxel (9.3 months) was not superior to that for paclitaxel. The safety profile of nab-paclitaxel revealed more hematologic and nonhematologic toxicity, including peripheral neuropathy, when compared with paclitaxel.

Taxane resistance is increasingly common with the general use of taxanes in the adjuvant setting. Several mechanisms of resistance exist, including overexpression and increased activity of the P-glycoprotein drug efflux pump, the development of mutations in the tubulin genes, and alterations in tubulin expression. Several chemotherapeutic agents have been developed in an attempt to overcome these various mechanisms of resistance. Other microtubule-targeting agents, such as the epothilones (e.g., ixabepilone), or the halichondrin B analog, eribulin, have demonstrated antitumor efficacy as second-line or more distant therapies in the setting of both anthracycline- and taxane-resistant disease.[336] In the EMBRACE trial, 762 women who had received between two and five prior chemotherapeutic regimens for metastatic disease, including anthracyclines and taxanes,[337] were randomly assigned to receive single-agent eribulin or the treatment of the attending physician's choice. Patients treated with eribulin achieved a significant improvement in OS (median, 13.1 months vs. 10.6 months).

Other effective single-agent chemotherapies available for the treatment of patients pretreated with anthracyclines and taxanes result in response rates of about 30% and include antimetabolites such as capecitabine (a 5-fluorouracil analog), the nucleoside analog gemcitabine, or the vinca alkaloid vinorelbine. The platinum salts, such as cisplatin and carboplatin, are DNA-damaging agents that appear to be more effective for the treatment of TNBC, particularly *BRCA*-mutant disease.

The anthracyclines contribute to cardiac toxicity on the basis of cumulative dosing and should be avoided in the setting of hyperbilirubinemia. Vinorelbine, ixabepilone, and taxanes increase peripheral neuropathy, with the duration and severity of symptoms dependent on individual risks (e.g., diabetes mellitus) and choice of drug. Caution must be used when capecitabine or platinum agents are administered in the setting of renal dysfunction, and ixabepilone should be avoided in patients with hepatic dysfunction.

The optimal duration of chemotherapy administration for metastatic disease remains unknown. Multiple studies investigating this issue have used regimens that are considered obsolete by today's standards. In general, the continuation of chemotherapy may result in prolonged DFS, especially in the first-line setting, but this has not yet translated into a significant improvement in OS. For this reason, the duration of treatment must be tailored to each individual patient, taking into account the toxicity of treatment, control of disease-related symptoms, and quality of life.[338] Patients whose disease is responding well to chemotherapy without significant toxicity do not need to stop after a prescribed number of cycles, whereas chemotherapy "holidays" are appropriate for patients who require time to recover from toxicity and whose disease may still be responsive to less-toxic targeted therapy, such as endocrine therapy or HER2-directed therapy. Patients with hormone receptor–positive or HER2-positive disease who achieve an adequate response can reasonably discontinue chemotherapy and begin or continue a targeted treatment, such as endocrine therapy or HER2-directed therapies, allowing for a break from chemotherapy-related toxicity.

The phase III OlympiAD trial evaluated the PARP inhibitor olaparib as monotherapy compared with chemotherapy in patients with germline *BRCA*-mutant, HER2-negative advanced breast cancer.[339] All 302 patients had received prior anthracycline- and taxane-based chemotherapy and none were allowed to have had progression on prior platinum chemotherapy. They were randomly assigned 2:1 to olaparib or single-agent chemotherapy of physician choice

(capecitabine, eribulin, or vinorelbine). Olaparib was associated with an ORR of 60% and a superior median PFS of 7.0 months compared with an ORR of 29% and a median PFS of 4.2 months for patients receiving conventional chemotherapy (HR; 0.58; p = 0.0009). There were more low-grade adverse events in those receiving olaparib (primarily nausea and vomiting), whereas there were more high-grade adverse events in those receiving chemotherapy (primarily neutropenia).

HER2-Directed Therapy

Pertuzumab and trastuzumab both target the extracellular domain of HER2; trastuzumab binds to subdomain IV and disrupts ligand-independent downstream signaling, whereas pertuzumab binds to subdomain II, which blocks dimerization of HER2 and subsequent ligand-dependent signaling. The CLEOPATRA trial assessed the added benefit of pertuzumab to combination docetaxel and trastuzumab for first-line treatment of metastatic, HER2-positive breast cancer.[340] This phase III trial randomly assigned 808 patients to receive pertuzumab, trastuzumab, and docetaxel (PTD) compared with trastuzumab and docetaxel with placebo (TD). The primary endpoint of PFS was significantly improved among patients who received both HER2-targeting agents and docetaxel compared with TD (18.5 months vs. 12.5 months; HR, 0.62; p < 0.001). A 6-month improvement in PFS was also seen in the subgroup that had been exposed to adjuvant trastuzumab. The ORR was superior in the PTD arm compared with the TD arm (80.2% vs. 69.3%, p = 0.001), as was the OS, with a 34% reduction in the risk of death with PTD compared with TD (p = 0.0008).[341] In June 2012, the FDA approved combination pertuzumab, trastuzumab, and either docetaxel or paclitaxel as the taxane backbone for first-line therapy of HER2-positive metastatic breast cancer. The final survival analysis in this trial revealed that PTD was associated with a median OS of 56.5 months, which compared with TD translated to an impressive absolute gain in OS of 15.7 months (hazard ratio favoring the pertuzumab group, 0.68; 95% CI; 0.56, 0.84; p < 0.001).[342] The PTD regimen is considered optimal first-line therapy per ASCO guidelines.[305]

Single-agent trastuzumab administered in the metastatic setting provides an ORR of 15 to 26%. The addition of chemotherapy to trastuzumab for first-line treatment improves this rate to 60 to 70%, regardless of which of several types of chemotherapy is administered (e.g., vinorelbine, docetaxel, weekly paclitaxel, or combination taxane plus carboplatin). Early studies that evaluated the efficacy of early administration of combination trastuzumab and chemotherapy in metastatic disease demonstrated an improvement in OS, specifically 1-year OS. The dramatic disease response observed when trastuzumab was added to chemotherapy for the treatment of metastatic HER2-positive disease prompted oncologists to empirically continue trastuzumab when progressive disease dictated a change in chemotherapy. The GBG 26/BIG 3-05 study subsequently confirmed the benefit of continuing trastuzumab with alternative chemotherapy following disease progression with combination chemotherapy and trastuzumab.[343] In this trial, 156 patients were randomly assigned to receive capecitabine alone or capecitabine with continued trastuzumab following disease progression during treatment with first-line trastuzumab or trastuzumab plus chemotherapy. The continuation of trastuzumab with capecitabine resulted in an improvement in PFS, but not OS; however, in further evaluation, allowing for crossover and the effects of third-line therapy, OS was significantly improved in those who continued administration of trastuzumab compared with those who did not.

Lapatinib, a dual tyrosine kinase inhibitor of epidermal growth factor receptor 1 (EGFR-1) and HER2, is also effective in the treatment of HER2-positive metastatic breast cancer, when

administered either in combination with trastuzumab or in combination with capecitabine.[344,345] Combination lapatinib plus capecitabine following disease progression during treatment with trastuzumab resulted in a doubling of the time to tumor progression compared with capecitabine alone.

Trastuzumab emtansine, T-DM1, is an antibody-drug conjugate of trastuzumab and the chemotherapy agent, DM1, a derivative of maytansine, which causes microtubule inhibition. The EMILIA study evaluated the effect of T-DM1 on PFS and OS, compared with combination lapatinib and capecitabine, among 991 patients with HER2-positive metastatic breast cancer whose disease had progressed following treatment with trastuzumab and a taxane.[346] Treatment with T-DM1 resulted in a 12.8% improvement in ORR, a 3-month improvement in PFS (HR, 0.65; 95% CI; 0.55, 0.77; $p < 0.001$), and a 32% reduction in the risk of death (HR, 0.68; 95% CI; 0.55, 0.85; $p < 0.001$) compared with lapatinib and capecitabine; this resulted in FDA approval of T-DM1 in 2013. The differences in PFS and OS in favor of T-DM1 were both highly significant. T-DM1 was also less toxic than the combination of capecitabine and lapatinib. The MARIANNE trial demonstrated no improvement in PFS when pertuzumab was combined with T-DM1 as first-line therapy for HER2-positive metastatic breast cancer.[347] Furthermore, T-DM1 alone or combined with pertuzumab did not result in superior PFS as compared with taxane-based chemotherapy with trastuzumab. The T-DM1 regimens were, however, associated with no febrile neutropenia and less neuropathy, diarrhea, and alopecia. A third trial, the TH3RESA study, involved 602 patients with recurrent, HER2-positive breast cancer and were randomly assigned to T-DM1 or to the treatment of physician's choice.[348] Approximately 30% of the patients enrolled had received more than five prior regimens for recurrent disease. The primary endpoint was PFS and was in favor of T-DM1, with an HR of 0.53 ($p < 0.0001$). The superiority of T-DM1 was also seen among patients who had received prior trastuzumab. Based on the consistent results from the EMILIA and TH3RESA studies, T-DM1 offers an effective and tolerable option for the treatment of HER2-positive disease that has progressed following trastuzumab and taxane chemotherapy, and it is recommended as a second-line treatment per ASCO guidelines.[305]

Approximately 45% of HER2-positive breast cancer is also hormone receptor–positive, which allows targeted therapy for both to be incorporated into the treatment of metastatic disease. Cross-talk exists between HER2 and the ER, resulting in relative resistance to endocrine therapy alone. The addition of trastuzumab to anastrozole, and lapatinib to letrozole, significantly improved PFS and clinical benefit compared with endocrine treatment alone in patients with hormone receptor–positive, HER2-positive metastatic disease; however, an OS advantage was not seen, likely because of the crossover study designs.[349]

KEY POINTS

- Metastatic breast cancer is primarily incurable; therefore, the goal of treatment is to control disease progression and improve quality of life.
- The choice of systemic therapy is based on the hormone receptor and HER2 status, as well as on the extent of metastatic disease, effect of disease on the patient's quality of life (i.e., symptoms and performance status), and pace of the metastatic disease.
- Endocrine therapy is the preferred initial treatment for hormone receptor–positive, HER2-negative metastatic disease unless visceral crisis or extensive visceral involvement is

present.

- Sequential single-agent chemotherapy is preferable to combination chemotherapy unless a rapid disease response is required.
- Combination pertuzumab, trastuzumab, and taxane therapy is the recommended first-line treatment for HER2-positive metastatic disease.
- Trastuzumab emtansine, an antibody-drug conjugate, is effective treatment for recurrent HER2-positive disease after progression during treatment with trastuzumab.

Bone-Modifying Agents

Approximately 65 to 80% of patients with metastatic breast cancer will have disease manifestation in the bone, most commonly among the hormone receptor–positive cancer subtype. Although bone involvement is associated with a more favorable prognosis than visceral metastases, patients are at higher risk of skeletal-related events (SREs) or other complications occurring over time, such as pathologic fracture, cord compression, pain, hypercalcemia, and the need for surgical interventions. Breast cancer that metastasizes to bone is treated with appropriate systemic therapy. Palliative radiation therapy to specific sites of disease can reduce the morbidity associated with pain and fracture, as well as control disease that may compromise the spinal cord.

Breast cancer that metastasizes to bone can produce osteoblastic or osteolytic bone lesions, both of which are associated with activation of osteoclasts. Breast cancer cells involving the bone can also secrete cytokines that stimulate receptor activator of nuclear factor kappa B ligand (RANKL) secretion by osteoblasts, which mediates osteoclast survival. Bisphosphonates are pyrophosphate analogs that are internalized by osteoclasts, which disrupt their function and result in apoptosis. Clinically available bisphosphonates (e.g., pamidronate and zoledronate) have been shown to reduce the incidence of SREs, the time to the occurrence of SREs, and pain.[350] Denosumab, a humanized monoclonal antibody to RANKL, delayed the advent of SREs by 18% over zoledronic acid among 2046 women with metastatic breast cancer.[351] Zoledronic acid use was associated with renal compromise, whereas hypocalcemia was more common with denosumab. Calcium and vitamin D supplementation should be employed for patients receiving bone-modifying agents, while renal function should be monitored in patients receiving bisphosphonates. Both drugs are associated with a 2% incidence of osteonecrosis of the jaw; ideally, physicians should avoid administering these agents to patients, for an undefined period of time, before or after any invasive dental procedure that involves manipulation of the bone. These agents should be considered once lytic bone metastases are diagnosed (see Chapter 21 Symptom Management). The optimal dosing intervals were not well studied until recently, when dosing interval studies were reported for zoledronate. Although recommendations had been monthly for both agents, results from a randomized trial that evaluated the use of the second year of zoledronate, following a year of monthly dosing demonstrated that dosing zoledronate monthly was equivalent to dosing every 3 months.[352] A randomized trial that compared up-front zoledronate at monthly versus 3-monthly intervals for 2 years also demonstrated equivalence.[353] Similar data are not available for denosumab, and the different mechanisms of action for denosumab and zoledronate do not allow for one to assume that the data would be similar for these two drugs. The optimal duration of treatment with either a bisphosphonate or denosumab is unknown, since the

therapeutic intervals in published studies vary from 3 months to indefinitely. Two years may be a reasonable duration for this treatment.[353]

Multiple clinical trials have been conducted to determine the role of bisphosphonates given in the adjuvant setting in an attempt to reduce the development of metastatic disease. Conflicting data exist, as the AZURE trial exhibited no effect of zoledronic acid on DFS among 3360 patients with stages II and III disease treated with chemotherapy, whereas the ABCSG-12 study demonstrated a 36% reduction in risk of disease recurrence among 1803 premenopausal women with stages I and II disease treated with ovarian suppression and endocrine therapy alone.[354,355] A meta-analysis of 13 studies that investigated the role of adjuvant bisphosphonates showed no impact on DFS or OS; however, there was a trend of improved DFS and a reduction in risk of death among postmenopausal women.[356] A subsequent meta-analysis of 17 trials and data from more than 21,000 patients demonstrated a 3.5% absolute reduction in the risk of distant relapse, predominantly bone metastatic relapse, as well as a 2.3% absolute improvement in all-cause mortality (OS) among postmenopausal women who received adjuvant bisphosphonate treatment.[357] In 2017, Cancer Care Ontario and ASCO published evidence-based recommendations, based on a systematic review of the literature.[358] The review determined that adjuvant bisphosphonates (either zoledronic acid 4 mg IV every 6 months or clodronate 1600 mg once daily orally) reduce the risk of recurrence and improve survival in patients who are postmenopausal by natural menopause or by ovarian suppression or ablation. The review also noted that long-term survival data for adjuvant denosumab are still lacking. It is recommended that adjuvant bisphosphonates be considered as adjuvant therapy for postmenopausal patients who are deemed candidates for systemic therapy.

KEY POINTS

- Bisphosphonates or denosumab decrease SREs when bone metastases are present.
- Adjuvant bisphosphonates have been associated with a reduction in risk of recurrence and improvement in OS. They should be considered for postmenopausal patients who are candidates for adjuvant systemic therapy.
- Renal function should be monitored with bisphosphonate use.
- Calcium and vitamin D supplementation should be strongly considered for patients receiving bone-modifying agents.

SPECIAL CIRCUMSTANCES

MALE BREAST CANCER

Like female breast cancer, most male breast cancers are of ductal origin (85 to 95%). The rate of hormone receptor expression is in excess of 90%, higher than what is observed in female breast cancer.[359] Male patients with breast cancer are usually diagnosed at a later disease stage compared with female patients. Local therapy is often mastectomy because of anatomical constraints, although BCT can be offered if standard criteria for BCT are met (see the Local Disease Control section under Stages I and II Disease). Recommendations for local disease treatment should be governed by the same criteria outlined for breast cancer in women.

Adjuvant therapy also should be administered using the same criteria as those used for women because randomized clinical trial data that specifically inform the treatment of men are not available. Adjuvant chemotherapy may be beneficial only in men with higher-grade and higher-stage cancers. Tamoxifen, however, is the mainstay of endocrine therapy in hormone receptor–positive male breast cancer. Few data exist to support the use of AIs alone or combined with LHRH agonists for adjuvant treatment among men. AI use may be best administered with medical (LHRH agonist) or surgical orchiectomy. In the metastatic setting, there are case reports of responses with an AI alone and in combination with an LHRH agonist. Although most clinicians favor the combination in this setting, and this is supported by biologic data, it is acceptable to start with an AI alone and follow closely.

ELDERLY PATIENTS

There has been a dramatic increase in breast cancer in older adults in the United States, with an expected increase to 72 million adults older than age 65 by 2030. Since more than one-half of all breast cancer diagnoses occur among older women, there is an expectation that this population will become more prevalent in the realm of oncologic care. The current life expectancy of a 70-year-old woman is 17.5 years, which is sufficient time for a high-risk breast cancer to recur. An assessment of comorbidities is essential, since more than 50% of patients older than age 50 have at least one comorbidity, and this percentage increases to 66% among patients older than age 75. Comorbidities are independent predictors of worse survival; however, among healthy elderly women, newer chemotherapy regimens, given without dose reduction, impart the same relative benefit as in younger women.[360] Older women can be more susceptible to some toxicities associated with chemotherapy. Hematologic toxicity is more common, often leading to dose reductions of chemotherapy, which may compromise outcome. Women older than age 65 have a 26% higher risk of congestive heart failure associated with anthracycline use.[361] An adequate interpretation of chemotherapy benefit among high-risk elderly women is difficult to make given that women older than age 65 comprise 8% of enrollment in clinical trials. The CALGB 49907 trial randomly assigned 633 women older than age 65 to receive adjuvant therapy with capecitabine compared with AC or CMF.[362] Two-thirds of the women were older than age 70, and 5% were older than age 80. The standard regimens of AC and CMF were associated with a 50% lower risk of recurrence or death compared with the *less toxic* oral capecitabine regimen. These data continue to support the benefit of standard chemotherapy in healthy elderly women who do not have substantial comorbidities.

PHYLLODES TUMOR

Phyllodes tumors of the breast are similar to fibroadenomas in that they contain both stromal and epithelial components. They are classified as benign, borderline, or malignant. Their prognosis depends largely on the status of surgical margins after resection. The greatest risk of recurrence is local, although metastasis can occur, primarily to the lungs. The primary treatment of a phyllodes tumor is surgical—either with excision or mastectomy, with both requiring generous negative margins (> 1 cm). ALND is not indicated, neither is routine adjuvant systemic therapy or radiotherapy. Because this tumor acts primarily like a stromal malignancy, options for the treatment of metastatic disease can be based on therapies for soft-tissue sarcomas.

KEY POINTS

- The treatment of male breast cancer is extrapolated from information about female breast cancer, with tamoxifen as the preferred agent for adjuvant endocrine therapy.
- There are limited data supporting the use of AIs for the treatment of metastatic disease in men.
- Performance status and comorbidities, but not age, should be the deciding factors for adjuvant therapy recommendations for male breast cancer.

SURVEILLANCE AND SURVIVORSHIP

With the increasing ability to detect earlier-stage breast cancer and the greater efficacy of adjuvant therapy, more women with breast cancer are expected to live long and prosperous lives following their diagnosis and treatment. Consequently, surveillance plans and survivorship issues play a large role in ongoing patient care. The primary goal of surveillance after completion of adjuvant therapy is to detect a new and curable cancer at an early stage (Table 7-9). Routine history and physical examinations and annual mammographic screening are important features of follow-up. ASCO recommendations for surveillance include a history and physical exam every 3 to 6 months for the first 3 years, then every 6 months for the next 2 years, then annually.[363] When breast conservation is used for local therapy, mammographic imaging of the affected breast should occur about 6 months after the completion of radiation therapy (which is often approximately 1 year after diagnosis) and then continue annually once mammographic stability is observed. There are no good data to support supplementary breast imaging in most breast cancer survivors, with exceptions being in women with hereditary breast cancer syndromes or those who had significant medical radiation exposure.

Table 7-9 **ASCO Recommendations for Follow-up Care of Patients with Primary Breast Cancer**

Mode of Surveillance	Summary of Recommendations
Recommended breast cancer surveillance	
History/physical examination	Every 3 to 6 months for the first 3 years after primary therapy; every 6 to 12 months for years 4 and 5; then annually
Patient education regarding symptoms of recurrence	Physicians should counsel patients about the symptoms of recurrence, including new lumps, bone pain, chest pain, abdominal pain, dyspnea, or persistent headaches; helpful websites for patient education include www.cancer.net and www.cancer.org
Referral for genetic counseling	Criteria include Ashkenazi Jewish heritage; history of ovarian cancer at any age in the patient or any first- or second-degree relatives; any first-degree relative with a history of breast cancer diagnosed before age 50; two or more first- or second-degree relatives diagnosed with breast cancer at any age; patient or relative with diagnosis of bilateral breast cancer; and history of breast cancer in a male relative
Breast self-examination	All women should be counseled to perform monthly breast self-examination
Mammography	First posttreatment mammogram 1 year after the initial mammogram that leads to diagnosis but no earlier than 6 months after definitive radiation therapy; subsequent mammograms should be obtained as indicated for surveillance of abnormalities
Coordination of care	Continuity of care is encouraged and should be performed by a physician experienced in the surveillance of patients with cancer and in breast examination, including the examination of irradiated breasts; if follow-up is transferred to a primary care physician (PCP), the PCP and the patient should be informed of the long-term options regarding adjuvant hormone therapy for the particular patient; this may necessitate referral for oncology assessment at an interval consistent with guidelines for adjuvant hormone therapy
Pelvic examination	Regular gynecologic follow-up is recommended for all women; patients who receive tamoxifen should be advised to report any vaginal bleeding to their physicians
Breast cancer surveillance testing: not recommended	
Routine blood tests	Complete blood counts and liver-function tests are not recommended
Breast MRI	Breast MRI is not recommended for routine breast cancer surveillance; MRI may be considered on an individual basis for high-risk women
Systemic imaging studies	Chest x-ray, bone scans, liver ultrasound, computed tomography (CT) scans, and fluorodeoxyglucose positron-emission tomography (FDG-PET) scans are not recommended
Tumor markers	CA 15-3, CA 27-29, and carcinoembryonic antigen testing are not recommended

The use of nonbreast imaging, tumor markers, or laboratory tests among asymptomatic patients has not been found to be beneficial and has been shown to adversely affect quality of life and increase downstream healthcare utilization.[364] Despite this, these tests, unfortunately, are commonly utilized in clinical practice. Most breast cancer recurrences are often identified between office visits; therefore, it is crucial to focus on patient education concerning signs and symptoms of disease recurrence. Once symptoms occur, appropriate imaging should be performed. The surveillance time should also be used to ensure that appropriate referrals for genetic counseling are made. Screening for second primary cancers among patients with genetic risks should occur, as outlined in the previous section on Screening.

Clinical outcomes have been shown to be identical when patients continue their posttreatment surveillance with either their oncologist or primary care provider. This emphasizes the need to understand other women's health issues in addition to breast cancer. Understanding potential long-term complications of treatment is also important. Chemotherapy-

induced amenorrhea or ovarian suppression can result in the onset of menopausal symptoms at an earlier-than-expected age. Hot flashes can often be controlled with venlafaxine or gabapentin, whereas the use of intravaginal estrogens to improve vaginal dryness and sexual dysfunction requires ongoing discussions with patients. Intravaginal DHEA has recently been demonstrated to be another option for treating vaginal dryness/dyspareunia.[365] The use of AIs can adversely affect bone density, which should be closely monitored. Awareness of potential cardiac toxicity from anthracyclines and trastuzumab may require the involvement of cardiologists. Focusing on good health activities, such as exercise and maintaining a normal BMI, appear to favorably impact the risk of disease recurrence. Cognitive dysfunction associated with cancer therapy is a subject of ongoing investigation. The psychosocial ramifications following the diagnosis and treatment of breast cancer cannot be minimized and may require ongoing support and therapy. In 2016, ASCO and the American Cancer Society developed a comprehensive set of guidelines that extend beyond cancer surveillance recommendations to further address symptom management, surveillance and management of late toxicities of cancer therapy, and general wellness (weight management, nutrition, activity, etc.) recommendations.[366]

KEY POINTS

- A complete history and physical examination with annual mammography is the primary schedule of disease monitoring after the completion of therapy.
- Anthracyclines and trastuzumab are associated with a risk of cardiac toxicity.
- AIs are associated with decreased bone density.
- Chemotherapy can result in premature amenorrhea, resulting in menopausal symptoms such as hot flashes, vaginal dryness, and sexual dysfunction.

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LUNG CANCER

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Recent Updates

- Important advances in immunotherapy for lung cancer continue to occur. The U.S. Food and Drug Administration (FDA) approved the anti–programmed cell death 1 (PD-1) antibody pembrolizumab for the treatment of advanced non-small cell lung cancer (NSCLC) as first-line treatment for NSCLC that harbors PD-1 ligand (PD-L1) expression ≥ 50%. (Reck M, *N Engl J Med* 2016)
- The ALK inhibitor alectinib was approved, on the basis of high response rates and prolonged progression-free survival, for the treatment of advanced ALK-rearranged NSCLC after disease progressed while being treated with crizotinib. (Larkins E, *Clin Cancer Res* 2016)

OVERVIEW

An estimated 222,500 new cases of lung cancer were expected in 2017, leading to approximately 155,870 deaths.[1] Although lung cancer accounts for approximately 13% of all cancer diagnoses, it is responsible for about 26% of all cancer deaths. Thus, unlike with breast, colon, and prostate cancers, most patients (about 84%) who are diagnosed with lung cancer will die of the disease. Lung cancer is the leading cause of cancer deaths for both men and women.[2] More women die of lung cancer each year than of breast, cervical, and uterine cancers combined; indeed, nearly twice as many women in the United States die from lung cancer than from breast cancer. More men die annually of lung cancer than of colorectal and prostate cancers combined. The incidence and death rates from lung cancer have been decreasing for men, and these numbers were rising for women until about 2000 and have since been leveling off.

The major cause of lung cancer is smoking. Numerous epidemiologic and laboratory studies, as well as in vitro data, have tied the present pandemic of lung cancer to the carcinogenic effects of tobacco smoke. Some data suggest that women with lung cancer who smoke and who are undergoing hormone-replacement therapy experience a less favorable outcome than those who are not undergoing such therapy.[3]

The incidence of lung cancer, although declining for both white and black men, is approximately 20% higher for black men.[2] Race-related variances in lung cancer, however, are complicated by differences in socioeconomic status, which are associated with disparities in smoking rates, types of cigarettes smoked, and exposures to inhaled agents in the workplace. In the United States, the most common form of lung cancer was squamous cell cancer until approximately 1987, when it was supplanted by adenocarcinoma. Small cell lung cancer once accounted for approximately 20% of all lung cancers, but its incidence has been declining, as

has large cell histology.[4]

KEY POINTS

- Lung cancer is the most common cause of cancer-related deaths in the United States for both men and women, and most patients (approximately 84%) will die of the disease.
- The epidemiology of lung cancer in the United States is changing somewhat, with a decrease in the incidence among men but an increase in women over the past 25 years, which has been leveling off since 2000. There also is a decrease in large cell and small cell histologic subtypes with an increase in the proportion of adenocarcinoma for both men and women.

ETIOLOGY

Cigarette smoking is the most common cause of lung cancer and is responsible for approximately 85% of all cases. Other risk factors include occupational or environmental exposure to substances such as arsenic, chromium or nickel, radon, air pollution, radiation, and environmental (secondhand) tobacco smoke.

The risk of lung cancer among cigarette smokers increases with the number of cigarettes smoked and the duration of smoking history—the latter of which is a stronger risk factor than the number of cigarettes smoked per day. A tripling of the number of cigarettes smoked per day is estimated to triple the risk of lung cancer, whereas a tripling of the duration of smoking is estimated to increase the risk 100-fold.[5] Of note, moderate- to high-intensity smoking (defined as ≥ 10 cigarettes per day) has dramatically declined in the United States since the 1960s.[6] The risk of lung cancer decreases with smoking cessation, and it approaches that of the nonsmoking population after 10 to 15 years of abstinence. However, one study among women reported that even after 30 years, the risk was not as low as for the population who had never smoked.[7] It is estimated that approximately half of all lung cancers in the United States occur in former smokers. The risks associated with e-cigarettes and their role in controlling tobacco use still require clarification.[8]

Passive smoking also is a risk factor; the risk of lung cancer for nonsmoking spouses of cigarette smokers is approximately 20 to 30% higher than the risk for nonsmoking spouses of nonsmokers.[5] It has been estimated that approximately 25% of lung cancer cases among never-smokers are caused by exposure to environmental tobacco smoke.[5] Nevertheless, data on molecular profiling of cancers from never-smoking patients show a very different pattern of abnormalities from those associated with smoking (*p53* and certain *KRAS* mutations), with a high incidence of mutations in the epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) fusions, as described in this chapter. These data suggest that the proportion of patients with lung cancer attributed to secondhand smoke may have been overestimated.[9]

Cigarette smoke contains thousands of constituents, many of which are carcinogenic. Two of the major classes of nicotine-related inhaled carcinogens include the polycyclic aromatic hydrocarbons and *N*-nitrosamines, which are metabolized to nitrosamine ketone and *N*′-nitrosonornicotine. Both compounds are activated by the cytochrome P450 enzyme system and exert carcinogenic effects through the formation of DNA adducts. The distribution of

benzo(a)pyrene diol epoxide adducts along the exons of the *TP53* gene occurs preferentially in codons 157, 248, and 273, which are the same mutational hot spots of *TP53.* Nitrosamine ketone has been postulated to be one factor that leads to the increased incidence of adenocarcinomas, because it predominantly induces these tumors in mice.[5]

Smoking causes each of the four major subtypes of lung cancer, although the dose–response relationship is steepest with small cell lung cancer. Indeed, small cell lung cancer is a disease that is found almost exclusively in smokers. Although adenocarcinoma in situ (AIS) is more likely to develop in nonsmokers than the other subtypes of lung cancer, smoking is still the major risk factor for this form of the disease.

Cigar smoking also is associated with an increased risk of lung cancer, although the risk is not as high as with cigarette smoking, most likely because cigar smokers do not inhale as deeply as do cigarette smokers. Similarly, risks related to pipe smoking also are lower because of differences in smoking frequency and depth of inhalation. Light cigarettes provide no benefit compared with other cigarettes; the lower tar and nicotine numbers on light cigarette packs and in advertisements are misleading because the low tar and nicotine levels recorded on smoking machines are artificial.[10]

Radon is a naturally occurring, chemically inert gas that is a decay product of uranium. The relative risk of lung cancer is increased for underground miners who are exposed to high levels of radon. For underground miners who smoke, the risk may exceed 10 times the risk for a nonsmoking miner. The relationship between indoor residential radon exposure and lung cancer risk is less well defined, although it is estimated that 2 to 10% of lung cancers may be caused by exposure to residential radon.[11] Exposure to asbestos combined with smoking acts to increase the risk of lung cancer. High doses of radiation also have been associated with an increased risk of lung cancer. For example, an increased risk has been observed for patients with breast cancer, as well as for long-term survivors of Hodgkin and non-Hodgkin lymphomas, particularly if patients continue to smoke after completing radiation therapy.

KEY POINTS

- Most cases of lung cancer (85%) are caused by carcinogens in tobacco smoke; a small percentage of cases are caused by passive smoking or exposure to radon, radiation, or other chemicals.
- Host differences may account for different susceptibilities to lung cancer.

HOST FACTORS

Genetic susceptibility to lung cancer has been postulated based on the fact that cigarette smoking causes lung cancer in a minority of people who smoke. Because many carcinogens in tobacco smoke are metabolized by the cytochrome P450 system—such as the polycyclic aromatic hydrocarbons—differences in subtypes or polymorphisms of these enzymes have been proposed as one mechanism of lung cancer risk. Other factors that may increase risk for some individuals include differences in glutathione *S*-transferase, an enzyme that detoxifies reactive metabolites of polycyclic aromatic hydrocarbons, and enzymes that modulate DNA repair capacity.

Epidemiologic studies have shown that a family history of lung cancer is a predictor of

increased risk. Familial aggregation of lung cancer has led to the hypothesis that there is a genetic susceptibility for lung cancer.[12] This may be related to inherited differences in carcinogen metabolism and activation and also to DNA repair capacity. For example, leukocyte DNA adduct levels have been associated with the risk of lung cancer, with an odds ratio (OR) of 1.86 (95% CI; 0.88, 3.93), particularly for never-smokers (OR, 4.04; 95% CI; 1.06, 15.42).[13] Germline polymorphisms in genes with products that activate (cytochrome P450 1A1 *[CYP1A1])* or detoxify (glutathione *S*-transferases M1 *[GSTM1]* and T1 *[GSTT1])* chemical carcinogens found in tobacco smoke have been associated with a risk of lung cancer from environmental tobacco smoke that is substantially greater than the risk for individuals who are heterozygous or homozygous carriers of the wild-type *GSTM1* allele.[14] However, some of the results from these studies are conflicting, suggesting that particular polymorphisms may predict increased risks in specific ethnic populations, limiting generalizability. Thus, germline polymorphisms should not be used to predict an individual person's lung cancer risk or for screening purposes. Genomewide association studies (GWAS) have identified the N allele of the D398N polymorphism of the nicotinic acid/acetylcholine receptor as well as polymorphisms in the reverse transcriptase component of telomerase (TERT) as potential increased risk factors for lung adenocarcinoma.[15] However, these results must also be interpreted with caution because the GWAS studies were not based on a functional hypothesis and therefore these alterations may not represent "drivers" of carcinogenesis.

The R331W missense mutation in *YAP1* was identified as a germline risk allele for lung adenocarcinoma, increasing the odds ratio of lung adenocarcinoma 5.9-fold. The *YAP1* oncogene plays an important role in the Hippo pathway, binding and activating many transcription factors that contribute to tumorigenesis.[16] The EGFR-T790M mutation, most frequently associated with resistance to EGFR–tyrosine kinase inhibitor (TKI), can also be present less frequently *de novo* and as a germline risk allele for lung cancer.[17] Detection of tumor EGFR-T790M before treatment with EGFR-TKI can be used to screen for familial EGFR-T790M and lead to suitable patients being referred for genetic counseling.[18]

Additional factors associated with increased lung cancer risk include previous lung damage, such as chronic obstructive pulmonary disease, and fibrotic disorders that restrict lung capacity, such as pneumoconiosis. Diets deficient in vitamins A and C and beta-carotene intake also have been associated with increased risk, whereas fruit and vegetable consumption may be weakly protective.

Preclinical evidence has suggested that higher dietary intake of retinol is associated with a decreased risk of lung cancer. Based on this evidence, three double-blind, placebo-controlled chemoprevention trials were conducted with beta-carotene, vitamin A, or one of their derivatives. A protective effect against lung cancer was not observed in any of the studies. Rather, beta-carotene supplementation was associated with an increased risk of lung cancer among high-risk populations of heavy smokers in two of the three trials.[19-21]

PATHOLOGY

More than 95% of lung cancers consist of one of the four major histologic types: squamous, adenocarcinoma, large cell, or small cell. Small cell lung cancer has scant cytoplasm, small hyperchromatic nuclei with a fine chromatin pattern, and indistinct nucleoli with diffuse sheets of cells, whereas non-small cell lung cancer (NSCLC) has abundant cytoplasm, pleomorphic nuclei with a coarse chromatin pattern, prominent nucleoli, and glandular or squamous architecture. Other subtypes, which are rare and therefore less well studied, include carcinoid, large cell

cancer with neuroendocrine features, and large cell neuroendocrine cancer.[22] Extremely rare primary tumors in the lung include sarcomas, cancers with sarcomatoid or sarcomatous elements (e.g., giant cell cancer, carcinosarcoma, pulmonary blastoma), and cancers of the salivary gland type (e.g., mucoepidermoid cancer, adenoid cystic cancer).

Adenocarcinoma, large cell cancer, and squamous cell cancer are collectively known as NSCLC. They exhibit differences in sensitivity to chemotherapy and radiation therapy when compared with small cell cancer, which is described in detail later in this chapter. Other clinical differences between small cell cancer and non-small cell cancer include the more rapid clinical course of small cell lung cancer and the enhanced association of small cell lung cancer with paraneoplastic syndromes and neuroendocrine features on pathologic examination. Adenocarcinoma in situ (AIS; discussed in the following section) is a subtype of adenocarcinoma that has received considerable attention because of its tendency to occur in women and in never-smokers.

PREINVASIVE LESIONS

Squamous Dysplasia

Squamous dysplasia may be mild, moderate, or severe, depending on the severity of the atypia and the thickness of the abnormality within the bronchial epithelium. There is increasing interest in using squamous dysplasia as an indicator of heightened risk when identifying patients for participation in chemoprevention studies.

Atypical Adenomatous Hyperplasia

Atypical adenomatous hyperplasia is considered a precursor to adenocarcinoma and is usually identified incidentally, often at the time of resection. The lesions are typically small (a few millimeters) and consist of discrete but ill-defined bronchoalveolar proliferation in which the alveoli are lined by monotonous, slightly atypical cuboidal to low-columnar epithelial cells. Their prognostic significance is unclear.

NON-SMALL CELL LUNG CANCER

Although the natural history of the subtypes of NSCLC differs somewhat when assessed on a stage-by-stage basis, histologic subtype is not a significant prognostic indicator. However, histologic subtype now has an influence on treatment selection, based on different chemosensitivity and safety profiles of squamous and nonsquamous tumors. Immunohistochemical (IHC) staining can help differentiate histology.

Adenocarcinoma

Adenocarcinoma is the most common histologic subtype in the United States and appears to be on the rise, although the reason for this is unknown. It accounts for more than 50% of all NSCLCs, has been associated with scarring, is more likely to be peripherally located than squamous cell or small cell cancer, and tends to metastasize frequently. It consists of four subtypes: acinar, papillary, AIS, and solid with mucus formation. Lung adenocarcinoma typically stains positive for cytokeratin 7 (CK7) and negative for cytokeratin 20 (CK20). The majority (but not all) of pulmonary adenocarcinomas also stain positive for thyroid transcription factor 1 (TTF-1).[23]

AIS (formerly known as “bronchioloalveolar cancer”) is defined as an adenocarcinoma of the

lung that grows in a lepidic fashion along alveolar septae. In the 1999 World Health Organization/International Association for the Study of Lung Cancer (WHO/IASLC) classification, the lack of invasive growth was added as an essential criterion because data suggested that surgical resection might cure disease in such patients. Histologically, pure AIS is rare; more common is adenocarcinoma, mixed subtype, with both AIS features and invasive components. The tumor typically presents in one of two forms: mucinous or nonmucinous. Mucin-producing tumors (30 to 40%) tend to be multicentric and TTF-1–negative and rarely harbor sensitizing *EGFR* mutations. Nonmucinous tumors (50 to 60%) tend to be solitary and TTF-1–positive and have high rates of *EGFR* mutations. This form of lung cancer develops in never-smokers more than the other subtypes. Although the prognosis is excellent for patients with small, solitary nonmucinous tumors, the prognosis for patients with advanced AIS is comparable with prognoses for other lung adenocarcinomas. Of note, small lesions discovered on screening computed tomographic (CT) scans, which are commonly found to have a “ground glass” appearance, are often AIS. The current staging classification is presented in Table 8-1.[24,25]

Table 8-1 **Definitions for Tumor-Node-Metastasis (TNM) Descriptors**[24]

T (Primary Tumor)	
TX	Primary tumor cannot be assessed, or tumor proven, by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* Squamous cell carcinoma *in situ* (SCIS) Adenocarcinoma in situ (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension
T1	Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 in greatest dimension) with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension
T1a	Tumor ≤1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.
T1b	Tumor >1 cm but ≤2 cm in greatest dimension
T1c	Tumor >2 cm but ≤3 cm in greatest dimension
T2	Tumor >3 cm but ≤5 cm or having any of the following features: • Involves the main bronchus regardless of distance to the carina, but without involvement of the carina • Invades visceral pleura (PL1 or PL2) • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung T2 tumors with these features are classified as T2a if ≤4 cm or if the size cannot be determined and T2b if >4 cm but ≤5 cm.
T2a	Tumor >3 cm but ≤4 cm in greatest dimension
T2b	Tumor >4 but ≤5 cm in greatest dimension
T3	Tumor >5 cm but ≤7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary
T4	Tumor >7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary
N (Regional Lymph Node)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M (Distant Metastasis)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial effusion. Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and not an exudate. If these elements and clinical judgement dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
M1b	Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
M1c	Multiple extrathoracic metastases in a single organ or in multiple organs

The original source for this material is the AJCC Cancer Staging Manual, 8th Edition (2017) published by Springer Science and Business Media LLC, www.springerlink.com.

Squamous Cell Cancer

Squamous cell cancers account for approximately 25% of all NSCLCs. These lesions tend to be located centrally and are more likely to cavitate than other histologic types. Squamous cell cancers, which most often arise in segmental bronchi and involve lobar and mainstem bronchi by extension, are recognized by the histologic features of intercellular bridging, squamous pearl formation, and individual cell keratinization. Squamous cell lung cancer often overexpresses squamous histology marker p63 and its isoform p40 as well as CK5/6.[26]

Large Cell Cancer

Large cell cancers account for approximately 10% of all lung cancers, and its incidence is

declining. These tumors are typically poorly differentiated and are composed of large cells with abundant cytoplasm and large nucleoli.

SMALL CELL LUNG CANCER

In the 1999 WHO/IASLC classification, small cell cancer is divided into two subtypes: so-called pure small cell lung cancer and combined histology lung cancer—the latter of which consists of elements of both non-small cell and small cell lung cancers. Histologically, the tumor is characterized by small cells with scant cytoplasm, finely granular nuclear chromatin, and absent or inconspicuous nucleoli. Nuclear molding and smearing of the nuclear chromatin may be present owing to crush artifact. Mitotic figures are common, and necrosis can be extensive. On electron microscopy, the cells may appear to have neuroendocrine granules. Neuroendocrine markers such as chromogranin and synaptophysin are frequently overexpressed.[27] Clinically, these tumors tend to be centrally located, are often found submucosally, and are more commonly associated with paraneoplastic syndromes. Because of the rapid growth and proliferation of these tumors, the clinical course tends to be more rapid than that of NSCLC. However, small cell lung cancers also are more responsive to both chemotherapy and radiation therapy, although resistance usually develops. Small cell lung cancer is on the spectrum of neuroendocrine cancers that consists of typical and atypical carcinoid, large cell, and small cell primary lung tumors.

OTHER PULMONARY NEUROENDOCRINE TUMORS

The normal lung contains neuroendocrine cells, although their significance is unclear. Neuroendocrine lung tumors represent a spectrum of pathologic entities, including typical carcinoid, atypical carcinoid, and large cell neuroendocrine cancer. Small cell lung cancer and large cell neuroendocrine cancer are high-grade neuroendocrine tumors, whereas typical carcinoid and atypical carcinoid are low and intermediate grades, respectively. Neurosecretory granules, particularly chromogranin A and synaptophysin, often are seen on electron microscopy. The presence of chromogranin, synaptophysin, and CD56 (neural cell adhesion molecule [NCAM]) may be detected by IHC. Approximately 20 to 40% of patients with both typical and atypical carcinoids are nonsmokers, whereas virtually all patients with small cell lung cancer and large cell neuroendocrine cancer are cigarette smokers.

Carcinoid Tumors

Carcinoid tumors are low-grade malignant neoplasms of neuroendocrine cells, which are divided into typical and atypical types, with the latter possessing more malignant histologic and clinical features. Surgery is the primary treatment for typical carcinoid tumors. The prognosis is excellent for patients with typical carcinoids.

Compared with typical carcinoids, atypical carcinoids tend to be larger, have a greater number of mitoses, and are associated with necrosis. Patients also are more likely to have distant metastases at presentation, and survival is significantly reduced.

Large Cell Neuroendocrine Cancer

Large cell neuroendocrine cancer is a high-grade, non-small cell neuroendocrine cancer. These tumors are characterized by histologic features similar to small cell cancer but are formed by larger cells. Large cell neuroendocrine cancer is defined as a tumor with neuroendocrine

morphologic characteristics, including organoid nesting, palisading, a trabecular pattern, and rosette-like structures. A mitotic count of 11 mitoses or more per 2 mm^2 is the main criterion for separating large cell neuroendocrine cancers and small cell lung cancers from atypical carcinoid tumors. The mitotic rates are usually high for both large cell neuroendocrine cancers and small cell lung cancers, with an average of 70 to 80 mitoses per 2 mm^2. Large cell neuroendocrine cancers are separated from small cell lung cancers by using the criteria listed in Table 8-2.[28]

Table 8-2 Characteristics of Large Cell Neuroendocrine Tumors That Distinguish Them from Small Cell Lung Cancers[28]

▪ Larger cell size
▪ Abundant cytoplasm
▪ Prominent nucleoli
▪ Vesicular or coarse chromatin
▪ Polygonal rather than fusiform shape
▪ Less prominent nuclear molding
▪ Less conspicuous DNA encrustation of blood vessel walls

Large cell cancers with neuroendocrine morphology are tumors that resemble large cell neuroendocrine tumors on light microscopy but lack proof of neuroendocrine differentiation on electron microscopy or IHC. The significance of this histology is unknown.

The prognosis for patients with large cell neuroendocrine cancer is worse than that for patients with atypical carcinoid and classic large cell cancer. Five-year survival is 21% for patients with large cell neuroendocrine cancer, 65% for atypical carcinoid, and 90% for typical carcinoid.[28]

KEY POINTS

- Preinvasive lung cancer lesions include squamous dysplasia and atypical adenomatous hyperplasia.
- Unlike other lung cancers, AIS occurs more commonly in never-smokers, is seen in men and women with the same frequency, and is associated more commonly with *EGFR* mutations than other types of lung cancer.
- Pulmonary neuroendocrine tumors represent a spectrum of neoplasms characterized by the presence of neurosecretory granules on electron microscopic evaluation and a distinct immunohistochemical phenotype.

BIOLOGY

Paradigm-changing studies have shifted the perspective on NSCLC from being considered a single disease or a few histology-based subgroups to the current concept of a large number of molecularly defined subtypes (Fig. 8-1) of variable prevalence.[29] Also, publications from The

Cancer Genome Atlas effort and other groups have revealed the impressive complexity of lung cancer, as demonstrated by both interpatient and intrapatient tumor heterogeneity.[30,31] Guidelines for molecular testing have been issued by multiple organizations, including the International Association for the Study of Lung Cancer, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network (NCCN). All recommend concurrent testing for *EGFR* mutations, *ALK* translocations, and *ROS1* translocations in lung adenocarcinoma, large cell carcinoma, and NSCLC not otherwise specified (NSLC-NOS), with a turnaround time of less than 2 weeks. In addition, NCCN recommends broad molecular profiling to identify other molecular alterations that could be matched to potential targeted treatment either as an off-label use or as part of a clinical trial (Current NCCN Guidelines Reference).[32] Molecular testing including broad molecular profiling and testing for *EGFR* mutations, *ALK* translocations, and *ROS1* translocations should also be considered in squamous cell histology, particularly for patients who are never-smokers or light smokers, have small biopsy specimens, or have mixed histology.[33]

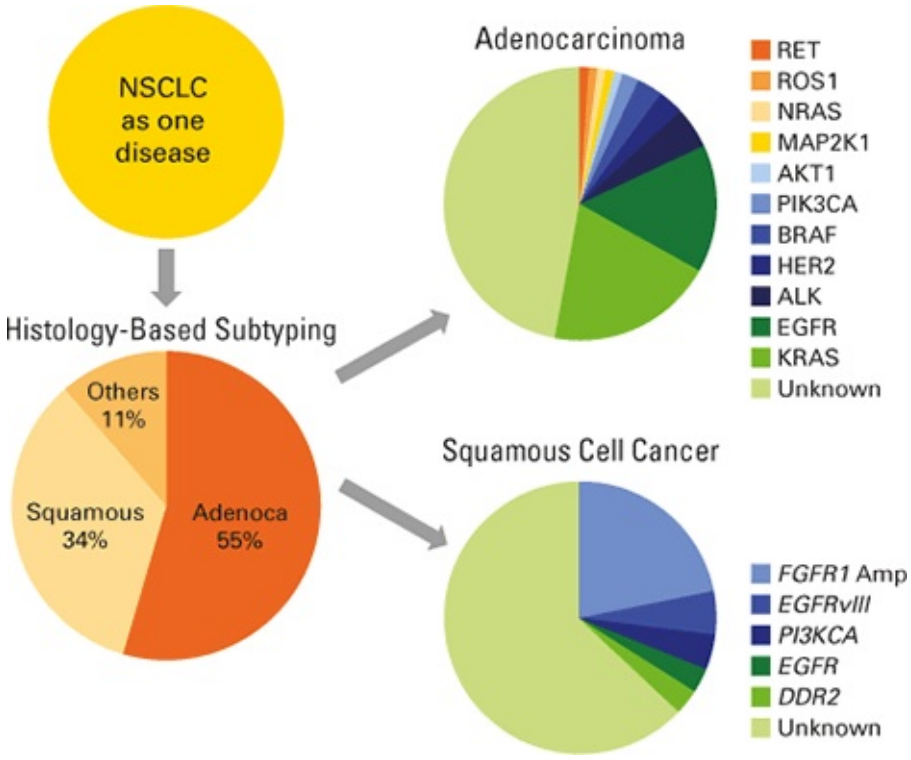

Fig. 8-1 Evolution of non-small cell lung cancer (NSCLC) subtyping from histologic- to molecular-based.[21]

Abbreviations: Adenoca, adenocarcinoma; EGFR, epidermal growth factor receptor; MAP2K1, mitogen- activated protein kinase kinase 1.

Adapted from Li T, Kung HJ, Mack PC, et al. Genotyping and genomic profiling of non-small-cell lung cancer: implications for current and future therapies. J Clin Oncol. *2013;31:1039–1049.*

The most common and clinically relevant molecularly defined subtypes found in non-squamous NSCLC are described in Fig. 8-1. Identifying actionable molecular drivers in squamous histology NSCLC is ongoing and is the subject of several clinical trials, including the Squamous Lung Master Protocol (LUNG-MAP).[34]

EPIDERMAL GROWTH FACTOR RECEPTOR

EGFR belongs to the HER/erbB family of growth factor receptors, which includes EGFR (HER1 or erbB1), HER2/neu (erbB2), HER3 (erbB3), and HER4 (erbB4). These cell-surface proteins

consist of an extracellular ligand-binding domain, a transmembrane structure, and an intracellular tyrosine kinase domain. The binding of ligand to receptor activates receptor dimerization and tyrosine kinase autophosphorylation, initiating a cascade of intracellular events and leading to increased cell proliferation, angiogenesis, metastasis, and a decrease in apoptosis. Inappropriate activation of this receptor-signal transduction pathway can be caused by ligand or receptor over expression, receptor mutation, binding of intracellular ligands, or dimerization with other receptors (heterodimerization or "receptor crosstalk") (Fig. 8-2).[35]

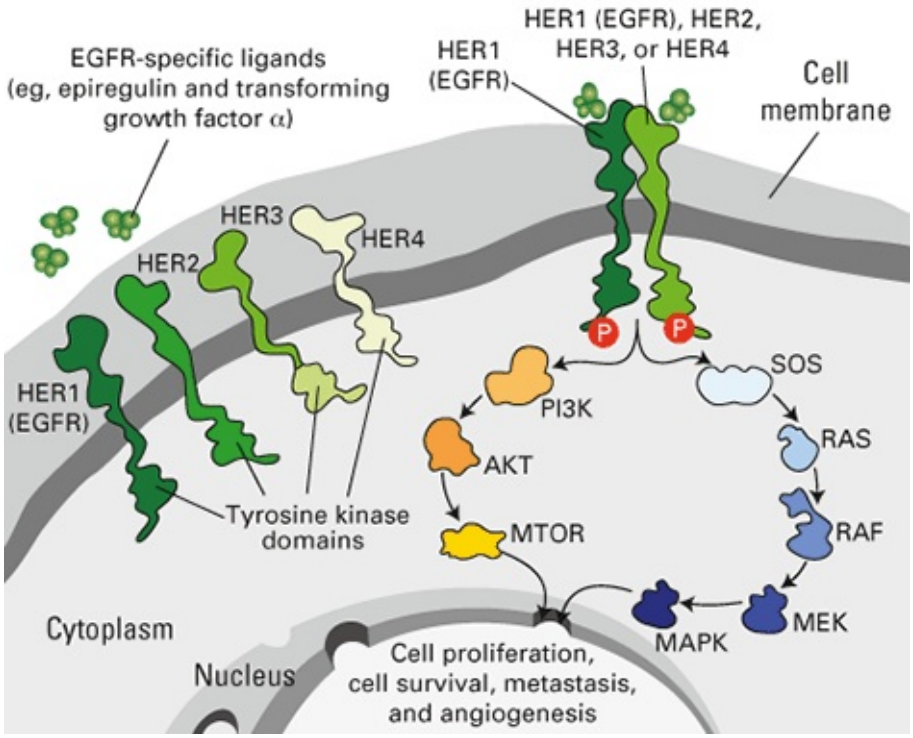

Fig. 8-2 Epidermal growth factor receptor (EGFR) signaling pathways.

Shown in the left portion of the figure are the four members of the ERBB (or HER) family of receptors. All four members of this family have tyrosine kinase domains in the cytoplasmic portion of the receptor. However, the tyrosine kinase domain of HER3 does not have catalytic activity. The right portion of the figure shows that binding of ligands to the HER family of receptors induces either homodimerization or heterodimerization of the receptors. Dimerization results in phosphorylation of the tyrosine residues of the EGFR kinase domain. The activated receptor may then phosphorylate a wide array of intracellular signaling cascades, such as the RAS–RAF–MEK–ERK and PI3K–AKT pathways, that induce cellular proliferation, angiogenesis, and metastases. EGFR amplification can obviate the requirement for ligand-induced dimerization.

Abbreviations: mTOR, mammalian target of rapamycin; P, phosphorylation; SOS, Son of Sevenless.

From Cataldo VD, Gibbons DL, Perez-Soler R, et al. Treatment of non-small-cell lung cancer with erlotinib or gefitinib. N Engl J Med. *2011;364:947–955. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.*

Overexpression of EGFR (which can be demonstrated by IHC) has been found in as many as 70% of NSCLCs and is an independent negative prognostic factor.[36] However, the most reliable biomarker to predict radiographic response to EGFR inhibitors is the presence of activating *EGFR* mutations. These mutations (detected by gene sequencing) hyperactivate the EGFR, rendering the cancer cell dependent on EGFR for survival and progression. These EGFR-mutant oncogene–addicted tumors are exquisitely sensitive to EGFR-TKIs. At diagnosis, these mutations appear mutually exclusive of *KRAS* and *ALK* aberrations and are associated with certain clinicopathologic features (i.e., females, East Asians, never-smokers or light smokers, and adenocarcinoma histology, especially nonmucinous AIS).

In NSCLC, activating mutations occur in the EGFR tyrosine kinase domain, centered around exons 18 to 21. Mutations in exons 19 and 21 (termed "classic" *EGFR* mutations) account for

approximately 90% of *EGFR* mutations. Exon 19 mutations are most commonly in-frame deletions of amino acids 747 to 750. Exon 21 mutations are characteristically L858R substitutions. The presence of *EGFR* mutations is both prognostic and predictive. Activating *EGFR* mutations are also associated with improved response to both conventional chemotherapy in general and EGFR-TKIs in particular. In NSCLC cases harboring classic *EGFR* mutations, EGFR-TKIs yield RRs over 60%—compared with RRs of approximately 10% in wild-type *EGFR* cases.

ANAPLASTIC LYMPHOMA KINASE

The *ALK* gene, which encodes a tyrosine kinase, was originally identified in a subset of anaplastic large cell lymphomas with a t(2;5)(p23;q35) translocation. In a rare subset (2 to 7%) of cases of NSCLC, chromosome 2p inversion results in fusion of the protein encoded by the echinoderm microtubule-associated protein-like 4 *(EML4)* gene with the intracellular signaling portion of the ALK receptor tyrosine kinase. Analogous to *EGFR* mutations, *EML4-ALK* fusions result in constitutive tyrosine kinase activity, dependence of the cancer cell on activated downstream mitogenic pathways, and sensitivity to ALK inhibition.[37]

Other genetic aberrations involving the *ALK* gene have been identified in anaplastic large cell lymphomas, inflammatory myofibroblastic tumors, and neuroblastomas. Efficacy of ALK inhibitors such as crizotinib or ceritinib for treatment of some of these other conditions highlights the increasing recognition that a tumor's molecular characteristics—and not anatomic site or histology—may ultimately guide treatment selection in oncology.[38]

The terms *"ALK* positivity," *"ALK* rearrangement," *"ALK* fusion," and *"ALK* translocation" are essentially synonymous and refer to the presence of the *EML4-ALK* translocation. Despite the rarity of this molecular aberration, because of the vast number of lung cancer cases worldwide, an estimated 40,000 such cases occur annually.[39] Similar to *EGFR* mutations, *EML4-ALK* translocations are associated with certain clinicopathologic features.[40,41] These include never or light smoking; adenocarcinoma histology (especially signet-ring subtype), and younger age. In contrast to *EGFR* mutations, *ALK* translocations do not appear to have a clear association with patient sex or race/ethnicity. *ALK* translocations are typically mutually exclusive of *EGFR* and *KRAS* mutations, though they sometimes can occur together, usually in the setting of acquired resistance to crizotinib.[42]

ALK rearrangements can be identified using IHC, fluorescence in situ hybridization (FISH), or polymerase chain reaction assay. Of these, FISH appears to be the most clinically applicable, although dual IHC and FISH may increase the detection of these cases, and IHC alone is being used more frequently.[41] *EML4-ALK* FISH employs differently labeled break-apart (split signal) probes on the 5′ and 3′ ends of the *ALK* gene. Normal *ALK* generates a fused (yellow) signal, while *ALK* rearrangements appear as separate red and green signals. The standard cutoff for a positive result is a split signal in more than 15% of cells examined.[43]

KRAS

RAS proteins are a family of guanine nucleotide–binding proteins that play an important role in the intracellular-signaling pathway. In response to the interaction between tyrosine kinase receptors and their ligands, RAS becomes activated in the triphosphate form, which leads to a cascade of downstream events responsible for the regulation of cell cycle and apoptosis, including the RAF-1/mitogen-activated protein kinase pathway and the RAC/RHO pathway. If mutated, the protein products of the mutated genes remain in an active state, resulting in a

continuous “on” signal that causes uncontrolled cell growth.

KRAS mutations, which occur primarily in exons 12, 13, and 61, are found mainly among patients with lung adenocarcinomas (approximately 25%) and in smokers. At diagnosis, they are typically mutually exclusive of *EGFR* mutations and *ALK* translocations. *KRAS* mutations have been associated with a poor prognosis and resistance to EGFR inhibitors.[44,45] Their effect on anti-EGFR monoclonal antibody therapy in NSCLC is not clear.

ROS1

ROS1 gene rearrangements are oncogenic drivers present in about 2% of NSCLC tumors.[46] ROS1 is an orphan tyrosine kinase of the insulin receptor family located on chromosome 6 and with sequence homology to *ALK.* Gene rearrangements of *ROS1* lead to constitutive activation of this tyrosine kinase. Like many oncogene-addicted lung cancers, *ROS1*-rearranged tumors commonly arise in young nonsmokers with lung adenocarcinoma histology. In addition to being an ALK and MET inhibitor, crizotinib is a potent inhibitor of ROS1 and has impressive activity in lung cancers with *ROS1* gene rearrangements, as evident from an exceptionally high overall RR (approximately 72%) and median progression-free survival (PFS) (19.2 months).[47]

RET

RET-gene fusions have been identified in 1 to 2% of NSCLCs.[48] Patients whose tumors harbor *RET* fusions can respond to RET inhibitors such as cabozantinib.[49] Clinical trials with *RET* inhibitors for patients with the *RET*-fusion gene are underway.

HER2

HER2 mutations have been described in about 1 to 2% of NSCLCs. *HER2* can be amplified in lung cancer as it is in breast cancer, but the *HER2* mutations found in NSCLC are distinct from *HER2* amplification and most commonly are insertions in exon 20.[50] Responses to afatinib among patients with HER2-mutated lung cancer have been documented.[51]

BRAF

BRAF mutations are present in 2 to 4% of lung adenocarcinomas. Unlike *EGFR* mutations and *ALK* rearrangements, *BRAF*-mutant lung adenocarcinoma is typically associated with patients who have been smokers.[52] Unlike melanoma, in which the majority of *BRAF* mutations are V600E, only about half of the *BRAF* mutations in NSCLC are V600E. Lung adenocarcinomas with *BRAF* V600E mutations can be sensitive to BRAF inhibitors either alone or in combination with downstream inhibition of MEK-ERK. In the phase II trial of the *BRAF V600E* inhibitor dabrafenib combined with the MEK inhibitor trametinib, the overall response rate (ORR) was 63% and the 12-week disease control rate (DCR) 88%.[53] Outcomes were better with combined *BRAF V600E* and MEK inhibition than inhibition of *BRAF V600E* with dabrafenib alone, which resulted in a lower, but still substantial, 32% ORR and 56% 12-week DCR.[54]

MET

MET exon 14 skipping mutations represent approximately 2.5% of NSCLCs and are higher in frequency in the rare sarcomatoid histology of NSCLC (~20 to 30% frequency). These juxtamembrane splice-site mutations lead to decreased MET degradation and appear to be

potent oncogenic drivers. Tumor responses to MET inhibitors such as crizotinib have been observed.

OTHER MUTATIONS

The paradigm of treatment of NSCLC has shifted over the past several years from a uniform chemotherapy approach to the identification and targeting of "actionable" driver mutations. This has led to the approval of EGFR tyrosine kinase inhibitors for first-line treatment of patients who have lung cancer with EGFR-activating mutations and of crizotinib for treatment of patients with *ALK and ROS1* rearrangements. Molecular profiling of 1000 patients with lung adenocarcinoma has identified other mutations that are being targeted in other clinical trials.[55] Mutations in *PIK3CA, Akt,* and others have also been documented. Research is ongoing to determine whether these mutations are oncogenic drivers and to match such mutations to effective targeted therapeutics.

LIQUID BIOPSIES FOR GENOMIC TESTING

Increasingly, liquid biopsies for genomic testing are being employed for molecular analyses of NSCLCs. Genomic testing is performed on blood using various nucleic acid sequencing methods examining a single gene of interest or an oncopanel of genes such as digital droplet polymerase chain reaction (ddPCR), BEAMing, real-time PCR, or next-generation sequencing of an oncopanel of genes. This examination of circulating tumor DNA (ctDNA) differs from examining whole circulating tumor cells because DNA shed in the blood is examined whether or not it is still contained in a tumor cell in the bloodstream.

The cobas real-time PCR test is approved by the U.S. Food and Drug Administration (FDA) in both tissue and plasma for the detection of the two most common EGFR-activating mutations (EGFR exon 19 and EGFR L858R) as well as EGFR-T790M (the most common resistance mutation to first- and second-generation EGFR-TKI (erlotinib, gefitinib, afatinib).

Broader genomic profiling of ctDNA using next-generation sequencing methods that examine multiple genes important in lung cancer (*EGFR, ALK, ROS1, BRAF,* etc.) is also sometimes used when tissue is insufficient or tissue biopsy for molecular testing is impractical.

A positive blood test is generally specific for the presence of the molecular aberration, and outcomes in EGFR-mutant NSCLCs have been shown to be similar whether the mutation was detected in tissue or plasma; however, a negative test should be interpreted with caution and followed by a tissue biopsy to more conclusively determine the presence or absence of the genomic aberration in question, particularly when there are approved therapies available such as osimertinib for acquired resistance to EGFR-TKI in the presence of an EGFR-T790M mutation.[56]

ANGIOGENESIS

Bevacizumab, a monoclonal antibody to vascular endothelial growth factor (VEGF), has been approved for the treatment of patients with nonsquamous histology in combination with carboplatin/paclitaxel for first-line treatment of NSCLC (see section on Non-Small Cell Lung Cancer Treatment).[57] Numerous previous randomized, phase III trials had not shown a benefit of VEGF receptor (VEGFR) TKIs when given in combination with chemotherapy.[58,59] However, one phase III trial showed improvement in overall survival (OS), PFS, and RR for patients with NSCLC treated with the VEGFR2 antibody ramucirumab when combined with docetaxel for

patients with progressive NSCLC during or after platinum-based chemotherapy.[60]

The major issues limiting the use and effect of antiangiogenic therapies are safety considerations and lack of predictive biomarkers. Bevacizumab and other antiangiogenic agents are associated with a distinct toxicity profile that reflects effects on normal vasculature and includes bleeding, clotting, hypertension, wound healing complications, gastrointestinal perforation, and proteinuria. The mechanisms of these adverse events are diverse and not fully understood. Bleeding may be a result of vascular endothelial cell apoptosis or tumor detachment from blood vessels in response to VEGF-directed therapy.[61,62] Hypertension is thought to arise from reduced nitric oxide production because of VEGF inhibition, which promotes vasoconstriction.[63] Proteinuria may be a result of disruption of glomerular endothelial integrity or by glomerular basement membrane damage caused by hypertension.[64]

The identification of markers predictive of benefit from anti-VEGF monoclonal antibodies and VEGFR-directed TKIs has proven elusive. Emerging but unproven biomarkers include tumor microvessel density, serum VEGF, soluble VEGFR2 and VEGFR3, intracellular adhesion molecule and other angiogenic and inflammatory markers, VEGF and VEGFR polymorphisms, circulating endothelial cells, noninvasive imaging of perfusion and oxygenation, and development of on-treatment hypertension.[65-69]

TUMOR SUPPRESSOR GENES

The *TP53* tumor suppressor is the most frequently mutated gene in cancer and is found in more than 50% of tumors. In lung cancer, loss of one *TP53* allele on chromosome 17p13 and mutational inactivation of the other allele occurs in more than 75% of small cell lung cancers and in 50% of NSCLCs. Although *TP53* mutations are common among patients with lung cancer, their prognostic significance is unclear.

LKB1 is another tumor suppressor inactivated or mutated in NSCLC. Inactivation of LKB1 is present in about 19% of cases of squamous cell lung cancer and 34% of lung adenocarcinoma. Inactivating mutations of *LKB1* contribute to lung cancer initiation, differentiation, and metastases.[70]

GENOMIC/PROTEOMIC PROFILING

Progress in the techniques for identifying proteins and genes over- and underexpressed in lung tumors has resulted in the ability to molecularly profile a tumor. For example, microarray techniques that profile the expression of thousands of genes can, in theory, simultaneously identify genetic signatures that may be able to identify patients with a favorable or unfavorable prognosis or patients likely to respond to a given therapy. A number of these genetic signatures have been described, but they have not been validated as predictive markers in prospective clinical trials.[71-75] It is also now possible to perform next-generation sequencing of hundreds of genes. This broad genomic profiling offers the opportunity to identify potential oncogenic drivers to treat with FDA-approved drugs or match to a clinical trial. Some current guidelines recommend broad genomic profiling beyond *EGFR* mutations; *ALK* and *ROS1* rearrangements are used to try to identify additional molecular alterations.[32] Caution must be exercised, in interpretation of this vast amount of genomic data. When “passenger” rather than “driver” mutations are targeted, treatment may be inferior to standard of care systemic therapy. Increasingly, institutions are adopting “Molecular Tumor Boards” to interpret this vast amount of data in a multidisciplinary fashion.

LUNG CANCER IMMUNOBIOLOGY

The past several years have seen a tremendous acceleration in our understanding of the immune microenvironment of lung cancer and translation of this understanding to the development of immunotherapies to treat advanced lung cancer. The most promising avenue of investigation has been the development of immune checkpoint inhibitors: monoclonal antibodies that overcome immune inhibition that tumors can exploit to prevent the immune system from attacking the tumor. See Chapter 4: Principles of Immuno-Oncology and Biologic Therapy for mechanistic details regarding the immune system and cancer.

KEY POINTS

- The most readily targeted molecular abnormalities associated with lung cancer are driver oncogenes, currently best represented by *EGFR* mutations and *ALK* and *ROS1* translocations. In contrast, targeting loss of tumor suppressor genes such as *p53* and *RB* has proven much more difficult. Although antiangiogenic therapy with bevacizumab and ramucirumab has proven active in NSCLC, at present these agents are employed in a "nontargeted" fashion, without the benefit of well-defined predictive biomarkers.
- Guidelines recommend concurrent testing for *EGFR* mutations and *ALK* and *ROS1* translocations, particularly in lung adenocarcinoma, large cell histology, and NSCLC not otherwise specified and with strong consideration for testing for never-smokers and light smokers with squamous cell histology, small biopsy samples, or mixed histology with a turnaround time of less than 2 weeks.
- Broad genomic profiling to identify molecular aberrations such as *HER2* insertions, *BRAF* mutations, and *RET* gene fusions among others that can be matched to clinical trials with targeted therapies should also be considered.

CLINICAL PRESENTATION

Most patients with lung cancer present with symptomatic disease (Table 8-3). The most common symptoms are anorexia, fatigue, weakness, and cough. Patients with AIS may have bronchorrhea (large quantities of foamy sputum) and shortness of breath out of proportion to radiographic findings.

Table 8-3 Symptoms Associated with Lung Cancer	
Typical	▪ Cough
	▪ Increased production of sputum
	▪ Shortness of breath
Common	▪ Fatigue
	▪ Weight loss
	▪ Anorexia
	▪ Low-grade fever
Less Common	▪ Chest pain (usually from a pleural-based lesion)
	▪ Hemoptysis
	▪ Hoarseness (secondary to laryngeal-nerve involvement)
	▪ Bone pain
	▪ Pleural effusion
Infrequent	▪ Signs and symptoms consistent with obstruction of the superior vena cava, superior sulcus, or Pancoast tumors
	▪ Pericardial tamponade
	▪ Paraneoplastic syndromes
	▪ Signs and symptoms consistent with brain metastases

Metastatic disease at presentation is common in small cell lung cancer (75%) and adenocarcinoma (50%), and many metastatic sites are possible, with brain, bone, liver, and adrenal gland being the most common sites of metastatic disease.[76] Liver and bone marrow metastases develop in approximately 20 to 30% of patients, and brain metastases occur in over 20%.[77,78]

Paraneoplastic syndromes are caused by humoral factors produced by cancer cells that act at a site distant from both the primary site and its metastases or by cross-reactivity between host antitumor antibodies and normal tissues.[79] For all paraneoplastic syndromes, treatment of the underlying cancer is recommended. Additionally, syndrome-specific therapies may be employed. The two most common paraneoplastic syndromes among patients with NSCLC are hypercalcemia and hypertrophic pulmonary osteoarthropathy. Although hypercalcemia is most often caused by diffuse skeletal metastases, it can be the result of ectopic production of a parathyroid hormone–related peptide or other humoral substances. Excessive production of corticotropin may result in Cushing syndrome with excess cortisol production, resulting in muscle weakness, weight loss, hypertension, hyperglycemia, and profound hypokalemia. This syndrome is most commonly found in small cell lung cancer. As a result of the rapid tumor growth, the classical physical stigmata of Cushing syndrome are often absent.

Small cell lung cancer also is associated with paraneoplastic neurologic abnormalities.

Central nervous system (CNS) paraneoplastic disorders include cerebellar degeneration, dementia, limbic encephalopathy, Lambert–Eaton syndrome, and visual paraneoplastic syndrome with optic neuritis and retinopathy.

Cerebellar degeneration is characterized by progressive cerebellar dysfunction with ataxia, dysarthria, hypotonia, and dementia. This syndrome is associated with four different antineuronal antibodies, the most common being an antibody against Purkinje cell proteins. Limbic encephalopathy is characterized by progressive dementia, hallucinations, depression, agitation, anxiety, or similar disturbances. Paraneoplastic sensory neuropathy often is caused by an anti-Hu antibody and is associated with subacute distal sensory loss and the absence of deep tendon reflexes with normal muscle strength. Anti-Hu is a circulating polyclonal immunoglobulin G that reacts with CNS neurons as well as the dorsal root and trigeminal ganglia. It can be associated with encephalopathy, autonomic neuropathy, and cerebellar degeneration.

Lambert–Eaton syndrome occurs in less than 1% of patients. It is caused by onconeural antibodies targeting presynaptic calcium channels and is characterized by proximal muscle weakness. Unlike with myasthenia gravis, muscle strength tends to improve with repeated activity.

KEY POINTS

- Common symptoms of lung cancer include local symptoms, such as cough and shortness of breath, and constitutional symptoms, such as fatigue, weakness, anorexia, and weight loss.
- The most common sites for metastatic disease in lung cancer are the lungs (both ipsilateral and contralateral), adrenal glands, liver, bone, and brain.
- Patients with lung cancer may present with a number of paraneoplastic syndromes.

SCREENING

Most patients with lung cancer present with advanced disease, raising a question about the role of screening to detect these tumors at an earlier and theoretically more curable stage (Fig. 8-3). The three screening interventions for lung cancer that have been explored include chest x-ray, cytologic analysis of sputum, and low-dose spiral CT. Although the role of screening patients at high risk for the development of early-stage disease was debated for many years, CT-based screening has been found to demonstrate a reduction in lung cancer mortality.

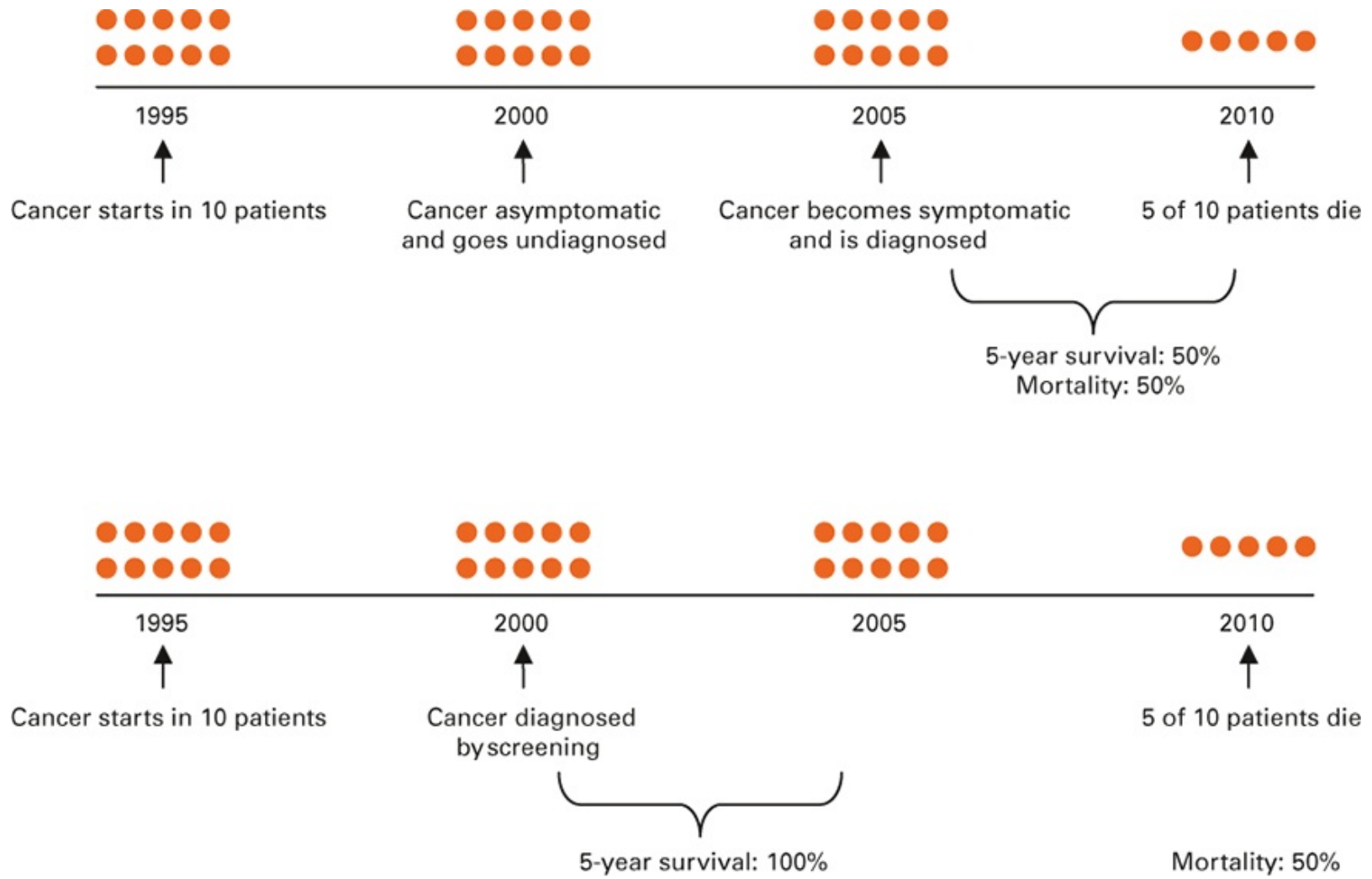

Fig. 8-3 Lead-time bias and its effects on survival and mortality rates.

Low-dose, noncontrast, thin-slice, helical or spiral CT is a scan in which only the pulmonary parenchyma is examined, negating the use of intravenous contrast medium and the necessity of a physician's presence. This type of scan can usually be done quickly (within one breath) and involves low doses of radiation. In a nonrandomized, controlled study from the Early Lung Cancer Action Project, low-dose CT was shown to be more sensitive than chest x-ray for detecting lung nodules and lung cancer in early stages.[80]

The National Lung Screening Trial (NLST) was a randomized multicenter study comparing low-dose helical CT scans with chest x-ray for the screening of older current and former heavy smokers for early detection of lung cancer.[81] From 2002 to 2004, more than 50,000 high-risk individuals from 33 U.S. centers were randomly assigned to three annual screenings with single-view posteroanterior chest x-ray or low-dose CT. The study enrolled individuals between ages 55 and 74 who had at least a 30 pack-year smoking history (former smokers needed to have quit within the previous 15 years). Individuals with a prior lung cancer diagnosis, hemoptysis, unexplained weight loss of more than 15 pounds, or chest CT within 18 months before enrollment were excluded. The rate of screening adherence exceeded 90%. The rate of positive screening tests was 24% with CT and 7% with chest x-ray. However, in both arms, there was a false-positive rate of 93 to 96%. There were 247 deaths from lung cancer per 100,000 person-years in the CT group and 309 deaths per 100,000 person-years in the chest x-ray group, corresponding to a 20% relative reduction in lung cancer mortality ($p = 0.004$). CT was also associated with a 6.7% reduction in all-cause mortality ($p = 0.02$). Based on these data from the NLST trial, the U.S. Preventive Services Task Force issued recommendations for

lung cancer screening with low-dose CT for patients ages 55 to 80 who had a smoking habit of 30 pack-years or more and who are currently smoking or had quit within the past 15 years. Although the NLST showed for the first time that CT-based screening reduced lung cancer mortality, numerous questions regarding implementation, cost, associated biomarkers to identify patients with high-risk disease and management of false-positive test results remain and will be important topics for future studies (Table 8-4).[82]

KEY POINTS

- Interpretation of screening studies requires an understanding of length-time bias, lead-time bias, overdiagnosis, and the distinction between survival and mortality.
- The NLST, which randomly assigned individuals with high-risk disease to three annual helical CT scans or chest x-rays, was the first study to demonstrate a 20% relative reduction in lung cancer mortality and a 6.7% relative reduction in all-cause mortality.
- In the NLST, there was a 24% rate of positive screening tests with helical CT, of which 96% were non–lung cancer diagnoses. The optimal means by which to implement screening and evaluate positive screening tests are not yet known.

Table 8-4 **Points about Screening for Lung Cancer to Share with Patients**[81,82]
▪ Results from observational studies of CT screening among patients at high risk (i.e., those with a history of heavy smoking) indicate a high rate of diagnosis of lung cancer in stage I (a relatively curable stage).
▪ CT screening reveals many noncalcified nodules, only a small fraction of which will be found to be lung cancer. The patient must be prepared to live with this uncertainty and must be able to commit to frequent follow-up scans.
▪ Costly invasive procedures that are associated with serious risks may be required to evaluate some nodules.
▪ Despite these considerations, the National Lung Screening Trial, which randomly assigned approximately 50,000 high-risk individuals to annual chest x-ray or low-dose spiral CT scan for 3 years, demonstrated a 20% reduction in lung cancer mortality with CT-based screening.
▪ A diagnostic workup should be done by physicians who are experienced in such evaluation.
▪ The selection of a facility with physicians who are experienced and credentialed in multidisciplinary fields (including thoracic surgery, pathology, and pulmonology) is critical to an optimal outcome.
▪ The most effective way for smokers to improve their health is to stop smoking.

PROGNOSTIC FACTORS

Prognostic factors predict a patient's outcome independently of treatment. Favorable prognostic factors for both NSCLCs and small cell cancers include stage, performance status (PS), lack of substantial weight loss (loss of < 5%), and female sex. Age is not an independent prognostic factor; fit older patients tend to fare as well as their younger counterparts. Further, older patients with good PS generally fare better than younger patients with poor PS. Histologic subtype also is not an independent prognostic factor for NSCLC, although adenocarcinoma is more likely to metastasize earlier than squamous cell carcinoma. However, once metastasized, these two histologies have similar prognoses.

PREDICTIVE FACTORS

Predictive factors forecast how a patient will fare with treatment. In lung cancer, *EGFR* mutation status is useful for predicting which patients are likely to derive the most benefit from EGFR-TKIs, particularly responses and improved time to progression.[83]

PREOPERATIVE EVALUATION FOR NSCLC

The suitability of a patient for a definitive resection depends on two factors: the stage of the

lesion and the ability of the patient to withstand surgery. A detailed discussion of the preoperative evaluation and comorbid conditions are beyond the scope of this chapter; however, assessment of pulmonary reserve is discussed here.

MEDICAL ASSESSMENT OF PULMONARY RESERVE

Preoperative evaluation for a thoracotomy starts with spirometry. General guidelines are described here, although it should be emphasized that a certified general thoracic surgeon, working as part of a multidisciplinary thoracic oncology team, is best qualified to determine whether a patient is a surgical candidate. The forced vital capacity is the value that has been used most commonly to assess suitability for surgery; a predicted postoperative forced vital capacity of less than 1 L or a preoperative value of less than 2 L for a pneumonectomy or less than 1.5 L for a lobectomy usually suggests that the patient is at risk for perioperative complications. Diffusion capacity should be measured if there is concern that the forced vital capacity may not be adequate or that the patient has signs or symptoms of interstitial lung disease. A low diffusion capacity (< 50% of predicted) suggests an increased risk of postoperative morbidity or mortality.

Pulmonary status should be optimized as much as possible before surgery. Treatment of bronchitis with antibiotics, bronchodilators, and/or oral corticosteroids is helpful. The patient should quit smoking, if applicable, and preoperative training with incentive spirometry and weight reduction should be considered when appropriate.

KEY POINTS

- Prognostic factors predict how a patient is likely to fare, regardless of which treatment is used. Positive clinical prognostic factors for lung cancer include stage of disease, PS, lack of substantial weight loss, and female sex.
- Predictive factors forecast how a patient is likely to fare with a specific treatment. For instance, *EGFR* mutations predict for higher RR and longer PFS with EGFR-TKIs.

NON-SMALL CELL LUNG CANCER

STAGING

The current (8th edition) tumor–node–metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) is based on an analysis of more than 94,000 cases of lung cancer internationally (Tables 8-1 and 8-5). Key changes include several modifications to T and M descriptors, including changes to tumor size cutoffs and additional designations for metastatic spread (M1a if contralateral lung and effusions, M1b if single extrathoracic metastases, M1c if multiple extrathoracic metastases in more than one organ). Certain stage groupings have also changed, reflecting the importance of size of the primary tumor to prognosis. It should be noted that a great majority of cases analyzed were surgical, regardless of stage, and that some stage changes reflect a selected database.[84]

Table 8-5 **Staging Groups by TNM Elements**			
	Descriptors		
Stage Groups	T	N	M
Occult Carcinoma	X	N0	M0
0	Tis	N0	M0
IA1	T1mi, T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a, T1b, T1c, T2a, T2b, T3	N1	M0
IIIA	T1a, T1b, T1c, T2a, T2b	N2, N3	M0
IIIA	T4	N0, N1	M0
IIIB	T1a, T1b, T1c, T2a, T2b	N3	M0
IIIB	T3, T4	N2	M0
IIIC	T3, T4	N3	M0
IVA	Any T	Any N	Any M1a
IVA	Any T	Any N	Any M1b
IVB	Any	Any	M1c
Clinical Stage (5-year Survival)		Pathological Stage (5-year Survival)	
IA1	92%	IA1	90%
IA2	83%	IA2	85%
IA3	77%	IA3	80%
IIB	68%	IB	73%
IIA	60%	IIA	65%
IIB	53%	IIB	56%
IIIA	36%	IIIA	41%
IIIB	26%	IIIB	24%
IIIC	13%	IIIC	12%
IVA	10%		
IVB	0%		

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OBTAINING A DIAGNOSIS

The diagnosis of lung cancer is most commonly made through cytologic or histologic evaluation of specimens obtained by transbronchial biopsy or percutaneous needle biopsy. Although the disease is usually discovered on chest x-ray, CT of the chest and upper abdomen is necessary to evaluate the extent of the primary disease, mediastinal extension, or lymphadenopathy, as well as the presence or absence of other parenchymal nodules in patients for whom surgical resection is a consideration. Positron-emission tomography (PET) scans are helpful primarily in detecting distant metastases, although they also assist in defining tumor size and in defining N2 stations appropriate for subsequent pathologic confirmation of cancer involvement. If a PET scan is done as part of the staging workup, a bone scan does not need to be performed. CT or magnetic resonance imaging (MRI) of the head is recommended for patients who are to be

treated with curative intent or for those with signs or symptoms suggestive of brain metastases.

Mediastinal nodal metastasis is a critical factor in determining tumor resectability (Table 8-1 and Fig. 8-4).[85,86] Mediastinoscopy has long been considered the gold standard for mediastinal staging and has been recommended for mediastinal lymph nodes larger than 1 cm on CT, even if they are not 18-fluorodeoxyglucose (FDG)–avid on PET. Patients with a normal mediastinum on CT whose lymph nodes also appear negative on a PET scan may not need to undergo preoperative mediastinoscopy, although the lymph nodes still must be sampled at the time of thoracotomy. The use of other techniques, including endobronchial ultrasound (EBUS) should be considered prior to definitive treatment (surgery or chemoradiation) for patients with a lower probability of mediastinal disease (CT and/or PET negative but with central mass or positive N1 nodes).

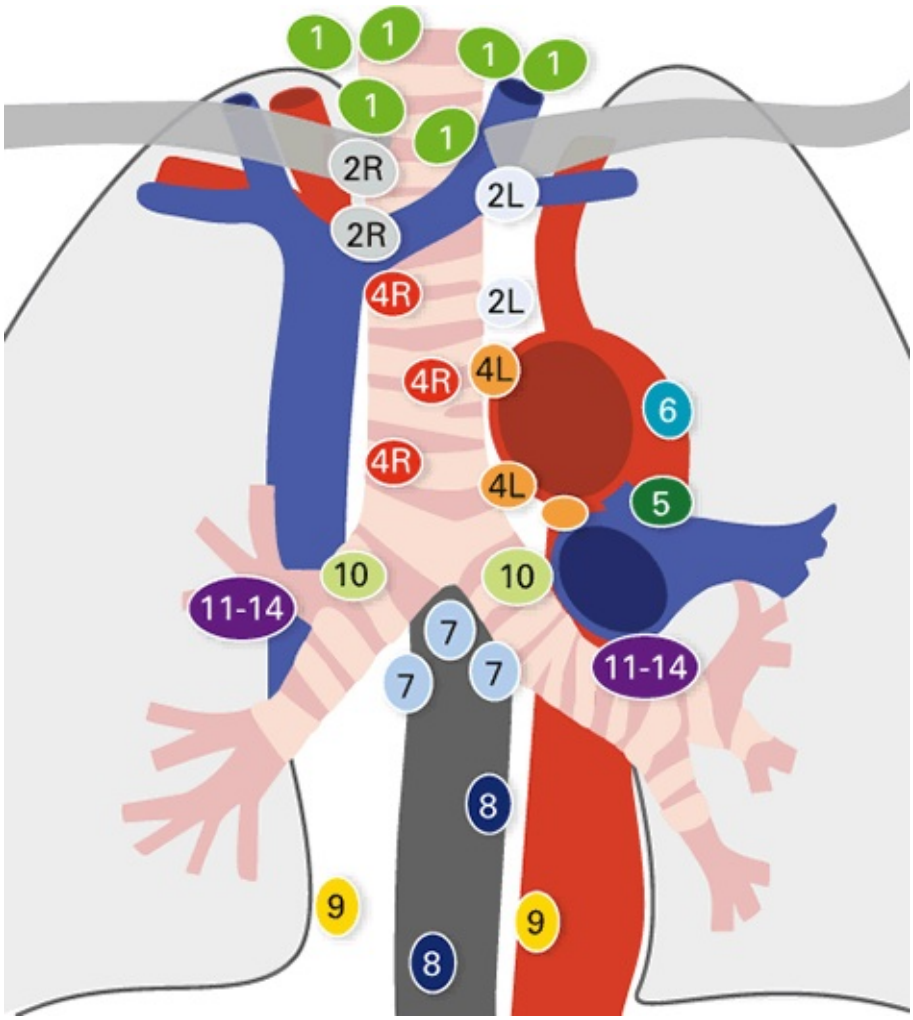

Fig. 8-4 Regional lymph node classification.

Supraclavicular nodes *1. Low cervical, supraclavicular and sternal notch nodes:* From the lower margin of the cricoid to the clavicles and the upper border of the manubrium. The midline of the trachea serves as border between 1R and 1L. **Superior mediastinal nodes 2 to 4** *2R. Upper paratracheal:* From the upper border of manubrium to the intersection of the caudal margin of innominate (left brachiocephalic) vein with the trachea. 2R nodes extend to the left lateral border of the trachea. *2L. Upper paratracheal:* From the upper border of manubrium to the superior border of aortic arch. 2L nodes are located to the left of the left lateral border of the trachea. *3A. Prevascular:* Nodes are not adjacent to the trachea, as are the nodes in Station 2, but they are anterior to the vessels. *3P. Prevertebral:* Nodes are not adjacent to the trachea, as are the nodes in Station 2, but behind the esophagus, which is prevertebral. *4R. Lower paratracheal:* From the intersection of the caudal margin of the innominate (left brachiocephalic) vein with the trachea to the lower border of the azygos vein. 4R nodes extend from the right to the left lateral border of the trachea. *4L. Lower paratracheal:* From the upper margin of the aortic arch to the upper rim of the left main pulmonary artery. **Aortic nodes 5 and 6** *5. Subaortic:* These nodes are located in the aortopulmonary window lateral to the ligamentum arteriosum. These nodes are not located between the aorta and the pulmonary trunk but lateral to these vessels. *6. Paraaortic:* These are ascending aorta or phrenic nodes lying anterior and lateral to the ascending aorta and the aortic arch.

Inferior mediastinal nodes 7 to 9 *7. Subcarinal. 8. Paraesophageal:* Nodes below carina. *9. Pulmonary ligament:* Nodes lying within the pulmonary ligaments. **Hilar, lobar, and (sub)segmental nodes 10 to 14**. These are all N1 nodes. *10. Hilar nodes:* These include nodes adjacent to the mainstem bronchus and hilar vessels. On the right, they extend from the lower rim of the azygos vein to the interlobar region; on the left, from the upper rim of the pulmonary artery to the interlobar region.

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INVASIVE STAGING IN THE MEDIASTINUM

Accurate staging of the mediastinum is critical for patients with NSCLC to guide optimal therapy. Clinical staging has been shown to differ markedly from pathologic staging at the time of resection.[87] In a review of numerous clinical trials, the performance of transthoracic, transbronchial, and endoscopic ultrasound-guided needle aspirations or biopsies was compared with mediastinoscopy for staging disease in the mediastinum.[87] Transthoracic and endoscopic needle aspirations had similar sensitivities to mediastinoscopies, although the transthoracic and endoscopic ultrasound needle aspirations were generally performed only for patients with enlarged nodes detected by CT, resulting in fewer false-negative results. However, mediastinoscopy has a higher negative predictive value. Mediastinoscopy does not provide access to Stations 5 and 6 lymph nodes (aortopulmonary nodes), which provide lymphatic drainage for the left lung; assessment of these nodes generally requires a Chamberlain procedure (anterior mediastinotomy). EBUS has emerged as an alternative means to evaluate the mediastinum. Thus far, EBUS appears accurate and safe. Although unlikely to completely replace mediastinoscopy, it may reduce the number of these more invasive procedures.[88]

POSITRON-EMISSION TOMOGRAPHY

PET, a metabolic imaging scan using FDG, is more sensitive, specific, and accurate than CT and has been shown to prevent unnecessary invasive procedures and/or “futile thoracotomies” for patients whose disease has been subsequently proven to be at a more advanced stage.[89]

In a prospective study, a standard approach to staging of NSCLC (CT, ultrasound, and bone scan) was compared with PET to determine which approach could more accurately detect metastases in mediastinal lymph nodes and distant sites.[85] Mediastinal involvement was confirmed histopathologically, and distant metastases were confirmed by other imaging tests. The results of PET and CT followed by pathologic staging were compared in a study involving 168 mediastinal nodes in 54 patients.[86] PET had higher sensitivity and specificity than CT in both studies (Table 8-6). However, the limitations of PET include the cost, availability, inability to detect lesions smaller than 8 mm, and lack of specificity, particularly for patients with inflammatory or granulomatous disease. Thus, PET cannot replace pathologic confirmation of malignancy because the scan can yield false-positive results when an inflammatory process is present and false-negative results when low-metabolic lung tumors such as AIS or carcinoid tumors are present.

Table 8-6 **Comparison of Sensitivity and Specificity of PET and CT**

	Sensitivity (%)	Specificity (%)	Accuracy (%)
Detection of Mediastinal Metastases[85]			
PET*	91	86	–
CT	75	66	–
Staging of Mediastinal Disease[86]			
PET	96	93	94
CT	68	65	66

*The sensitivity and specificity of PET for detecting distant metastases were 82% and 93%, respectively.

Despite these problems, preoperative PET (in addition to a conventional workup) has been demonstrated to reduce the number of "futile" thoracotomies, as defined by benign disease, exploratory thoracotomy, pathologic stage IIIA (N2) or IIIB disease, postoperative relapse, or death within 12 months,[90] although it may not affect OS.[91] PET also has been used to detect distant metastases; indeed, it is in this area that some investigators believe PET may have its primary role in staging.[89] Negative results on PET for patients without symptomatic disease probably obviates the need for bone imaging.[89] PET may be useful for judging response to therapy, depending on the clinical context; PET scans done early after treatment have been demonstrated to be better predictors of survival than CT, although these data need to be confirmed in larger trials.[92]

KEY POINTS

- Preoperative evaluation should include determinations of forced vital capacity and a predicted postoperative value, a diffusing capacity, and the maximum oxygen consumption.
- Although PET is more sensitive and specific than CT for staging disease in the mediastinum, it does not replace mediastinoscopy, because of the incidence of false-positive and false-negative results (the one exception may be patients with a normal mediastinum on CT and a normal PET scan).
- PET is useful to guide lymph node biopsy and to evaluate for metastatic disease.
- Mediastinal lymph node sampling, with mediastinoscopy and/or EBUS, should be performed for all patients with enlarged or abnormal nodes detected on either CT or PET.

NON-SMALL CELL LUNG CANCER TREATMENT

Treatment of NSCLC is stage-specific. Within a given stage category, a number of additional relevant factors enter therapeutic decision-making, including histology and molecular profiling

for driver oncogenes. Of course, PS, comorbid conditions, and relevant social factors must also be taken into account.

STAGES I AND II DISEASE

Approximately one-third of all patients with lung cancer present with stage I or II disease. The treatment of choice for fit patients is surgical resection, which can result in cure for many patients. The preferred surgical procedure is lobectomy, although for patients in whom disease crosses a major fissure or involves the proximal mainstem bronchus, pneumonectomy may be required. Lobectomy has traditionally been the procedure of choice, even for patients with small, peripheral lesions, because wedge resections have been shown to be associated with increased local recurrence and decreased survival.[93] Lobectomy should include resection of bronchial, hilar, and selected mediastinal nodes based on published guidelines (at least 4R and 7 for right-sided tumors; at least 5/6 and 7 for left-sided tumors). Research is ongoing regarding the management of the small, ground-glass–appearing lesions discovered on low-dose, non–contrast-enhanced, thin-slice, helical CT. For example, because pure AIS does not feature lymphatic or hematogenous spread, it has been proposed that wedge resection without lymph node dissection may be adequate for localized tumors. For multifocal disease, some centers have performed lung transplantation, albeit with somewhat discouraging outcomes.[94]

For patients with medical contraindications to surgery but with adequate pulmonary function, conventional fractionated radiotherapy (e.g., 6000 cGy, or rads, in 30 fractions of 200 cGy each) results in cure for about 20% of patients. Advances in imaging and radiation delivery have resulted in the use of stereotactic radiation for lung tumors. With this technology, radiation delivery to surrounding normal lung parenchyma is substantially less than that seen with conventional radiotherapy. It is therefore possible to administer much higher, ablative, doses of radiation over a small number of fractions (e.g., up to 2000 cGy per fraction given every 2 to 3 days for three fractions). To date, outcomes with this technique appear promising. In a multicenter, phase II, U.S. trial of patients with medically inoperable stage I NSCLC, the 3-year rate of primary tumor control was 98%, 3-year distant failure rate 22%, 3-year disease-free survival 48%, and 3-year OS 56%.[95]

Stereotactic radiation, which entails radiation to the primary tumor but not to the draining lymph nodes, is considered only for patients with clinical stage I (T1N0M0 or T2N0M0) disease. Because of toxicities, stereotactic radiation is usually not performed when the tumor lies within 2 cm of the proximal bronchial tree. This technique is also usually restricted to tumors less than 5 cm.

In contrast to surgically resected early-stage tumors (see section on Adjuvant Chemotherapy), the role of chemotherapy following radiation therapy for medically inoperable early-stage NSCLC is unclear.

The risk of second lung cancers developing is high (approximately 2 to 3% annually) for patients with resected stage I NSCLC. Vitamin A and one of its derivatives (beta-carotene or *cis*-retinoic acid) have been found to be ineffective as chemopreventive therapy and actually deleterious in current smokers.[19-21] A study of secondary chemoprevention with selenium[96] also did not demonstrate a reduction in the incidence of second primary cancers.[97]

Patients with peripheral chest wall invasion (T3N0; stage IIB) should have an en bloc resection of the involved ribs and underlying lung. Five-year survival rates as high as 50% have been reported.[98]

PANCOAST TUMORS

Pancoast, or superior sulcus, tumors in the upper lobe adjoining the brachial plexus are frequently associated with Horner syndrome (ptosis, miosis, and anhidrosis) or shoulder and arm pain; the latter is caused by rib destruction, involvement of the seventh cervical vertebra or T1 nerve roots, or both. The Southwest Oncology Group (SWOG) intergroup phase II trial involving patients with T3/4N0/1M0 superior sulcus NSCLC established the current standard of care, which consists of cisplatin/etoposide and concomitant radiation therapy 45 Gy followed by attempted surgical resection and then two cycles of consolidation chemotherapy after surgery.[99] Among patients with available surgical specimens, 54 (65%) showed either a complete pathologic response or minimal microscopic disease on pathologic evaluation. The 2-year survival rate was 55% for all eligible patients and 70% for patients who had a complete resection.

Adjuvant Chemotherapy

The rationale for adjuvant chemotherapy for patients with early-stage lung cancer is based on the observation that distant metastases are the most common site of failure following potentially curative surgery. Interest in this treatment strategy grew after publication of a 1995 meta-analysis of more than 4300 patients in which those who received cisplatin-based regimens had an improved survival rate of approximately 5% at 5 years, with borderline statistical significance ($p = 0.08$).[100] Since that time, a number of randomized trials have evaluated the role of adjuvant chemotherapy following surgical resection of early-stage NSCLC (Table 8-7).[101-106] In a pooled analysis of five of these trials, there was a 5.4% absolute survival benefit at 5 years (hazard ratio [HR], 0.89; 95% CI; 0.82, 0.96; $p = 0.005$).[107] The Lung Adjuvant Cisplatin Evaluation study performed an individual patient meta-analysis of the five largest cisplatin-based adjuvant trials (ALPI, BLT, IALT, JBR.10, and ANITA). Importantly, the benefit of adjuvant chemotherapy varied considerably by disease stage. For stage IA NSCLC, adjuvant chemotherapy was associated with a trend toward worse survival (HR for death 1.40; 95% CI; 0.95, 2.06). For patients with stage IB disease, the HR was 0.93 (95% CI; 0.78, 1.10). In the Cancer and Leukemia Group B (CALGB) 9633 trial, patients with stage IB disease were randomly assigned to surgery alone or surgery followed by carboplatin/paclitaxel.[104] In long-term follow-up of this trial, only the subset of patients with tumors 4 cm or larger demonstrated a significant survival difference in favor of adjuvant chemotherapy (HR, 0.69; 95% CI; 0.48, 0.99; $p = 0.04$). The fact that this trial employed a carboplatin-based regimen further confounds interpretation, as cisplatin/paclitaxel was proved superior to carboplatin-paclitaxel in stage IV NSCLC, with a median survival of 9.8 months, versus 8.5 months ($p = 0.0019$).[108] Given these data, whether patients with stage IB disease and tumors 4 cm or larger should be offered adjuvant chemotherapy remains controversial. For patients with resected stage IA NSCLC, there are no supporting data in favor of adjuvant chemotherapy, and some trials and meta-analyses even suggest a detrimental effect. The reason for a potentially negative effect in stage IA disease is speculative.

Table 8-7 **Adjuvant Therapies Following Surgical Resection of Early-Stage Non-Small Cell Lung Cancer**

Study (Stage)*	Treatment	Patients	5-Year Survival (%)	Median Survival	Hazard Ratio	p Value
ECOG 3590 (II-IIIA)[101]	Surgery → radiation therapy vs. postoperative concurrent radiation therapy plus cisplatin and etoposide	242		39 months	0.92	0.56
		246		38 months		
ALPI (I-IIIA)[102]	Surgery vs. postoperative mitomycin, vindesine, and cisplatin	603	51		0.96	0.589
		606	43			
IALT (IB-IIIA)[103]	Surgery vs. postoperative cisplatin and etoposide, or vinca alkaloids	405	40		0.86	0.03
		361	44.5			
CALGB (IB)[104]	Surgery vs. postoperative carboplatin and paclitaxel	172	57		0.83	0.12
		172	59			
NCI-C (IB-II)[105]	Surgery vs. postoperative cisplatin and vinorelbine	241	54		0.80	0.03
		241	69			
ANITA (IB, II, IIIA)[106]	Surgery vs. postoperative cisplatin and vinorelbine	433	43	44 months	0.80	0.017
		407	51	66 months		

Abbreviations: ALPI, Adjuvant Lung Project Italy; ANITA, Adjuvant Navelbine International Trialist Association; CALGB, Cancer and Leukemia Group B; ECOG, Eastern Cooperative Oncology Group; IALT, International Adjuvant Lung Cancer Trial; NCI-C, National Cancer Institute of Canada.
*These studies used American Joint Commission on Cancer staging prior to 8th edition.

The role of adjuvant chemotherapy for resected stage II NSCLC is well established. In the Adjuvant Navelbine International Trialist Association (ANITA) trial, patients with stage IB to IIIA cancer were randomly assigned to surgery alone or surgery followed by four cycles of cisplatin/vinorelbine.[106] OS was significantly improved at 5 years (51% vs. 43%), although the survival benefit was limited to patients with stage II or IIIA disease. In a pooled analysis of cisplatin-based chemotherapy trials, there was a significant survival benefit (HR, 0.83; 95% CI; 0.73, 0.95) for stage II NSCLC. Accordingly, adjuvant chemotherapy is recommended following complete resection of stage II and stage III NSCLC.

The optimal regimen for adjuvant chemotherapy remains unclear. Almost all studies have employed cisplatin-containing doublets. The principal exception, CALGB 9633, which employed carboplatin/paclitaxel after resection of stage IB disease, did not meet statistical significance for OS (HR, 0.83; 95% CI; 0.6, 1.08; p = 0.12).[104] Whether this result is because of the stage IB population, the relatively small sample size (344 patients), or the chemotherapy regimen is not known. Nevertheless, cisplatin rather than carboplatin is recommended in the adjuvant, potentially curative, setting. Vinca alkaloids and etoposide have most commonly been combined with cisplatin in adjuvant trials. In the International Adjuvant Lung Trial (IALT), patients with resected stage I to IIIA disease were randomly assigned to either observation or chemotherapy (cisplatin plus either etoposide, vinorelbine, vinblastine, or vindesine).[103] Although the study was terminated early because of slow accrual, there was a significant improvement in median survival, disease-free survival, 5-year survival, and 5-year disease-free survival in favor of the chemotherapy arm (HR for survival, 0.86). A randomized trial by the National Cancer Institute of Canada (NCIC JBR.10) randomly assigned 482 patients with stage IB or II disease to postoperative observation or to treatment with vinorelbine and cisplatin. OS was significantly prolonged for the chemotherapy group compared with the observation group (94 months vs. 73 months; HR for death, 0.69; p = 0.04), as was relapse-free survival (not reached vs. 46.7

months; HR for recurrence, 0.60; p < 0.001). Five-year survival rates were 69% and 54% for the two groups, respectively (p = 0.03).[105] Of note, this 15% absolute benefit at 5 years is among the highest in all adjuvant chemotherapy trials across cancer types. In the ANITA trial, 840 patients with postoperative stage I (T2N0), II, or IIIA disease were assigned to surgery alone or surgery followed by cisplatin/vinorelbine. Median survival was 65.8 months in the treatment arm and 43.7 months in the observation arm (HR, 1.264; 95% CI; 1.05, 1.52; p = 0.013). Survival at 2, 5, and 7 years was 68%, 51%, and 45%, respectively, in the treatment arm and 63%, 43%, and 37% in the observation arm. Five-year survival by stages I, II, and IIIA were 62%, 52%, and 42%, respectively, in the treatment arm and 63%, 39%, and 26% in the observation arm.[105]

Efforts to improve on the efficacy of platinum doublet chemotherapy have focused on antiangiogenesis agents and targeted therapies. The ECOG 1505 clinical trial randomly assigned patients with resected early-stage NSCLC to adjuvant platinum-based chemotherapy with or without bevacizumab; bevacizumab added to platinum-based chemotherapy did not improve OS (HR, 0.99; 95% CI; 0.81, 1.21; p = 0.93) or disease-free survival (DFS) (HR, 0.98; 95% CI; 0.84, 1.14; p = 0.75). Median OS was more than 72 months in both cohorts, and no differences in OS or DFS were observed between four different adjuvant cisplatin-based chemotherapy regimens (docetaxel, vinorelbine, gemcitabine, and pemetrexed [pemetrexed in non-squamous cell only]). Though efficacy was comparable, patients with non-squamous cell carcinoma who received pemetrexed had significantly less total grade 3 to 5 toxicity (p < 0.001), vinorelbine was associated with more neutropenia, and gemcitabine was associated with more thrombocytopenia.

There is growing interest in the incorporation of molecularly targeted agents into the treatment of early-stage NSCLC. At this time, however, such an approach cannot be recommended outside a clinical trial. In the NCIC JBR.19 trial, which was terminated early, administration of the EGFR inhibitor gefitinib after resection of stages I to III NSCLC did not improve OS. Surprisingly, a subset analysis of a small number of patients with tumors harboring activating *EGFR* mutations—a population expected to derive particular benefit from such an approach—suggested the possibility of a detrimental effect from gefitinib.[109] In the RADIANT trial, 973 patients with stage IB to IIIA NSCLC were randomly selected to receive erlotinib or placebo for 2 years. In the 161 (16.5%) of patients in RADIANT whose tumors harbored an *EGFR* mutation, a trend toward increased DFS was observed with erlotinib but the change was not statistically significant. Similarly, the use of ALK inhibitors after surgery for advanced disease remains investigational. The ALCHEMIST trial is currently randomly assigning patients with stage IB to IIIA disease with *EGFR* mutations or *ALK* rearrangements to 2 years of adjuvant erlotinib or crizotinib or placebo.[110] The ALCHEMIST trial also has added an immunotherapy arm to see if the addition of a programmed cell death 1 (PD-1) antibody can improve on standard-of-care treatments in the adjuvant setting.

Neoadjuvant Chemotherapy

The potential advantages of neoadjuvant chemotherapy include:

- Improved tolerability when administered before surgery (90% of patients will receive the planned dose preoperatively and 60% postoperatively);
- Micrometastases treated earlier rather than later; and
- Downstaging with chemotherapy that may allow complete resection.

Two small randomized studies published in 1994 raised considerable interest in the role of neoadjuvant chemotherapy.[111,112] In these trials, each of which involved 60 patients, surgery alone was compared with surgery plus preoperative chemotherapy for stage IIIA disease. Both studies found improved survival for patients receiving neoadjuvant chemotherapy, although criticisms of these studies include their small size, imbalances between the two arms, and poor survival in the control arms.

In a larger randomized French trial, preoperative chemotherapy with mitomycin, ifosfamide, and cisplatin plus surgery was compared with surgery alone for 355 patients with resectable stages I (except T1N0), II, and IIIA (including N2) disease. No benefit with neoadjuvant chemotherapy was found.[113] A subset analysis suggested a survival advantage for neoadjuvant chemotherapy for N0 and N1 disease but not for N2 disease. A European intergroup study (Medical Research Council [MRC] LU22/Dutch Society of Physicians for Pulmonology and Tuberculosis [NVALT] 2/European Organisation for the Research and Treatment of Cancer [EORTC] 08012) randomly assigned 519 patients to receive surgery alone or to receive three cycles of platinum-based chemotherapy followed by surgery. There was no evidence of a benefit in survival (HR, 1.02; 95% CI; 0.80, 1.31; p = 0.86).[114]

Although level 1 evidence supports the role of adjuvant chemotherapy, the exact role of neoadjuvant chemotherapy is less clear. Randomized trials have shown that patients tolerate preoperative chemotherapy better, that dose delivery is better, and that a higher percentage of patients complete preoperative compared with postoperative therapy. Nevertheless, one study has demonstrated a survival advantage for preoperative therapy.[115] However, a meta-analysis of the hazard ratio for neoadjuvant chemotherapy in 15 randomized, controlled trials (2385 patients) showed a significant benefit of preoperative chemotherapy on survival (HR 0.87, 95% CI; 0.78, 0.96, p = 0.007) with an absolute survival improvement of 5 percentage points at 5 years (from 40% to 45%) that is comparable to the LACE meta-analysis of adjuvant chemotherapy clinical trials.[116]

KEY POINTS

- Treatment of stages I and II NSCLC involves surgical resection (if the patient is a candidate) or radiation therapy (if the patient is not a surgical candidate).
- Optimal management of Pancoast tumors consists of concurrent chemoradiation followed by surgical resection.
- Adjuvant chemotherapy consisting of a cisplatin-based combination is indicated for patients with stages II and IIIA disease after surgical resection; though controversial, it should be discussed with patients with larger tumors ≥ 4 cm with negative lymph nodes. Cisplatin is the preferred platinum compound in this curative setting because it has been shown to be more effective than a carboplatin-based regimen, even in stage IV disease. Level 1 evidence from randomized trials suggests that the second drug should be vinorelbine or etoposide, although many clinicians extrapolate from the advanced disease setting and use other cisplatin-based doublets as well, which is supported by current NCCN guidelines.

STAGE III DISEASE

Treatment of locally advanced NSCLC is one of the most controversial issues in the management of lung cancer. Treatment options include surgery or radiation therapy for local control plus chemotherapy to enhance local therapy and to control micrometastases. Interpretation of the results of clinical trials involving patients with locally advanced disease has been clouded by a number of issues, including changing diagnostic techniques, different staging systems, and heterogeneous patient populations with tumors that range from nonbulky stage IIIA (clinical N1 nodes with N2 nodes discovered only at the time of surgery or mediastinoscopy) to bulky N2 nodes (enlarged adenopathy clearly visible on chest x-rays or involvement of multiple node levels) to clearly inoperable stage IIIB disease.

For some subsets of stage IIB (T3N0), IIIA (T3N1), or IIIA (T4N0±1) tumors, the outcome may be less related to the potential of micrometastatic disease and more to the location of the tumor and its resectability (e.g., superior sulcus, chest wall, proximal airway). For each location, a determination must be made on the basis of the potential of surgical resectability and the likelihood of distant metastases, as evidenced by mediastinal metastases.

Nonbulky Stage IIIA Disease

The optimal treatment for nonbulky stage IIIA disease generally consists of a local approach (surgery and/or radiation therapy) plus a systemic treatment (chemotherapy). Possible combinations include surgery followed by adjuvant chemotherapy (with or without thoracic radiation), neoadjuvant chemotherapy (or chemoradiation) followed by surgery, or concurrent or sequential chemotherapy and radiation.

The potential benefit of adding surgery to combined chemoradiation for stage IIIA disease has been evaluated in a randomized, phase III intergroup trial (INT 0139).[117] This study randomly assigned 396 patients with stage T1-3N2M0 NSCLC to concurrent chemoradiation (45 Gy) plus two cycles of cisplatin/etoposide, followed by either surgical resection or continuation of radiation to 61 Gy total plus an additional two cycles of cisplatin/etoposide. Although PFS was significantly longer in the surgery arm (12.8 vs. 10.5 months; $p = 0.02$), there was no significant difference in OS (23.6 vs. 22.2 months; $p = 0.24$). There were more treatment-related deaths in the surgery arm (8% vs. 2%), with the majority of deaths among patients who required pneumonectomy. However, the survival curves subsequently separated so that by the third year, 5-year OS rates were 27.2% and 20.3% (OR for 5-year survival 0.63; 95% CI; 0.36, 1.10; $p = 0.10$). In the trimodality arm, more patients were alive without disease progression ($p = 0.008$), but more patients died without progression ($p = 0.021$). Consistent with other trials, achievement of pathologic N0 status at the time of surgery was associated with improved clinical outcomes (median OS, 34 months).

Occasionally, despite preoperative staging, patients thought to have stage I or II disease are found to have N2 nodal involvement at the time of surgery. For these patients with stage III disease, postoperative radiation therapy (PORT; 50 to 54 Gy) may be considered, usually after completion of adjuvant chemotherapy. In a PORT meta-analysis, this approach reduced locoregional recurrence but did not prolong survival.[118] However, in a more contemporary review of the National Cancer Data Base, patients who received PORT after complete surgical resection and adjuvant chemotherapy for N2 disease had prolonged OS compared with no PORT.[119]

Bulky Stage IIIA (N2) and Stage IIIB Disease

Bulky stage IIIA and stage IIIB tumors are generally considered unresectable, with the

preferred treatment consisting of combined chemoradiation. Chemotherapy plus radiation therapy is the treatment of choice for patients with bulky or inoperable stage IIIA or IIIB disease. Randomized studies have demonstrated an improvement in median and long-term survival with chemotherapy followed by radiation therapy compared with radiation therapy alone.[120,121]

The results from two randomized studies, one conducted in Japan and the other by the Radiation Therapy Oncology Group (RTOG), showed a survival advantage with concurrent chemoradiation compared with a sequential approach, albeit at the expense of increased toxicity. In the Japanese trial, two cycles of mitomycin C/vindesine/cisplatin (MVP) were given concurrently or sequentially with 56 Gy of radiation.[122] Patients in either arm who experienced a response received another two cycles of MVP after radiation therapy was completed. The RR and median survival were significantly improved with concurrent chemoradiotherapy (84% vs. 66%, p = 0.0002; 17 vs. 13 months, p = 0.04). The confirmatory randomized RTOG 9410 trial also showed improved survival with concurrent cisplatin, vinblastine, and radiation therapy compared with sequential chemoradiation (median survival, 17 vs. 13 months; p = 0.08).[123] Notably, the concurrent approach appeared to provide particular benefit to patients older than age 70.

Chemotherapy can be administered in either full systemic doses with radiation therapy, in weekly radiosensitizing doses, or in a combination of the two. Although single-agent weekly carboplatin has not resulted in a survival benefit when administered with radiation therapy, preliminary results from phase I and II studies (Locally Advanced Multimodality Protocol [LAMP]) of weekly doses of paclitaxel (50 mg/m^2) and carboplatin (AUC 2) with concurrent radiation therapy followed by consolidation paclitaxel and carboplatin proved promising.[124] A CALGB trial compared concomitant chemoradiotherapy, consisting of low-dose weekly carboplatin and paclitaxel, with induction therapy prior to the same concomitant chemoradiotherapy regimen. Median survival with chemoradiation was 11.4 months, compared with 14 months for induction chemotherapy followed by chemoradiation (p = 0.154). The median survival achieved in each of the treatment groups was low compared with other reports in the literature, possibly indicating that chemoradiation with induction chemotherapy followed by low-dose weekly carboplatin and paclitaxel is not optimal.

Thus, major questions remain unanswered regarding the best combination and scheduling of chemotherapy and radiation therapy. Although results from the Japanese trial demonstrated a slightly superior outcome with concurrent chemoradiotherapy, the mitomycin-based approach is not widely used in the United States. The RTOG trial involved an older chemotherapy regimen; none of the newer agents, such as carboplatin, paclitaxel, docetaxel, gemcitabine, and vinorelbine, have been tested in this context. SWOG 9504 demonstrated promising results with consolidation docetaxel following full-dose cisplatin/etoposide and concurrent radiation therapy, but these results were not confirmed in a randomized trial.[125-127] Indeed, consolidation docetaxel after concurrent chemoradiation led to more febrile neutropenia, pneumonitis, and hospitalizations and cannot be recommended. The efficacy of sensitizing doses of concurrent chemotherapy also has not been compared with full doses of chemotherapy in randomized trials. Thus, at this point, there is level 1 evidence for concurrent chemoradiation therapy with full-dose cisplatin and etoposide, and level 2 evidence (based on randomized phase II data) supporting weekly low doses of paclitaxel and carboplatin with concurrent radiation therapy followed by consolidation paclitaxel and carboplatin. One phase III trial[128] showed that standard 60-Gy thoracic radiotherapy is superior to a 74-Gy radiation dose with chemotherapy in terms of OS and locoregional control for treatment of stage III NSCLC.[129] These results are not

explained simply by an increase in toxicity. In the phase 3 PROCLAIM trial, 598 patients with stage IIIA/IIIB non-squamous NSCLC were randomly assigned to receive thoracic radiation (60-66 Gy) with either concurrent cisplatin/etoposide for two cycles followed by two cycles of consolidation platinum-based doublet chemotherapy or concurrent cisplatin/pemetrexed for three cycles followed by four cycles of pemetrexed consolidation. The cisplatin/pemetrexed arm was not superior to the cisplatin/etoposide arm in terms of OS (HR, 0.98; 95% CI, 0.79, 1.20; median, 26.8 vs. 25.0 months; p = .831), though the cisplatin/pemetrexed arm had a lower incidence of any drug-related grade 3 to 4 adverse events (64.0% vs. 76.8%; p = .001), including neutropenia (24.4% vs. 44.5%; p < .001).[130]

Currently, there is no established role for molecularly targeted agents in the treatment of locally advanced NSCLC. In SWOG 0023, patients with stage III NSCLC whose disease had not progressed after concurrent chemoradiation (with cisplatin/etoposide) and consolidation docetaxel were randomly assigned to the EGFR-TKI gefitinib or to placebo maintenance therapy.[131] Unexpectedly, though the sample size was small, OS was significantly worse in the gefitinib arm (median, 23 vs. 35 months; p = 0.01). This result remains largely unexplained, though the sample size was small. The antiangiogenic drug bevacizumab has been added to concurrent chemoradiotherapy for stage III NSCLC. In small series, this combination was associated with substantial toxicities, including an increased incidence of tracheoesophageal fistulae, and should not be used with concurrent thoracic radiotherapy.[132]

Stage III Recommendations

Treatment of patients with stage III, N2 NSCLC is not standardized, as indicated in the previous discussion. Although results from ongoing or recently completed randomized studies are maturing, some general guidelines for treating a patient can be identified:

- Clinical N0 disease by CT and PET—A resection should be performed, with mediastinal sampling or complete dissection at the time of surgery. If microscopic N2 (or N1) disease is detected at surgery, postoperative chemotherapy should be administered. For N2 disease detected at surgery, PORT can be considered.
- Nonbulky N2 by CT (e.g., one node measuring 1 to 2 cm) and/or by PET—The patient's age, PS, and comorbid conditions should be considered. Level 1 evidence exists for a combined modality approach with chemotherapy and radiation therapy. If the patient is a surgical candidate, it is not unreasonable to have a discussion regarding the use of surgery plus preoperative chemotherapy and/or radiation therapy, stressing that the optimal treatment sequence has not been clearly identified. Some surgeons recommend resampling the mediastinal nodes after two cycles of the induction chemotherapy, rationalizing that if the N2 nodes remain positive following chemotherapy, a definitive resection should not be attempted and the patient should proceed with definitive radiation therapy or with combined chemotherapy and radiation. Combined preoperative chemoradiation should be administered cautiously and only to a fit patient who will be undergoing resection by an experienced thoracic surgeon (given the high incidence of postoperative deaths). Particular caution should be exercised for patients undergoing a right-sided pneumonectomy. Overall, chemotherapy plus concurrent thoracic radiation therapy remains the standard of care in this setting.
- Bulky N2 nodes—Chemotherapy plus concurrent radiation therapy is indicated. The presence of pathologically involved N2 nodes should be confirmed when possible,

because enlarged nodes detected on CT will be pathologically negative for approximately 30% of patients. The patient's age, PS, and comorbid conditions must be considered. Concurrent chemoradiotherapy provides a small survival benefit, albeit at the expense of an increase in toxicity, and thus should be reserved for patients with good PS. Weekly, low-dose, concurrent chemotherapy has not been compared with full-dose chemotherapy in randomized trials, although it is often administered concurrently with radiation therapy if followed by two to three cycles of standard-dose chemotherapy.

KEY POINTS

- Optimal treatment of "nonbulky" stage IIIA disease (e.g., small, single-station node) continues to evolve but optimally involves both systemic chemotherapy and local therapy (surgery and/or radiation). For patients with multistation N2 disease or bulky N2 nodes (3 cm or larger), concurrent chemotherapy plus radiation therapy is considered standard of care.
- For nonbulky N2 disease, a trimodality approach with chemoradiotherapy followed by surgery can be considered, though patients requiring pneumonectomy (particularly right-sided pneumonectomy) had poor survival. Management decisions regarding stage IIIA NSCLC should be made by a multidisciplinary thoracic tumor board.
- Curative intent treatment of stage IIIB NSCLC similarly involves combined-modality treatment with chemotherapy and radiation therapy. Evidence from randomized trials suggests that concurrent chemotherapy and radiation therapy will result in the best survival, albeit with an increase in toxicity.
- The optimal chemoradiation schedule remains debatable; there is level 1 evidence for concurrent chemoradiation therapy with full-dose cisplatin and etoposide, and level 2 evidence (based on randomized, phase II data) supporting weekly low doses of paclitaxel and carboplatin with concurrent radiation therapy, followed by consolidation paclitaxel and carboplatin.

STAGE IV DISEASE

Chemotherapy improves survival for patients with metastatic NSCLC (a 1-year survival rate of approximately 10% for untreated patients compared with 35 to 40% for treated patients). In addition, chemotherapy may reduce symptoms and improve quality of life; therefore, it is usually recommended for patients with good PS. Because chemotherapy is not curative, goals for treatment should be discussed with the patient, including palliation of symptoms and a modest improvement in survival.

The principal factors predictive of response to chemotherapy and survival are PS and bulk of disease. Favorable prognostic factors include no weight loss, female sex, normal level of serum lactate dehydrogenase, and no bone or liver metastases.

First-Line Treatment

Chemotherapy. Chemotherapy for metastatic NSCLC has traditionally consisted of a platinum-based doublet regimen. Results from randomized studies have shown an improvement in

survival, symptoms, and quality of life for patients treated with cisplatin-based therapy compared with patients receiving best supportive care. Median survival and 1-year survival rates have increasingly improved with use of second- and third-generation chemotherapy regimens (Table 8-8).

Table 8-8 Survival Rates for Chemotherapy for Non-Small Cell Lung Cancer

	Chemotherapy Agents	Median Survival (months)	1-Year Survival (%)	2-Year Survival (%)
Best supportive care only		4–5	5–10	< 5
First-generation chemotherapy regimens	Cisplatin, vinblastine, mitomycin, vindesine	5–6	10–15	< 5
Second-generation chemotherapy regimens	Carboplatin, etoposide	6	20–25	< 10
Third-generation chemotherapy regimens	Paclitaxel and docetaxel, gemcitabine, vinorelbine, pemetrexed, nab-paclitaxel	8–9	35–40	10
Nonsquamous histology (no hemoptysis)	Carboplatin and paclitaxel plus bevacizumab	12	50	20
Nonsquamous histology	Cisplatin plus pemetrexed	12	50	20
EGFR mutations	EGFR-TKI before or after doublet chemotherapy	18–27		

Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

Until recently, findings from numerous randomized studies have not shown a clinically significant advantage of any platinum-based doublet regimen, although there are differences in toxicity, cost, schedule, and convenience. However, there are now data supporting different treatment approaches depending on the histologic subtype of NSCLC, based on efficacy (pemetrexed) and safety (bevacizumab). Pemetrexed is an inhibitor of thymidylate synthase and other folate-dependent enzymes, including dihydrofolate reductase and glycinamide ribonucleotide formyltransferase. A phase III trial of more than 1700 patients with chemotherapy-naive disease has been reported, comparing pemetrexed/cisplatin with gemcitabine/cisplatin.[133] OS was the same in the two arms, with an improved toxicity profile in the pemetrexed arm. However, in a prespecified subset analysis, OS was statistically superior for cisplatin/pemetrexed compared with cisplatin/gemcitabine for patients with adenocarcinoma (12.6 vs. 10.9 months) and large cell carcinoma histology (10.4 vs. 6.7 months). Conversely, patients with squamous cell histology experienced a significant improvement in survival with cisplatin/gemcitabine compared with cisplatin/pemetrexed (10.8 vs. 9.4 months). This and other studies have led to approval of pemetrexed for the first-line, maintenance, and second-line treatment of nonsquamous cell NSCLC. One proposed explanation for the differential pemetrexed sensitivity of squamous and nonsquamous NSCLC is higher expression and activity of thymidylate synthase in squamous tumors.[134]

Bevacizumab. Bevacizumab has been approved for the management of non–squamous cell carcinoma based on results from the Eastern Cooperative Oncology Group (ECOG) 4599 phase III trial of 878 patients randomly assigned to chemotherapy (paclitaxel and carboplatin) or to chemotherapy plus 15 mg/kg of bevacizumab every 3 weeks.[57] Median survival for patients who received chemotherapy plus bevacizumab was 12.3 months, compared with 10.3 months for patients who received chemotherapy alone (HR. 0.79; p = 0.003). Median duration

of PFS for patients who received chemotherapy plus bevacizumab was 6.2 months, compared with 4.5 months for those who received chemotherapy alone (HR, 0.66; $p < 0.001$), with corresponding RRs of 35% and 15%, respectively ($p < 0.001$). However, because of the grade 3 to 4 bleeding episodes observed in the phase II study that preceded this one, it should be noted that eligibility for this study was restricted to patients with non–squamous cell carcinoma (because of higher levels of severe hemoptysis observed in squamous tumors) and no brain metastases, as well as no hemoptysis, bleeding disorders, or anticoagulation requirement. Despite these restrictions, significant bleeding was more frequent for patients who received chemotherapy plus bevacizumab (4.4% vs. 0.9%; $p = 0.001$). There were 15 treatment-related deaths in the group of patients who received chemotherapy plus bevacizumab, including 5 resulting from pulmonary hemorrhage. Thus, the risks and benefits of bevacizumab should be clearly delineated to patients with advanced NSCLC.

A second randomized study of bevacizumab involving more than 1000 patients has been conducted (the Avastin in Lung [AVAiL] trial).[135] Unlike the ECOG study, this study involved gemcitabine and cisplatin and randomly assigned patients to chemotherapy plus placebo, chemotherapy with 7.5 mg/kg of bevacizumab every 3 weeks, or chemotherapy with 15 mg/kg of bevacizumab every 3 weeks. The study met its primary endpoint of PFS, with HRs of 0.75 and 0.82 for the low- and high-dose bevacizumab arms, respectively. However, the absolute benefit was modest (median PFS, 6.7 and 6.5 months vs. 6.1 months), with no improvement in survival. It is unclear whether the lack of survival benefit is a result of the differences in chemotherapy doublets between the ECOG study and the AVAiL trial, differences in bevacizumab dose, or differences in study design, of which there were many.

Subsequent experience with bevacizumab and other antiangiogenic agents in lung cancer and other malignancies has provided further insight into the nature of their vascular complications, in some instances suggesting that it may be feasible to expand patient eligibility for these agents. Squamous cell tumors remain an absolute contraindication to bevacizumab therapy. Although it has been proposed that squamous cell histology may be a surrogate marker of central tumor location and proximity to vascular structures, neither of these anatomic characteristics has emerged as an independent risk factor for severe pulmonary hemorrhage. In the AVAiL trial, central lesions (defined as tumors in which the center of the mass was within the hilar structure) were present in 38% of patients and were not associated with increased rates of grade 3 to 4 pulmonary hemorrhage. The only potential radiographic risk factor identified to date is baseline tumor cavitation (OR, 4.5; 95% CI; 0.73, 28.33; $p = 0.06$).[136]

The FDA approval of bevacizumab for the treatment of glioblastoma multiforme has supported the concept of using bevacizumab for patients with intracranial malignancy. The phase II PASSPORT trial administered bevacizumab plus chemotherapy to 115 patients with brain metastases previously treated with radiation or surgery. No cases of CNS hemorrhage occurred.[137] The use of bevacizumab for patients receiving antiplatelet agents was evaluated in a pooled analysis of five randomized trials in NSCLC, colorectal cancer, and breast cancer, in which the concurrent administration of bevacizumab, chemotherapy, and low-dose prophylactic aspirin did not increase the risk of bleeding compared with chemotherapy and aspirin alone.[138] The use of bevacizumab for patients receiving therapeutic anticoagulation has not been described extensively. In the AVAiL trial, 86 patients in whom venous thromboembolism developed during the study were treated with full-dose anticoagulation. Once on a stable anticoagulation regimen, patients who had been randomly assigned to receive bevacizumab were permitted to resume it. Patients who were taking anticoagulants experienced higher bleeding rates than patients not taking them, regardless of whether they received

bevacizumab.[139] As a result of these and other reports, bevacizumab is now being used for patients with previously treated brain metastases. Although not an absolute contraindication, given the limited data available, caution should be exercised before initiating bevacizumab for patients receiving anticoagulants.

Immunotherapy—First Line. Because of the success and approval of PD-1 and PD-1 ligand (PD-L1) antibodies as second-line treatment for metastatic NSCLC, these drugs are increasingly being studied as first-line NSCLC treatment (Table 8-9). In the KEYNOTE-024 trial, 305 patients with PD-L1 expression on at least 50% of tumor cells and no *EGFR* mutation or *ALK* translocation were randomly assigned to receive either pembrolizumab or the investigator's choice of platinum-based chemotherapy. Crossover from the chemotherapy group to the pembrolizumab group was allowed at disease progression. The primary endpoint of PFS was superior in the pembrolizumab arm compared to chemotherapy arm (median PFS, 10.3 months; 95% CI; 6.7, not reached, vs. median PFS, 6.0 months; 95% CI; 4.2, 6.2) (HR, 0.50; 95% CI; 0.37, 0.68; $p < 0.001$). OS was also significantly and substantially improved in the pembrolizumab arm (HR, 0.60; 95% CI; 0.41, 0.89; $p = 0.005$). The response rate (RR) was higher with pembrolizumab (44.8% vs. 27.8%), and treatment-related adverse events of any grade were less frequent (occurring in 73.4% vs. 90.0% of patients), as were serious treatment-related adverse events (26.6% vs. 53.3%).[140] Based on these data, pembrolizumab is now FDA-approved as first-line treatment for stage IV NSCLC with PD-L1 expression on at least 50% of tumor cells using the companion diagnostic DAKO 22C3 antibody.

Table 8-9 **Selected Trials of Immunotherapy Agents in Non-Small Cell Lung Cancer**

Checkpoint Inhibitor	Target	Biomarker Antibody	Randomized First-Line Trials (vs. Platinum-Based Chemotherapy)	Randomized Second-Line Trials (vs. Single-Agent Docetaxel)
Pembrolizumab[140,217]	PD-1	DAKO 22C3 (PD-L1)	KEYNOTE-024; 305 patients; eligibility, ≥ 50% PD-L1 expression; PFS HR, 0.50; 95% CI; 0.37, 0.68; $p < 0.001$; OS HR 0.60; 95% CI; 0.41, 0.89; $p = 0.005$; ORR, 44.8% vs. 27.8%	KEYNOTE-010; 1034 patients; eligibility ≥ 1% PD-L1 expression; for 2 mg/kg: HR, 0.71; 95% CI; 0.58, 0.88; $p = 0.0008$; for 10 mg/kg HR, 0.61; 95% CI; 0.49, 0.75; $p < 0.0001$
Nivolumab[214]	PD-1	DAKO 28-8 (PD-L1)	CHECKMATE 026; 541 patients; ≥ 5% PD-L1 expression; PFS HR, 1.15; 95% CI; 0.91, 1.45; OS HR 1.02; 95% CI; 0.8, 1.3	CHECKMATE 017; 272 patients; squamous NSCLC; median OS, 9.2 months vs. 6.0 months, $p < 0.001$; HR, 0.59; 1-year OS, 42% vs. 24%; CHECKMATE 057; 582 patients; non-squamous; median OS, 12.2 months (95% CI; 9.7, 15.0) vs. 9.4 months (95% CI; 8.1, 10.7) HR, 0.73; $p = 0.002$). 1 year OS 51% vs. 39%
Atezolizumab[218]	PD-L1	Ventana SP142 (TC/IC)	Final results pending	OAK; 850 patients; median OS, 13.8 months vs. 9.6 months; HR 0.73, 95% CI 0.62, 0.87, $p = 0.0003$

More recently, the FDA approved pembrolizumab in combination with carboplatin and pemetrexed agnostic of PD-L1 expression in non–squamous NSCLC. This approval was based on data from the KEYNOTE-021 trial. In one cohort of this phase II trial, 123 untreated patients were randomly assigned to either the triplet carboplatin/pemetrexed/pembrolizumab or the

doublet carboplatin/pemetrexed. The primary endpoint of ORR was superior with the triplet (55% vs. 26%; p = 0.0016) as was PFS (HR, 0.53; p = 0.01).[141] Thus, for NSCLC for non–squamous NSCLC, the combination of carboplatin/pemetrexed and pembrolizumab is a potential treatment option. OS data for the combination is immature and it is unclear at this point whether the triplet enhances OS compared to sequencing platinum-based chemotherapy and pembrolizumab separately. Results from the confirmatory randomized phase 3 trial of this triplet (KEYNOTE-189) are eagerly anticipated.

The CHECKMATE 026 trial randomly assigned 541 patients whose tumors were PD-L1–positive. The primary endpoint was PFS in patients with 5% or greater PD-L1 expression. Among these patients, nivolumab did not improve median PFS compared to investigators' choice of chemotherapy (4.2 months vs. 5.9 months; HR, 1.15; 95% CI; 0.91, 1.45). Overall survival was also not improved (median OS, 14.4 months for nivolumab vs. 13.2 months for chemotherapy; HR, 1.02; 95% CI; 0.8, 1.3). The discrepancy between the survival outcomes for pembrolizumab and nivolumab in the first-line setting is unclear and cannot be explained just by selection of the 50% versus 5% PD-L1 expression cutpoint, since in the CHECKMATE 026 subset analysis, survival endpoints were not improved with nivolumab even when PD-L1 expression was 50% or greater.

EGFR Inhibitors. There are two main approaches to targeting EGFR: TKIs and monoclonal antibodies. TKIs (e.g., erlotinib, gefitinib) cross the cell membrane, binding to and inhibiting the function of the intracellular tyrosine kinase domain. Monoclonal antibodies bind to the extracellular domain of EGFR, interfering with ligand binding and receptor activation.

It is clear that EGFR-TKIs provide superior radiographic RR and PFS compared with conventional chemotherapy for patients with tumors harboring activating *EGFR* mutations (Table 8-10).[142-161] Although no survival benefit has been observed in randomized studies, this has been postulated to be a result of patients whose disease has progressed crossing over from the chemotherapy arm to the EGFR-TKI arm. Importantly, clinicopathologic features appear insufficient to predict the presence of *EGFR* mutations. In the Iressa Pan-Asian Survival Study (IPASS) trial, only 60% of East Asians with adenocarcinoma who were never- or former light smokers had *EGFR* mutations.[148] It should be noted that despite the emphasis on the use of EGFR-TKIs in *EGFR*-mutated cancers, randomized studies such as BR.21 have demonstrated a benefit in PFS and OS in an unselected patient population in the second- and third-line settings.[83]

Table 8-10 **Selected Phase III Trials of Epidermal Growth Factor Receptor (EGFR) Inhibitors for Non-Small Cell Lung Cancer (NSCLC)**

Trial*	Population	Line of Therapy	Treatment	Number of Patients	Primary Outcome(s)
RADIANT	*EGFR* FISH-positive stage IB-IIIA	Adjuvant	Adjuvant erlotinib × 2 yr vs. placebo	973	DFS, 50.5 mo (EGFR FISH + erlotinib) vs. 48.2 mo (placebo) (p = 0.32); 46.4 mo (*EGFR* mutation + subset erlotinib) vs. 28.5 mo (placebo) (p = 0.039; not significant because of hierarchical testing)
NCIC JBR.10[142]	Unselected stage IB-IIIA	Adjuvant	Adjuvant gefitinib vs. placebo	Closed after 500 (of 1200 planned)	OS median survival: 5.1 yr (gefitinib) vs. not reached (placebo) (p = 0.130)
Rigas et al.[143]	Unselected, unresectable stage III	Stage III maintenance	Chemoradiation (cisplatin/docetaxel) ± maintenance erlotinib	253	PFS, 13.5 mo (erlotinib) vs. 10.4 mo (placebo) (p = 0.12)
SWOG 0023[131]	Unselected, unresectable stage III	Stage III maintenance	Chemoradiation (cisplatin/etoposide) then consolidation docetaxel ± maintenance gefitinib	Closed after 243 (of 672 planned)	OS, 23 mo (gefitinib) vs. 35 mo (placebo) (p = 0.01)
RTOG 0617[126]	Unselected, unresectable stage III	Stage III	Chemoradiation (carboplatin/paclitaxel) ± cetuximab	465	OS, 23.1 mo (cetuximab) vs. 23.5 mo (placebo) (p = 0.484)
TALENT[144]	Unselected stage IIIB-IV	First-line metastatic	Cisplatin/gemcitabine ± erlotinib	1172	OS, 10.8 mo (chemo plus erlotinib) vs. 11.0 mo (chemo alone) (p = 0.49)
TRIBUTE[145]	Unselected stage IIIB-IV	First-line metastatic	Carboplatin/paclitaxel ± erlotinib	1059	OS, 10.6 mo (erlotinib) vs. 10.5 mo (placebo) (p = 0.95)
INTACT-1[146]	Unselected stage IIIB-IV	First-line metastatic	Cisplatin/gemcitabine ± gefitinib	1093	OS, 9.9 mo (gefitinib 500 mg/day) vs. 9.9 mo (gefitinib 250 mg/day) vs. 10.9 mo (placebo) (p = 0.46)
INTACT 2[147]	Unselected stage IIIB-IV	First-line metastatic	Carboplatin/paclitaxel ± gefitinib	1037	OS, 8.7 mo (gefitinib 500 mg/day) vs. 9.8 mo (gefitinib 250 mg/day) vs. 9.9 mo (placebo) (p = 0.64)
IPASS[148]	East Asian nonsmokers or former light smokers with stage IIIB-IV adenocarcinoma	First-line metastatic	Gefitinib vs. carboplatin/paclitaxel	1217	12-mo PFS, 24.9% (gefitinib) vs. 6.7% (carboplatin/paclitaxel) (p < 0.001)
WJTOG3405[149]	Stage IIIB-IV with *EGFR* mutations in Japan	First-line metastatic	Gefitinib vs. cisplatin/docetaxel	172	PFS, 9.2 mo (gefitinib) vs. 6.3 mo (cisplatin/docetaxel) (p < 0.001)
First-SIGNAL[150]	Korean never-smokers with IIIB-IV	First-line metastatic	Gefitinib vs. cisplatin/gemcitabine	313	OS, 20.3 mo (gefitinib) vs. 23.1 mo (cisplatin/gemcitabine) (p = 0.43)
NEJ002[151]	Stage IIIB-IV with *EGFR* mutations in Japan	First-line metastatic	Gefitinib vs. carboplatin/paclitaxel	200	PFS, 10.4 mo (gefitinib) vs. 5.5 mo (carboplatin/paclitaxel) (p < 0.001)
OPTIMAL[152]	Stage IIIB-IV with *EGFR* mutations in China	First-line metastatic	Erlotinib vs. gemcitabine/carboplatin	165	PFS, 13.1 mo (erlotinib) vs. 4.6 mo (gemcitabine/carboplatin) (p < 0.0001)
FLEX[153]	EGFR-positive stage IIIB-IV	First-line metastatic	Cisplatin/vinorelbine ± cetuximab	1125	OS, 11.3 mo (chemo plus cetuximab) vs. 10.1 mo (chemo alone) (p = 0.04)
BMS099[154]	Unselected stage IIIB-IV	First-line metastatic	Carboplatin/taxane ± cetuximab	676	PFS, 4.4 mo (chemo plus cetuximab) vs. 4.2 mo (chemo alone) (p = 0.24) [secondary endpoint, OS, 9.7 mo (chemo plus cetuximab) vs. 8.4 mo (chemo alone) (p = 0.17)]
SATURN[155]	Unselected stage IIIB-IV	First-line maintenance	4 cycles platinum doublet chemotherapy followed by maintenance erlotinib vs. placebo	889	6-mo PFS, 31% vs. 17% (p < 0.0001) [secondary endpoint, OS, 12 mo (erlotinib) vs. 11 mo (placebo); p < 0.05)]
ATLAS[156]	Non-squamous stage IIIB-IV	First-line maintenance	4 cycles platinum doublet chemotherapy followed by maintenance bevacizumab ± erlotinib	768	PFS, 4.8 mo (bevacizumab + erlotinib) vs. 3.7 mo (bevacizumab alone) (p = 0.001)
BR21[83]	Unselected stage IIIB-IV	Second- and third-line	Erlotinib vs. placebo	731	OS, 6.7 mo (erlotinib) vs. 4.7 mo (placebo) (p < 0.001)
ISEL[157]	Unselected stage IIIB-IV	Second-line	Gefitinib vs. placebo	1692	OS, 5.6 mo (gefitinib) vs. 5.1 mo (placebo) (p = 0.09)
INTEREST[158]	Unselected stage IIIB-IV	Second-line	Gefitinib vs. docetaxel	1466	OS, 7.6 mo (gefitinib) vs. 8.0 mo (docetaxel) (p > 0.05)
EURTAC[159]	Stage IV *EGFR*-mutation-positive in Europe	First-line metastatic	Erlotinib vs. carboplatin/docetaxel or carboplatin/gemcitabine	174	PFS, 9.7 mo vs. 5.2 mo (p < 0.0001)
LUX-Lung 3[160]	Stage IV, *EGFR*-mutation-positive	First-line, metastatic	Afatinib vs. cisplatin/pemetrexed	345	PFS, 13.6 mo vs. 6.9 months (p = 0.001)
LUX-Lung 6[161]	Stage IV, *EGFR*-mutation-positive	First-line, metastatic	Afatinib vs. cisplatin/gemcitabine	364	PFS, 11.0 mo vs. 5.6 mo (p < 0.0001)
LUX-Lung 7[163]	Stage IV, *EGFR*-mutation-positive	First-line, metastatic	Afatinib vs. gefitinib	319	PFS, 11.0 months vs. 10.9 months; HR, 0.73; 95% CI; 0.57, 0.95; p = 0.017
LUX-Lung 8[211]	Stage IV squamous NSCLC	Second-line, metastatic	Afatinib vs. erlotinib	795	OS, 7.9 mo vs. 6.8 mo, p = 0.0077). PFS, 2.6 mo [95% CI vs. 1.9 mo; HR, 0.81; p = 0.0103)
ILND[196]	Stage IV EGFR wt NSCLC	Maintenance therapy vs. second-line, metastatic	Erlotinib maintenance vs. second-line erlotinib	643	OS, 9.7 mo vs. 9.5 mo; HR, 1.02; 95% CI; 0.85, 1.22; log-rank p = 0.82.

Abbreviations: chemo, chemotherapy; DFS, disease-free survival; OS, overall survival; PFS, progression-free survival; wt, wild-type.
*These studies used American Joint Commission on Cancer staging prior to 8th edition.

Afatinib is an irreversible EGFR inhibitor and a HER2 inhibitor approved by the FDA for first-line treatment of patients with metastatic NSCLC with tumors harboring *EGFR*-activating mutations.[160,161] Approval was based on afatinib's improving median PFS compared with cisplatin/pemetrexed for patients with NSCLC with *EGFR*-mutated tumors (median PFS, 11.1 vs. 6.9 months; HR, 0.58; p < 0.001). Despite an initial dramatic response to EGFR inhibitors among patients with *EGFR*-mutated NSCLC, resistance generally develops within 2 years. Approximately half of these cases are associated with a secondary *T790M* mutation, which results in steric hindrance to EGFR-TKI binding (analogous to the *T315I* mutation in chronic myeloid leukemia) and altered ATP handling.[162,163] Additional cases with secondary resistance develop because of overexpression of c-Met, a receptor tyrosine kinase that activates downstream components of the EGFR signal transduction cascade ("molecular cross talk").[164]

A subset of *EGFR*-mutated tumors can become resistant to EGFR-TKI therapy by transforming their histology into small cell lung cancer histology and may respond to regimens such as those used for small cell lung cancer.[165] Mutations in PI3CA and HER2 amplification, among other bypass tracts, have also been implicated as resistance mechanisms. Therapeutic strategies to overcome these processes, including EGFR inhibitors with potent activity against EGFR-T790M (the most common resistant mechanism to currently approved EGFR TKIs and with novel combination regimens such as afatinib and the EGFR-monoclonal antibody cetuximab[166]), remain under investigation.

Indeed, the third-generation EGFR TKI osimertinib that binds potently to mutant EGFR harboring the *T790M* gatekeeper resistance mutation has been approved for use in advanced *EGFR*-mutant NSCLC with the *T790M* mutation after progression on prior EGFR-TKI. For these patients, the median PFS was 9.6 months and the objective RR was 61%. PFS and objective RR was substantially lower in treated patients with EGFR-T790M–negative tumors (PFS, 2.8 months; ORR, 21%).[167] Based on these data demonstrating high ORR and prolonged PFS, osimertinib was approved by the FDA for *EGFR*-mutant NSCLC harboring EGFR-T790M.

Although EGFR inhibitors improve PFS as first-line therapy for patients with tumors harboring activating *EGFR* mutations, it has not been shown that the order in which these EGFR inhibitors are received affects OS. In the IPASS trial, the gefitinib arm had clinically and significantly longer PFS as compared with the carboplatin/paclitaxel arm in *EGFR*-mutated tumors. There was no significant difference in OS, presumably because of the high proportion of crossover to gefitinib in the carboplatin/paclitaxel arm. Similarly, a registry study of *EGFR*-mutated NSCLC from Spain has demonstrated no difference between first- or second-line administration of EGFR inhibitors in OS.[168] In the Northeast Japan Study Group (NEJ) 002 trial, 200 patients with EGFR-mutated tumors were randomly assigned to carboplatin/paclitaxel or gefitinib. Gefitinib yielded superior PFS (10.8 vs. 5.4 months; HR, 0.3; 95% CI; 0.22, 0.41; $p < 0.001$) and radiographic RR (74% vs. 31%; $p < 0.001$). Although there was a numerical improvement in median OS (30.5 vs. 23.6 months), it was not statistically significant ($p = 0.31$).[151] A key observation from the IPASS trial is that, for patients with *EGFR* wild-type tumors, PFS with gefitinib in the first-line setting is substantially inferior to PFS with chemotherapy (HR, 2.85; 95% CI; 2.05, 3.98; $p < 0.001$), which is not the case in the second-line setting. A clinical trial in a predominantly European population that compared erlotinib to cisplatin-based doublet chemotherapy also showed much higher RRs and median PFS for patients with metastatic lung cancers harboring *EGFR* mutations (RR, 58 vs. 15%; median PFS, 9.7 vs. 5.2 months; $p < 0.0001$).[159]

Results combining EGFR inhibitors with cytotoxic chemotherapy are mixed. Four randomized trials (INTACT [Iressa NSCLC Trial Assessing Combination Treatment]-1, INTACT-2, TALENT [Tarceva Lung Cancer Investigation], and TRIBUTE [Tarceva Responses in Conjunction with Paclitaxel and Carboplatin]) failed to demonstrate a survival benefit, an outcome that has been attributed to enrollment of an unselected population and to potential pharmacodynamic interference between cytostatic EGFR-TKIs and cell-cycle–dependent chemotherapeutic agents.[169] Achieving pharmacodynamic separation by sequencing treatment to prevent G1-cell-cycle arrest from EGFR inhibitors from interfering with optimal chemotherapeutic effect was tested in the FASTACT-2 trial. In a predominantly Asian population enriched for *EGFR*-activating mutations, combination platinum and gemcitabine was intercalated with erlotinib. Compared with platinum/gemcitabine alone, this combination yielded improved PFS and OS (7.6 months vs. 6 months, $p < 0.0001$; 18.3 months vs. 15.2 months, $p = 0.042$). Patient benefit was restricted primarily to patients with tumors harboring *EGFR*-activating mutations (PFS,

16.8 vs. 6.9 months, p < 0.0001; OS, 31.4 vs. 20.6 months, p = 0.009).[170] Despite the FASTACT-2 results, single-agent EGFR-TKI still remains the first-line standard of care for patients with advanced NSCLC harboring *EGFR*-activating mutations.

In contrast to EGFR-TKIs, the effect of anti-EGFR monoclonal antibodies in NSCLC does not appear to be associated with the presence of activating *EGFR* mutations, nor is the effect associated with the presence of *KRAS* mutations, as has been shown in colorectal cancer.[171,172] Two phase III clinical trials incorporating anti-EGFR monoclonal antibodies have been performed. The BMS099 trial randomly assigned patients to platinum/taxane chemotherapy with or without cetuximab.[154] No difference in OS was noted. The First-line in Lung cancer with ErbituX (FLEX) trial randomly assigned patients to cisplatin/vinorelbine with or without cetuximab.[153] The cetuximab-containing arm demonstrated a statistically significant improvement in OS (HR, 0.87; 95% CI; 0.76, 0.99; p = 0.04), with an increase in median OS from 10.1 to 11.3 months. Whether differences in the chemotherapy regimen, geographic setting, or inclusion criteria (FLEX mandated EGFR-positive tumors, defined as at least one cell staining positive on IHC) underlie the different results of the BMS099 and FLEX trials is not known. As for first-line treatment in stage IV squamous cell NSCLC, another EGFR monoclonal antibody, necitumumab, modestly improved OS when added to cisplatin and gemcitabine. In the SQUIRE trial, 1093 patients were randomly assigned to receive either cisplatin/gemcitabine or cisplatin/gemcitabine plus necitumumab. The addition of necitumumab modestly improved OS (median OS, 11.5 vs. 9.9 months; HR, 0.84; p = 0.012) and PFS (HR, 0.85; p = 0.020). No difference in ORR was noted (31% vs. 29%; p = 0.400).[173]

Treatment of ALK and ROS1 Rearranged NSCLC

Crizotinib. In 2011, the FDA approved the ALK inhibitor crizotinib for the treatment of NSCLC harboring *EML4-ALK* fusions. The efficacy of crizotinib in ALK-positive NSCLC was initially seen in an expanded cohort of a multicenter phase I study.[174] Tumor specimens from approximately 1500 patients with advanced NSCLC were screened for *ALK* translocations. A total of 82 patients, most of whom were treated previously, were enrolled. The radiographic RR was 57% and stable disease was 33%, yielding a clinical benefit rate of 90%. The estimated 6-month PFS rate was 72%. A retrospective analysis looked at outcomes of 82 patients with *ALK*-positive disease who were given crizotinib and compared them with 23 control patients with *ALK*-positive disease who did not receive crizotinib. Survival of 30 patients with *ALK*-positive disease who were given crizotinib in the second- or third-line setting was significantly longer than in the 23 control patients with *ALK*-positive disease given any second-line therapy other than crizotinib (median OS, not reached vs. 6 months; 1-year OS, 70% vs. 44%; and 2-year OS, 55% vs. 12%; p = 0.004).[175] A phase III clinical trial (PROFILE 1007) confirmed that crizotinib had a higher RR and PFS compared with investigators' choice of docetaxel or pemetrexed for patients with *ALK*-positive tumors whose disease progressed after first-line chemotherapy (ORR, 65% vs. 20%; median PFS, 7.7 vs. 3 months; p < 0.0001).[176] As for first-line treatment, in a phase III trial (PROFILE 1014), crizotinib improved median PFS compared with standard platinum and pemetrexed chemotherapy (10.9 months vs. 7 months; HR, 0.45; p < 0.001) in *ALK*-rearranged metastatic NSCLC.[177] Thus, crizotinib should be employed as first-line treatment in *ALK*-rearranged NSCLC.

A high RR (72%) and exceptional median PFS (19.2 months) for patients with NSCLC harboring a *ROS1* gene rearrangement treated with crizotinib has also been observed in clinical trials; and crizotinib is now FDA approved for advanced ROS1 rearranged NSCLC.[47]

Ceritinib. Ceritinib is an oral TKI of ALK that is 20 times more potent than crizotinib. The FDA approved ceritinib in 2014 for the treatment of *ALK*-rearranged NSCLC after progression of the disease on crizotinib. This approval was based on a clinical trial in metastatic *ALK*-rearranged NSCLC showing an RR of 58% for patients who received at least 400 mg of ceritinib daily. For patients who had progressive disease on crizotinib, the RR was 56% and PFS 7.0 months.[178]

Alectinib. Alectinib is another oral TKI of ALK that is more potent than crizotinib. The FDA approved alectinib in 2015 for the treatment of *ALK*-rearranged NSCLC after progression of the disease on crizotinib. This approval was based on clinical trials in metastatic *ALK*-rearranged NSCLC showing an RR of 50% in patients with progressive disease on crizotinib with a median duration of response of 11.2 months.[179] It is also highly active in the CNS, with a CNS response rate of 64.0% (95% CI; 49.2, 77.1), a CNS disease control rate of 90.0% (95% CI; 78.2, 96.7), and a median CNS duration of response of 10.8 months in a pooled analysis.[180] Alectinib is currently being studied in the first-line setting and has superior PFS compared to crizotinib in two phase III, randomized clinical trials in the first-line setting (the ALEX study and the J-ALEX study). Impressively, in the ALEX study, investigator-assessed median PFS was not reached for alectinib (95% CI; 17.7 months to not estimable) and was 11.1 months for crizotinib (HR, 0.47; 95% CI; 0.34, 0.65; $p < 0.001$).[181] In the Japanese J-ALEX study results were comparable with median PFS not reached (95% CI: 20.3-Not Estimated) with alectinib while it was 10.2 months (95% CI: 8.2-12.0) with crizotinib.[182] Overall survival data are not yet mature, but based on these strongly positive studies in terms of PFS, alectinib will likely become the standard first-line treatment for *ALK*-rearranged NSCLC.

Additional ALK Inhibitors in Development. Brigatinib is another next-generation ALK inhibitor that was granted accelerated approval by the FDA for crizotinib-refractory *ALK*-rearranged NSCLC. This approval was based on the ALTA study, in which 222 patients were randomly assigned to brigatinib at doses of either 90 mg once daily (112 patients) or 180 mg once daily following a 7-day lead-in at 90 mg once daily (110 patients).

On independent review, the ORR was 48% (95% CI; 39, 58) in the 90-mg arm and 53% (95% CI, 43, 62) in the 180-mg arm. Median progression-free survival was 9.2 months (95% CI, 7.4 to 15.6) and 12.9 months (95% CI, 11.1 to not reached) in the 90-mg arm and 180-mg arm, respectively.[183] A small subset of patients (6%) experienced early pulmonary toxicity, which is why the 90-mg daily lead-in dose escalating to 180 mg daily is the FDA-approved dose.

Lorlatinib has in vitro activity against a broad spectrum of *ALK-TKI* resistance mutations and has received breakthrough designation for the treatment of *ALK*-rearranged NSCLC in patients who have previously received an ALK inhibitor. In a phase I–II trial, lorlatinib demonstrated activity in *ALK*-rearranged NSCLC, including *ALK* tumor harboring the *ALK G1202R* mutation that is refractory to other ALK-TKIs, such as alectinib.[184]

Oligoprogressive Disease in Metastatic *EGFR*-Mutant and *ALK*-Rearranged NSCLC. Among patients with tumors harboring *ALK* translocations or *EGFR* mutations treated with TKIs, occasionally progression occurs in limited sites, such as the CNS, while the remainder of the cancer remains controlled (oligoprogressive disease). In these situations, irradiating the site of progression or resecting isolated brain metastasis, for example, and then continuing the TKI may result in a lengthening of clinical benefit.[185]

Older Patients. Treatment of patients age 65 or older tends to be complicated by comorbid conditions and by patients taking multiple medications. However, studies show that fit older patients are likely to benefit as much from chemotherapy as their younger counterparts. Evidence from a phase III study in which patients older than age 70 with advanced disease were randomly assigned to best supportive care or to weekly vinorelbine indicated that patients who received vinorelbine had better scores on quality-of-life scales than the control group, as well as fewer lung cancer–related symptoms. However, patients in the chemotherapy group experienced more severe toxicity-related symptoms.[186] There was a significant survival advantage for patients who received vinorelbine (median survival, 28 weeks vs. 21 weeks). More recently, it has been shown that, despite an increase in toxic effects, platinum-based doublet chemotherapy yields superior outcomes to single-agent chemotherapy in fit elderly individuals. In a phase III trial conducted by the Intergroupe Francophone de Cancerologie Thoracique, 451 previously untreated patients ages 70 to 89 (median, 77) with ECOG PS of 0 to 2 were randomly assigned to carboplatin/paclitaxel or monotherapy with vinorelbine or gemcitabine. A total of 27% of patients in each arm had an ECOG PS of 2. Median OS was 10.3 months in the carboplatin/paclitaxel arm, compared with 6.2 months in the monotherapy arm (HR, 0.64; 95% CI; 0.62, 0.78; $p < 0.0001$).[187] Subset analyses of other randomized trials show that the RR, toxicity, and survival for fit older patients receiving a platinum-based treatment for NSCLC appears to be similar to the same variables for younger patients; however, for patients age 70 or older, comorbidity is greater and the frequency of leukopenia and neuropsychiatric toxicity are higher. Hence, advanced age alone should not preclude appropriate treatment.

Patients with Poor PS. The survival rates for patients with a poor PS (ECOG PS of 2, 3, or 4) are significantly shorter than the rates for patients with a good PS. Patients with a poor PS also are less likely to be able to tolerate treatment. Retrospective subset analyses suggest that patients with a PS of 2 may derive a modest benefit from chemotherapy. However, given the overall short survival—particularly for patients with a PS of 3 or 4—and the minimal benefit derived from chemotherapy, these patients probably should not be treated outside of a clinical study. A possible exception is patients with tumors harboring activating *EGFR* mutations or ALK or ROS1 fusions, especially if poor PS is a result of the lung cancer. In general, EGFR and ALK inhibitors may be better tolerated than conventional chemotherapy and, for these patients, may result in rapid clinical and radiographic responses.

One clinical trial compared carboplatin (AUC 5) and pemetrexed to pemetrexed alone for patients with stage IV NSCLC with a Zubrod PS of 2. A substantial improvement was observed in median OS with the combination compared with pemetrexed alone (9.3 vs. 5.3 months; $p = 0.001$).[188]

Duration of Therapy and Maintenance Therapy. The role of maintenance treatment for patients with metastatic NSCLC remains under active investigation. Although results from earlier randomized studies did not show a survival difference with prolonged (more than six) cycles of chemotherapy compared with fewer (four to six) cycles (Table 8-11),[189-194] several additional clinical trials have challenged that paradigm. Two maintenance strategies have been investigated: so-called switch maintenance and continuation maintenance. The goal of continuation maintenance is to delay progressive disease by continuing an effective agent. Switch maintenance seeks to initiate a new second-line agent early to delay onset of progressive disease.

Table 8-11 **Selected Randomized Trials of Maintenance Therapy for Advanced Non-Small Cell Lung Cancer**

Reference	Treatment Comparison	Type of Trial	Median Survival (months)	1-Year Survival (%)	p Value
Westeel et al.[189]	6 months of vinorelbine	Switch maintenance	13	53	Not significant
	Best supportive care		10	40	
Socinski et al.[190]	Four cycles of carboplatin plus paclitaxel	Continuation maintenance	7	28	Not significant
	Carboplatin plus paclitaxel until disease progression		9	35	
Smith et al.[191]	Three cycles of mitomycin C, vindesine, and cisplatin	Three cycles vs. six cycles	6	22	Not significant
	Six cycles of same regimen		7	25	
Fidias et al.[192]	Four cycles of gemcitabine plus carboplatin, with docetaxel on disease progression	Switch maintenance	9.1	38	Not significant
	Four cycles of gemcitabine plus carboplatin, followed immediately by docetaxel for six cycles		11.9	48.5	
Ciuleanu et al.[193]	Four cycles of platinum-based therapy, followed by placebo	Switch maintenance	10.6		0.012
	Four cycles of platinum-based therapy, followed by pemetrexed		13		
Cappuzzo et al.[155]	Four cycles of platinum-based therapy, followed by placebo	Switch maintenance	11		0.0088
	Four cycles of platinum-based therapy, followed by erlotinib		12		
Paz-Ares et al.[194]	Four cycles of cisplatin and pemetrexed, followed by placebo	Continuation maintenance	11		0.0195
	Four cycles of cisplatin and pemetrexed, followed by pemetrexed		13.9		

Three trials have been reported that suggest a benefit with prolonged-duration therapy.[195-197] In one study, patients who had stable or responsive disease following their initial four cycles of gemcitabine/carboplatin were randomly assigned to receive maintenance docetaxel immediately following induction chemotherapy or at progression.[192] Median PFS for immediate docetaxel was significantly greater than for delayed docetaxel (5.7 vs. 2.7 months; p = 0.0001). Median OS for immediate docetaxel also was greater than for delayed docetaxel, although the difference was not significant (12.3 months vs. 9.7 months; p = 0.0853). Interestingly, the median OS for patients assigned to immediate docetaxel and those assigned to delayed docetaxel who received the specified therapy at the time of progression was identical. These findings raise the question of whether switch maintenance therapy may actually be similar to early use of second-line therapy at the first sign of progressive disease. A second study investigating maintenance pemetrexed employed a slightly different trial design.[193] A total of 633 patients with stable or responsive disease were randomly assigned in a 2:1 fashion to observation or pemetrexed following induction chemotherapy with platinum-based chemotherapy. Pemetrexed resulted in significantly better survival (13.4 months vs. 10.6 months; HR, 0.79; 95% CI; 0.65, 0.95; p = 0.012) and PFS. The improvement in survival was

observed primarily among patients with nonsquamous histology (15.5 months vs. 10.3 months, OS HR, 0.70; it was not the primary endpoint, but it was a preplanned secondary analysis). A third phase III study has examined the role of erlotinib maintenance therapy.[155] In the Sequential Tarceva in Unresectable NSCLC (SATURN) trial, 889 patients whose disease did not progress during first-line platinum-based chemotherapy were randomly assigned to receive erlotinib or placebo. There was a statistically significant improvement in PFS (HR, 0.71; 95% CI; 0.62, 0.82; $p < 0.001$) and OS (HR, 0.81; 95% CI; 0.70, 0.95; $p = 0.009$), with a median OS of 12 months (erlotinib) compared with 11 months (placebo). However, in one phase III clinical trial (IUNO), OS and PFS with maintenance erlotinib were not superior to those for second-line erlotinib treatment (OS, 9.7 vs. 9.5 months; HR, 1.02; 95% CI; 0.85, 1.22; log-rank $p = 0.82$) in patients whose tumor did not harbor an *EGFR*-activating mutation.[198] Based on the failure of erlotinib maintenance to improve any clinical outcomes, the FDA modified the approved indication of erlotinib to NSCLC harboring *EGFR*-activating mutations.

A phase III clinical trial (PARAMOUNT) randomly assigned patients with advanced nonsquamous NSCLC to four cycles of cisplatin and pemetrexed followed by observation compared with continuation maintenance pemetrexed every 3 weeks until progression or intolerable toxic effects occurred. Continuation pemetrexed improved PFS, with a median PFS of 4.4 months compared with 2.8 months (HR, 0.62; 95% CI; 0.49, 0.79; $p < 0.0001$), and OS, with a median OS of 16.9 months compared with 14.0 months after induction (HR, 0.78; 95% CI; 0.64 to 0.96; $p = 0.0195$).[194]

Currently, switch-maintenance therapy with pemetrexed is FDA-approved, as is continuation maintenance with pemetrexed. This new treatment paradigm has raised many questions, including whether the apparent benefit is a result of the timing of therapy or the higher rates of administering effective second-line agents and how maintenance strategies should be implemented for patients receiving pemetrexed- or bevacizumab-containing first-line regimens.

Number of Drugs. Although findings from numerous phase I and II studies have demonstrated the feasibility of triplet chemotherapy combinations, the results of most randomized trials have not demonstrated a survival advantage and have been at the expense of enhanced toxicity and cost. Thus, regimens that employ three cytotoxic drugs cannot be routinely recommended for patients with advanced NSCLC.

In randomized studies, single-agent paclitaxel, gemcitabine, or docetaxel was compared with double-agent cisplatin plus paclitaxel, gemcitabine, or docetaxel.[195-199,199-203] Findings from all of these trials showed a survival advantage for the two-drug regimens. These results can be interpreted either as demonstrating the advantages of cisplatin for the treatment of advanced NSCLC or as evidence of the superiority of doublet compared with single-agent therapy.

Cisplatin Compared with Carboplatin. Meta-analyses have suggested that cisplatin may have a modest benefit in terms of survival as compared with carboplatin for patients with advanced disease, albeit with a different toxicity profile.[204,205] In one direct comparison, a phase III trial of the Spanish Lung Cancer Group randomly assigned patients to paclitaxel with either cisplatin or carboplatin. Efficacy endpoints showed superiority of the cisplatin-based regimen with about a 1-month improvement in OS.[205] Although this difference may be of limited clinical consequence for patients with metastatic disease, it may be more important in the adjuvant or locally advanced setting, where cure is the goal. In metastatic, incurable disease, where the goal is palliation, carboplatin is acceptable, since administration of cisplatin with higher rates of renal insufficiency, neuropathy, and hearing loss may impact quality of life.

Nonplatinum-Based Regimens. Given the toxicities associated with cisplatin, there has been considerable interest in utilizing nonplatinum agents. In general, randomized studies have failed to show superiority of any nonplatinum regimen compared with platinum-based, third-generation regimens, although toxicities vary.[206] Consequently, nonplatinum regimens are not commonly used in current practice.

KEY POINTS

- Cytotoxic chemotherapy improves survival and symptoms for patients with metastatic NSCLC.
- Platinum-based doublet chemotherapy is considered standard of care and typically administered for four to six cycles for patients with good PS.
- Bevacizumab (15 mg/kg every 3 weeks) prolongs survival when administered with carboplatin/paclitaxel to eligible patients with advanced non–squamous cell carcinoma as demonstrated in a large randomized trial.
- Fit elderly patients tolerate chemotherapy and derive the same survival benefit as their younger counterparts.
- EGFR-TKIs should be considered standard of care in the first-line setting for patients with tumors harboring *EGFR*-activating mutations.
- Crizotinib should be considered standard of care in the first-line setting for patients with tumors harboring ALK and ROS1 fusions. For ALK fusions recent clinical trials indicate that next-generation ALK inhibitors such as alectinib may supplant crizotinib for first-line therapy of ALK rearranged NSCLC.
- Pembrolizumab is standard first-line therapy for metastatic NSCLC with high PD-L1 expression (≥ 50%).

Second- and Third-Line Therapy and Beyond

Currently, four agents (docetaxel, pemetrexed, and ramucirumab in combination with docetaxel and nivolumab) are approved for second-line therapy for advanced NSCLC regardless of the tumor's molecular characteristics. In two randomized trials, second-line docetaxel was evaluated for patients who did not respond to first-line therapy. In one trial, docetaxel at a dose of 75 mg/m^2 significantly prolonged survival compared with best supportive care.[207] Although this dose of docetaxel resulted in an RR of only 7%, improved time to disease progression and survival was seen for patients treated with docetaxel. Moreover, docetaxel also improved quality of life and reduced weight loss and the need for pain medications. Previous exposure to paclitaxel did not affect response to docetaxel, suggesting non–cross-resistance between the two agents. In the second study, docetaxel was compared with either vinorelbine or ifosfamide.[208] Although OS was not significantly different among the three groups, the 1-year survival associated with docetaxel was notably better than that associated with the control treatment (32% vs. 19%; p = 0.025).

For a number of years, single-agent chemotherapy was considered the standard treatment for metastatic NSCLC after progression on platinum-based chemotherapy. Until recently, a

large number of clinical trials pairing a second drug with single-agent chemotherapy failed to show an OS benefit. Ramucirumab (a monoclonal antibody that targets VEGFR2) was the first drug to show an OS benefit when paired with chemotherapy in this setting. This antiangiogenesis agent, in combination with docetaxel has been approved for the treatment of metastatic NSCLC with progression of disease on or after platinum-based treatment. Unlike bevacizumab, which is contraindicated in squamous histology NSCLC, ramucirumab is approved and has benefit in this disease. Approval was based on the randomized, phase III REVEL trial, which randomly assigned 1253 patients with stage IV NSCLC after progression on platinum-based chemotherapy to docetaxel with or without ramucirumab. OS (median 10.5 vs. 9.5 months; $p = 0.023$), PFS (median, 4.5 vs. 3.0 months; $p < 0.0001$), and RR (23% vs. 14%; $p < 0.001$) were all improved with the addition of ramucirumab.[60]

A phase III study compared pemetrexed with docetaxel.[209] Although no difference in survival was observed (1-year survival of 29.7% in both arms), patients randomly assigned to receive docetaxel were more likely to have febrile neutropenia (12.7% vs. 1.9%; $p = 0.001$), infections (3.3% vs. 0%; $p = 0.004$), and hospitalizations for neutropenic fevers (13.4% vs. 1.5%; $p = 0.001$) than patients who received pemetrexed, resulting in the FDA's approval of pemetrexed as second-line therapy for NSCLC.

In a randomized, placebo-controlled, double-blind clinical trial conducted by the National Cancer Institute of Canada (BR.21), patients with stage IIIB or IV NSCLC and a PS of 0 to 3 who had received one or two prior chemotherapy regimens were randomly assigned in a 2:1 ratio to receive either oral erlotinib at a dose of 150 mg daily or placebo.[83] Median survival rates were 6.7 months and 4.7 months for erlotinib and placebo, respectively (HR, 0.70; $p < 0.001$). The only predictive factor for survival benefit was smoking status, for which current or former smokers had an HR of 0.9, and never-smokers had an HR of 0.4. The VeriStrat serum proteomic test can predict lack of benefit to second-line erlotinib for patients with NSCLC unselected for an EGFR-activating mutation. In the prospective randomized PROSE trial, patients with a poor VeriStrat proteomic classification had worse OS when treated with erlotinib compared with standard chemotherapy (HR, 1.72; $p = 0.022$).[210] No differences in survival were noted with a VeriStrat good classification.

As discussed earlier, approval of erlotinib has been narrowed by the FDA to canonical *EGFR*-activating mutations. However, the irreversible EGFR-TKI afatinib has been granted FDA approval for the treatment of advanced squamous NSCLC as second-line treatment. Approval was based on a large randomized, phase III study (LUX-LUNG 8).[211] This trial randomly assigned 795 patients with advanced squamous cell lung cancer to afatinib or erlotinib. PFS was the primary endpoint and was significantly longer with afatinib than with erlotinib (median, 2.4 months vs. 1.9 months; HR 0.82; $p = 0.0427$). OS was also modestly greater in the afatinib group than in the erlotinib group (median, 7.9 months vs. 6.8 months; $p = 0.0077$).

The following points may be taken into consideration: even in highly clinically enriched populations, *EGFR* mutations occur in only about 60% of patients, and *EGFR* mutations occur in up to 10% of patients who lack typical clinical predictors[28,212]; for patients with tumors harboring *EGFR* mutations, PFS is similar if an EGFR-TKI is administered as first-, second-, or third-line therapy[168]; in the first-line setting, patients with *EGFR* wild-type tumors have superior PFS with conventional chemotherapy compared with EGFR-TKI therapy.[83] Afatinib is approved for squamous histology advanced NSCLC, but erlotinib did not show a benefit in the IUNO[198] trial in *EGFR* wild-type advanced NSCLC. EGFR-TKIs are generally well tolerated, with rash and diarrhea the principal toxic effects. Interstitial pneumonitis occurs rarely in North American and western European populations.

Immunotherapy: Second Line and Beyond

Immunotherapy has assumed a prominent role in the treatment of lung cancer. Immune checkpoint inhibitors such as PD-1 and PD-L1 antibodies were the first immunotherapies approved for the treatment of advanced NSCLC. The PD-1 checkpoint acts to regulate T-cell antigen recognition in the tumor microenvironment. Tumors can express the ligand to PD-1 (PD-L1) that binds to PD-1 to downregulate the immune response within the tumor microenvironment. Three PD-1/PD-L1 antibodies are currently approved for second-line treatment of advanced NSCLC: atezolizumab (PD-L1), nivolumab (PD-1), and pembrolizumab (PD-1). As discussed previously, pembrolizumab is the only PD-1 antibody approved for first-line treatment.

Nivolumab is a monoclonal antibody to PD-1 and was the first immunotherapy approved for the treatment of lung cancer. It is currently approved for advanced NSCLC with progression during or after platinum-based chemotherapy. The approval in squamous NSCLC was based on the phase III CHECKMATE 017 trial, which randomly assigned 272 patients with stage IV squamous cell lung cancer with progression during or after platinum-based chemotherapy to nivolumab or docetaxel. OS was substantially improved (median, 9.2 vs. 6.0 months, $p < 0.001$; HR, 0.59; 1-year OS, 42% vs. 24%).[213] RRs are not high (approximately 17%), but some patients can achieve long-term clinical benefit. A similar phase III clinical trial randomly assigned 588 patients with advanced nonsquamous NSCLC (CHECKMATE 057) and demonstrated an impressive OS benefit with nivolumab as compared with docetaxel. Median OS was 12.2 months (95% CI; 9.7, 15.0) in the nivolumab group and 9.4 months (95% CI; 8.1, 10.7) in the docetaxel group (HR, 0.73; 95% CI; 0.59, 0.89; $p = 0.002$).[214] At 1 year, the OS was 51% (95% CI; 45, 56) with nivolumab compared to 39% (95% CI; 33, 45) with docetaxel. The RR was 19% with nivolumab compared to 12% with docetaxel ($p = 0.02$). Interestingly, median PFS did not favor nivolumab over docetaxel (median, 2.3 and 4.2 months, respectively), but the rate of PFS at 1 year was higher with nivolumab (19% and 8%, respectively). The clear separation of the Kaplan–Meier curve at later points past the median for OS and PFS highlights that a subset of patients with advanced NSCLC can derive long-term benefit from PD-1 blockade. In advanced squamous NSCLC, tumor PD-L1 expression was not predictive of benefit. However, in advanced nonsquamous NSCLC, tumor-membrane expression of the PD-1 ligand was associated with greater efficacy. Treatment-related adverse events of grade 3 or 4 were reported in 10% of patients in the nivolumab group compared to 54% of patients in the docetaxel group. Immune-mediated adverse events, including pneumonitis, endocrine dysfunction, hepatitis, and colitis, are potential side effects; immune-mediated pneumonitis is the most frequent cause of treatment-related death (approximately 2%).[215]

Pembrolizumab is another PD-1 inhibitor approved for the treatment of advanced NSCLC. Among 495 patients who received pembrolizumab in the KEYNOTE-001 trial, ORR was 19.4%, with median duration of response of 12.5 months, median PFS of 3.7 months, and median OS of 12 months. With pembrolizumab, tumor expression of PD-L1 correlated with efficacy; for patients whose proportion of tumor PD-L1 expression was at least 50%, ORR was over 45%.[216] In the larger KEYNOTE-010 trial, patients with advanced NSCLC postprogression during or after platinum-based chemotherapy and tumors expressing at least 1% PD-L1 were enrolled. Of the 1034 patients, 345 were allocated to pembrolizumab 2 mg/kg, 346 were allocated to pembrolizumab 10 mg/kg, and 343 were allocated to docetaxel. Median OS was 10.4 months with pembrolizumab 2 mg/kg, 12.7 months with pembrolizumab 10 mg/kg, and 8.5 months with docetaxel. OS was longer for pembrolizumab 2 mg/kg and for pembrolizumab 10 mg/kg as compared with docetaxel (HR, 0.71, 95% CI; 0.58, 0.88; $p = 0.0008$; and HR, 0.61,

95% CI; 0.49, 0.75; p<0.0001, respectively).[217]

Among patients with at least 50% of tumor cells expressing PD-L1, OS was significantly longer with pembrolizumab than with docetaxel (2 mg/kg: median, 14.9 months vs. 8.2 months; HR, 0.54; 95% CI; 0.38, 0.77; p = 0.0002; 10 mg/kg: 17.3 months vs. 8.2 months; HR, 0.50; 95% CI; 0.36, 0.70; p < 0.0001). Likewise, for this patient population, PFS was significantly longer with pembrolizumab than with docetaxel (2 mg/kg: median, 5.0 months vs. 4.1 months; HR, 0.59; 95% CI; 0.44, 0.78; p = 0.0001; 10 mg/kg: 5.2 months vs. 4.1 months; HR, 0.59, 95% CI; 0.45, 0.78; p < 0.0001). Approval for second-line pembrolizumab for patients with NSCLC harboring 1% or more PD-L1 expression by the companion diagnostic DAKO22C3 antibody is based on this KEYNOTE-010 trial.

In comparison with nivolumab, which was approved without a companion diagnostic for advanced NSCLC, pembrolizumab was granted accelerated approval for patients with advanced NSCLC whose tumors express PD-L1 on IHC. Several other PD-1 and g63 PD-L1 antibodies are in advanced stages of clinical development, with different IHC companion diagnostic assays. Efforts to harmonize differing companion assays for detection of PD-L1 and tumor-infiltrating lymphocytes to associate with clinical benefit for these immunotherapies are underway. PD-L1 IHC assays for lung cancer were compared in the Blueprint Project, which was undertaken by the International Association for the Study of Lung Cancer. It found agreement in patient tumor comparison for nivolumab and pembrolizumab companion PD-L1 immunohistochemistry (For ≥ 1% PD-L1 expression 94.7% agreement between DAKO 28-8 and DAKO 22C3 antibodies by IHC).[218,219]

Approval of the PD-L1 antibody atezolizumab in advanced NSCLC is based on the phase III OAK trial, which randomly assigned 850 patients to receive either atezolizumab or docetaxel. OS was significantly longer with atezolizumab compared with docetaxel (median OS, 13.8 months; 95% CI; 11.8, 15.7; vs. median OS, 9.6 months; 95% CI; 8.6, 11.2; HR, 0.73; 95% CI; 0.62, 0.87; p = 0.0003). OS in the TC1/2/3 or IC1/2/3 population was also improved with atezolizumab compared with docetaxel (median OS, 15.7 months; 95% CI; 12.6, 18.0 with atezolizumab; vs. median OS, 10.3 months; 95% CI; 8.8, 12.0] with docetaxel; HR, 0.74; 95% CI; 0.58, 0.93]; p = 0.0102). Patients in the PD-L1 low or undetectable subgroup (TC0 and IC0) also had improved survival with atezolizumab (median OS, 12.6 months vs. 8.9 months; HR, 0.75; 95% CI; 0.59, 0.96). Improvement in OS was similar in patients with squamous histology (HR, 0.73; 95% CI; 0.54, 0.98]; 112 patients in the atezolizumab group and 110 in the docetaxel group) or non–squamous histology (HR, 0.73; 95% CI; 0.60, 0.89]; 313 and 315 patients, respectively). Fewer patients had treatment-related grade 3 or 4 adverse events with atezolizumab (90 [15%] of 609 patients) versus docetaxel (247 [43%] of 578 patients).[220] Additional PD-L1 antibodies, such as avelumab and durvalumab are in development and are being studied in later-stage clinical trials.

ISOLATED BRAIN METASTASES

For patients with controlled disease outside the brain who have an isolated cerebral metastasis in a resectable area, resection followed by whole-brain radiation therapy is superior to whole-brain radiation therapy alone and may improve survival. Another therapeutic option for tumors smaller than 3 cm in diameter is stereotactic radiosurgery (SRS), which uses a stereotactic fixation system and non-coplanar convergent beams that create a sharp peripheral dose fall-off along the edge of the target. SRS spares the surrounding normal tissue, enabling the use of a single, large fraction of radiation. Previous trials suggested that survival is improved when SRS

is administered with whole-brain radiation therapy. However, in a meta-analysis from the three largest randomized clinical trials of SRS and whole-brain radiation therapy that included patients with solid tumors and one to four brain metastases, SRS alone was superior to SRS plus whole-brain radiation therapy for OS in patients age 50 or younger (HR, 0.64; 95% CI; 0.42, 0.99).[221]

PARANEOPLASTIC SYNDROMES

Humoral-associated hypercalcemia is most commonly related to squamous cell cancers and least commonly to small cell lung cancer. Manifestations of hypercalcemia depend more on the rate of onset than on the degree of elevation and include mental status changes, polydipsia, gastrointestinal symptoms, and nephrolithiasis. In addition to treatment of the malignancy, therapy includes intravenous hydration and administration of bisphosphonates and calcitonin. Use of diuretics, which may exacerbate volume depletion, is discouraged. Hypertrophic pulmonary osteoarthropathy is characterized by clubbing of the digits and, when severe, painful periostitis of the long bones. Hypertrophic pulmonary osteoarthropathy is most common with adenocarcinoma, although it is not pathognomonic for cancer; it may also occur with other pulmonary diseases.

KEY POINTS

- PD-1 or PD-L1 blockade with nivolumab, atezolizumab, or pembrolizumab improves OS compared with docetaxel as second-line treatment of advanced NSCLC and is approved for treatment in this setting. Pembrolizumab is currently the only PD-1/PD-L1 antibody approved for first-line treatment of patients with advanced NSCLC whose tumors harbor PD-L1 expression of ≥ 50%.
- The addition of the VEGFR2 antibody ramucirumab to docetaxel modestly improves OS.

SMALL CELL LUNG CANCER

STAGING

Small cell lung cancer is usually classified as either limited or extensive because of its propensity to metastasize quickly and the fact that micrometastatic disease is presumed to be present in all patients at diagnosis. Limited-stage disease is typically defined as being encompassed within one radiation port and is usually limited to the hemithorax and to regional nodes, including mediastinal and ipsilateral supraclavicular nodes. Extensive-stage disease is usually defined as disease that has spread outside those areas. Though small cell lung cancer is typically graded using the Veterans Administration staging system of limited-stage disease compared to extensive-stage disease, current guidelines also recommend staging by the AJCC TNM staging system.

PROGNOSTIC FACTORS

As with NSCLC, the major pretreatment prognostic factors for small cell lung cancer are stage of disease, PS, serum lactate dehydrogenase, and sex. If the patient's initial poor PS is the result of the underlying malignant disease, symptoms often disappear quickly with treatment,

resulting in a net improvement in quality of life. However, major organ dysfunction from nonmalignant causes often results in a patient's inability to tolerate chemotherapy.

PRETREATMENT EVALUATION

Common sites of metastases include the brain, liver, bone marrow, and bone. For this reason, a full staging workup consists of a complete blood-cell count, liver-function tests, CT scan with contrast of chest and upper abdomen, CT or MRI of the brain, and consideration of PET or bone scan. Bone marrow aspiration is not recommended unless an otherwise unexplained hematologic abnormality is present (e.g., nucleated red blood cells are seen on peripheral-blood smear, neutropenia, or thrombocytopenia).

This complete workup should probably not be undertaken unless the patient is a candidate for combined-modality treatment with chest radiation and chemotherapy, the patient is being evaluated for a clinical study, or the information is helpful for prognostic reasons. If the patient is not a candidate for combined-modality treatment or a clinical study, it is usually appropriate to stop the staging at the first evidence of extensive-stage disease. In addition, because the chance of metastasis to the bone marrow only is less than 10%, biopsy of bone marrow is usually unnecessary except in certain cases of limited-stage disease in which demonstration of localized disease may be important for prognostic or psychosocial reasons or for clinical trial eligibility. PET scanning can provide useful information and can replace bone scanning.

TREATMENT

The cornerstone of treatment for patients with small cell lung cancer is combination platinum-based chemotherapy. Until recently, no clear survival advantage was demonstrated for any regimen. With standard chemotherapy—etoposide with either cisplatin or carboplatin—an ORR of 75 to 90% and a complete RR of 50% for localized disease can be anticipated. For extensive-stage disease, an ORR of approximately 50% and a complete or near-complete RR of approximately 25% are common. Tumor regressions usually occur quickly, often within the first two cycles of treatment, and provide rapid palliation of tumor-related symptoms. Despite these high RRs, median survival time remains approximately 14 months for limited-stage disease and 9 months for extensive-stage disease. Less than 5% of patients with extensive-stage disease survive more than 2 years. Although initial results of treatment with irinotecan plus cisplatin showed improved survival (compared with etoposide plus cisplatin) in a Japanese population, these results were not confirmed in U.S. studies.[222,223]

Dose Intensity

Dose intensity has been evaluated in a number of randomized studies. Most—although not all—failed to show a benefit in survival, regardless of whether the chemotherapy was delivered in higher doses or more frequently (dose density). In addition, a meta-analysis of chemotherapy dose intensity for small cell lung cancer in which doses not requiring bone marrow transplantation support were evaluated showed no consistent correlation between dose intensity and outcome.[224] The role of marrow-ablative doses of chemotherapy with subsequent progenitor cell replacement (e.g., autologous bone marrow transplantation) was evaluated in several phase I and II clinical trials, and results for survival were not promising. In a randomized, phase III study comparing high-dose chemotherapy with conventional-dose chemotherapy, the high-dose regimen with stem cell support prolonged relapse-free survival but

not OS.[225]

Duration and Maintenance of Therapy

The findings from most randomized studies do not show a survival benefit for prolonged administration of chemotherapy or for consolidation chemotherapy. The results of several randomized studies have demonstrated no survival benefit for prolonged first-line treatment when compared with treatment initiated on relapse. The optimal duration of treatment for patients with small cell lung cancer is four to six cycles.

Second-Line Therapy

The chance of response to second-line agents correlates with the relapse occurred following induction chemotherapy; patients who experience relapse more than 3 months after completing first-line chemotherapy are considered to have sensitive disease and are more likely to have a response than patients who experience disease progression during or within 2 to 3 months after receiving a first-line regimen (resistant disease). The only drug approved for second-line therapy for small cell lung cancer in the United States is topotecan, which is associated with a 20 to 40% RR for patients with sensitive disease and with a median survival of 22 to 27 weeks.[226] A phase III trial comparing the novel anthracycline amrubicin to topotecan as second-line treatment of small cell lung cancer showed no difference in OS, although PFS was modestly superior.[227] Temozolomide also has modest activity in second- or third-line treatment for extensive-stage small cell lung cancer, including among patients with platinum-refractory disease and brain metastases. As in glioma, tumor methylguanine methyltransferase (MGMT) methylation status may predict benefit.[228] For patients with refractory disease, the RR in phase II studies has ranged from 3 to 13%. Median survival is approximately 20 weeks. Patients with sensitive disease also may have a response to repeat treatment with the first-line regimen. Other drugs that have modest activity in phase II studies in the second-line setting include combination cyclophosphamide/doxorubicin/vincristine and single-agent paclitaxel.

Immune checkpoint inhibitors (both PD-1/PD-L1 and cytotoxic T-lymphocyte antigen 4 [CTLA-4] antibodies) have been studied alone and in combination in extensive-stage small cell lung cancer. Nivolumab in combination with the CTLA-4 antibody ipilimumab appears to increase the response rate (26% ORR) and duration of response, but with an increase in immune-related adverse events.[229] Given the propensity for paraneoplastic syndromes in small cell lung cancer and the potentially fatal immune-related adverse events, caution must be used when treating patients who have small cell lung cancer with immune checkpoint inhibitors.

Older Patients

As is the case with NSCLC, treatment of older patients is often complicated by poor PS and comorbid conditions. However, unlike older patients with NSCLC, older patients with small cell lung cancer may not benefit from single-agent therapy. Two randomized studies in which single-agent etoposide was compared with standard combination chemotherapy were stopped early because the single-agent arm was associated with a shorter median and long-term survival and a decreased quality of life.[230,231] Therefore, the standard treatment of fit older patients remains combination chemotherapy administered on a 3-week schedule.

Chemotherapy plus Radiation to the Thorax

Radiation therapy to the thorax in addition to chemotherapy is associated with a small but significant improvement in long-term survival for patients with limited-stage disease, providing an additional 5% improvement in 3-year survival compared with chemotherapy alone.[232] Chemotherapy given concurrently with thoracic radiation is superior to sequential chemoradiation in terms of survival; however, it is associated with substantially more esophagitis and hematologic toxicity. To decrease the morbidity associated with such treatment, as well as to improve overall outcome, investigative efforts have focused on optimizing the radiation fields, fractionation, and schedule. In one randomized study, twice-daily hyperfractionated radiation was compared with a once-daily schedule; both were administered concurrently with four cycles of cisplatin and etoposide. Survival was significantly higher with the twice-daily regimen (median survival, 23 months vs. 19 months; 5-year survival, 26% vs. 16%), albeit at the expense of more grade 3 esophagitis.[233] In another randomized trial, early administration of thoracic radiation as part of the combined-modality therapy for limited-stage disease was superior to late or consolidative thoracic radiation.[234] These data suggest that patients with good PS who have limited disease should receive concurrent chemoradiation, preferably administered twice daily in an accelerated, hyperfractionated approach. However, because of logistical considerations, once-daily radiation is the most commonly used treatment schedule in clinical practice.

A randomized clinical trial of 498 patients with extensive-stage small cell lung cancer with a response to platinum-based induction chemotherapy showed that thoracic radiotherapy, when added to prophylactic cranial radiation, significantly increased PFS. Though median OS, regardless of whether patients received thoracic radiotherapy, was 8 months, and OS at 1 year was not significantly prolonged (33% vs. 28%; $p = 0.066$), an improvement in 2-year OS was statistically significant (13% vs. 3%; $p = 0.04$).[235] Some of the features of the overall patient population were atypical for extensive-stage small cell lung cancer, such as 46% isolated intrathoracic progression in the control group. Thus, thoracic radiotherapy can be considered for patients with extensive-stage small cell lung cancer that responds to platinum-based chemotherapy; though, in view of the atypical features of the trial population, more studies are required before this approach can be considered the standard of care.

Prophylactic Cranial Irradiation

Brain metastases are the first site of relapse for approximately one-third of patients who have relapsing small cell lung cancers. Another third of such patients will have both brain and systemic metastases as the first sites of relapse and the remaining one-third will have systemic-only disease. Because of the morbidity associated with brain metastases, the role of prophylactic cranial irradiation has been studied in numerous randomized trials. These findings have generally demonstrated that prophylactic cranial irradiation decreases the risk of brain metastases by approximately half without enhanced neurotoxicities, including cognitive dysfunction, ataxia, and seizures. A meta-analysis of seven randomized trials concluded that prophylactic cranial irradiation increased 3-year survival, with a net gain of 5%.[236] In the United States, patients are typically administered 24 Gy in 12 fractions. The optimal dose and schedule are not clear; however, the meta-analysis demonstrated a trend toward improved control with higher doses.

Although prophylactic cranial irradiation had generally been reserved for patients with limited-stage disease in whom a complete response is achieved with induction chemotherapy, a study from the EORTC showed a survival benefit for patients with extensive-stage disease who had a

response to induction chemotherapy.[237] Patients with extensive-stage small cell lung cancer who had a response to chemotherapy were randomly assigned to undergo prophylactic cranial irradiation or no further therapy. Irradiation was associated with an increase in median OS from 5.4 to 6.7 months and an improvement in the 1-year survival rate (27.1% vs. 13.3%) in the radiation group and control group, respectively, in addition to a lower risk of brain metastases (risk of metastases at 1 year, 14.6% vs. 40.4%). Thus, prophylactic cranial irradiation should be considered for all patients who have a complete or very good partial response after induction therapy.

Treatment of Paraneoplastic Syndromes

In small cell lung cancer, the most common paraneoplastic syndrome is syndrome of inappropriate secretion of antidiuretic hormone (SIADH), which occurs in up to 5% of patients. The hallmark of SIADH is euvolemic, hypotonic hyponatremia (in the absence of thyroid or adrenal dysfunction). Clinical features include confusion, seizures, and altered sensorium. In addition to treatment of the underlying malignancy, treatment includes fluid restriction, demeclocycline, and hypertonic saline in severe cases. Care must be taken to avoid overly rapid correction of hyponatremia, which could result in central pontine myelinolysis. Treatment of Lambert–Eaton syndrome and other neurologic paraneoplastic syndromes with corticosteroids, other immunosuppressive agents, intravenous gamma globulin, and plasmapheresis have been used with varying success.[80] Response to edrophonium is poor.[238]

KEY POINTS

- Small cell lung cancer often demonstrates features of neuroendocrine differentiation, which may be identified histopathologically, and it may be associated with paraneoplastic syndromes.
- Small cell lung cancer is exquisitely sensitive to both chemotherapy and radiation therapy, although resistant disease often develops.
- Etoposide with either cisplatin or carboplatin remains the standard of care for the treatment of patients with small cell lung cancer, with an optimal duration of four to six cycles.
- Concurrent chemotherapy and thoracic radiation confers a survival benefit and potential cure for patients with limited-stage small cell lung cancer.
- Prophylactic cranial irradiation reduces the incidence of symptomatic brain metastases and prolongs disease-free survival and OS for patients with limited-stage disease and in those with extensive-stage disease that has a major response to therapy.
- The addition of thoracic radiotherapy to prophylactic cranial irradiation can be considered for patients with extensive-stage small cell lung cancer and response to chemotherapy based on a clinical trial showing improved PFS and 2-year OS.
- Results with second-line chemotherapy for small cell lung cancer are poor for patients with “refractory” disease, in whom first-line treatment failed within 2 to 3 months.

PALLIATION FOR PATIENTS WITH LUNG CANCER

BISPHOSPHONATES

Bisphosphonates (zoledronate) have resulted in the reduction of skeletal-related complications such as pain, hypercalcemia, pathologic fractures, and spinal cord and nerve compression, as well as improvements in the quality of life for patients with metastatic bone disease who are likely to have a prolonged clinical course (Table 8-12).[238]

Table 8-12 Palliative Approaches for Complications of Lung Cancer

Superior Vena Cava Syndrome	▪ Chemotherapy alone (mild symptoms)
	▪ Concurrent chemoradiation therapy (severe symptoms)
	▪ Radiation therapy to the thorax (patients with non-small cell lung cancer)
	▪ Placement of stent
Pleural Effusion	▪ Intermittent thoracentesis
	▪ Pleurodesis
	▪ Long-term catheter drainage
	▪ Systemic chemotherapy
Bronchial Obstruction	▪ High-dose endobronchial radiation therapy
	▪ Placement of stent
	▪ Neodymium–yttrium–aluminum-garnet (Nd-YAG) endobronchial laser therapy
	▪ Electrocautery
	▪ Photodynamic therapy
Cachexia	▪ Megestrol acetate (160 to 800 mg daily)
Bone Metastases	▪ Bisphosphonates (zoledronate)
	▪ RANK-ligand inhibitor (denosumab)
Brain Metastases	▪ Corticosteroids
	▪ Resection or stereotactic radiation and whole-brain radiation (for isolated brain metastases for patients with non-small cell lung cancer)
	▪ Whole-brain radiation therapy (for multiple metastases)

RANK-LIGAND INHIBITOR

The monoclonal antibody to the receptor activator of nuclear kappa B (RANK) ligand denosumab was noninferior to zoledronate in delaying or preventing skeletal-related complications for patients with advanced cancer, including patients with lung cancer, in a

randomized, double-blind study of denosumab compared with zoledronic acid in the treatment of bone metastases for patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma.[240] The incidence of osteonecrosis is similar to that with bisphosphonates.

RADIATION THERAPY

Palliative radiation therapy often is helpful for controlling pain related to bone metastases or for improving neurologic function for patients with brain metastases. Radiation therapy to the thorax may help control hemoptysis, superior vena cava syndrome, airway obstruction, laryngeal-nerve compression, and other local complications.

CHEMOTHERAPY

Randomized trials involving patients with NSCLC and patients with small cell lung cancer have shown that chemotherapy reduces the incidence of cancer-related symptoms such as pain, cough, hemoptysis, and shortness of breath.

COLONY-STIMULATING FACTORS

Filgrastim, a granulocyte colony-stimulating factor, decreases the incidence of neutropenic fevers, the median duration of neutropenia, days of hospitalization, and days of antibiotic treatment for patients with extensive-stage small cell lung cancer. However, as discussed previously, the clinical benefit of maintaining a dose-intense approach for patients with this disease has not been established. In addition, caution must be exercised when using myeloid growth factors for patients receiving combined-modality treatment that consists of both chemotherapy and radiation therapy to the thorax, as this combination has been associated with an increase in thrombocytopenia.[241]

SUPERIOR VENA CAVA SYNDROME

Superior vena cava syndrome occurs when the superior vena cava becomes obstructed either directly by a tumor or by metastases to regional lymph nodes. Common symptoms include distention of the collateral veins over the anterior chest wall and neck; swelling and puffiness of the neck, face, throat, eyes, and arms; headache; and cyanosis. Although once thought to represent a medical emergency, in almost all cases, the symptoms are mild enough that treatment can be delayed until a histologic diagnosis has been determined. Radiation therapy is used to treat patients with NSCLC or other less chemosensitive tumors, whereas patients with extensive-stage small cell lung cancer and mild symptoms often may be treated with chemotherapy alone. Concurrent chemoradiation therapy usually is necessary for patients with both small cell lung cancer and NSCLC who present with severe symptoms. Other options include the placement of vascular stents, although the literature regarding their role is relatively sparse.

PLEURAL EFFUSION

Palliative thoracentesis should be performed for patients who are symptomatic from pleural effusions, and management with intermittent thoracentesis can frequently be effective if the effusion does not reaccumulate quickly. When reaccumulation is rapid, pleurodesis may be considered. The two most common methods of a pleurodesis are through a chest tube or via

thoracoscopy. Common sclerosing agents include doxycycline, talc, and bleomycin; talc is the most effective. Unfortunately, the procedure is effective in only about 50% of cases and is associated with discomfort and a prolonged hospital stay. For these reasons, long-term drainage through a semipermanent catheter is being used more frequently. Systemic therapy often reduces the effusion for patients with small cell lung cancer.

KEY POINT

- Every attempt should be made to palliate the symptoms of patients with lung cancer. In addition to systemic anticancer therapies, these include multidisciplinary management of painful bone metastases, dyspnea caused by pleural effusions, and maintenance of adequate analgesia.

THYMIC MALIGNANCIES

The thymus contains two major cell populations: epithelial cells and lymphocytes. A number of different tumors can arise in the anterior mediastinum, including thymomas, Hodgkin and non-Hodgkin lymphomas, carcinoid tumors, and germ cell neoplasms. Thymomas are malignant neoplasms originating within the epithelial cells of the thymus, which often contain admixtures of lymphocytes.[242] Thymic carcinomas also are tumors of the thymic epithelium, but they are associated with a paucity of lymphocytes and are more aggressive and have a worse prognosis. Most thymomas are well encapsulated, but they are considered malignant because of their invasive potential. Cytokeratin is a useful diagnostic marker to distinguish thymomas from non–epithelial cell malignancies.

Thymomas are the most common (~20 to 30%) of all anterior mediastinal tumors in adults. Although they usually present in the fourth and fifth decades of life, cases have been reported from infancy into the ninth decade. At presentation, one-third of patients have an asymptomatic anterior mediastinal mass on chest x-ray; one-third have local symptoms such as cough, superior vena cava syndrome, and dysphagia; and one-third have myasthenia gravis. Distant metastases are uncommon, with the most common metastatic site being the pleura.

A number of paraneoplastic syndromes have been associated with thymomas. Myasthenia gravis—an autoimmune disorder caused by circulating acetylcholine-receptor antibodies resulting in acetylcholine-receptor deficiency at the motor end plate—occurs in approximately one-third of patients with thymoma, although it is rarely seen with thymic cancers. Surgical removal of all thymic tissue, not just tumor tissue, usually results in an attenuation of the severity of myasthenia gravis, although complete disappearance of all symptoms of the disorder is uncommon. Patients should have their serum antiacetylcholine receptor antibody levels measured prior to surgery to determine whether they have myasthenia gravis (to avoid respiratory failure during surgery).

Approximately two-thirds of patients with myasthenia gravis will have thymic lymphoid hyperplasia, and 10 to 15% will have thymoma. Myasthenia gravis is characterized by diplopia, dysphagia, weakness of the ocular muscles, and easy limb fatigability (proximal > distal). Interestingly, thymomas associated with myasthenia gravis tend to be less aggressive, and histologically, they tend to have a larger lymphocyte-to-epithelial-cell ratio. Other paraneoplastic syndromes include pure red cell aplasia, vasculitides, hypogammaglobulinemia, and other

autoimmune disorders. Thymectomy may result in normalization of the bone marrow for up to 40% of patients with pure red cell aplasia, although the procedure rarely results in a return to normal immunoglobulin levels for patients with immunodeficiency.

The Masaoka staging for thymoma is based on encapsulation of the tumor and invasion into surrounding organs and distant sites outside the chest (Table 8-13).[243] Important prognostic factors include WHO histologic grade, complete resection status, and size.[242,243] Negative prognostic factors include:

- Tumor size > 10 cm;
- Tracheal or vascular compromise;
- Age < 30;
- Presence of hematologic paraneoplastic syndromes;
- Incomplete surgical resection;
- Thymic carcinoma histology.

Table 8-13 **Modified Masaoka Clinical Staging of Thymoma**[242]

Masaoka Stage	Diagnostic Criteria
Stage I	Macroscopically and microscopically completely encapsulated
Stage II	(A) Microscopic transcapsular invasion
	(B) Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium
Stage III	Macroscopic invasion into neighboring organs (i.e., pericardium, great vessels, lung)
	(A) Without invasion of great vessels
	(B) With invasion of great vessels
Stage IV	(A) Pleural or pericardial dissemination
	(B) Lymphatic or hematogenous metastasis

The treatment of choice for thymoma is resection. Long-term survival for patients with encapsulated, noninvasive (stage I) tumors is excellent, approaching 90 to 95% at 10 years. The role played by postoperative radiation after an R0 resection is controversial but sometimes the procedure is used for completely resected stage II–IV thymomas. Adjuvant PORT is often recommended for patients with invasive disease.[243] For patients in whom complete resection is not possible because of extensive invasion, debulking with a subtotal resection followed by radiation therapy may result in improved survival. One small study suggested that chemotherapy plus radiation therapy may be more beneficial than either treatment alone.[244]

The optimal management of incompletely resected or unresectable thymomas is

controversial. Achieving a complete (R0) resection is an important prognostic indicator. Thymomas are generally chemosensitive tumors; thus, debulking with chemotherapy for locally advanced thymomas to attempt to increase the potential for an R0 (complete) resection is sometimes performed. Given the small number of patients, no randomized trials have been performed to identify the best chemotherapy regimen for inoperable or recurrent thymomas. Comparing response across trials, anthracycline-containing regimens increase the RR.[245] Commonly used regimens include cisplatin/doxorubicin/cyclophosphamide,[246] etoposide/ifosfamide/cisplatin,[247] and cisplatin/etoposide.[248]

Thymic carcinomas are aggressive and characterized by a high degree of histologic anaplasia and architectural atypia. A number of different subtypes have been described, although more than half are undifferentiated. These tumors often metastasize to regional lymph nodes and distant sites; thus, they have a worse prognosis than thymomas, with 5-year survival rates of 20 to 30%. Responses to carboplatin and paclitaxel have been described.[249]

KEY POINTS

- Thymomas are often encapsulated, well differentiated, and associated with paraneoplastic syndromes such as myasthenia gravis.
- The optimal treatment of thymoma is thymectomy and complete surgical resection, in which case the survival is excellent.
- The most important prognostic factors after resection are Masaoka stage, histology, complete resection status, and size.
- Thymic carcinomas are more aggressive than thymomas.
- Regimens incorporating anthracyclines increase RRs in thymoma.

MESOTHELIOMA

Mesothelioma arises from mesothelial cells—the cells that form the serosal lining of the pleura, pericardium, and peritoneal cavities. Although benign mesotheliomas have been described, most are malignant and have an aggressive clinical course.[250]

Malignant mesotheliomas are rare, with approximately 2500 new cases diagnosed annually in the United States. Although approximately 80% are associated with exposure to asbestos, only approximately 5% of asbestos workers are diagnosed with mesothelioma. In contrast to lung cancer and asbestosis, smoking does not increase the risk of mesothelioma. Unlike asbestosis, in which there is a dose–response relationship, this association does not exist for mesothelioma, with the exception of chrysotile asbestos, which may be oncogenic only at high doses.

The various types of asbestos are divided into two major groups: serpentine, represented by chrysotile, the most common form of asbestos in the Western world; and rodlike amphiboles, which include crocidolite, the most oncogenic type of asbestos.

Carcinogenic effects of asbestos appear to result from its physical properties rather than from its chemical structure, with long, rodlike fibers of narrow diameter being more likely to induce tumors in laboratory animals. It has been postulated that chrysotile asbestos fibers are less carcinogenic because the fibers can be partially digested and removed from the lungs,

whereas amphibole asbestos is more resistant to solubilization by cellular enzymes and therefore accumulates in the lungs. The fibers cause mutagenic changes by several different mechanisms, including direct physical effects on chromosomes; the production of hydroxyl radicals and superoxide anions leading to DNA strand breaks and deletions; stimulation of EGFR autophosphorylation, activation, and signal transduction; and increased production of inflammatory cytokines. The expression of the simian virus 40 large-tumor antigen in mesothelioma cells and not in nearby normal cells, as well as the capacity of antisense T-antigen treatment to arrest mesothelioma cell growth in vitro, suggest that simian virus 40 may also contribute to the development of mesothelioma, particularly for patients exposed to asbestos. Mesothelioma also has been associated with exposure to Thorotrast and its radiation effects.

Three histologic variants of mesothelioma have been described: epithelial, which is the most common form and is associated with the best prognosis; sarcomatoid; and mixed. To distinguish mesotheliomas from metastatic adenocarcinomas, the periodic acid–Schiff stain is frequently used before and after diastase digestion. Neutral mucopolysaccharides that are strongly positive on periodic acid–Schiff staining are found in intracellular secretory vacuoles and in intra-acinar vacuoles in most adenocarcinomas but are rarely found in most mesotheliomas. In addition, immunohistochemical staining for CD15, Ber-EP-4, TTF1, and carcinoembryonic antigen are usually absent in mesotheliomas but are positive in most adenocarcinomas, whereas mesothelioma is characterized by staining for calretinin, Wilms tumor antigen (WT1), vimentin, CK5/6, mesothelin, or HBME-1 (an antimesothelial cell antibody).[251]

Mesothelioma most commonly develops in the fifth to seventh decade, and it affects men and women in a 5:1 ratio. The onset of disease occurs 20 to 50 years after exposure. Family members also are at higher risk of mesothelioma, presumably because of exposure to asbestos fibers brought home on the clothing and bodies of individuals who work with asbestos.

The typical presentation consists of dyspnea or chest-wall pain secondary to a pleural effusion. Most mesotheliomas (60%) occur on the right side, and bilateral involvement of the chest wall is present at the time of diagnosis in less than 5% of cases. Repeated cytologic examination of pleural fluid may be negative, necessitating either a thoracoscopy or thoracotomy, despite the risk of seeding the biopsy site or surgical scar with tumor. Mesothelin-related peptide is a serum marker that may be predictive of disease recurrence after surgical resection.[252] Osteopontin is a glycoprotein that binds integrin and CD44 receptors, and it may distinguish patients with malignant mesothelioma from those with benign disease.[225] Fibulin-3 levels in pleural fluid and plasma has also emerged as a diagnostic and prognostic marker with potentially better sensitivity, specificity, and reproducibility than osteopontin levels.[253]

Mesotheliomas tend to be locally invasive. For approximately 20% of patients, a chest-wall mass develops over tracts resulting from thoracentesis, chest tubes, or thoracotomy. Direct involvement of the ribs, diaphragm, pericardium, and vertebrae is common. Although various staging classifications have been described, the staging system proposed by the International Mesothelioma Interest Group emphasizes the importance of the local extent of the tumor and node involvement.[254]

Evaluation of surgical resectability often includes echocardiography to delineate cardiac involvement and MRI to delineate diaphragmatic involvement, in addition to chest CT and PET scans. The choice of surgical resection for mesothelioma is controversial. Extrapleural pneumonectomy results in a lower local recurrence rate and has traditionally been considered the procedure of choice, though no conclusive OS benefit has been demonstrated. Extrapleural

pneumonectomy includes en bloc resection of the parietal pleura, lung pericardium, and diaphragm. Given the extent of the resection and long duration of anesthesia needed, this procedure should be reserved for patients younger than age 65 who are in good health.

Treatment of resectable mesothelioma traditionally consists of a trimodality approach. The best results have been described in a retrospective series reported by Sugarbaker et al. in which median survival was 19 months for 176 patients treated with extrapleural pneumonectomy (EPP), four to six cycles of adjuvant chemotherapy, and adjuvant radiation therapy to the ipsilateral hemithorax and mediastinum.[254] Patients with pure epithelial type and no node involvement had a significantly better outcome than patients with sarcomatoid/mixed histology or node involvement. Survival at 2 and 5 years for the 103 patients with epithelial cell–type tumors were 38% and 15%, respectively, compared with 16% at 2 years, with no 5-year survival for the 74 patients with sarcomatous or mixed cell types. Indeed, given the poor outcomes noted with sarcomatoid tumors, in some centers the presence of this histology guides treatment away from aggressive surgical intervention.

A large retrospective review suggested that pleurectomy with decortication may also provide long-term benefit.[255] Surgical management of mesothelioma and whether to perform pleurectomy with decortication compared with EPP for patients with resectable disease is controversial. The small randomized Mesothelioma and Radical Surgery (MARS) feasibility study showed a survival benefit for 26 patients who did not undergo EPP compared with the 24 patients who did (14.4 months for the EPP group vs. 19.5 months for the no-EPP group; HR, 1.90; 95% CI; 0.92, 3.93; exact p = 0.082).[256]

The role of preoperative (neoadjuvant) chemotherapy is also being explored. A multicenter phase II trial of neoadjuvant pemetrexed and cisplatin followed by EPP and hemithoracic radiation showed a median survival in the overall population of 16.8 months (77 patients) and of 29 months for patients completing all therapy (40 patients; 2-year survival, 61%).[257]

For patients with unresectable disease, effusions may be controlled by thoracoscopy with talc pleurodesis. Pleurectomy with decortication, although rarely curative, also can be used to control effusions. Smaller doses of radiation (21 Gy in three fractions) may prevent seeding of the surgical wound by mesothelioma cells.

The prognosis is poor for patients who have unresectable disease at presentation, with a median survival of approximately 12 months. Single-agent chemotherapy yields RRs of 5 to 20%, with the active agents including doxorubicin, cisplatin, pemetrexed, and gemcitabine.[258,259] Combination chemotherapy, which is usually cisplatin-based, has increased response rates as initial systemic treatment. Single-agent gemcitabine is associated with an RR of 12% or less, findings from a phase II study of gemcitabine plus cisplatin showed a 48% RR.[260] The best results have been reported with pemetrexed and cisplatin. A phase III study in which cisplatin was compared with cisplatin plus pemetrexed demonstrated a 9-month median survival for patients treated with cisplatin alone and a 12-month survival for patients treated with the combination (p = 0.02), making this regimen until recently the standard of care for patients with advanced mesothelioma. RRs were 41.3% and 16.7% in the pemetrexed/cisplatin arm and control arm, respectively.[261] In a randomized, phase 3 trial, bevacizumab added to cisplatin and pemetrexed improved OS (median, 18.8 months; 95% CI; 15.9, 22.6, vs. 16.1 months, 95% CI; 14.0, 17.9; HR, 0.77; 95% CI; 0.62, 0.95; p = 0.0167). More grade 3 or higher hypertension (23 vs. 0%) and thrombotic events (6 vs. 1%) were noted with bevacizumab. Thus, cisplatin and pemetrexed with bevacizumab should be considered the new standard of care in unresectable malignant pleural mesothelioma patients who are bevacizumab eligible.[262]

KEY POINTS

- Approximately 80% of pleural mesotheliomas are associated with exposure to asbestos, including indirect exposure.
- The epithelial histologic form of mesothelioma is associated with a better prognosis than the sarcomatoid or mixed histology forms.
- A trimodality approach consisting of surgery, chemotherapy, and radiation therapy should be considered for younger patients with good PS, particularly patients with negative mediastinal nodes and the epithelial variant.
- First-line chemotherapy for patients with mesothelioma consists of cisplatin and pemetrexed with the addition of bevacizumab for unresectable mesothelioma in bevacizumab-eligible patients.

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HEAD AND NECK CANCERS

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Recent Updates

- Cisplatin/gemcitabine improved survival compared to cisplatin/5-fluorouracil as first line treatment for recurrent or metastatic nasopharyngeal cancer. (Zhang L, *Lancet* 2016)
- PET/CT can effectively be used to determine need for neck dissection following completion of chemoradiation. (Mehanna H, *N Engl J Med* 2016)
- Nivolumab and pembrolizumab have been approved by the FDA for treatment of platinum refractory recurrent or metastatic head and neck squamous cell carcinoma. (Ferris R, *N Engl J Med* 2016; Seiwert TY, *Lancet Oncol* 2016; Baum J, *J Clin Oncol* 2017)
- In the American Joint Committee on Cancer (AJCC) 8th edition, p16-positive oropharyngeal tumors will be staged using a unique staging system to reflect the better prognosis associated with HPV-related oropharyngeal tumors. (Lydiatt WM, *Cancer J Clin* 2017)

OVERVIEW

The term “head and neck cancer” refers to a heterogeneous group of malignant tumors arising from the epithelial lining of the upper aerodigestive tract. The specific primary sites are subdivided by anatomic boundaries: lip and oral cavity, pharynx (nasopharynx, oropharynx, and hypopharynx), larynx, and nasal cavity and paranasal sinuses (Table 9-1, Fig. 9-1). Squamous cell cancer or a variant is the most common histologic type, accounting for 85 to 95% of head and neck cancers. Etiologic factors include tobacco and alcohol use and viruses, such as the human papillomavirus (HPV) and the Epstein–Barr virus (EBV) (Table 9-2). Head and neck cancers are generally categorized as early-stage disease (stage I or II), locally advanced disease (stage III, IVa, or IVb), or metastatic disease (IVc). Early-stage disease is usually treated with single modality therapy with either surgery or radiation, whereas locally advanced disease is generally treated with multimodality therapy, which commonly includes chemotherapy. Systemic therapy by itself is palliative and is the mainstay for metastatic disease. The other two anatomic sites included in the head and neck region are the thyroid and salivary glands. Surgical resection remains the standard of care for localized and resectable thyroid and salivary gland tumors. Depending on the pathologic findings, there is a role for radioactive iodine for the former and external-beam radiation for the latter. For patients with differentiated thyroid cancer, radioactive iodine is the first treatment of choice for metastatic disease. Two tyrosine kinase inhibitors are approved for treatment of radioactive iodine–refractory disease. Two tyrosine kinase inhibitors are approved for the management of medullary thyroid cancer. There is no standard systemic therapy licensed for patients with

unresectable salivary gland cancers.

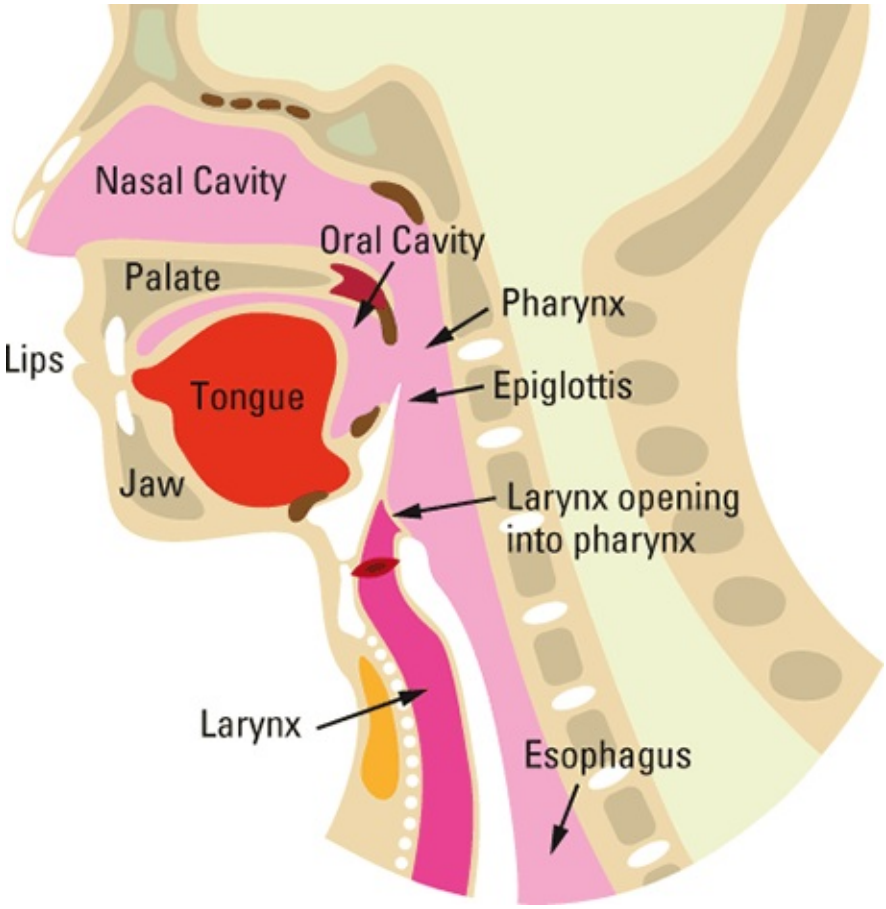

Fig. 9-1 Head and neck cancer regions.
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Table 9-1 **Head and Neck Cancer: Primary Sites**	
Oral Cavity and Lip	▪ Floor of mouth
	▪ Oral tongue
	▪ Buccal mucosa
	▪ Alveolar ridges
	▪ Hard palate
	▪ Retromolar trigone
Pharynx	▪ Nasopharynx (includes superior surface of soft palate)
	▪ Oropharynx (includes inferior surface of soft palate, uvula, base of tongue, tonsil, posterior pharyngeal wall)
	▪ Hypopharynx (pyriform sinus, postcricoid, posterior wall)
Larynx	▪ Supraglottic larynx (false cords, arytenoids, epiglottis)
	▪ Glottic larynx (includes commissures)
	▪ Subglottic larynx
Nasal Cavity and Paranasal Sinuses	▪ Nasal cavity
	▪ Maxillary sinuses
	▪ Ethmoid sinuses
	▪ Frontal sinuses
	▪ Sphenoid sinuses

Table 9-2 Characteristics of Virus-Associated Head and Neck Cancers		
	Human Papillomavirus	**Epstein–Barr Virus**
Anatomic site	Oropharynx	Nasopharynx
Anatomic subsite	Lingual and palatine tonsils, base of tongue	Pharyngeal walls, fossa of Rosenmüller
Percent virus associated		WHO I: 70–80%
	60–70%	WHO II and III: 100%
Associated histopathology	Basaloid	Lymphoepithelioma
Viral transmission	Sexual	Oral
Viral genome	Episomal/integrated	Episomal/ integrated
Viral oncogenes	*E6* and *E7*	*LMP-1* and *EBNA1*
Cofactors	Tobacco and alcohol	Diet and genetics
Clinical presentation	Unknown primary neck mass	Distant metastases, neck mass
Prognosis controlled for stage	Improved	Improved

EPIDEMIOLOGY

In 2016, it was estimated that head and neck cancers would account for approximately 3% (61,760) of all estimated new cancers and about 2% (13,190) of all estimated cancer deaths in the United States.[1] Worldwide, head and neck cancer accounts for more than 550,000 cancer cases and 380,000 deaths from cancer annually.[2] Head and neck cancer affects men and women in a ratio of 2.5:1, although the ratio varies according to the primary site (e.g., 4:1 for cancer of the oropharynx, 7:1 for cancer of the larynx). The median age at diagnosis is approximately 60. Oropharyngeal cancer incidence has increased significantly since the 1980s, predominantly in developed countries and among younger individuals, likely because of the role of HPV infection, particularly among men, and is associated with a better prognosis.[3] The age-adjusted incidence and mortality for head and neck cancer overall are highest among black men, and the stage-specific survival rates are lower for this group.

RISK FACTORS

TOBACCO AND ALCOHOL

Epidemiologic data document a multiplicative risk relationship between tobacco and alcohol. For example, the relative risk of oral and pharyngeal cancer is increased nearly 40-fold for patients with a 40 pack-year smoking history who consume 30 or more alcoholic drinks per week.[4] Age

younger than 18 years at onset and a duration of smoking of more than 35 years are significant risk factors. Overall, an estimated 75% of head and neck cancers can be attributed to tobacco and alcohol use, highlighting the importance of tobacco and alcohol counseling in medical practice and as part of prevention strategies. The carcinogens found in significant levels in tobacco that are considered directly mutagenic are benzopyrene and nicotine-derived nitrosamine ketone (NNK), or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. The type of tobacco product used affects the distribution of observed primary sites. Smokeless tobacco and other orally chewed carcinogens—such as betel quid, a combination of betel leaf, lime, and areca nut, commonly used in India and parts of Asia—are associated with the development of cancers of the oral cavity. Black, air-cured tobacco (commonly found in cigars and pipe tobacco) is more irritating to the respiratory mucosa than blonde or flue-cured tobacco (more commonly found in cigarettes) and is associated with a higher risk for head and neck cancer.

DIET

Because many patients with head and neck cancer are malnourished at the time of diagnosis, dietary deficiencies have been postulated as risk factors, and both laboratory and epidemiologic data suggest that vitamin A and its analogues may be protective. Plummer–Vinson syndrome, which is most commonly seen in women younger than age 50, is associated with iron deficiency anemia, hypopharyngeal webs, dysphagia, and a higher risk for cancers of the postcricoid region and hypopharynx.

OCCUPATIONAL EXPOSURE

Most tumors of the sinonasal tract originate in the maxillary sinus, and the proportion that have squamous cell histology is lower than other more common head and neck cancers (approximately 50%). Of note, these cancers are associated with certain occupational exposures (e.g., nickel, radium, mustard gas, chromium, and byproducts of leather tanning and woodworking).

VIRUSES

Human Papillomavirus (HPV)

HPV has emerged as an important cause of oropharyngeal cancer.[5] In the United States between 1984 and 1989, only 16% of oropharyngeal cancers were related to HPV, as compared with 73% of oropharyngeal cancers between 2000 and 2004, revealing a 4-fold increase during the past two decades.[6] This trend has been striking, given the decrease in tobacco use in the United States.[7] The rapid increase in the incidence of oropharyngeal cancers among men younger than age 60, with no or minimal use or history of alcohol or tobacco abuse, has become particularly apparent during the past decade.[8,9]

Genetic material from high-risk oncogenic strains (most commonly HPV types 16 and 18) is found in approximately 60% of oropharyngeal cancers arising from the palatine and lingual tonsils.[6,10] The transforming potential results from viral proteins E6 and E7, which inactivate the tumor suppressor proteins p53 and retinoblastoma protein (pRb) and result in loss of cell-cycle regulation, cellular proliferation, and chromosome instability.[11] More recently, HPV 16 E6 seropositivity has been reported to be present more than 10 years before the diagnosis of oropharyngeal cancer.[12] These tumors are clinically and molecularly distinct from HPV-negative tumors. The histology of HPV-associated tumors is frequently described as basaloid or poorly

differentiated squamous cell cancer, and the initial presentation often is as an unknown primary or small primary tumor with large cystic neck node(s). The verrucous cancer subtype of squamous cell cancer is strongly associated with HPV. Patients with HPV-associated tumors tend to be younger, have a history of minimal tobacco and alcohol exposure, and often have a history of high-risk sexual behavior.

Patients with oropharynx carcinoma who are HPV-positive have a strikingly improved survival compared with patients who are HPV-negative. A retrospective multivariate analysis of patients treated in the RTOG 0129 trial revealed significantly improved 3-year survival among patients who were HPV-positive compared with patients who were HPV-negative (84% vs. 57%).[10] Patients with HPV-positive tumors had a 58% reduction in risk for death compared with patients with HPV-negative tumors (hazard ratio [HR], 0.42; 95% CI; 0.27, 0.66). Patients with HPV-associated tumors also appear to have a lower risk for the development of a second primary malignancy (SPM).[13]

In a multicenter Eastern Cooperative Oncology Group study, patients with newly diagnosed stage III or IV head and neck squamous cell carcinoma (HNSCC) were treated with induction chemotherapy followed by concomitant chemotherapy and radiation; 60% of oropharynx primary tumors were found to be HPV-positive.[14] Two-year progression-free (86% vs. 53%; $p = 0.02$) and overall survival rates (95% vs. 62%; $p = 0.005$) were significantly better for patients with HPV-associated cancer than for those with HPV-negative cancers. In a retrospective analysis of Surveillance, Epidemiology, and End Results Program data, patients with HPV-positive oropharyngeal cancer had a 4-fold higher survival than patients who were HPV-negative (131 months vs. 20 months).[6]

More recently, retrospective data have confirmed that patients with HPV-positive oropharyngeal tumors have better survival in the setting of recurrent or metastatic disease compared with patients with HPV-negative disease.[15] The same survival benefit does not extend to HPV-positive or p16-positive tumors from non-oropharyngeal head and neck sites.[16] In the phase III EXTREME study, which evaluated the addition of cetuximab to a platinum and 5-fluorouracil doublet in patients with recurrent or metastatic HNSCC, HPV- or p16-positive disease had improved overall survival compared with patients with HPV- or p16-negative patients, regardless of treatment arm.[17] In a retrospective analysis of locally advanced oropharyngeal cancers treated in the RTOG 0129 or 0522 trial, patients with p16-positive tumors had an improved survival after disease progression compared with patients with p16-negative tumors, with a median overall survival of 2.6 years compared with 0.8 years, respectively ($p < 0.001$).[15] In a review of patients for whom archival tissue was available and treated in Eastern Cooperative Oncology Group trials for recurrent or metastatic head and neck cancer, the observed response rates to treatment and overall survival were improved in HPV- or p16-positive patients compared with patients with tumors negative for both HPV and p16.[18]

Although in situ hybridization, which is available at a limited number of referral centers, is considered an important test to confirm the presence of HPV, tumoral expression of p16 protein reflects biologically relevant HPV infection, is not genotype-specific, and is an excellent surrogate for HPV status.[19] Expression of p16 is upregulated when HPV E7 oncoprotein degrades pRb, whereas p16 expression in HPV-negative tumors is silenced by epigenetic promoter methylation or genetic mutation.[8] In RTOG 0129, immunohistochemical analysis of tumoral p16 protein expression performed numerically better than detection of HPV DNA in identifying the good prognostic group (HR, 0.33; 95% CI; 0.21, 0.53). With this in mind, the 8th edition of AJCC will use p16 overexpression by immunohistochemistry, defined as ≥ 75% tumor

expression with at least a moderate staining intensity marker, as a surrogate for HPV-positivity in oropharyngeal cancers and will stage this tumor independently from non-HPV-positive oropharyngeal cancers.[20]

There is also a new oral rinse that can detect DNA from HPV subtype 16. Rettig et al. demonstrated that patients with oropharyngeal cancer with detectable HPV-16 DNA have a poorer prognosis than those whose rinse is negative.[21]

Epstein–Barr Virus

Nasopharyngeal cancer is strongly associated with EBV. Cancer of the nasopharynx is especially common among individuals from endemic areas in southern China and northern Africa, where World Health Organization (WHO) type II (nonkeratinizing) and III (undifferentiated cancer) are more common. WHO type I (keratinizing) is more common in Western countries and appears to more likely be related to tobacco exposure or possibly HPV.[22,23] The EBV genome can be found in nasopharyngeal cancer tissues and dysplastic lesions that progress to invasive disease. However, the exact role of this virus in etiology is still being defined, and evidence of EBV can be found in nonmalignant nasopharyngeal tissue as well.

KEY POINTS

- Tobacco and alcohol use are the major risk factors for squamous cell cancer of the head and neck, and the use of both results in a multiplicative increase in risk.
- There is evidence for a causal association between high-risk oncogenic HPV and cancers of the oropharynx (e.g., tonsil, base of tongue); these cancers are increasing in incidence in the United States.
- The survival prognosis is substantially better for HPV-positive cancers than for HPV-negative cancers.
- The incidence of second primary cancers for patients with a history of squamous cell cancer of the head and neck is 3 to 7% annually; common sites include the head and neck, lung, and esophagus.

HEAD AND NECK CARCINOGENESIS

MOLECULAR PROGRESSION MODEL

A molecular progression model of multistep carcinogenesis has been elucidated for the transformation of normal mucosa to invasive squamous cell cancer.[24] The earliest genetic alteration noted during transition from normal mucosa to hyperplastic mucosa is the loss of genetic material from chromosome region 9p21 and inactivation of the *p16* tumor suppressor gene. The next step during the transition from hyperplastic mucosa to dysplasia is the loss of 3p and 17p with inactivation of the *p53* gene. Transition from dysplasia to carcinoma in situ is associated with loss of chromosome regions 11q, 13q, and 14q; during transition to invasive squamous cell carcinoma, there is loss of chromosome regions 6p, 8p, and 4q.[24] More than half of patients with tobacco- and alcohol-associated HNSCC have disease with the *TP53* gene

mutation and downregulation of p16 protein. In contrast, HPV-associated HNSCC characteristically demonstrates wild-type *TP53* and *RB1* genes and upregulation of p16 protein levels.

ORAL PREMALIGNANCY

Patients with head and neck cancer, specifically oral cancers, often have diffuse mucosal abnormalities related to tobacco use, alcohol use, and betel quid chewing. Oral premalignancy, or intraepithelial neoplasia, is the precursor to invasive oral cancer. Understanding the stepwise molecular events that define the risk for progression to invasive disease and identifying potential targets for intervention are areas of intense research interest. The loss of genomic material containing tumor suppressor genes (loss of heterozygosity or allelic imbalance) of regions on chromosomes 3p, 9p, 11q, and 17p, as well as p16 promoter hypermethylation and *p53* mutation, are steps in the progression of intraepithelial neoplasia to invasive cancer.

Leukoplakia

Histologically, leukoplakia is the most common precancerous lesion in the oral mucosa. Clinically, it appears as white plaques distributed on the lip, buccal mucosa, floor of the mouth, hard palate, tongue, and soft palate. The majority (approximately 80%) are benign lesions that can be kept under observation without treatment. The sites of leukoplakia at highest risk for severe (high-grade) dysplastic change or transformation to cancer are lesions on the tongue, lip vermilion, and floor of the mouth. Understanding molecular events such as loss of 3p and/or 9p in the transformation of leukoplakia to invasive cancer may allow for stratification of patients by risk; this also may enable novel therapies to be tested in this population.

Erythroplakia

In contrast with leukoplakia, erythroplakia presents as a red, velvety patch that is separated from the surrounding normal tissue by a distinct interface, and it occasionally has a pebbled or granular appearance. Erythroplakia is associated with a 90% incidence of severe dysplasia, carcinoma in situ, or invasive disease on microscopic examination. Erythroplakia may occur on the tongue, lower lip, floor of the mouth, buccal mucosa, and oral commissure. Dysplasia is a common finding in most erythroplakic lesions, and the degree of dysplasia is increased compared with dysplasia associated with leukoplakia. The molecular changes noted with leukoplakia are also noted in the erythroplakic lesions.

FIELD CARCINOGENESIS AND SECOND PRIMARY TUMORS OF THE AERODIGESTIVE TRACT

Field carcinogenesis is a concept proposed in the 1950s that has been supported by many epidemiologic and molecular studies. Exposure to risk factors such as alcohol and tobacco results in carcinogen distribution over large areas in the upper aerodigestive tract, and the exposed mucosa (the field) is a potential site for development of premalignant and invasive cancer. Given the central role of tobacco in the genesis of many head and neck cancers, medical comorbidity and synchronous or metachronous SPMs are common among these patients (3 to 7% per year, depending on whether tobacco use continues).[25] A tumor is considered synchronous if it occurs within 6 months after detection of the first primary tumor; a metachronous tumor is one that occurs more than 6 months after detection of the first primary

tumor. Geographically, these tumors should be separate and distinct with at least 1 cm of normal mucosa intervening. Synchronous lesions tend to present as premalignant mucosal lesions located in the head and neck, whereas metachronous lesions present as distinct tumors in the head and neck, lung, or esophagus.[26] Within the aerodigestive tract, the most frequent site of an SPM is the lung, followed by the esophagus.

The risk and distribution of SPMs vary significantly according to the subsite of the index cancer. In a population-based cohort study of 75,087 patients with HNSCC in the Surveillance, Epidemiology, and End Results program, the risk of SPM was highest for hypopharyngeal cancer. Since the 1990s, during the HPV era, the risk for an SPM associated with oropharyngeal cancer has declined to the lowest risk level of any subsite. The most common SPM site for patients with oral cavity and oropharyngeal cancer was the head and neck; for patients with laryngeal and hypopharyngeal cancer, the most frequent site was the lung.[13] A solitary pulmonary nodule is not rare in the workup of a new pharyngeal or laryngeal cancer and should not be assumed to be a metastasis, particularly for a patient with early-stage head and neck cancer. For example, a patient with early glottic cancer, no involved neck nodes, and a lung nodule is much more likely to have an SPM than metastatic disease, mandating a curative treatment approach for both primary tumors.

PREVENTION AND CHEMOPREVENTION

Stopping the use of tobacco and alcohol (the two primary risk factors for HNSCC) is central to any prevention program. Counseling combined with the use of a pharmacologic intervention, such as a tapering nicotine patch, doubles success rates; however, very few smokers succeed in quitting on their first attempt. Important reasons for smoking cessation that clinicians can discuss with their patients include the fact that the rate of SPM is higher among patients who continue to smoke and that continuing to smoke may adversely influence the effectiveness and tolerance of cancer treatment.

PREVENTION TRIALS USING RETINOIDS

Testing of retinoids to halt or reverse the processes that ultimately lead to epithelial carcinogenesis began in the mid-1980s. Trials investigating 13-cis-retinoic acid in high and low doses for primary prevention showed that high-dose 13-cis-retinoic acid was able to reverse oral intraepithelial neoplasia for approximately two-thirds of premalignant lesions and was able to maintain the effect for the duration of treatment. However, intolerable side effects precluded chronic, long-term dosing.[27] As secondary prevention after curative treatment of early-stage head and neck cancer, placebo-controlled, randomized trials of isotretinoin have failed to demonstrate benefit for prevention of a second primary tumor,[28,29] overall survival,[29] and disease-free survival,[28] although a favorable effect of tobacco cessation has been reported.[29] No systemic therapy to prevent head and neck cancer can be recommended at present. Enrollment of patients with oral premalignant mucosal changes in suitable clinical trials is encouraged.

CLINICAL PRESENTATION, DIAGNOSIS, AND STAGING

In general, cancers of the oral cavity, pharynx, and larynx are characterized by disease confined to the primary site with or without spread to regional nodes at the time of diagnosis and late metastatic spread. Less than 10% of patients have distant disease at presentation. Thus, initial disease staging and management focus on the extent of local–regional involvement

and the effect of the choice of treatment on speech and swallowing function, as well as on the risk for recurrence.

KEY POINTS

- Stopping the use of tobacco and alcohol, the two primary risk factors for squamous cell cancer of the head and neck, is central to any prevention program.
- Chemopreventive agents currently are not part of standard clinical practice but remain under active investigation.

PRESENTING SIGNS AND SYMPTOMS

Clinical signs and symptoms vary with the anatomic site affected. For example, patients with oral cavity cancer may present with mouth sores, a nonhealing ulcer, or pain. Symptoms of oropharyngeal cancer can range from sore throat to chronic dysphagia, persistent odynophagia, and otalgia. Patients with hypopharyngeal or supraglottic laryngeal cancer often seek medical attention at a later stage with sore throat, hoarseness, difficulty swallowing, or neck mass as the initial presenting sign. Tumors of the glottic larynx tend to be diagnosed at an earlier stage than those of the supraglottic larynx or hypopharynx because hoarseness is an early symptom at the glottic subsite. The Eustachian tubes are frequently invaded by nasopharyngeal disease, leading to ear fullness, otalgia, or otitis media—a diagnosis in an adult patient that mandates careful assessment of the nasopharynx. With more advanced nasopharyngeal tumors, double vision may be the presenting symptom because of invasion of the cavernous sinuses and the branches of the third, fourth, and particularly sixth cranial nerves, which track with these vascular structures. Spread to distant metastatic sites is more common at presentation in patients with advanced neck disease and in patients who have nasopharyngeal or hypopharyngeal primary sites.

Cervical Lymphadenopathy

The discovery of a painless lump in the neck is a common presenting symptom for a patient with head and neck cancer. The location of cervical adenopathy, denoted by dividing the neck into levels, may direct the physician to the primary site (Fig. 9-2). For example, cancers of the oral cavity typically spread to lymph nodes in the submental and submandibular areas (level I); oropharyngeal and laryngeal cancer spread to the upper and midneck (levels II and III); nasopharyngeal cancer spreads to the upper neck and posterior triangle (levels II and V); and disease confined to the lower part of the neck or supraclavicular area should raise suspicion about a primary lesion below the clavicle or in the thyroid (levels IV and V). Spread to the neck is uncommon for patients with primary cancers of the glottic larynx or paranasal sinuses. Involvement of the neck nodes is prognostically significant, reducing the cure proportion for a given tumor stage by approximately 50%.

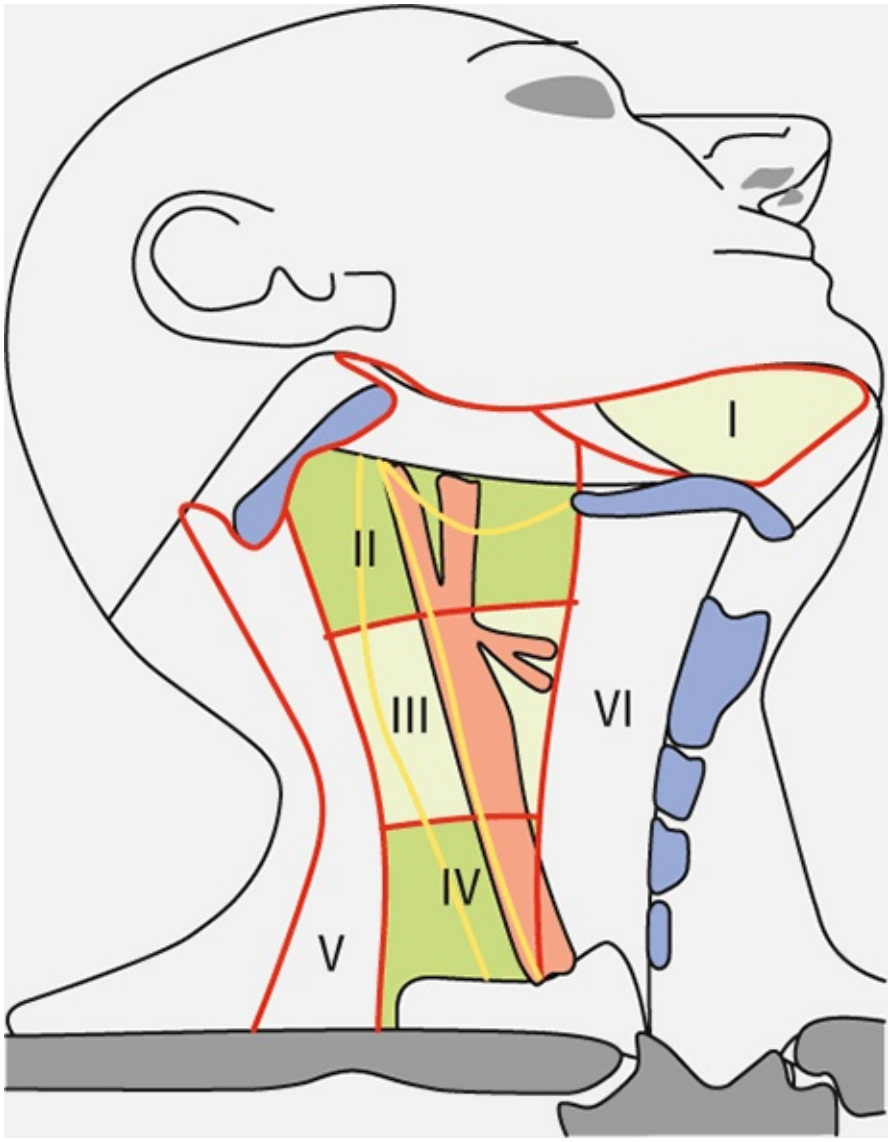

Fig. 9-2 Cervical lymph node levels.

From Moergel M, Jahn-Eimermacher A, Krummenauer F, et al. Effectiveness of adjuvant radiotherapy in patients with oropharyngeal and floor of mouth squamous cell carcinoma and concomitant histological verification of singular ipsilateral cervical lymph node metastasis (pN1-state)—a prospective multicenter randomized controlled clinical trial using a comprehensive cohort design. *Trials*. 2009;10:118. PMID 20028566. © *Moergel et al; licensee BioMed Central Ltd. 2009*

DIAGNOSTIC EVALUATION

A comprehensive examination of the head and neck with the assistance of mirrors or fiber-optic scopes is central to the evaluation. Because lymph nodes track along the internal jugular vein, examination of the neck for enlarged lymph nodes is facilitated by rotating the head toward the side being examined to promote relaxation of the sternocleidomastoid muscle on that side.

Endoscopy

Examination under anesthesia often is necessary and important, especially for patients with tumors of the larynx or pharynx. The routine application of so-called “triple endoscopy” (laryngoscopy or pharyngoscopy plus bronchoscopy and esophagoscopy) to rule out synchronous tumors is controversial. If the primary site is known, the diagnostic yield of bronchoscopy or esophagoscopy is generally low. However, most clinicians agree that these procedures are indicated for patients with evidence of diffuse mucosal abnormalities in the setting of a malignant neck node without a clear primary site, particularly when the lymph node

is located in the lower part of the neck, which increases the likelihood of a lung or esophageal primary tumor. In addition, endoscopy has a low yield in nonsmokers, as a synchronous second primary cancer is less likely in these patients.

Imaging

Recommendations for imaging the primary site and the neck include computed tomography (CT) or magnetic resonance imaging for demarcating the extent of disease. A high-quality CT scan performed with contrast medium is less expensive than magnetic resonance imaging (MRI) and is sufficient in most cases. An extensive search for distant metastases for patients with head and neck cancer who do not have suspicious symptoms is not routinely done because the overall incidence of spread below the clavicle at the time of presentation is low (10% or less), particularly in the absence of lymph node involvement. Hence, routinely performing positron-emission tomography (PET)/CT or other body imaging in all patients is neither clinically indicated nor cost-effective. A chest x-ray is performed as much to rule out a second primary lung cancer or to document chronic obstructive pulmonary disease as to identify lung metastases.

A high-resolution CT scan is more sensitive than a chest x-ray for identifying a new primary site or metastases, and it could have a specific indication for patients presenting with bulky N2 or N3 neck disease or a primary site of the hypopharynx, both of which are risk factors for distant metastatic spread. Formal imaging of the liver and bones should be carried out only if clinically indicated based on symptoms or a biochemical abnormality, such as hypercalcemia or an elevation in serum alkaline phosphatase. By contrast, evaluation for metastatic disease with a body CT scan and bone scan, or by using 18-fluorodeoxyglucose (FDG)-PET/CT, is an appropriate part of the workup for patients with nasopharyngeal cancer with lymph node involvement. In this setting, the incidence of distant metastases approaches 60%, and bone is the most common site of metastasis.

FDG-PET is appropriate when the primary site is unknown or to evaluate an equivocal finding on cross-sectional imaging; however, routine application of this test is expensive, and if disease management will not be affected, it is not indicated. FDG-PET does not replace cross-sectional imaging of the primary site and neck, and is best interpreted in the context of a separate or fused cross-sectional study performed with contrast. As with any diagnostic test, FDG-PET is not without fault. False-positive results can be related to dental disease or to an inflammatory process in the neck or elsewhere, and uptake by lesions smaller than 1 cm is inconsistent. FDG-PET with a fused, contrast-enhanced CT scan may be useful for identifying spread to regional nodes in the N0 neck, the identification of which would alter radiation portals or the choice of neck dissection to be performed.[30-32] The sensitivity and specificity to detect nodal metastases is 90% and 94%, respectively.

Tissue Diagnosis

Histologic proof of cancer typically is obtained by performing a biopsy of the primary site, a neck node, or both. At least initially, needle aspiration of a lymph node is preferred to excisional biopsy, especially for an apparently malignant node with an occult primary lesion. This approach is both safe and feasible, and the theoretical risk of seeding malignant cells along the needle track has not been a problem in the clinic. Straightforward squamous cell cancers should pose few challenges to the cytopathologist; poorly differentiated tumors or lymphomas are more problematic. If an excisional biopsy is necessary, its results may be incorporated into the

definitive treatment of the patient. A surgeon capable of performing a neck dissection should be involved if squamous cell cancer is suspected.

STAGE CLASSIFICATION

The stage groupings for all primary sites are based on the tumor, node, and metastasis (TNM) classification of the AJCC 8th edition and the Union for International Union Against Cancer (UICC). The TNM system is based on both clinical examination and radiographic information. A few general rules for clinical staging can be identified:

- Primary tumors of the oral cavity and oropharynx that are 4 cm or larger are classified as T3; those with massive local invasion of adjacent structures are classified as T4.
- Vocal cord paralysis in the setting of a primary tumor of the larynx or hypopharynx indicates a stage of no less than T3.
- The nasopharynx is the one primary site for which an alternative staging system—the Ho staging system—is commonly used, particularly in Asia. Because definitions for component stages vary between the AJCC/UICC and Ho systems, these differences must be considered when reviewing the published results of therapy.
- For all primary sites (Table 9-3) except the nasopharynx and p16-positive oropharyngeal cancers (Table 9-4), the TNM stage grouping is the same; clinical lymph node involvement indicates an overall stage of at least stage III; the presence of distant metastases indicates stage IVC disease, and locally advanced resectable and unresectable stage IV disease (without distant metastases) are designated as IVA and IVB, respectively.
- Oral cavity T stage has been updated to incorporate depth of invasion into staging in addition to previously included size and sites of local invasion.
- The general nodal staging system now incorporates extranodal extension into the N staging to reflect the poorer prognosis associated in tumors with positive extranodal extension.
- The term “early-stage disease” refers to stages I and II disease and to low-volume stage III disease (e.g., T1 or T2 and N0 or N1); the term “locally” or “locally regionally advanced disease” refers to stages III and IV disease, specifically a large primary tumor (T3 or T4) or the presence of multiple or bulky neck nodes (N2 or N3).

Table 9-3 **American Joint Committee on Cancer Staging: Lip and Oral Cavity, Oropharynx, Hypopharynx, and Larynx**

Primary Tumor (T)	**Tx**	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ
Lip and Oral Cavity	**T1**	Tumor 2 cm or less in greatest dimension
	T2	Tumor greater than 2 cm but no more than 4 cm in greatest dimension
	T3	Tumor greater than 4 cm in greatest dimension
	T4	(lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose)
	T4a	(oral cavity) Tumor invades adjacent structures (e.g., through cortical bone, into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)
	T4b	Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery
Oropharynx	**T1**	Tumor 2 cm or less in greatest dimension
	T2	Tumor greater than 2 cm but no more than 4 cm in greatest dimension
	T3	Tumor greater than 4 cm in greatest dimension
	T4a	Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
	T4b	Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery
Hypopharynx	**T1**	Tumor limited to one subsite of hypopharynx and 2 cm or less in greatest dimension
	T2	Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures greater than 2 cm but no more than 4 cm in greatest diameter without fixation of hemilarynx
	T3	Tumor greater than 4 cm in greatest dimension or fixation of hemilarynx
	T4a	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue
	T4b	Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures
Larynx-Supraglottis	**T1**	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
	T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
	T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)
	T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
	T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Glottis	**T1**	Tumor limited to the vocal cord(s) with normal mobility
	T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
	T3	Tumor limited to the larynx with vocal cord fixation and/or invades paraglottic space, and or minor thyroid cartilage erosion
	T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
	T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Regional Lymph Nodes (N)	NX	Regional lymph nodes cannot be assessed		
	N0	No regional lymph node metastasis		
	N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension		
	N2	Metastasis in a single ipsilateral lymph node, greater than 3 cm but no more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none greater than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none greater than 6 cm in greatest dimension		
	N2a	Metastasis in a single ipsilateral lymph node, greater than 3 cm but no more than 6 cm in greatest dimension		
	N2b	Metastasis in multiple ipsilateral lymph nodes, none greater than 6 cm in greatest dimension		
	N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
	N3	Metastasis in a lymph node, greater than 6 cm in greatest dimension		
Distant Metastasis (M)	MX	Distant metastasis cannot be assessed		
	M0	No distant metastasis		
	M1	Distant metastasis		
Stage Grouping	Stage 0	Tis	N0	M0
	Stage I	T1	N0	M0
	Stage II	T2	N0	M0
	Stage III	T3	N0	M0
		T1	N1	M0
		T2	N1	M0
		T3	N1	M0
	Stage IVA	T4a	N0	M0
		T4a	N1	M0
		T1	N2	M0
		T2	N2	M0
		T3	N2	M0
		T4a	N2	M0
	Stage IVB	T4b	Any N	M0
		Any T	N3	M0
	Stage IVC	Any T	Any N	M1

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Unresectable T4 Lesion

There is general agreement among surgeons regarding the following criteria for unresectability: base of skull involvement, fixation to the prevertebral fascia, carotid encasement, and involvement of the pterygoid musculature. Additional criteria that many would consider appropriate are the inability to perform an adequate reconstruction for a functional result, a low likelihood of achieving negative margins, and a requirement for total glossectomy. Assignment to the stage IVB category has implications for prognosis (i.e., less favorable) and treatment (i.e., primary surgical management not planned). For these primary sites, stage IVB disease now includes patients with T4b, any N category, and no metastasis (M0), or any T category and N3 (any neck node larger than 6 cm in greatest diameter). Stage IVC includes any T and N category as well as M1 disease.

HPV-Related Oropharyngeal Cancer

The AJCC staging system was updated to account for p16 status in staging of oropharyngeal tumors given the marked difference in prognosis between patients with p16-positive and p16-negative tumors. Based on the work of groups such as the International Collaboration on Oropharyngeal Cancer Network for Staging and others, the new staging system for p16-positive oropharyngeal tumors uses the nasopharyngeal classification for nodal disease without the lower neck lymph node variable and combining of T4a and T4b into a single T4 category. The new system has three stages for nonmetastatic disease: stage I (T0-T2N0-N1), stage II (T0-T2N2 or T3N0-N2), and stage III (T4 or N3) and stage IV (M1) for metastatic disease.[33] Additionally, cancers of unknown primary origin in patients who are HPV- or EBV-positive may now be regarded as oropharyngeal cancers or nasopharyngeal cancers, respectively.[20]

KEY POINTS

- Many presenting signs and symptoms are associated with a particular primary site (e.g., hoarseness may refer to the larynx or hypopharynx, and a unilateral otitis media may refer to the nasopharynx).
- The location of pathologic lymph nodes in the neck may suggest the primary site.
- The initial staging evaluation for head and neck cancer includes comprehensive examination of the head and neck, imaging of the primary site and neck, chest imaging, and routine lab screenings.
- Early-stage disease is defined as disease limited to a small primary tumor (T1 or T2) with low risk nodal involvement. Locally or locally regionally advanced disease is defined as the presence of a large primary tumor (T3 or T4) or the presence of large, multiple, or contralateral regional node involvement (N2 or N3).
- Criteria for unresectable disease include base of skull involvement, fixation to the prevertebral fascia, carotid encasement, and involvement of the pterygoid musculature.

Table 9-4 American Joint Committee on Cancer Staging: Nasopharyngeal Carcinoma

Classification of Nasopharyngeal Carcinoma	WHO Classification	Former Terminology		
	Type I: Squamous cell carcinoma	Squamous cell carcinoma		
	Type II: Nonkeratinizing carcinoma	Transitional cell carcinoma		
	Without lymphoid stroma	Intermediate cell carcinoma		
	With lymphoid stroma	Lymphoepithelial carcinoma (Regaud)		
	Type III: Undifferentiated carcinoma	Anaplastic carcinoma		
	Without lymphoid stroma	Clear cell carcinoma		
	With lymphoid stroma	Lymphoepithelial carcinoma (Schminke)		
Primary Tumor (T)	TX	Primary tumor cannot be assessed		
	T0	No evidence of primary tumor		
	Tis	Carcinoma in situ		
	T1	Tumor confined to the nasopharynx, extends to oropharynx and/or nasal cavity without parapharyngeal extension		
	T2	Tumor with parapharyngeal extension		
	T3	Tumor involves bony structures and/or paranasal sinuses		
	T4	Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space		
Regional Lymph Nodes (N)	NX	Regional lymph nodes cannot be assessed		
	N0	No regional lymph node metastasis		
	N1	Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa		
	N2	Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa		
	N3	Metastasis in a lymph node(s) greater than 6 cm and/or to supraclavicular fossa		
	N3a	Greater than 6 cm in dimension		
	N3b	Extension to the supraclavicular fossa		
Distant Metastasis (M)	MX	Distant metastasis cannot be assessed		
	M0	No distant metastasis		
	M1	Distant metastasis		
Stage Grouping	Stage 0	Tis	N0	M0
	Stage I	T1	N0	M0
		T1	N1	M0
	Stage II	T2	N0	M0
		T2	N1	M0
		T1	N2	M0
		T2	N2	M0
	Stage III	T3	N0	M0
		T3	N1	M0
		T3	N2	M0
		T4	N0	M0
	Stage IVA	T4	N1	M0
		T4	N2	M0
	Stage IVB	Any T	N3	M0
	Stage IVC	Any T	Any N	M1

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PRINCIPLES OF DISEASE MANAGEMENT

Historically, surgery and radiation therapy have been the central treatment modalities for head and neck cancers because they have curative potential. Management of the primary site and management of the neck are separate but related concerns that influence decisions about which modality is used or the integration of combined-modality therapy. Although chemotherapy may enhance the effects of radiation therapy, chemotherapy by itself is not curative. TNM stage groupings are helpful for defining prognosis and treatment options. Management of head and neck cancer is best served by multidisciplinary treatment planning that involves not only a surgeon, medical oncologist, and radiation oncologist but also dentists, prosthodontists, nutritionists, audiologists, speech and swallowing therapists, physical and occupational therapists, social workers, and psychiatrists, as necessary. Plans for rehabilitation are an

integral part of this process.

NEWLY DIAGNOSED T1 OR T2, N0 OR N1, AND M0 (STAGES I, II, AND LOW-BULK III) DISEASE

Single-modality treatment with surgery or radiation is typically used for previously untreated stage I, stage II, or low-bulk stage III disease—essentially, a small primary tumor with or without a single ipsilateral node measuring 3 cm or less in diameter. Cure rates for this group are quite favorable, ranging from 52 to 100%, depending on the primary site. Strategies to decrease the morbidity associated with treatment and to prevent SPMs have been research priorities. The chosen modality depends on local expertise, anticipated functional outcome, and patient preference. For example, a T1N0M0 tumor of the glottic larynx can be managed with surgery or radiation. The 5-year overall survival rates associated with primary surgery (e.g., cordectomy and hemilaryngectomy) and primary radiation therapy (with salvage surgery as necessary) have been comparable (approximately 90%).[34] A cordectomy requires less time than radiation therapy and initially is cheaper, but repeat procedures may be necessary and could lead to a related decrease in function. Radiation therapy is associated with excellent control rates and voice function outcome, but it requires a 6-week course and initially may be more expensive.

NEWLY DIAGNOSED, HIGHER-VOLUME STAGE III AND STAGES IVA AND IVB DISEASE

If a higher-volume stage III or a stage IV tumor is resectable, the standard approach is surgery followed by adjuvant radiation therapy with or without concomitant chemotherapy based on pathologic risk features (see section on Principles of Surgery), or combined chemotherapy and radiotherapy if organ preservation is desired. If the tumor is unresectable, the approach is radiation and concomitant chemotherapy. Cure rates are less favorable for this group, ranging from 10 to 65%, depending on the primary site and disease extent. Data from randomized trials support integrated chemotherapy and radiation as standard treatment options for patients with advanced, resectable cancers of the larynx and hypopharynx (with the intent of avoiding total laryngectomy) and for patients with cancers of the oropharynx when a nonsurgical approach is chosen. For patients with advanced tumors of the oropharynx, nasopharynx, or unresectable squamous cell cancers of the upper aerodigestive tract, combined-modality therapy with chemoradiation improves survival compared with radiation alone[35-41] (Table 9-5). When primary chemoradiation therapy is used, surgery is reserved for persistent disease or for recurrence of resectable disease.

Table 9-5 Concurrent Chemoradiotherapy Standard of Care	
Organ Preservation	**Regimen**
Larynx	RT/cisplatin[38]
Oropharynx	RT/cisplatin or RT/carboplatin/5-FU[39,40] Consider RT/cetuximab if not candidates for platinum therapy[43,44]
Nasopharynx	RT/cisplatin followed by cisplatin/5-FU[42]
Unresectable disease	RT/cisplatin[41]
Postoperative adjuvant	RT/cisplatin[45,46]

Abbreviations: 5-FU, 5-fluorouracil; RT, radiotherapy.

For locally advanced, resectable cancers of the oral cavity, primary surgical management with appropriate reconstruction and/or postoperative radiation therapy is the mainstay of treatment because anticipated functional outcomes are favorable even for more advanced tumors.

RECURRENT DISEASE WITHOUT A SURGICAL OR RADIATION OPTION, OR M1 DISEASE

For patients who receive chemotherapy but for whom surgery or radiation therapy is not an option (including patients with distant metastases), disease is generally not curable, and the median survival ranges from 5 to 10 months with various available standard drugs based on prior clinical trials. Data now indicate that survival for patients with HPV-positive disease is longer than for patients with HPV-negative tumors even in the metastatic setting.[18] The identification of more effective chemotherapy and integration of targeted agents have been a priority for this patient group. Immunotherapy, using programmed death 1 antibodies, has now been approved for patients in whom platinum-based therapies have failed.

KEY POINTS

- Single-modality treatment with surgery or radiation therapy is typically used with curative intent for previously untreated stage I, stage II, or low-bulk stage III (T1-2N1) disease.
- Combined-modality treatment with surgery and radiation or chemoradiation therapy is typically used with curative intent for previously untreated, higher-volume stage III (T3N0-1) and stage IV disease without distant metastases.
- Metastatic disease below the clavicle and local–regional recurrent disease without a surgical or radiation option are generally incurable and treated with palliative intent.

PRINCIPLES OF SURGERY

SURGERY OF THE PRIMARY TUMOR

Complete removal of a tumor with negative margins defines an adequate surgical resection. Transoral robotic and endoscopic technology is now available and facilitates the accomplishment of such resections in a less invasive manner, but these techniques require special expertise and experience to apply well. Depending on the primary site and the size of the tumor, complete surgical extirpation may necessitate removal of key structures, such as the larynx, eye, or mandible. The potential adverse effect on cosmesis and function underscores the importance of rehabilitation as part of the treatment strategy. A variety of skin and bone flaps, as well as customized obturators and prosthetics, successfully address many defects that arise from surgery. Function-preserving procedures are applicable for selected patients in whom negative margins are achieved, while uninvolved structures necessary for function are preserved. Examples include various subtotal laryngectomy procedures, for which adding a postoperative course of radiation therapy often compromises the functional outcome. Thus, all of these factors must be considered when deciding the best therapeutic option for each patient.

As the spectrum of reconstructive options increases, defining precise, reproducible criteria for tumor unresectability remains a challenge and complicates interpretation of the literature. A patient with an unresectable tumor should be distinguished from a patient with disease that is clearly resectable but for whom there are medical contraindications to surgery (i.e., medically inoperable).

SURGERY OF THE NECK

Different types of neck surgery or dissection are used to address suspected or proven disease in the cervical lymph nodes. This is performed up front or after completion of chemoradiation, at the discretion of treating physicians. A comprehensive neck dissection involves the en bloc removal of all five lymph node levels (Fig. 9-2). Three important structures are potentially jeopardized by this procedure: the sternocleidomastoid muscle, the internal jugular vein, and the spinal accessory nerve. If none of these structures are spared, the procedure is considered a radical neck dissection, which is associated with the highest likelihood of postoperative shoulder pain and weakness. Different types of comprehensive neck procedures that spare one, two, or three of these structures (modified radical neck dissections) may be performed for selected patients, without compromising disease control. Comprehensive neck dissections generally are done with therapeutic intent, such as when cancerous lymph nodes are suspected or known to be present. In other settings, selective neck dissections are used, whereby fewer than five lymph node levels are removed. Selective procedures usually are performed electively in part to improve staging precision (such as when there are no palpable lymph nodes, but the estimated risk for occult metastases exceeds 15 to 20%, and negative findings on specimen analysis may obviate the need for postoperative radiation therapy).

PET imaging 3 months after treatment is useful in the assessment of patients with node-positive disease who were treated with chemoradiation therapy. Rather than all patients proceeding to adjuvant neck dissection, given the high negative predictive value of FDG-PET, observation can be considered for patients with non–FDG-avid neck lymph nodes measuring less than 1 cm. In a randomized study of patients with N2 or N3 neck disease, PET/CT-guided surveillance resulted in noninferior survival at 36 months as compared with up-front neck dissection, and these patients underwent fewer neck dissections.

KEY POINTS

- Function-conserving procedures are applicable for select patients in whom negative margins can be achieved with preservation of structures important for function.
- Conservative or debulking surgery is not part of routine clinical practice for head and neck cancer.
- Comprehensive neck dissections involve removal of all five lymph node levels and are usually performed with therapeutic intent. Selective neck dissections involve removal of fewer than all five levels and are generally done electively to improve staging precision.

PRINCIPLES OF RADIATION THERAPY

The curability of head and neck cancer with radiation therapy is inversely related to tumor bulk. The rate of disease control with radiation alone decreases with increasing T stage. This finding explains why radiation can be used as a single modality to treat early-stage disease but is generally applied as an adjunct to surgery or combined with chemotherapy for more advanced tumors.

RADIATION DOSE AND FRACTIONATION

The dose of radiation necessary to sterilize squamous cell cancer varies with the fractionation size and schedule used. Standard, once-daily fractionation consists of 2.0 Gy per day with a total dose of 70 Gy or greater to the primary site and gross adenopathy and 50 Gy or greater to uninvolved nodal stations at risk. When given postoperatively, the total dose to the primary site and involved nodal stations is 60 Gy or greater, and the dose to uninvolved nodal stations at risk is 50 Gy or greater. Postoperative radiation generally begins 4 to 6 weeks after surgery. The delivery of radiation requires careful treatment planning. In particular, the spinal cord must be blocked to prevent radiation-induced cervical myelopathy.

Potential improvements in the therapeutic index of radiation for head and neck cancer may be achieved by altering the radiation fractionation (more than one fraction per day, often with a change in the fraction size). The results of randomized trials have established the therapeutic benefits of an altered-fractionation strategy, particularly with regard to local–regional control. In one seminal study by the RTOG,[42] more than 1000 previously untreated patients with stage II, III, or IV HNSCC were randomly assigned to four different radiation-only treatment arms: standard fractionation, 2 Gy daily and 70 Gy for 7 weeks; hyperfractionation, 1.2 Gy twice daily and 81.6 Gy for 7 weeks; accelerated fractionation with a split, 1.6 Gy twice daily and 67.2 Gy for 6 weeks; and accelerated fractionation with a concomitant boost, 1.8 Gy daily, 1.5 Gy daily as a boost for the last 12 days only, and 72 Gy for 6 weeks.

With a median follow-up of 41.2 months among surviving patients, the hyperfractionation and concomitant boost arms yielded significantly improved local–regional control ($p = 0.045$ and $p = 0.050$, respectively), as well as a trend toward improved disease-free survival ($p = 0.067$ and $p = 0.054$). More acute toxicity, but no late effect, was seen in the three altered-fractionation groups. Although no significant differences in overall survival were demonstrated, the meta-analysis known as MARCH indicated a significant improvement in absolute survival at 5 years with altered-fractionation approaches (3.4%; HR, 0.92; 95% CI; 0.86, 0.97; $p = 0.003$). This

assessment included 15 randomized trials involving 6515 patients and compared conventional radiotherapy with hyperfractionated radiotherapy, accelerated radiotherapy, or both.[43] The benefit was significantly higher with hyperfractionated radiotherapy than with accelerated radiotherapy (8% vs. 2% at 5 years). Altered-fractionation programs are increasingly being incorporated into standard practice for patients who can tolerate the added local–regional toxicity and also are being investigated in combination with concomitant chemotherapy. In RTOG 0129, researchers investigated adding chemotherapy to different radiation delivery plans. Specifically, patients with locally advanced disease were treated with cisplatin plus accelerated fractionation with a concomitant boost or standard fractionation. With a median follow-up of 7.9 years, there were no significant differences between the standard fractionation group and the accelerated fractionation plus concomitant boost group in overall survival (HR, 0.96, p = 0.37; 5-year, 57% vs. 60%; 8-year estimate, 48% vs. 48%), progression-free survival (HR, 1.02; p = 0.52; 5-year, 49% vs. 50%; 8-year estimate, 42% vs. 41%), local–regional failure rate (HR, 1.08; p = 0.78; 5-year, 31% vs. 34%; 8-year estimate, 37% vs. 39%), or rate of distant metastases (HR, 0.83; p = 0.16; 5-year, 14.5% vs. 11.5%; 8-year estimate, 15% vs. 13%).[44]

With recent advances in technology, improved planning and delivery of radiotherapy has helped overcome some of the major side effects of conventional radiotherapy. One advancement is intensity-modulated radiotherapy, which is regularly used in the treatment of head and neck cancer. This therapy delivers therapeutic radiation doses specifically around the tumor and the at-risk lymph nodes with improved conformality, defined as the ratio of the dose to tumor relative to the dose to normal tissues. Increasingly, conformal plans are able to deliver the same dose to the tumor while sparing progressively more of the surrounding tissues. The advantages of this technique are that the surrounding normal tissue can be spared and that anatomic structures (e.g., the pharyngeal constrictor muscles necessary for swallowing and the salivary glands) can be preserved. In the randomized, phase III PARSPORT study, patients treated with intensity-modulated radiotherapy had less incidence of xerostomia compared with patients treated with conventional radiation therapy, albeit with higher rates of fatigue during treatment.[45] Another more recent advancement is the use of proton-beam therapy. Compared with typical photon therapy, in proton-beam therapy the physical properties of a proton allow the administration of lower doses of radiation beyond the tumor, leading to better conformality. However, definitive data that one method leads to better tumor control than the other in the management of head and neck cancer are lacking, and their relative side-effect profiles with and without the addition of systemic therapy are in the process of being better defined.

RADIATION-RELATED TOXICITY

Radiation at the doses outlined previously is associated with predictable acute mucosal and skin toxicities. More aggressive dosing and fractionation schedules and the addition of concomitant chemotherapy generally increase the severity of these acute toxicities. Depending on the amount of salivary tissue included in the radiation portal, xerostomia and loss of taste are common. Because adequate saliva is an important component of oral hygiene, careful dental assessment is necessary before the start of radiation therapy, followed by ongoing dental prophylaxis and fluoride treatments. Pain management, nutritional support, swallowing evaluation and therapy, and aggressive oral care are required. Other potential complications include hypothyroidism, especially for patients receiving treatment to the neck; Lhermitte syndrome, a self-limited, shocklike sensation extending down the spine and extremities with

neck flexion; long-term induration and fibrosis; and osteoradionecrosis of the mandible.

Some degree of xerostomia is common. Pilocarpine (a cholinomimetic, muscarinic agent), cevimeline (a parasympathomimetic and a muscarinic agonist), and amifostine (a thiol with chemoprotectant and radioprotectant properties) are used to treat dry mouth.[46-48] Amifostine is approved only for use with postoperative adjuvant radiotherapy and not in the definitive setting.

KEY POINTS

- Compared with standard schedules, altered-fractionation radiotherapy improves local–regional control of advanced tumors, albeit with increased acute local toxicity.
- Head and neck radiation commonly causes acute toxicities, including mucositis, edema, and xerostomia. Other potential toxicities include hypothyroidism, Lhermitte syndrome, long-term induration and fibrosis, and osteoradionecrosis of the mandible.
- Intensity-modulated radiotherapy is associated with less dry mouth after treatment than that seen with conventionally planned radiation therapy.
- Pilocarpine, cevimeline, and amifostine may ameliorate radiation-induced xerostomia.

PRINCIPLES OF CHEMOTHERAPY

A number of drugs have activity against HNSCC, including methotrexate, cisplatin, carboplatin, 5-fluorouracil, paclitaxel, docetaxel, and cetuximab. Gemcitabine (for nasopharynx cancer),[49,50] vinorelbine, bleomycin, ifosfamide, and irinotecan also are active but are used less frequently in current clinical practice. The reported response proportions vary with the setting (untreated or pretreated) and the drugs used (single agent or combination). Platinum-based regimens are most commonly used as first-line therapy. The anticipated major response rate in patients with previously untreated disease is 60 to 90%, with clinical complete responses in 20 to 50%. By contrast, the activity of platinum-based drug combination therapy in patients with recurrent disease is 30 to 40% and complete responses are rare. Rates of complete and partial responses from single-agent therapy are approximately half of those observed with combination chemotherapy.

The use of chemotherapy for patients with potentially curable, advanced, local–regional disease is generally distinguished from the treatment of patients with incurable, recurrent, metastatic disease. For patients with potentially curable cancer, the chemotherapy literature can be divided into the following four groups:

- induction or neoadjuvant chemotherapy administered for several cycles prior to definitive local therapy (surgery, radiation therapy, or chemoradiotherapy);
- chemoradiation in the setting of locally advanced, unresectable disease;
- local curative therapy (surgery) followed by adjuvant chemoradiation; and
- organ-preservation techniques for patients with resectable cancers of the oropharynx, larynx, and hypopharynx.

The goals of these multimodality approaches are to improve survival by reducing rates of local–regional recurrence and metastases as well as to achieve preservation of the organ and

its function without a decrement in the survival rates achievable with primary surgery. The latter specifically refers to preservation of the larynx for patients with primary cancers of the larynx or hypopharynx and preservation of structures in the oropharynx for speech and swallowing function, such as the tongue.

INDUCTION CHEMOTHERAPY

Studies evaluating the integration of induction chemotherapy with local–regional treatment dominated the literature of head and neck cancer during the 1980s and early 1990s. The results of randomized controlled trials evaluating two to four courses of cisplatin-based combination chemotherapy as induction followed by local therapy demonstrated a decrease in distant metastases in some trials, but no significant or consistent differences were observed in either local–regional control or overall survival when compared with the standard of care for most trials and meta-analyses.[39,51,52] This result was found despite the high major response rates seen after treatment with cisplatin-based combination chemotherapy in these previously untreated patients.

A meta-analysis of 63 randomized trials of local–regional treatment with or without chemotherapy was performed using updated patient data. This comprehensive review showed no significant survival benefit from the addition of induction chemotherapy (31 trials involving 5269 patients; HR, 0.95; 95% CI; 0.88, 1.01; p = 0.10). A subgroup analysis focusing on trials in which induction cisplatin/5-fluorouracil were used showed a significant survival benefit for this regimen (HR, 0.88; 95% CI; 0.79, 0.97; p = 0.05), but a similar subset analysis focusing on platinum-based concomitant therapy demonstrated an approximately 3-fold higher survival benefit.[52]

Taken collectively, these data did not support a role in standard clinical practice for induction chemotherapy in the setting of planned surgery and radiation (with improvement in overall survival as the endpoint).

The next phase of induction studies added taxanes to the backbone of previously tested cisplatin/5-fluorouracil. The results from three randomized controlled trials comparing three or four cycles of induction docetaxel/cisplatin/5-fluorouracil with standard cisplatin, 100 mg/m^2 plus 5-fluorouracil daily, and 1000 mg/m^2 per day by continuous infusion for 5 days are noteworthy.[53-55] The TAX 323 trial enrolled more than 300 patients with locally advanced unresectable disease. The control arm consisted of four cycles of the two-drug combination followed by radiotherapy, and the experimental arm consisted of four cycles of the three-drug combination (docetaxel, 75 mg/m^2; cisplatin, 75 mg/m^2; 5-fluorouracil, 750 mg/m^2 per day by continuous infusion for 5 days) followed by radiotherapy.[54] The response rate to the three-drug induction regimen was significantly higher than that of the two-drug regimen (68% vs. 54%; p = 0.006) as was overall survival (HR, 0.73; 95% CI; 0.57, 0.94; p = 0.016). There also was less nonhematologic toxicity with the three-drug combination than with the two-drug combination; however, hematologic toxicity was more common with the former. Similarly, the TAX 324 trial randomly assigned 501 patients with unresectable or resectable disease (all sites) to three cycles of standard cisplatin/5-fluorouracil or to combination docetaxel, 75 mg/m^2; cisplatin, 100 mg/m^2; 5-fluorouracil, 1000 mg/m^2 per day by continuous infusion for 4 days.[53] Definitive local therapy in both arms consisted of standard radiotherapy plus weekly carboplatin (area under the curve, 1.5). Overall survival was significantly improved for patients who received the three-drug therapy (HR, 0.70; 95% CI; 0.54, 0.90; p = 0.0058). The differences between groups persisted with longer follow-up. At a median follow-up of 72 months, median survival was 70.6

months (95% CI; 49.0, 89.0) in the triplet arm compared with 34.8 months (95% CI; 22.6, 48.0) in the doublet arm (p = 0.014).[56] The third trial was conducted by the GORTEC study group for organ preservation in patients with either locally advanced cancer of the larynx or hypopharynx.[55] A total of 220 patients were randomly assigned, and of these, just over half had a hypopharyngeal primary tumor. The stage of the primary tumor was T3 for the majority of patients. The two treatment arms were standard cisplatin/5-fluorouracil for three cycles (control) or combination docetaxel/cisplatin/5-fluorouracil for three cycles (dosing same as in TAX 323). After induction, patients with responsive disease received 70 Gy of standard radiation; patients whose disease did not respond to chemotherapy underwent total laryngectomy followed by radiotherapy with or without additional chemotherapy The three-drug therapy was shown to be statistically superior for the endpoints of response to the induction regimen (83% vs. 61%) and preservation of a functional larynx at 3 years (63% vs. 41%). More details of the patient population and outcomes are needed for interpretation of the results in the context of other larynx-preservation trials for these two primary sites.

These three trials demonstrate that combination of docetaxel/cisplatin/5-fluorouracil followed by radiotherapy alone or chemoradiation with carboplatin is superior to cisplatin/5-fluorouracil followed by the same definitive local therapy. Also, the three-drug regimen administered in TAX 323 seems to have an acceptable toxicity profile with lower rates of severe and life-threatening myelosuppression than those observed with the two-drug regimen. A fourth phase III trial has been published in final form.[57] This trial compared induction paclitaxel/cisplatin/5-fluorouracil with induction cisplatin/5-fluorouracil in a heterogeneous population of patients with resectable and those with unresectable disease. Chemoradiation was planned following induction chemotherapy, but the actual treatment was not uniform. The taxane-containing treatment group experienced a higher overall response rate (80% vs. 68%). However, the difference in overall survival was not significant, although the trend favored the paclitaxel-containing arm.

In addition to the trials reviewed earlier, a meta-analysis of five randomized trials representing 1772 patients comparing cisplatin/fluorouracil induction therapy with a taxane/cisplatin/5-fluorouracil regimen confirmed the superiority of the taxane-containing induction regimen, with a significant reduction in progression, local–regional failure, and distant failure compared with cisplatin/5-fluorouracil.[58]

These data provided the rationale for three phase III trials comparing induction chemotherapy with taxane/cisplatin/5-fluoruracil followed by chemoradiation therapy compared with chemoradiation therapy alone.[59-61] There was no evidence of a survival benefit in any of these three studies. The first was a phase III study that compared induction chemotherapy, including a docetaxel/cisplatin/5-fluorouracil induction arm, followed by chemoradiation therapy with chemoradiation therapy alone.[60] Next published was the PARADIGM study, which enrolled 145 patients with locally advanced head and neck cancer and randomly assigned them to docetaxel/cisplatin/5-fluorouracil induction therapy followed by chemoradiation therapy (with either docetaxel or carboplatin) or cisplatin-based chemoradiation therapy alone (with two cycles of bolus cisplatin).[61] After a median follow-up of 49 months, the 3-year overall survival was 73% in the induction chemotherapy therapy followed by chemoradiation therapy group and 78% in the chemoradiation-alone group (p = 0.77). More patients had febrile neutropenia on the induction therapy arm. In the DeCIDE trial, patients with N2/N3, locally advanced head and neck cancer were randomly assigned to receive two cycles of docetaxel/cisplatin/5-fluorouracil induction therapy followed by chemoradiation therapy or chemoradiation therapy alone. The concomitant therapy was similar in the two arms and consisted of cisplatin/5-fluorouracil/hydroxyurea. A total of 280 patients were enrolled. With a minimum follow-up of 30

months, the incidence of distant failure was higher in the chemoradiation-alone arm (29 vs. 17 in the induction therapy arm), but this difference was not statistically significant ($p = 0.11$); the overall survival was similar in the two arms at 72% in the induction arm and 69% in the chemoradiation-alone arm ($p = 0.69$). The incidence of grade 3 to 4 leukopenia and neutropenia was higher in the induction arm.[59]

Therefore, at this time, although induction chemotherapy with taxanes/cisplatin/5-fluorouracil followed by chemoradiation therapy remains an option, it cannot be concluded that it is superior to chemoradiation therapy alone in the management of locally advanced head and neck cancer. The role of induction chemotherapy followed by surgery and postoperative radiation therapy was investigated in a phase III trial that evaluated 256 patients with locally advanced (stages III and IVa) oral squamous cell cancers.[62] Patients received either two cycles of docetaxel/cisplatin/5-fluorouracil induction followed by surgery and postoperative radiation therapy or up-front surgery and postoperative radiation therapy. There was no increased perioperative morbidity noted with the induction arm. At a median follow-up of 30 months, there was no significant difference in overall survival between the two arms of the study. This approach of induction chemotherapy followed by surgery and postoperative therapy, therefore, cannot be considered as a standard treatment paradigm.

CONCOMITANT CHEMOTHERAPY AND RADIATION

The major role for chemotherapy in patients with nonmetastatic disease is its use as a radiation sensitizer. Therefore, the main focus has been on drugs that show activity against the disease and radiation-enhancement properties (e.g., cisplatin, cetuximab, and 5-fluorouracil). The two general strategies that can be identified amid a broad spectrum of approaches are

- concomitant single-agent or combination chemotherapy with continuous-course radiation, or
- combination chemotherapy with planned split-course radiation.

More recently, altered-fractionation approaches have become an added variable. Historically, the use of chemotherapy in this manner was applied to patients with unresectable disease and generally increased the severity of acute mucosal and skin toxicities but also improved local–regional control compared with radiation alone. These encouraging efficacy results led to studies of other patient groups (e.g., resectable, organ-preservation intent, and poor-risk adjuvant).

A study first reported in 1992 was the turning point for the growing interest in chemoradiation therapy for advanced head and neck cancer.[63] In this study, the investigators randomly assigned 157 patients with unresectable HNSCC to radiation alone (up to 70 Gy, conventional fractionation) or to a cisplatin/5-fluorouracil combination alternating with radiation (up to 60 Gy). The complete response rate (43%) and the survival rate (41%) in the group treated with chemoradiation therapy were significantly superior to those in the radiation alone group (22% and 23%, respectively; $p = 0.01$).

Another trial randomly assigned 295 patients with unresectable HNSCC to one of three treatment groups: radiation alone (70 Gy, 2 Gy daily); the same radiation with concomitant cisplatin (100 mg/m^2) on days 1, 22, and 43; or split-course radiation (60 Gy to 70 Gy, 2 Gy daily) with three cycles of concomitant bolus cisplatin/infusional 5-fluorouracil. In the third arm, the option existed to pursue surgical resection after the second cycle of chemotherapy, if possible; resection was available for all three groups if feasible after the completion of

treatment.[38] With a median follow-up of 41 months, there was a significant survival advantage at 3 years associated with chemoradiation compared with radiation alone (37% and 23%; p = 0.014). The split-course concomitant regimen offered no survival advantage over the control group (27%). Toxicity of grade 3 or higher was significantly more common with concomitant chemotherapy (52% with radiotherapy alone vs. 89% with chemoradiation therapy; p < 0.0001). This trial established chemoradiation with high-dose cisplatin as the standard of care for locally advanced unresectable head and neck cancer.

The meta-analysis by Pignon et al. that included the 1992 study highlights the favorable results seen with a chemoradiation approach in these early trials. Although significant heterogeneity among designs was noted, the chemoradiation regimen was associated with an 8% absolute benefit in survival at 5 years compared with radiation alone (HR, 0.81; 95% CI; 0.76, 0.88; p < 0.0001).[54] An updated analysis of 87 trials involving more than 16,000 patients showed the same absolute benefit for survival with concomitant treatment (HR, 0.81; p < 0.0001).[64]

Once-daily fractionation radiation therapy for 7 weeks with high-dose cisplatin (100 mg/m^2 on days 1, 22, and 43) was compared with accelerated boost radiation therapy (42 fractions for 6 weeks) in combination with two cycles of cisplatin (100 mg/m^2 on days 1 and 22) in the RTOG 0129 trial. There was no statistically significant difference in overall survival between the arms.[44]

The use of targeted therapies with radiotherapy is an area of great interest. Epidermal growth factor receptor (EGFR) is highly expressed in virtually all HNSCC, and expression is inversely associated with prognosis. Therefore, EGFR inhibitors have been the focus of most targeted therapy trials for head and neck cancer. Cetuximab was approved by the U.S. Food and Drug Administration (FDA) for use in combination with radiotherapy for patients with advanced head and neck cancer based on a multicenter trial published by Bonner and colleagues.[65] This important, proof-of-principle trial randomly assigned patients with locally advanced squamous cell cancers of the oropharynx, larynx, and hypopharynx to treatment with radiotherapy alone (standard or altered-fractionation schedules) or to the same radiotherapy with weekly cetuximab. Local–regional failure-free survival and overall survival rates were significantly improved with the addition of cetuximab. The updated median overall survival for patients treated with cetuximab and radiation was 49.0 months (95% CI; 32.8, 69.5) compared with 29.3 months (95% CI; 20.6, 41.4) in the radiotherapy-alone group (HR, 0.73; 95% CI 0.56, 0.95; p = 0.018). Five-year overall survival was 45.6% in the cetuximab and radiation group and 36.4% in the radiotherapy-alone group. Further, survival was improved in patients who experienced at least a grade 2 acneiform rash compared with patients with grade 0 or 1 rash (HR, 0.49; 95% CI; 0.34, 0.72; p = 0.002).[66] Cetuximab had no effect on distant metastases. In a retrospective evaluation, patients with oropharyngeal cancer demonstrated improved local–regional control, progression-free survival and overall survival with the addition of cetuximab to radiation, regardless of HPV/p16 status.[67] Whether this combination of radiotherapy plus a biologic therapy is as effective as the standard cisplatin-based chemoradiation is unknown; therefore, the exact role and indications for cetuximab with radiotherapy are not clear. More recently, the international phase II CONCERT-2 study, which randomly assigned patients with locally advanced HNSCC to standard radiation with either two cycles of cisplatin (100 mg/m^2) or three cycles of panitumumab (9 mg/kg), reported a 2-year local–regional control rate of 61% compared with 51%, respectively. The HR for progression-free survival was 1.73 (95% CI; 1.07, 2.81; p = 0.03), and no statistical difference in overall survival was reported.[68]

At present, the only indication for cetuximab with radiotherapy in lieu of platinum-based chemotherapy is for the treatment of patients in whom the use of cisplatin is precluded or there is patient preference because of concern for cisplatin-related side effects. Numerous trials are testing the addition of EGFR inhibition with monoclonal antibodies or small-molecule tyrosine kinase inhibitors (TKIs) to chemotherapy and radiation in various disease settings. One such trial, RTOG 0522, directly compared cisplatin and radiation with or without cetuximab.[69] After a median of 3.8 years, there was no statistically significant improvement in the 3-year progression-free survival (61.2% vs. 58.9%; p = 0.76) and overall survival (72.9% vs. 75.8%; p = 0.32) or distant metastasis (13.0% vs. 9.7%; p = 0.08) with the addition of cetuximab to cisplatin and radiation. In CONCERT-1, a randomized international phase II study in patients with locally advanced squamous cell, investigators compared three cycles of panitumumab (9 mg/kg) with cisplatin (75 mg/m^2) with standard three cycles of cisplatin (100 mg/m^2) and failed to show any benefit of adding panitumumab in local–regional control at 2 years.[70] Similarly, the addition of erlotinib, an oral small-molecule TKI acting on EGFR, failed to show any improvement compared with cisplatin and radiation alone in the management of locally advanced HNSCC.[71]

Given the favorable prognosis of HPV-related oropharyngeal cancer, recent efforts have focused on attempts to "deintensify" the definitive standard modalities of radiation and chemotherapy. The disease control rates for HPV-positive low-risk (N0-2a or N2b patients with ≤ 10 pack-year smoking history) were similar for radiation therapy alone and chemoradiation therapy in one retrospective series.[72] However, the rate of disease control was lower in the N2c subset managed by radiation therapy alone (73% vs. 92% for chemotherapy and radiation; p = 0.02). Besides T and N staging, stratification by smoking exposure may also help risk stratify these patients. These data are considered exploratory and at this time any deintensification approach, although attractive in reducing long-term toxicities, should be considered investigational.

In summary, chemoradiation therapy leads to improved disease control compared with radiation alone for patients with unresectable HNSCC and represents a standard treatment for patients who are able to tolerate the anticipated added treatment-related toxicity. There also is a role for this approach in the organ-preservation and larynx-preservation settings and for advanced local–regional nasopharyngeal cancer. The data showing improvement are best established for platinum-based chemoradiation therapy regimens; an advantage persists even when newer altered-fractionation approaches are employed.

ADJUVANT CHEMORADIATION

The results of two randomized controlled trials have clarified the role of chemotherapy and radiation in the postoperative adjuvant setting when compared with radiotherapy alone. These studies, conducted by the EORTC,[36] as well as the trial by the RTOG[35] addressed the question of whether the addition of cisplatin to standard postoperative radiotherapy (based on pathologic criteria) would improve the outcome for patients. The experimental arms of both studies consisted of standard fractionation radiation with concomitant cisplatin (100 mg/m^2) on days 1, 22, and 43. The 5-year results of the EORTC study indicated significant improvement in progression-free survival (47% vs. 36%; p = 0.04) and overall survival (53% vs. 40%; p = 0.02) in favor of chemoradiation therapy with cisplatin.[36] The findings of the RTOG study initially demonstrated a significant advantage with combined-modality adjuvant therapy for the first two outcomes, but not for overall survival (3-year survival, 56% vs. 47%; p = 0.09).[35] In both

studies, toxicity was greater with concomitant chemoradiation therapy.

Although the treatment was very similar in these two studies, the high-risk pathologic features were not uniform and the study populations differed. The entry criteria for the RTOG study were the presence of multiple positive nodes, an extracapsular extension of tumor, or a positive margin. In contrast, the EORTC trial defined *high risk* as a positive margin, an extracapsular extension of nodal disease, vascular embolism, or perineural disease; for oral cavity or oropharynx primary sites, *high risk* was defined as positive nodes at level IV or V. These differences may, in part, explain the variable outcome of the two trials. In an effort to reconcile the results of these two trials, a pooled analysis was performed, which indicated that the subsets of patients in both trials who experienced a significant benefit from cisplatin added to radiotherapy had either microscopically involved margins or extracapsular extension of disease in neck nodes.[73] Therefore, the presence of either or both of these risk factors is considered a definite indication for adjuvant chemotherapy and radiation. Since these initial analyses were performed, the RTOG trial has been reanalyzed with a median follow-up of 9.4 years, and data demonstrated a significant advantage for chemoradiation therapy in terms of improvement of local–regional control and disease-free survival in patients with either positive margins or extracapsular nodal extension, but only a trend for overall survival benefit ($p = 0.07$).[74]

COMBINED-MODALITY TREATMENT: ORGAN PRESERVATION

Initial organ-preservation studies were designed around the use of induction chemotherapy for patients with resectable disease and, subsequently, have focused on chemoradiation therapy. Avoidance of total laryngectomy received the greatest attention in these early studies.[75,76]

Larynx and Hypopharynx Organ Preservation

The U.S. Department of Veterans Affairs Laryngeal Cancer Study Group (VALCSG) conducted a seminal randomized trial in which induction cisplatin/5-fluorouracil infusion (three cycles) followed by radiation therapy (with surgery reserved for patients whose disease had an inadequate response, disease persistence, or relapse) was compared with total laryngectomy followed by radiation therapy.[75] All 332 patients had advanced, resectable, T2 to T4 laryngeal cancer. There was no significant difference in survival between the groups with more than 10 years of follow-up subsequent to the original publication; total laryngectomy was avoided for approximately two-thirds of survivors who received chemoradiation therapy. On multivariate analysis, T4 and N2 disease were both significant predictors of treatment failure, with 56% of T4 cases eventually requiring laryngectomy. The pattern of failure differed between the two treatment groups, with a significant reduction in distant failure but a higher rate of local failure for the patients randomly assigned to induction chemotherapy compared with those in the surgery control arm.

Long-term quality-of-life outcomes were also assessed. Among the 46 long-term survivors surveyed, those who received induction chemotherapy plus radiation had significantly better quality-of-life scores ($p < 0.05$), better pain scores, and less depression. After 2 years, communication (speech) scores favored the induction chemotherapy group, but at longer follow-up, the two treatment groups had similar speech scores.[77]

The EORTC performed a similar study involving patients with advanced, resectable (T2 to T4) cancer of the hypopharynx.[76] There was no difference in survival between the two groups; the 5-year estimate of successful larynx preservation (i.e., local control and no tracheostomy or

feeding tube) was 35%. The EORTC and VALCSG studies established induction cisplatin/infusional 5-fluorouracil followed by radiation (for the patients whose disease responded) as an alternative to initial surgical management. This combined-modality approach became a standard treatment option for patients with locally advanced, resectable laryngeal or hypopharyngeal cancer who sought to avoid total laryngectomy. Close monitoring for recurrence and timely integration of salvage surgery are important parts of these combined approaches and are necessary for survival to remain comparable with the survival rates associated with primary surgical management.

During the 1990s, the use of chemotherapy shifted from induction to concomitant use with radiation not only as definitive treatment for unresectable squamous cell cancers but also for patients with resectable disease who chose a nonsurgical organ-preservation approach. Multiple studies demonstrated that concurrent administration of chemotherapy with radiation resulted in improved tumor control compared with radiation alone or induction chemotherapy followed by radiation.

In one randomized study of patients with resectable stage III or IV squamous cell carcinoma of the head and neck, primary radiation therapy (68 to 72 Gy, 1.8 to 2 Gy daily) was compared with the same radiation regimen plus concomitant daily cisplatin (20 mg/m^2/day) and 5-fluorouracil (1000 mg/m^2/day) for 4 days starting on days 1 and 22.[78] Surgery was recommended for both groups if no response was evident at 50 to 55 Gy or for disease persistence or recurrence at the completion of treatment. Most of the 100 patients enrolled had primary lesions of the larynx, hypopharynx, or oropharynx. With a median follow-up of 5 years, overall survival was not significantly different between the two groups, but survival with successful primary-site preservation was superior in the chemotherapy and radiation group (laryngeal preservation at 5 years, 34% vs. 42%; $p = 0.004$), albeit at the expense of greater acute hematologic toxicity, mucositis, cutaneous reactions, weight loss, and the need for a feeding tube during treatment. The lack of a significant difference in overall survival was attributed to effective salvage surgery and competing causes of death.

Intergroup RTOG 91-11, a follow-up to the VALCSG study, addressed two questions unresolved in the prior trial, including the optimal sequencing of chemotherapy and radiotherapy (induction chemotherapy followed by radiation or concomitant chemotherapy and radiation) and the precise contribution of chemotherapy added to radiotherapy.[39] A total of 547 patients with T2 to low-volume T4, nonmetastatic, squamous cell cancer of the larynx were randomly assigned to one of three treatment arms: radiation alone (70 Gy, 35 fractions); concomitant cisplatin (100 mg/m^2), administered intravenously on days 1, 22, and 43, with the same radiation dose; or induction cisplatin/5-fluorouracil followed by radiation for patients who had a complete or partial disease response of the primary site. In all groups, laryngectomy was reserved for patients with insufficient response, suspected disease persistence, or local recurrence. A planned neck dissection was performed approximately 8 weeks after completion of radiation in patients who had N2 or N3 disease at initial staging. The results at 2 years showed significant improvement in the larynx-preservation rate for the concomitant-treatment arm (88%) compared with the induction arm (75%; $p = 0.005$) and the radiation-alone arm (70%; $p < 0.001$). Local–regional control also was significantly better with concomitant treatment compared with the other two treatments (78% vs. 61% and 56%, respectively). Chemotherapy suppressed distant metastases, with rates of 8%, 9%, and 16% for the concomitant, induction, and radiation-alone arms, respectively. Disease-free survival was significantly better in both the concomitant (61%) and the induction (52%) arms compared with

the radiation-alone arm (44%); however, the overall survival rates did not differ among the three groups. Chemotherapy-related toxicities (grades 3 to 4 mucositis in the concomitant arm and grades 3 to 4 myelosuppression in the induction arm) were more common in the combination-treatment groups than in the radiation-alone group, although rates for possible treatment-related deaths were not significantly different. Mature data (reported after a minimum follow-up of almost 5 years and, more recently, 10.8 years) for all patients confirmed these results (Table 9-6).[79] Laryngectomy-free survival is an endpoint that combines survival and a quality-of-life parameter and does not account for patients dying from other causes with an intact larynx. Although this would not be chosen as the primary endpoint in modern practice, laryngectomy-free survival was the endpoint used to generate the statistical hypothesis in 1990. In the initial 2-year data analysis of this endpoint, only the concomitant arm showed significant improvement when compared with radiation alone; however, in the mature analysis, both induction and concomitant arms reached statistical significance compared with radiation alone for laryngectomy-free survival. The importance of this finding for clinical practice is unclear because the larynx-preservation and local-control results were not different for patients treated with induction chemotherapy followed by radiotherapy or with radiotherapy alone; these results were significantly inferior to the results with concomitant cisplatin and radiotherapy. Late toxicity did not differ across the three arms of the study. It is intriguing, however, that overall survival favored the induction arm numerically, but not statistically, by 11%. The clinical relevance of this finding and its rationale remain unclear at this time.

Table 9-6 **RTOG 91-11 Results: 5- and 10-Year Outcomes**

Treatment Arm	Time (years)	LFS (%)	LP (%)	DM (%)	DFS (%)	OS 5-Year (%)
Cis/5-FU followed by RT	5	44	71	14.7	37.7	58.1
	10	29 ($p = 0.02$ as compared with CRT)	68	16.6	20.4	38.8
CRT	5	47	83.6	13.6	38	55.1
	10	24 ($p = 0.68$ as compared with induction; $p = 0.03$ as compared with RT alone)	81.7 ($p = 0.005$ as compared with induction; $p < 0.001$ as compared with RT alone)	16.1	21.6 ($p = 0.04$ as compared with RT alone)	27.5 ($p = 0.08$ as compared with induction; $p = 0.53$ as compared with RT alone)
RT alone	5	34	66	22	28	53.8
	10	17	64	24	14.8	31.5 ($p = 0.29$ as compared with induction)

Abbreviations: 5-FU, 5-fluorouracil; cis, cisplatin; CRT, concomitant chemoradiation; DFS, disease-free survival; DM, distant metastases; LFS, laryngectomy-free survival; LP, larynx preservation; OS, overall survival; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group.

In summary, mature results from Intergroup RTOG 91-11 demonstrated that induction cisplatin/5-fluorouracil followed by radiation and chemoradiation with cisplatin demonstrate similar efficacy for the endpoint of laryngectomy-free survival. However, local–regional control and larynx preservation were significantly improved with concomitant chemoradiation compared with induction or radiation alone. Overall survival did not differ significantly across the three

arms. For patients who wish to preserve their larynx, 100 mg/m^2 of daily cisplatin administered on days 1, 22, and 43 during radiotherapy is the standard of care, with surgery reserved for patients with persistent or recurrent disease after treatment completion.

A randomized larynx-preservation trial for patients with locally advanced, resectable cancer of the larynx or the hypopharynx was completed by the EORTC; it compared induction cisplatin/5-fluorouracil chemotherapy followed by radiotherapy with an alternating schedule of chemotherapy and radiotherapy (four cycles of cisplatin/5-fluorouracil during weeks 1, 4, 7, and 10 with alternating weeks of radiotherapy with 20 Gy during the three 2-week intervals). In long-term follow-up, there was no difference in larynx preservation. The two arms performed equally in terms of survival with a larynx, overall survival, progression-free survival, and in severity of toxicities observed.[51]

Oropharynx Organ Preservation

Given the results of these larynx-preservation studies, the chemoradiation approach also has been of investigational interest for locally advanced, resectable tumors of other primary sites for which surgical management may lead to substantial cosmetic or functional morbidity. GORTEC reported a noteworthy site-specific trial in which 226 patients with stage III or IV squamous cell cancer of the oropharynx were randomly assigned to either radiotherapy alone (70 Gy, 35 fractions) or to the same radiation program with concomitant bolus doses of carboplatin (70 mg/m^2 daily for 4 days) and 5-fluorouracil (600 mg/m^2 as a daily 24-hour infusion for 4 days) starting on days 1, 22, and 43. Concomitant treatment yielded a better 3-year survival rate (51% vs. 31%; p = 0.02) and disease-free survival (42% vs. 20%; p = 0.04), albeit at the expense of greater toxicity. Mucositis, weight loss, and the need for a feeding tube, as well as hematologic toxicity, occurred more frequently in the chemoradiation therapy group. Therefore, this treatment approach is considered an evidence-based standard treatment option and is particularly applicable for the management of T3 to T4 or N2 to N3 disease located at the base of the tongue or tonsils.[41]

Available data indicate that chemoradiation therapy is feasible for oropharynx cancer, and disease-control outcomes compare favorably with those obtained historically with primary surgical management. However, a series of site-specific, direct, randomized comparisons with standard surgery and postoperative radiation therapy are lacking for this malignancy. Nonetheless, most head and neck oncologists believe that the evidence is sufficiently compelling to support the use of chemoradiation therapy in standard practice as initial management for advanced oropharyngeal cancer, even if it is resectable. For other sites of advanced resectable disease, especially the oral cavity (for which good reconstructive options exist), primary surgical management is better established and remains the standard of care.

In general, for patients with locally advanced squamous cell cancer of the larynx, hypopharynx, or oropharynx, chemoradiation therapy yields better disease control compared with radiation alone, albeit at the expense of greater acute toxicity. This is the preferred organ-preservation approach for cancer of the primary sites. It must be emphasized that successful application of a chemotherapy and radiation strategy for organ preservation requires a team approach that includes not only the head and neck surgeon, radiation oncologist, and medical oncologist but also a nutritionist, swallowing therapist, oncology nurses, advanced care practitioners (physician assistants and nurse practitioners), and social workers. Close monitoring with comprehensive head and neck examinations and timely integration of salvage surgery, when necessary, are part of the treatment plan and are necessary to avoid

compromising survival. The evaluation of functional and quality-of-life outcomes is another parameter for assessing the overall benefit of organ-preservation therapies and will be an important factor in comparing therapeutic approaches.

KEY POINTS

- Induction chemotherapy with the three-drug regimen docetaxel/cisplatin/5-fluorouracil improves disease control outcomes compared with cisplatin/5-fluorouracil alone.
- There are no definitive data that induction chemotherapy followed by chemoradiation therapy leads to better survival compared with chemoradiation alone.
- For patients with unresectable HNSCC, chemoradiation with high-dose cisplatin significantly improves survival compared with radiotherapy alone and is the standard of care.
- In locally advanced laryngeal cancer (T2 to low-volume T4), local-regional control and larynx preservation were significantly improved with concomitant cisplatin and radiation therapy compared with induction chemotherapy followed by radiation or radiation alone.
- Cetuximab added to radiation improves survival compared with radiation alone in locally advanced head and neck cancer, but there are insufficient data for it to replace chemoradiation with cisplatin therapy as the standard of care.
- Chemoradiation with high-dose cisplatin is the standard of care for postoperative adjuvant treatment for patients with positive resection margins or extracapsular extension of nodal disease.

NASOPHARYNGEAL CANCER

Cisplatin-based chemoradiation therapy is the cornerstone of therapy for newly diagnosed, advanced, local–regional nasopharyngeal cancer. Although this treatment is widely used, disagreements occur regarding the role of adjuvant chemotherapy in this setting. The clinical behavior of nasopharyngeal cancer varies somewhat according to its histologic subtype.

WHO type I (keratinizing squamous cell cancer) is more common in Western countries and has a local–regional behavior more similar to that of other smoking-related head and neck cancers. WHO types II (nonkeratinizing, differentiated) and III (undifferentiated cancer), both of which can occur with lymphoid stroma (lymphoepithelioma; Table 9-4), predominate in endemic areas (such as southern China and northern Africa) and have a higher propensity for distant metastases. There is also a category known as basaloid squamous cell carcinoma of the nasopharynx. WHO types II and III also are more responsive to radiotherapy and chemotherapy than the differentiated squamous histology, and more than 90% of cases are associated with EBV. Radiation is the historic mainstay of treatment for disease above the clavicle. The same drugs used in the management of squamous cell cancers arising from other sites in the head and neck, such as cisplatin, 5-fluorouracil, and the taxanes, also are active against nasopharyngeal cancer.

The management of locally advanced nasopharyngeal cancer was dramatically changed after the results of the Intergroup nasopharynx study were published.[37] In this trial, patients with

stage III or IV nasopharyngeal cancer were randomly assigned to either radiation alone (70 Gy, 35 fractions for 7 weeks) or to the same radiation schedule with three planned doses of concomitant cisplatin (100 mg/m^2) administered every 21 days, followed by three cycles of adjuvant cisplatin (80 mg/m^2) and 5-fluorouracil (1000 mg/m^2 per day for 4 days). Most patients (91%) had stage IV disease, and WHO type I histology was more common as compared with a series from endemic areas. With a minimum follow-up of 5 years, overall survival was significantly improved for patients who received combined-modality therapy that included the adjuvant chemotherapy (67% vs. 37%; $p < 0.001$), as was progression-free survival (58% vs. 29%; $p < 0.001$). This improvement in survival was observed even though only 63% of patients received all three planned cycles of cisplatin during radiation and only 55% received all three cycles of adjuvant cisplatin/5-fluorouracil.

The Intergroup study was criticized because the relative contributions of the concurrent cisplatin and the adjuvant therapies could not be determined, and the trial results may be less applicable to endemic areas where WHO type I histologic subtypes are infrequent. That being said, subsequent randomized trials[80,81] in endemic areas and two meta-analyses[82,83] have confirmed the significant survival advantage afforded by cisplatin chemotherapy concurrent with radiation as compared with radiation alone. By contrast, randomized trials of induction chemotherapy followed by radiation compared with radiation alone have shown no significant improvement in overall survival,[84,85] although some reported improved relapse-free survival. Three meta-analyses of trials that compared any sequence of chemotherapy and radiotherapy with radiotherapy alone have been published. The meta-analysis reported by Huncharek et al. was a pooled analysis of the published results of six randomized trials involving 1528 patients.[82] In this analysis, at 4 years, chemotherapy improved progression-free survival by 34% and overall survival by 20%. The second meta-analysis used updated individual patient data from eight randomized trials (1753 patients with locally advanced disease) conducted from 1966 to 2003.[83] The effect on overall survival of adding chemotherapy to radiotherapy was an absolute survival benefit of 6% or from 56 to 62% alive at 5 years (HR for death, 0.82; 95% CI; 0.71, 0.94; $p = 0.006$). The effect observed on event-free survival was an absolute benefit of 10% or from 42 to 52% alive at 5 years (HR for tumor failure [local, regional, or distant] or death, 0.76; 95% CI; 0.67, 0.86; $p < 0.0001$). A significant interaction between the timing of chemotherapy and overall survival was observed, with the highest benefit resulting from concomitant chemoradiation therapy ($p = 0.005$). In a third meta-analysis, Blanchard and colleagues pooled the data from 4806 patients treated across 19 studies and also confirmed that adding chemotherapy to radiotherapy significantly improved overall survival (HR, 0.79; 95% CI; 0.73, 0.86; $p < 0.0001$), with an absolute benefit at 5 years of 6.3%.[86] The interaction of timing of the chemotherapy with radiation and overall survival favored concomitant plus adjuvant therapy followed by concomitant without adjuvant therapy, but the benefit was not present for chemotherapy alone either as induction or adjuvant therapy.

Based on these data as a whole, the survival benefit from cisplatin-based chemoradiation seems clear and is the accepted standard of care for patients with locally advanced nasopharyngeal cancer. The benefit of adjuvant chemotherapy, theoretically used to suppress distant metastases common in nasopharyngeal cancer, is less widely accepted. An important study in that regard is the trial by Chen et al., which compared chemoradiation with or without adjuvant chemotherapy in 251 patients with nonmetastatic stage III or IV nasopharyngeal carcinoma.[85] The primary endpoint was failure-free survival. After a median follow-up of 37.8 months, the estimated 2-year failure-free survival rate was 86% in the chemoradiation plus adjuvant chemotherapy arm and 84% in the chemoradiation-only group ($p = 0.13$). This

controversial issue will hopefully be addressed by the results of an ongoing international study (NRG 001) that uses plasma EBV DNA to prognosticate which patients are at risk for recurrence following definitive chemoradiation. Patients who clear EBV DNA during definitive treatment are randomly assigned to observation or standard adjuvant treatment. In a second arm, patients with posttreatment EBV DNA in the blood are randomly assigned to two different adjuvant chemotherapy regimens. While awaiting further follow-up, National Comprehensive Cancer Network guidelines have been modified to include chemoradiation therapy alone without adjuvant chemotherapy as an acceptable option (category 2B). In the United States, the standard of care for treatment of patients with stages IIB, III, IVA (T4N0-2M0), and IVB (T1-4N3M0) nasopharyngeal cancer is radiotherapy (70 Gy) with chemoradiation therapy utilizing high-dose cisplatin on days 1, 22, and 43 followed by three courses of adjuvant cisplatin/infusional 5-fluorouracil.[37] Radiotherapy alone is indicated for stage I disease.

The general management of recurrent or metastatic nasopharyngeal carcinoma is a platinum-based doublet. In one randomized, phase III study, patients treated with gemcitabine/cisplatin experienced an improved median progression-free survival of 7.0 months (range, 4.4–10.9) compared to 5.6 months (range, 3.0–7.0) in patients receiving 5-fluorouracil/cisplatin (HR, 0.55; 95% CI; 0.44, 0.68, $p < 0.0001$).[87]

KEY POINTS

- WHO type I nasopharyngeal cancer (keratinizing) is more commonly found in the United States, whereas WHO types II (nonkeratinizing, differentiated cancer) and III (undifferentiated cancer) overwhelmingly predominate in endemic areas, such as southern China and northern Africa, and are associated with EBV.
- The standard of care (according to stage) is radiotherapy alone for stage I and chemoradiation therapy with cisplatin followed by three cycles of adjuvant cisplatin/5-fluorouracil for stages II to IVB nasopharyngeal cancer. However, results with regard to the benefits of adjuvant chemotherapy are inconclusive.
- Cisplatin/gemcitabine is an active combination therapy for the treatment of recurrent or metastatic nasopharyngeal cancer; it is more efficacious than treatment with cisplatin/5-fluorouracil.

INCURABLE RECURRENT OR DISTANT METASTATIC DISEASE

Systemic Therapy

Disease that cannot be resected and has been previously irradiated or involves distant organs is considered incurable. Cisplatin, carboplatin, docetaxel, paclitaxel, 5-fluorouracil, and methotrexate are the most commonly used cytotoxic agents to treat recurrent or metastatic HNSCC; cetuximab is an active targeted agent that is also commonly used. Activity also has been demonstrated for bleomycin, irinotecan, gemcitabine (in nasopharyngeal cancer), vinorelbine, capecitabine, oxaliplatin, ifosfamide, and pemetrexed. Randomized trials comparing combination chemotherapy and single-agent therapy show a near doubling of the response rate with platinum-based combinations, but unless a clinical complete response is achieved, the duration of response is brief (2 to 4 months) and does not have a significant effect on overall

survival.

Toxicity is generally greater when combination chemotherapy is used. As an example, one meta-analysis included all studies in which cisplatin/5-fluorouracil, the historical gold-standard combination regimen, was compared with single-agent therapy. A significant improvement in response was documented, which translated into only a 2-week difference in the median survival (odds ratio, 0.43; 95% CI; 0.29, 0.63). No formal quality-of-life data were available, but toxicity was greater for patients who received combination therapy. Numerous single agents have activity and can be used, but weekly methotrexate is the historical gold standard because of its ease of administration, toxicity profile, and relatively low cost.[88] Combination chemotherapy should be limited to patients with a good performance status (e.g., ECOG performance status of 0 to 1), who are better able to tolerate the added toxicity; for these patients, the higher response rate may translate into better palliation, although there are no objective quality-of-life data to support this notion. Factors associated with poor response in this population are well known and include poor performance status, the presence of comorbidities, bulky local–regional disease or high tumor volume, and prior treatment for recurrent disease.

It was hoped that the introduction of the taxanes in the 1990s would result in improved survival for patients with recurrent disease, but this has not occurred. Two different weekly schedules of paclitaxel offered no advantage compared with weekly single-agent methotrexate.[89] Results from another study showed that paclitaxel/cisplatin did not differ significantly from standard cisplatin/5-fluorouracil in terms of the median survival rate (9 vs. 8 months) and the 1-year survival rate (30% vs. 41%), although the paclitaxel regimen was generally better tolerated.[90]

Cetuximab is the only molecularly targeted drug to be approved for use in the United States for metastatic head and neck cancer; its indication is for platinum-refractory disease. Phase II trials of cetuximab alone or combined with cisplatin for patients who had experienced either stable or progressive disease as the best response to a standard platinum-based doublet were in the range of 10 to 13%.[91-93] In a randomized trial in which the combination of cisplatin/placebo was compared with cisplatin/cetuximab for 123 patients, no significant difference was found in median progression-free survival (2.7 vs. 4.2 months; $p = 0.27$), although the rate of major response (complete plus partial) was significantly higher for patients who received cisplatin/cetuximab (10% vs. 26%; $p = 0.03$).[94]

In the phase III EXTREME trial, 440 patients with recurrent or metastatic HNSCC were randomly assigned to either the intervention arm (cisplatin or carboplatin with 5-fluorouracil/cetuximab) or standard arm (cisplatin or carboplatin with 5-fluorouracil) as first-line treatment.[95] It was found that adding cetuximab to cisplatin/5-fluorouracil significantly prolonged the median overall survival from 7.4 months to 10.1 months (HR for death, 0.80; 95% CI; 0.64, 0.99; $p = 0.04$), significantly prolonged the median progression-free survival from 3.3 months to 5.6 months (HR for progression, 0.54; $p < 0.001$), and increased the response rate from 20% to 36% ($p < 0.001$). This is the first trial to show any improvement in overall survival when compared with the standard regimen of cisplatin/5-fluorouracil.

In a randomized, phase II study, patients with platinum-refractory disease were randomly assigned to treatment with single-agent afatinib, an oral small-molecule TKI that irreversibly inhibits EGFR and HER2, or cetuximab with crossover permitted at progression. Although both single-agent afatinib and cetuximab had modest activity, with a mean tumor shrinkage of 16.6% and 10.1%, respectively ($p = 0.30$), patients who progressed on either agent had clinical benefit after crossover, with disease control rates of 33.3% for afatinib and 18.8% for

cetuximab, suggesting a lack of cross-resistance between these agents.[96] In a randomized study comparing afatinib to single-agent methotrexate as a second-line treatment for recurrent/metastatic head and neck cancer, afatinib led to a statistically significant improvement in progression-free survival of 2.6 months, compared with 1.7 months for methotrexate ($p = 0.03$).[97] Other TKIs targeting EGFR have been studied, including gefitinib and erlotinib, which have modest activity in this setting (including responses for patients who received prior chemotherapy). However, a phase III study failed to show any overall survival benefit of either 250 mg or 500 mg of gefitinib daily compared to standard methotrexate therapy in recurrent metastatic head and neck cancer.[98]

Checkpoint Inhibitors

Pembrolizumab and nivolumab, monoclonal antibodies directed at programmed death 1 protein, were approved by the FDA for the treatment of platinum-refractory recurrent or metastatic HNSCC based on the results of three large clinical trials. In KEYNOTE-012, a nonrandomized study, 174 patients with platinum-refractory HNSCC were treated with pembrolizumab 10 mg/m^2 every 2 weeks or 200 mg flat dose every 3 weeks. A total of 28 patients (16%) experienced a tumor response, and the tumor response lasted for 6 months or longer in 23 (82%) of these and several have lasted for more than 2 years. [99] In KEYNOTE-055, a second nonrandomized study of pembrolizumab in patients with cetuximab- and cisplatin-refractory disease, a flat dose of 200 mg was administered every 3 weeks. Among the 171 patients treated, the overall response rate was 16% with a median duration of 8 months with three-fourths of responses continuing at time of publication.[100] The final approval is for a dose of 200 mg every 3 weeks. The approval for nivolumab treatment for HNSCC resulted from the positive results of a randomized, phase III study in which patients were randomly assigned 2:1 to nivolumab 3 mg/kg every 2 weeks or the physician's choice of weekly docetaxel, methotrexate, or cetuximab. Patients treated with nivolumab had improved median overall survival of 7.5 months (95% CI; 5.5, 9.1) versus 5.1 months (95% CI; 4.0, 6.0) in patients treated with standard treatment ($p = 0.01$). The response rate to nivolumab is 13.3%. At 1 year, 36.0% of patients in the nivolumab arm were alive compared to 16.6% of patients treated with standard therapy.[101] Though patients with HPV-positive (p16-positive) disease and those whose tumors expressed programmed death ligand 1 (PDL-1) performed somewhat better with nivolumab than with chemotherapy, those whose tumors did not express PDL-1 or were p16-negative, also attained benefit. Hence, PDL-1 expression is not required for administration of checkpoint inhibitors in the recurrent/metastatic setting.

Re-Irradiation for Second Primary or Recurrent Head and Neck Tumors

Repeat radiation therapy is increasingly feasible with the greater availability of conformal technology. Building on the improved disease control seen with concurrent chemoradiation for primary treatment, this approach also has been investigated in the recurrent disease setting. Phase II trials suggest that for a proportion of patients (up to 25% in some studies), disease control is more durable than what would be anticipated with chemotherapy alone. This re-irradiation approach may represent a good option for selected patients, but it requires special expertise in radiation planning. In one study, investigators reported the results with full-dose repeat radiation therapy with or without chemotherapy for 169 patients; 13 patients experienced complete remissions ranging from 12 months to 111 months.[102] Two successive phase II RTOG trials that used split-course radiation and twice-daily fractionation at a total

dose of 60 Gy have been completed.[103,104] The concurrent chemotherapy used in the first trial (RTOG 96-10) was 5-fluorouracil/hydroxyurea; the second trial (RTOG 96-11) utilized cisplatin/paclitaxel. At median follow-up of just under 2 years, the overall survival rates were 17%[103] and 25%,[104] respectively, suggesting that for a subset of patients, re-irradiation might provide a survival advantage compared with palliative chemotherapy alone. When analyzed for factors that predicted a favorable survival outcome, an interval of at least 3 years from the original radiation was seen in RTOG 96-10 but not in RTOG 96-11. However, a phase III trial (R04-21) comparing re-irradiation with chemotherapy to chemotherapy alone was terminated because of poor accrual. In another study, 130 patients with recurrent or new tumors within a previously irradiated field were randomly assigned after surgical resection to receive chemotherapy and radiation versus observation alone. This study found an improvement in disease-free survival but no difference between the two arms in overall survival.[105] Identifying which patients are most likely to benefit from the acute and potential long-term toxicities resulting from re-irradiation remains an important area of investigation.

KEY POINTS

- Combination chemotherapy leads to increased response rates compared with sequential single-agent therapy but has not demonstrated an improvement in survival and comes at the expense of increased toxicity.
- The exception is the combination of cetuximab/cisplatin/5-fluorouracil, which demonstrated a survival benefit compared with cisplatin/5-fluorouracil.
- Re-irradiation with or without concurrent chemotherapy may provide long-term survival for a select subset of patients.

CANCER OF UNKNOWN PRIMARY SITE

Although a malignant neck lymph node without a clear primary tumor is a common occurrence in the head and neck, for most patients the primary site will be found after comprehensive examination of the head and neck, assessment under anesthesia, and diagnostic imaging. The location of the lymph node in the neck directs the examiner toward the likely potential primary sites, and PET scanning may be helpful. In recent years, FDG-PET has become an effective diagnostic tool in identifying the primary site for patients who present with cervical lymph node metastases with an unknown primary site. A meta-analysis of 16 studies revealed an overall sensitivity of 88% and specificity 75%.[106] FDG-PET is now considered part of the standard evaluation for squamous cell carcinoma of unknown primary site.

Fine-needle aspiration of the lymph node is the first choice for initial biopsy. If negative, repeating fine-needle aspiration with consideration of a core needle biopsy, if feasible, is appropriate. Viral testing of the nodal specimen (HPV and EBV) may help suggest a particular primary site. If the histologic diagnosis remains inconclusive, subsequent excisional biopsy should be performed in such a way that the incision can be incorporated into an appropriate neck dissection. Open biopsy done inappropriately may contaminate the surgical field and create a larger problem.

If pathologic findings from the neck indicate a diagnosis of squamous cell cancer and a

primary lesion above the clavicle is suggested, especially if the lymph node is high in the neck, a comprehensive head and neck examination under anesthesia is the next step. Directed biopsies should be performed for suspicious mucosal areas as well as locations known to be a source of occult tumors, such as the hypopharynx, base of the tongue, and nasopharynx. In addition, a bilateral simple tonsillectomy is recommended based on the increasing incidence of tonsillar cancers associated with HPV.[5] Of note, the skin, upper part of the esophagus, and lung are other potential sources of squamous cell cancer spread to the neck. If the findings on biopsy of a cervical lymph node indicate an adenocarcinoma, the primary lesion sites, such as the thyroid gland, salivary gland, or sites below the clavicle, should be considered. Lymphoma is another important diagnostic possibility and may require a core needle biopsy for diagnostic purposes. Similarly, distinguishing lymphoma from anaplastic and undifferentiated or poorly differentiated cancers can be difficult on the basis of cytologic analysis alone and may require additional immunohistochemical studies or more tissue.

The choice of treatment of patients with squamous cell cancer in a neck node of unknown primary site is controversial and evolving. Historically, either surgery or radiation was used to treat patients with low-bulk disease in a single lymph node, whereas both modalities were necessary for patients with more advanced disease. The extent of radiation to the potential primary sites requires clinical judgment regarding the likely source of the tumor because a larger portal will increase the morbidity associated with treatment. Findings from clinical series indicate that with longitudinal follow-up, the primary site will ultimately be found for approximately 30% of patients. Long-term survival is better for patients in whom the primary lesion remains occult than for those in whom it does not. The mainstay of treatment is still neck dissection followed by radiation with concomitant cisplatin when extracapsular extension of nodal disease is present. However, integrated primary chemoradiation therapy is used increasingly for these patients based on the physician's impression of the likely primary site(s).

KEY POINTS

- The search for the primary site should include fused FDG-PET/CT imaging and an examination under anesthesia with directed biopsies of the base of the tongue, nasopharynx, and hypopharynx and ipsilateral tonsillectomy.
- Standard treatment consists of neck dissection followed by radiotherapy to include the likely primary sites, and concurrent chemotherapy is added if extracapsular extension of nodal disease is present.
- In selected patients, chemoradiation therapy is another treatment option.

MALIGNANT LESIONS OF THE SALIVARY GLANDS

Cancers of the major salivary glands (parotid, submandibular, sublingual) and the minor salivary glands are uncommon, accounting for fewer than 10% of epithelial head and neck tumors. Tobacco and alcohol use are not risk factors for tumors of the salivary glands, but there may be an association with prior exposure to radiation. The WHO classification lists 24 histologic subtypes of malignant epithelial salivary tumors. Their small numbers, as well as their histologic and prognostic heterogeneity, make them difficult to study; therefore, there are few adequately

tested histologic regimens to guide the medical oncologist.

The most common types of salivary gland cancers are adenoid cystic carcinoma and adenocarcinoma, which originate from the intercalated ducts, and mucoepidermoid carcinoma, which originates from the secretory ducts. A histologic reading of high-grade mucoepidermoid or adenocarcinoma correlates with aggressive behavior and greater likelihood of eventual metastasis, whereas low-grade cancers of these histologies are more likely to be cured with initial local therapies. Adenoid cystic cancer is the most common tumor found in the minor salivary glands, is prone to neurotropic spread, and has the highest propensity of the histologic subtypes for distant metastases, yet it can grow in a very indolent manner. Salivary duct carcinoma is an aggressive subtype of adenocarcinoma with a rapid appearance of metastases.

Surgery is the mainstay of treatment for all primary and recurrent resectable disease with adjuvant radiation, as indicated by the presence of adverse pathologic features.[107] There is a tendency among medical oncologists to recommend the addition of cisplatin or other chemotherapy as a radiosensitizer to improve local–regional control when poor-risk features are present (e.g., positive margins or extracapsular nodal spread) based on the experience with HNSCC, but there are no definitive data to support this addition. However, an ongoing cooperative group trial is attempting to answer this question.

Definitive radiation-based therapy is used for unresectable tumors. Neutron-beam therapy has shown promise in this setting, especially for adenoid cystic cancer, but toxicity is a concern and the RTOG-MRC randomized trial that suggested therapeutic benefit with neutron compared with photon therapy had significant methodologic limitations.[108] Concurrent chemotherapy with radiation is feasible—given the data from the management of squamous cell cancers of the upper aerodigestive tract—and not uncommonly applied for unresectable salivary gland tumors as an extrapolation of benefits seen with this strategy in several other primary tumors, although there are no randomized trial data in these less common tumors to demonstrate improved efficacy with this approach compared with radiation alone.

The available data regarding the activity of different chemotherapy agents are limited and commonly include mixed histologic subtypes; most older reports are case series rather than true clinical trials. A trial of single-agent paclitaxel showed activity for patients with mucoepidermoid carcinoma and adenocarcinoma but not for adenoid cystic carcinoma, emphasizing the importance of histology-specific trials.[109] The available data for other single agents and standard cytotoxic combinations were reviewed by Laurie and Licitra.[110] The most commonly used regimens include cyclophosphamide, doxorubicin, cisplatin, and 5-fluorouracil in various two- and three-drug combinations. Responses are reported across histologic types, but no one trial or case series includes enough patients with a given histology to yield statistical confidence.

Adenoid cystic carcinoma and selected other salivary gland cancer subtypes may be more indolent tumors; therefore, palliative chemotherapy should be attempted only for a symptomatic patient or when substantial tumor growth can be appreciated on serial imaging within a 6-month time frame. In this setting, doxorubicin, cisplatin, and 5-fluorouracil have been used as single agents; combination cyclophosphamide/doxorubicin/cisplatin is a regimen commonly used.[111] Even with combination chemotherapy, the rates of complete and partial responses will be low, and it is appropriate to consider investigational therapy. Epirubicin, mitoxantrone, and vinorelbine have demonstrated activity in adenoid cystic cancer,[112-114] but no such activity has been observed for paclitaxel.[109]

The search for molecular targets for which there are available therapies is the focus of

investigation. The *c-kit* target is expressed in approximately 80% of adenoid cystic cancers, whereas *EGFR* expression is quite variable; the hormone receptors and HER2 are rarely expressed. Imatinib has been evaluated in adenoid cystic carcinoma in a phase II trial with no objective responses observed.[110] Overexpression of *EGFR* is commonly seen in mucoepidermoid carcinoma, whereas *c-kit,* HER2, and hormone receptors are rarely expressed. In adenocarcinoma, *c-kit* is variably expressed depending on the histologic subtype; hormone receptor expression is rare, and *EGFR* expression is uncommon. With the proliferation of targeted agents, there is considerable interest in evaluating multitargeted agents, such as lapatinib (dual inhibitor of *EGFR* and HER2),[115] as well as agents that affect vascular endothelial cell proliferation, such as sorafenib and axitinib. Investigational agents for adenoid cystic carcinoma and the other salivary gland histologies are best evaluated in multicenter collaborations.

Microscopically, salivary duct carcinoma looks identical to ductal breast cancer, is commonly androgen receptor–positive, and may also overexpress *HER2* and *EGFR* on immunohistochemical analysis. Responses to antiandrogen therapy have been reported.[116]

KEY POINTS

- Metastatic adenoid cystic cancer and selected other salivary gland cancers are often characterized by an indolent natural history.
- Systemic treatment should be delayed until substantial tumor growth can be appreciated on serial imaging studies within a 6-month time frame or if disease is located such that symptom development is imminent (e.g., bronchial obstruction).
- The activity of chemotherapy may vary by histologic subtype.

THYROID CANCER

The American Cancer Society estimated 56,870 new cases of thyroid cancer in the United States and 2010 deaths from the disease in 2016.[1] The incidence of this cancer continues to increase in the United States, with a 2.4-fold increase in incidence noted between 1973 (3.6 cases per 100,000 people) and 2002 (8.7 cases per 100,000 people); however, the mortality rate is stable at 0.5 deaths per 100,000 people.[117] This change in incidence is accounted for by an increase in papillary thyroid cancer but not other histologic types. Nearly 90% of these cancers are subclinical or smaller than 2 cm, which suggests that earlier diagnosis may account for most of the observed change in incidence.

Thyroid cancers are classified on the basis of the two main parenchymal cells of origin: the follicular cells involved in thyroid hormone production and the parafollicular cells that produce calcitonin. The former give rise to well-differentiated thyroid cancer (which constitutes 90% of thyroid malignancies) and to anaplastic thyroid cancer (1 to 2% of thyroid cancers); the latter gives rise to medullary thyroid cancer (5 to 9% of thyroid cancers). The histologic subtypes within the well-differentiated thyroid cancer classification are papillary, mixed tumors with areas of papillary and follicular histologic features, follicular, follicular variant of papillary, and Hürthle cell, a follicular variant.

ETIOLOGY

The only well-documented etiologic factor for thyroid cancer is radiation exposure, with an inverse relationship between age at exposure and risk for development of a thyroid malignancy. The thyroid gland of children younger than age 10 is highly vulnerable to developing thyroid cancer if it is exposed to ionizing radiation. The risk for the development of thyroid cancer is much higher for individuals who have been exposed to radioactive iodine isotopes from nuclear reactor accidents and atomic bomb testing, as well as for children and young adults who have received external radiotherapy for other cancers (e.g., Hodgkin lymphoma, neuroblastoma, or Wilms tumor) compared with individuals irradiated during childhood for benign conditions (as was common until 1960). Data from Chernobyl show that nearly all thyroid cancers developing in children after exposure to radioiodine fallout were the well-differentiated papillary type but had a higher rate of local invasion and lymph node involvement than usually observed for this histology. More than 90% of well-differentiated thyroid cancers, however, are unrelated to radiation exposure. Familial syndromes should be suspected when there is a family history of thyroid cancer or a history of a familial syndrome associated with thyroid cancer. Approximately 5% of the differentiated thyroid cancers are associated with hereditary syndromes such as Gardner syndrome, familial adenomatous polyposis, Cowden syndrome, multiple endocrine neoplasia type 2A, familial medullary thyroid carcinoma, and Carney complex.

CLINICAL PRESENTATION AND WORKUP

The sporadic differentiated thyroid cancers are usually asymptomatic for long periods and present as a solitary nodule. The familial papillary thyroid cancers appear to be clinically more aggressive than the sporadic ones. The familial differentiated thyroid cancers are usually multifocal and bilateral and have a tendency to recur both local-regionally and in distant sites. Papillary thyroid cancer and its variants tend to recur locally in the regional lymph nodes, whereas follicular and Hürthle cell cancers tend to recur distantly, especially in bone and lung.

Various prognostic systems have been developed to assist in the risk classification of patients with differentiated thyroid cancer, with potential implications for management based on risk group. Several factors have been widely accepted as being associated with a poor prognosis: age older than 45 years, male sex, poorly differentiated histology, tumor size, and extrathyroidal extension at diagnosis. In contrast, involvement of the regional lymph nodes is associated with greater risk for nodal recurrence but does not confer a worse prognosis for survival.[118] Overall, the 10-year survival rate for differentiated thyroid cancer is excellent (90%). The median age at diagnosis is 45, and the median age at death is 75.[119]

Most thyroid cancers are detected as incidental thyroid nodules found on physical exam or by the patient presenting to the physician with a neck mass. The diagnostic evaluation should include high-resolution ultrasonography to aid in performing a fine-needle aspiration biopsy and to assess the number and characteristics of the nodules, including whether the nodules are solid or cystic. Fine-needle aspiration has high sensitivity and specificity and is the test of choice when evaluating solitary thyroid nodules.[120] Routine thyroid scanning with iodine-123 or technetium-99 is not recommended. This test provides information on whether a nodule is functional; however, the majority of benign and malignant nodules are “cold” or nonfunctioning, meaning that the test is nonspecific and not cost-effective. All patients with a thyroid nodule and suspected familial medullary thyroid cancer should have calcitonin level testing.

TREATMENT

Surgery

The mainstay of treatment is thyroid surgery; for differentiated thyroid cancer, levothyroxine suppression and administration of radioactive iodine are the standards. External-beam radiotherapy and chemotherapy are reserved for palliation of refractory or metastatic disease. The extent of initial surgical therapy is controversial. Many experts recommend removal of the entire thyroid, with the caveats that removal of only the affected lobe and the isthmus is necessary for patients with better risk (e.g., young patients with small tumors) and that total thyroidectomy is associated with a greater risk for complications, such as recurrent laryngeal nerve injury leading to vocal cord paralysis and hypocalcemia secondary to hypoparathyroidism.[121]

Radioactive Iodine

Although the practice is controversial, most U.S. physicians will administer a single dose of radioactive iodine to ablate any normal thyroid remnant and to destroy any microscopic deposits of the remaining thyroid cancer after a total thyroidectomy. It should be emphasized that recent use of iodinated contrast medium, an iodine-rich diet, and inadequate elevation of the level of thyroid-stimulating hormone (thyrotropin) can all undermine the effectiveness of radioactive iodine treatment. Human recombinant thyrotropin has replaced the need for a patient to be put into a hypothyroid state. Dosing strategies for radioactive iodine—ablative compared with higher therapeutic doses—are determined by the patient's prognostic risk, and they range from 50 mCi to 75 mCi for ablation of remnants after total thyroidectomy for low-risk patients, 100 mCi to 150 mCi for the treatment of local–regional lymph nodes, and 150 mCi to 250 mCi for the treatment of lung and bone metastases.

Ablation of remnants enables improved surveillance because normal thyroid cells are also removed, which could cause false-positive results on whole-body scans or false-positive elevations of serum thyroglobulin. In the absence of all normal thyroid tissue, the serum thyroglobulin is a highly sensitive and specific tumor marker.[122] After total thyroidectomy and ablation of remnants, the serum thyrotropin level generally should be suppressed to below normal levels with thyroxine because this hormone is a potential growth factor for microscopic cancer deposits.

Six to 12 months after initial therapy, measurement of the serum thyroglobulin should be performed while the patient is receiving suppressive doses of thyroxine. If the serum thyroglobulin is undetectable and the findings of ultrasound imaging of the neck are negative, an annual analysis of thyroglobulin levels and physical examination are sufficient for most low-risk patients. If there is no detectable level of serum thyroglobulin during treatment with suppressive doses of thyroxine at 1 year after surgery and ablation, the thyroglobulin level should be determined after two doses of recombinant human thyrotropin. If the level rises above 2 ng/mL, a search for remaining disease is warranted. Diagnostic whole-body imaging with iodine scanning should be performed. If this is negative, FDG-PET scanning has been shown to be helpful for localizing disease in more than 60% of such cases.[123]

If metastases develop, radioactive iodine is the treatment of choice. Complete response to treatment has been observed for 45% of patients with distant metastases, although a higher complete response rate has been noted for younger patients and those with small pulmonary metastases.[124] Following the approval of two TKIs for radioactive iodine–refractory thyroid cancers, chemotherapy plays a lesser role in the treatment of this disease. Some thyroid tumors grow very slowly, so a period of careful observation is reasonable before committing to

treatment.

MOLECULAR PATHWAYS IN THYROID CANCER

Interest in targeted therapies has been stimulated by the discovery of activating point mutations of the *BRAF* gene that occur early, are associated with more advanced disease at diagnosis,[125] and independently predict for recurrence. *RET/PTC* rearrangement is found in approximately 20% of adult sporadic papillary carcinomas.[126] Point mutations of the *BRAF* gene are found in 45% of thyroid papillary carcinomas.[127,128] *BRAF* serine–threonine kinase can lead to activation of the mitogen-activated protein kinase (*MAPK*) signaling pathway. Together, mutations involving one of these three genes (*RET/PTC, BRAF,* or *RAS*) are found in more than 70% of papillary carcinomas, and they rarely overlap in the same tumor. *PAX8-PPAR-gamma* is found in about 35% of follicular carcinomas and a small number of Hürthle cell carcinomas.[129]

Sorafenib, an orally active inhibitor of vascular endothelial growth factor (VEGF) receptors 1 to 3 and Raf kinases, was approved by the FDA for treatment of radioactive iodine–refractory thyroid cancer in 2013 based on the positive results of the phase III placebo-controlled DECISION trial.[130] A total of 417 patients, who had locally advanced or metastatic thyroid cancer that was refractory to radioactive iodine and had progression within the past 14 months, were randomly assigned to receive 400 mg of oral sorafenib twice daily or matching placebo. Patients receiving placebo were allowed to receive sorafenib open-label if they had progression. The primary endpoint was progression-free survival. Tumor histology was 57% papillary, 25% follicular, and 10% poorly differentiated; 96% of patients had metastatic disease. The most common site of metastatic disease was lung (86%), lymph nodes (about 50%), and bone (about 25%). Sorafenib was shown to extend the median progression-free survival of 5.8 months (placebo arm) compared with 10.8 months (sorafenib arm; $p < 0.0001$). Median overall survival had not been reached at the time of the presentation. The disease control rate (complete response + partial response + stable disease > 6 months) was 54% in the sorafenib arm, compared with 38% in the placebo arm ($p < 0.0001$). The majority of these responses were stable disease with no complete responses and 12% partial responses reported. Expected toxicities of sorafenib were reported. The most common grade 3 or 4 toxicities included hand–foot syndrome, hypertension, and hypocalcemia.

Lenvatinib, an oral, multitargeted TKI, was approved by the FDA for the treatment of radioactive iodine–refractory thyroid cancer in 2015 based on the positive results of the SELECT trial, a phase III placebo-controlled trial.[131] Lenvatinib inhibits VEGF receptors 1 to 3, fibroblast growth factor receptor 1-4, platelet-derived growth factor α, RET, and KIT. In a 2:1 design, 261 patients were randomly assigned to lenvatinib 24 mg daily and 131 patients were randomly assigned to placebo. The median progression-free survival was 18.3 months compared with 3.6 months, favoring lenvatinib with an HR for progression or death of 0.21 (95% CI; 0.14, 0.31; $p < 0.001$). The response rate to lenvatinib was 64.8%, with four complete responses and 165 partial responses. Treatment-related adverse events (grade 3 or higher) occurred in 75.9% of patients taking lenvatanib versus 9.9% in those taking placebo. The most common toxicities included hypertension, diarrhea, fatigue, anorexia, and weight loss.

Other TKIs are under evaluation in differentiated thyroid cancer. One drug with activity is axitinib (AG-013736), which targets VEGF receptors 1 to 3, platelet-derived growth factor receptor β, and c-kit. A multiinstitutional study assessed its safety and activity in 60 patients with radioactive iodine–resistant thyroid cancer of any histology. The drug was given at a dose of 5 mg twice daily. Partial responses were observed in 30% of patients, and stable disease

lasting at least 16 weeks was reported in another 38%. Median progression-free survival was more than 18 months.[132]

Pazopanib is a potent small-molecule TKI that targets all subtypes of VEGF receptor without activity against the RET receptor and has predominantly antiangiogenic activity. A phase II study with 37 evaluable patients with rapidly progressive, metastatic, radioiodine-refractory, differentiated thyroid cancer were treated with 800 mg of pazopanib administered once daily.[133] Partial response was seen in 49% (95% CI; 35, 68) and lasted longer than 1 year in 66% of the patients whose disease responded. Dose reduction was required in 43% of patients. The most common treatment-related adverse events were consistent with class effect, including hypertension, fatigue, diarrhea, bleeding tendencies, and skin and hair changes. Despite good clinical response, the effect on survival has not been determined and needs to be clarified by controlled trials.

ANAPLASTIC THYROID CANCER

Unlike the case with differentiated thyroid cancer, the anaplastic or “giant cell” variant is associated with an extremely poor prognosis, with the best available therapy producing a median survival of less than 1 year. An association with prior well-differentiated thyroid cancer or benign thyroid nodule disease is not uncommon. Patients are older, generally in their 60s or 70s, and the distribution between the sexes is balanced. Distinguishing the tumor from a large cell lymphoma of the thyroid is of fundamental importance. Clinically, anaplastic thyroid cancer is characterized by a rapidly growing mass in the thyroid that invades the trachea or larynx and causes symptoms of dysphagia, hoarseness, or hemoptysis. A total of 20 to 50% of patients have distant metastases at the time of presentation (most often pulmonary), and the remainder usually manifest metastases within 1 or 2 months of diagnosis. However, most deaths are a result of aggressive local–regional spread and upper airway respiratory failure. If resection is feasible, it should be pursued, although these tumors are typically unresectable at presentation, and the patient often requires an urgent tracheostomy. Initial external-beam radiation therapy, both for definitive treatment and as an adjuvant (often with doxorubicin sensitization),[134] is commonly used and considered the standard of care. Chemotherapy alone has limited efficacy. Doxorubicin/cisplatin is probably the most widely used combination.[135] Radioactive iodine generally plays no role in the treatment of these tumors. Combretastatin A4 phosphate is a novel drug whose precise mechanism of action is unknown; it has antitumor effects by binding tubulin and disrupting vascular supply within tumors. In a phase I trial, in combination with paclitaxel, a single patient with anaplastic thyroid cancer had a complete response that lasted more than 30 months after treatment.[136] A randomized, open-label, controlled, phase II/III multinational trial was done to assess the safety and efficacy of carboplatin and paclitaxel with or without combretastatin. A total of 80 patients were treated in the study, which was stopped early because of poor accrual. The median overall survival was 5.2 months (95% CI; 3.1, 9.0) in the experimental arm compared with 4.0 months (95% CI; 2.8, 6.2) in the control arm (HR, 0.72; 95% CI; 0.43, 1.20). The 1-year survival was 25.5% (95% CI; 15, 38) in the experimental arm compared with 8.7% in the control arm (95% CI; 2, 24). Deaths were primarily caused by disease progression.[137]

MEDULLARY THYROID CANCER

Medullary thyroid cancer is a neoplasm of the calcitonin-producing cells that reside in the thyroid. It constitutes approximately 5 to 9% of all thyroid cancers and is associated with a

mutation in the *RET* proto-oncogene. Both sporadic and familial types occur. The sporadic form is more common (60 to 70% of cases) and tends to occur in an older age group than the familial form (40 to 45 years vs. 15 to 25 years). Three distinct familial syndromes account for the remaining 30 to 40% of cases. The *RET* mutation is transmitted in the germline, and familial medullary thyroid cancer may be part of multiple endocrine neoplasia type 2A (medullary thyroid cancer, pheochromocytoma, and parathyroid hyperplasia) or type 2B (medullary thyroid cancer, pheochromocytoma, and intestinal and mucosal ganglioneuromatosis with characteristic marfanoid habitus); it also may be a familial form of medullary thyroid cancer not associated with multiple endocrine neoplasia.

The clinical presentation of the sporadic type of medullary thyroid cancer is usually a painless thyroid mass; however, high calcitonin levels may result in a watery secretory diarrhea as the primary symptom. The diagnosis is made on the basis of a constellation of a thyroid mass, a high calcitonin level, and a fine-needle aspiration specimen that stains positive for calcitonin. Screening for pheochromocytoma (catecholamine excess) is important in order to exclude a familial syndrome for a patient otherwise believed to have the sporadic type. CT and PET imaging are useful to detect metastases, but radioactive iodine scans are not useful. For the familial syndromes, a dominant inheritance pattern is recognized, and family members of patients with newly diagnosed cases of the disease should be screened for *RET* mutations because germline mutations are substantially higher than might be expected on the basis of family history alone. Total thyroidectomy often results in complete cures for young, at-risk family members (based on *RET* gene testing), even in the absence of clinically detectable thyroid abnormalities. Studies show that a minority of family members undergoing prophylactic thyroidectomy actually have histologically normal thyroid glands. More often, there is evidence of C-cell hyperplasia and microscopic or macroscopic medullary thyroid cancer, which underscores the importance of operating early.

The treatment of choice for medullary thyroid cancer is total thyroidectomy with bilateral central compartment node dissection and unilateral neck dissection (at the very least). The risk for multifocal disease is high for both familial and sporadic types. Radiation has disappointing efficacy for macroscopic disease, and postoperative radiation therapy is not routinely used. After resection of all disease in the neck, patients should be monitored with two tumor markers: calcitonin and carcinoembryonic antigen. The survival outcome has improved with genetic testing and prophylactic surgery. Ten-year survival rates are 70 to 80% for combined series of familial and sporadic types.[138]

Vandetanib is an oral inhibitor that targets VEGF receptor, RET, and EGFR and has clinically relevant antitumor activity in advanced medullary thyroid cancer with an acceptable safety profile.[139] In a randomized, phase III trial of 300 mg of vandetanib daily compared with placebo in 331 patients with advanced medullary thyroid cancer, a median follow-up of 24 months revealed a statistically significant difference favoring vandetanib with prolongation of progression-free survival when compared with placebo (HR, 0.46; 95% CI; 0.31, 0.69; $p < 0.001$). This study also revealed a statistically significant difference with objective response rate, disease control rate, and biochemical response favoring vandetanib when compared with placebo.[139] Common adverse events of any grade included diarrhea, rash, nausea, hypertension, and headache. Overall survival data has not yet been reported. Based on the results of this study, the FDA granted approval for vandetanib for the treatment of symptomatic or progressive medullary cancer in patients with unresectable, locally advanced, or metastatic disease in April 2011. QT prolongation, torsades de pointes, and sudden death are included in a boxed warning for this drug. Because of the risk of QT prolongation, vandetanib is available

only through the FDA Vandetanib Risk Evaluation and Mitigation Strategy program. The recommended daily dose of vandetanib is 300 mg orally. The starting dose should be reduced to 200 mg in patients with moderate or severe renal impairment.

Cabozantinib is an oral TKI that targets MET, VEGF receptor 2, and RET. In a randomized, phase III, double-blind, placebo-controlled, international trial, 330 patients with radiographic progression of metastatic medullary thyroid cancer were enrolled and randomly assigned (2:1) to cabozantinib (140 mg per day) or placebo.[140] The primary endpoint was progression-free survival. Patients assigned to cabozantinib therapy achieved a statistically significant improvement in progression-free survival of 11.2 months, compared with 4.0 months for the placebo arm ($p < 0.001$). Response rates were 28% for cabozantinib and 0% for placebo. Common adverse effects of cabozantinib included diarrhea, palmar–plantar erythrodysesthesia, decreased weight and appetite, nausea, and fatigue. Dose reductions were required in 79% of patients. On the basis of this study, the FDA approved cabozantinib for the treatment of progressive metastatic medullary thyroid cancer in November 2012. A black box warning for gastrointestinal perforations and fistula formation, occurring in 3% and 1% of patients, respectively, has been issued.

Local recurrences are usually treated surgically. Metastatic disease (commonly to the mediastinum, lung, bone, and liver) often follows an indolent course, and in this case, observation is reasonable. The newly approved agents vandetanib and cabozantinib have not been directly compared with each other and, although both agents have been shown to decrease carcinoembryonic antigen and calcitonin levels and improve progression-free survival, no overall survival benefit has been reported thus far. Therefore, the choice of agent may depend on expected side effects, and the indications for starting therapy will need to be individualized and balanced with toxicity profiles and quality-of-life outcomes. In an editorial, Haddad supported using certain parameters such as calcitonin doubling time and the presence of symptomatic disease as important considerations prior to initiating these currently approved therapies.[141]

Palliative surgery, including tumor debulking, or radiotherapy may be used as indicated for symptom control or to manage tumor encroachment on critical structures. Diphenoxylate, octreotide, and interferon alpha-2a may palliate the diarrhea that can occur. Doxorubicin, cisplatin, dacarbazine, 5-fluorouracil, streptozocin, and somatostatin analogs have some reported activity; however, medullary thyroid cancer generally is resistant to standard cytotoxic agents, making investigational therapy appropriate.

KEY POINTS

- For differentiated thyroid cancers, poor prognostic features include age older than 45 years, male sex, poorly differentiated histology, tumor size, and extrathyroidal extension at diagnosis. In contrast, involvement of the regional lymph nodes does not confer a worse prognosis for survival.
- Radioactive iodine is the treatment of choice for metastatic disease. Standard chemotherapy has disappointing activity. Radioactive iodine generally has no role in the treatment of anaplastic or medullary thyroid cancers.
- Sorafenib and lenvatinib are approved by the FDA for the treatment of locally recurrent or metastatic, progressive differentiated thyroid cancer that no longer responds to

radioactive iodine treatment.

- Screening for germline *RET* gene mutation in patients with medullary thyroid carcinoma should be considered because total thyroidectomy, based on the results of genetic testing, often results in complete cures for young, at-risk family members.
- Vandetanib and cabozantinib have been approved by the FDA for the treatment of symptomatic or progressive, locally advanced or metastatic medullary thyroid cancers.

MANAGEMENT OF DISEASE IN THE ELDERLY

Although head and neck cancer is mostly diagnosed in patients in their 50s/60s, with increasing lifespans, a substantial proportion of patients with head and neck cancer will be elderly. Elderly patients present with age-specific problems such as multiorgan dysfunction, depression, alteration of mental status, reduced nutritional status, and limited social support, all of which can interfere with the diagnosis and treatment of cancer. However, biologic age, not chronologic age, is more important and takes into account comorbid illnesses and performance status. In a large, single-institution study, the percentage of patients with head and neck cancer with moderate to severe comorbidity was 21%, and there was a significant relationship between severity of comorbidity and overall survival.[142] A comprehensive geriatric assessment can be used to evaluate functional status, mental status, medications, nutritional status, social support, and comorbid illnesses to provide physicians with a better sense of a patient's life expectancy and tolerance to different treatment modalities when making therapeutic decisions.[143-145]

A multidisciplinary team with both oncologic and nononcologic providers is needed to optimize a treatment strategy in elderly patients. Surgery remains an appropriate option for the management of head and neck cancer in elderly patients once a full risk assessment is completed and medical optimization is initiated. Postsurgical mortality is associated with older age, severity of comorbid illnesses, and length of the operation.[146] Given the concern about the time under anesthesia, reconstructive surgery with free flaps in elderly patients remains controversial.

Radiation is a potentially curative option for patients diagnosed with early-stage disease or those with nonmetastatic disease who are deemed ineligible for surgical resection. Radiation can be safely administered in an elderly population, and most patients are able to complete their planned treatment.[147] There are no data demonstrating poorer tolerance or need to reduce radiation dose because of age.[148,149] However, the functional consequences of toxicities may be more severe in a more frail or debilitated patient.

As discussed earlier, concurrent chemoradiation improves both local tumor control and overall survival by 8% at 5 years in patients with head and neck cancer with locally advanced disease when compared with radiation alone.[64] However, patients age 70 or older derived little or no incremental survival benefit from adding chemotherapy to radiation in the large meta-analysis.[47] Yet, the use of chemoradiation in patients older than age 65 has steadily increased during the past 15 years.[150] This trend has further increased with the use of cetuximab with radiation. However, even with this less toxic agent, overall survival benefit in an older patient population is not clear.[43] In some patients, the benefit of chemoradiation may be offset by acute, often severe, treatment-related toxicities, particularly among older patients and those with comorbid medical conditions or poor performance status. In a population-based study, older patients who received chemoradiation were more than twice as likely to experience severe acute toxic effects compared with patients who received radiation alone.[151] Older

patients can be more susceptible to the toxic effects of chemotherapy because of potential delayed clearance from renal or hepatic impairment, decreased bone marrow reserve, malnutrition, and cognitive impairment.[152]

SURVIVORSHIP

Survivorship is an important area that needs attention. Studies involving survivors of head and neck cancer have mainly focused on the social supports, tobacco and alcohol use, the risk for second primary cancers, functional status, and depression and how these factors influence quality of life.[13,153-156] Chronic pain, xerostomia, impairments of speech and swallowing, alterations of taste and smell, and poor cosmesis are some of the long-term sequelae associated with treatment for head and neck cancer. These variable long-term toxicities can have a profound psychosocial effect on cancer survivors and their families. Fortunately, advances in reconstructive techniques and organ-preservation strategies are having a positive effect on quality of life relative to the functional and cosmetic consequences of radical local therapies of the past. Nevertheless, quality-of-life and survivorship issues must be a focus of future research and an integral component of those efforts.[154]

KEY POINTS

- Older patients can safely be treated with radiation-based therapy for head and neck cancer but require additional attention for management of comordid illnesses.
- Measures of biologic rather than chronologic age are relevant when determining appropriate treatment for patients with locally advanced head and neck cancer.
- Survivors of head and neck cancer can experience issues with swallowing, breathing, pain, and neck mobility that require ongoing management.

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GASTROINTESTINAL CANCERS

Manish A. Shah, MD

Recent Updates

Esophageal Cancer

- In patients who receive definitive chemoradiation for locally advanced esophageal cancer, delayed esophagectomy may be associated with increased operative morbidity including a significantly higher risk of esophageal anastomotic leaks. (Farinella E, *J Surg Oncol* 2016)

Gastric Cancer

- The phase III CRITICS study evaluating postoperative chemotherapy versus chemoradiotherapy in patients with locally advanced gastric cancer who received neoadjuvant epirubicin, platinum, fluoropyrimidine therapy failed to demonstrate improved patient survival with postoperative chemoradiation. (Verheij M, *J Clin Oncol* 2016)
- The three-drug combination of docetaxel/oxaliplatin/fluorouracil–leucovorin improved patient survival when compared with epirubicin/cisplatin/fluorouracil in the perioperative treatment of locally advanced gastric and gastroesophageal junction adenocarcinoma. (Al-Batran SE, *J Clin Oncol* 2017)
- The HELOISE study confirmed the standard dose of trastuzumab in combination with platinum/ fluorouracil as first-line therapy for HER2-positive gastric cancer. (Shah MA, *J Clin Oncol* 2017)
- The GATSBY study failed to demonstrate that second-line trastuzumab emtansine, the novel drug-antibody conjugate, is superior to taxane therapy in second-line treatment for HER2-positive gastric cancer. (Thuss-Patience PC, *Lancet Oncol* 2017)
- A series of studies evaluating mesenchymal-epithelial transition (MET) pathway antibody inhibition in combination with chemotherapy in advanced gastric cancer failed to improve patient survival in first-line treatment. (Shah MA, *JAMA Oncol* 2017; Cunningham D, *J Clin Oncol* 2015)

Pancreatic Cancer

- Although the phase II clinical trial in metastatic pancreatic cancer involving the Janus kinase 1/2 inhibitor ruxolitinib was encouraging, the phase III update of ruxolitinib and capecitabine in advanced pancreas cancer was negative. (Hurwitz H, *J Clin Oncol* 2017)
- The ESPAC-4 study demonstrated a survival advantage of gemcitabine with capecitabine in the adjuvant setting in advanced pancreatic cancer. (Neoptolemos JP, *Lancet* 2017)

Hepatocellular Carcinoma

- The RESORCE study confirmed the benefit of regorafenib in second-line treatment for advanced hepatocellular carcinoma. (Bruix J, *Lancet* 2017)

Colorectal Cancer

- There may be a role for vemurafenib in combination with irinotecan and cetuximab in BRAF V600E mutant colorectal cancer, according to the updated results of a random assignment phase II study. (Kopetz S, *J Clin Oncol* 2017)
- For tumors that are mismatch repair–deficient (e.g., microsatellite instability–high), the programmed death 1 inhibitor pembrolizumab demonstrated significant efficacy and was granted accelerated FDA approval. (Le DT, *N Engl J Med*

2015)

OVERVIEW

In 2017, approximately 310,440 new cancers of the digestive system will be diagnosed in the United States, making it the most common physiologic system afflicted by cancer and, importantly more common than breast cancer (255,180), lung and respiratory tract cancers (243,170), and genitourinary cancers (279,800).[1] About 157,700 patients will die of gastrointestinal malignancies, including 50,260 patients with colon cancer, 43,090 patients with pancreatic cancer, 28,920 patients with liver and intrahepatic bile duct cancers, and 26,650 patients with gastroesophageal cancers. The spectrum of diseases encountered in this field varies from rather indolent malignancies such as low-grade neuroendocrine tumors with overall survival measured in years to very aggressive and rapidly fatal cancers, such as pancreas and hepatocellular carcinomas, for which, in advanced stages, survival is measured in months. Several cancers of the digestive tract are linked to hereditary syndromes, which require genetic counseling of patients and family members. Medical oncologists are feeling significant pressure because of advances in the development of medical therapies, which now routinely include targeted agents beyond conventional chemotherapy in most gastrointestinal malignancies, as well as the identification of specific biomarkers, which allow tailoring medical therapy to subsets of patients with cancer. The complexity associated with the diagnosis and treatment of gastrointestinal cancers is further increased by the fact that most of these malignancies require multimodality management involving close interaction between gastroenterologists, interventional radiologists, surgeons, radiation oncologists, and medical oncologists. One of the medical oncologist's key roles is, therefore, to coordinate the multimodality team and counsel the patient on various potential, sometimes competing, treatment options for his or her disease.

ESOPHAGEAL CANCER

Esophageal cancers exhibit great variation in histology, geographic distribution, and incidence over time. Historically, the most common type of esophageal cancer was a squamous cell cancer of the upper to middle esophagus. However, during the past 3 to 4 decades, the incidence of squamous cell cancers has decreased, as the incidence of adenocarcinoma of the esophagus and gastroesophageal junction has continued to increase rapidly. In the United States, esophageal cancers represent the fifth most common gastrointestinal cancer (after colorectal, pancreas, liver, and gastric cancers) and rank among the 10 most common cancers worldwide.[2,3] Areas of high incidence include portions of Iran, Russia, and northern China where squamous cell cancers dominate.[4] In the United States, carcinoma of the esophagus is infrequent, constituting approximately 1% of all cancers and approximately 6% of gastrointestinal malignancies. During the past 3 decades, the incidence of adenocarcinoma of the distal esophagus and gastroesophageal junction has increased, paralleling the rise of gastroesophageal reflux disease (GERD) in the general population, most notably for patients with a high body mass index (BMI).[5,6] Squamous cell tumors are more likely to occur in patients who are black, and these tumors are associated with achalasia, caustic injury, tylosis, Plummer–Vinson syndrome, cigarette smoking, and excessive alcohol consumption. Patients with squamous cell carcinoma of the head and neck are at increased risk of a synchronous or metachronous esophageal cancer of the same histology.

Adenocarcinomas of the distal esophagus and gastroesophageal junction more typically arise

in metaplastic epithelium—a condition known as Barrett's esophagus.[6] This premalignant condition is characterized by the replacement of stratified squamous epithelium by columnar epithelium that develops as a consequence of chronic GERD. The incidence of Barret's esophagus is 10 to 20% among symptomatic patients who undergo endoscopy and 30 to 50% for patients with peptic strictures. Risk factors for Barrett's esophagus include GERD, white or Hispanic race, male sex, advanced age, smoking, and obesity.[6,7] Although it is associated with chronic reflux disease, the mechanism by which chronic irritation leads to epithelial changes is unknown. Approximately 60% of cases of distal esophageal or gastroesophageal adenocarcinomas have evidence of Barrett's esophagus. In a nationwide population study from Denmark, the relative risk of adenocarcinoma among patients with Barrett's esophagus was 11.3 (95% CI; 8.8, 14.4) compared with the risk in the general population.[8] The annual risk of esophageal adenocarcinoma was 0.12% (95% CI; 0.09, 0.15). Detection of low-grade dysplasia on the index endoscopy was associated with an incidence rate for adenocarcinoma of 5.1 cases per 1,000 person-years. In contrast, the incidence rate among patients without dysplasia was 1.0 case per 1000 person-years. Risk estimates for patients with high-grade dysplasia were slightly higher.

It is unclear whether rigorous medical management of reflux disease with long-term proton-pump inhibitors can affect the natural history of the disease or the development of malignancy. The typical treatment for patients with Barrett's esophagus is surveillance using upper endoscopy and biopsy to examine tissue for evidence of dysplasia.[7] High-grade dysplasia is an indication for more aggressive management, including surgical resection. Tumor markers, such as *TP53,* may be predictors of potential progression to malignant disease. There is an inverse association between *Helicobacter pylori (H. pylori)* infection and adenocarcinomas of the lower esophagus, presumably a result of the reduced acidity associated with atrophic gastritis.[9] On the other hand, infection with human papillomavirus (HPV) has been correlated with an increased incidence of squamous cell cancers of the upper esophagus.[10]

CLINICAL PRESENTATION AND DIAGNOSIS

The most common clinical presentation of esophageal cancer is dysphagia. Cachexia and substantial weight loss are complications of this presenting symptom, which cause many patients to be debilitated at the time of the diagnosis. Bleeding (hematemesis, tarry stools, anemia) can be present as well. Other symptoms include treatment-refractory heartburn, and patients with tracheobronchial invasion may present with laryngeal nerve paralysis, cough, and/or postobstructive pneumonia.[11]

An upper endoscopic examination should be performed to obtain a minimally invasive biopsy. Computed tomography (CT) of the thorax should be performed with tomographic slices through the liver to evaluate the extent of disease in the upper abdomen with special attention to potential liver metastases and celiac lymphadenopathy. A thorough clinical examination with careful attention paid to the lymph nodes in the supraclavicular and axillary regions is essential.

Endoscopic ultrasound (EUS) can accurately assess the depth of penetration in up to 90% of tumors and determine involvement of mediastinal lymph nodes in nearly all patients; it has become a standard component when evaluating patients with esophageal cancer eligible for local–regional therapy.[12] In addition, EUS allows the biopsy of suspicious lymph nodes to confirm the presence of lymph node metastases. Positron emission tomography (PET), preferably as a PET/CT scan, has become part of the routine pretreatment diagnostic workup for patients with esophageal cancers. PET allows for the determination of lymph node status

and the detection of occult sites of distant metastatic spread; therefore, it may spare the patient the morbidity of an aggressive local–regional treatment approach.[13,14]

TREATMENT

The treatment of choice for patients with esophageal cancer had long been controversial, but accumulating evidence from meta-analyses and clinical trials has led to a consensus regarding the practical management of esophageal cancers. The most frequently used initial treatment had long been primary surgical resection. However, the results of surgical resection alone have been discouraging, spawning a series of clinical trials to determine the efficacy of chemotherapy and radiation in addition to surgical resection.

Esophageal cancers limited to the mucosa (T1, T1a) may be managed with endoscopic mucosal resection. For lesions that have penetrated into the submucosa without lymph node involvement on staging studies (T1b), surgical resection with lymphadenectomy is recommended because of the risk of lymph node involvement. For any lymph node-positive disease and lesions T2 or greater amenable to surgical resection, multimodality management with chemotherapy and/or radiation therapy has become the standard.[11]

Surgery

The two most commonly used surgical techniques are transhiatal esophagectomy, which is generally reserved for patients with tumors of the lower esophagus, and a transthoracic approach (e.g., an Ivor-Lewis resection), which utilizes a combination of thoracotomy and laparotomy. The latter procedure is a more traditional operation for esophageal cancer. The results associated with the two approaches are similar.[15,16] Reports suggest a higher retrieval rate of lymph nodes with an Ivor-Lewis approach.[17,18] Operative mortality rates should be less than 5% when the operation is performed by an experienced surgeon. Historically, survival has been poor for patients treated with surgery only, with 5-year survival rates ranging from 5 to 34%.[11]

It is important to monitor and maintain patients' nutritional status in light of weight loss and continued difficulty with alimentation both before and during treatment. To palliate tumor-related esophageal obstruction, and alleviate local swallowing dysfunction, there has been a shift away from surgical resection in favor of newer techniques such as the use of esophageal stents, laser therapy, endoscopic dilation, and gastric/jejunal tube feeding.

Combined-Modality Neoadjuvant Treatment

The poor surgical outcome and the relatively advanced nature of disease at the time of diagnosis (stages II and III) in most cases, led to investigations regarding combined-modality approaches for the treatment of patients with esophageal cancer. Combined-modality treatment involves both chemotherapy and radiation therapy and has been the focus of most of the research for esophageal cancer over the past several decades. The addition of chemotherapy is designed to treat micro-metastases and enhance the local effects of radiation. An original landmark clinical trial, performed by Herskovic et al., was the first to demonstrate the benefit of combined-modality therapy.[19] In this trial, patients with locally advanced, unresectable esophageal cancer were randomly assigned to receive either radiation therapy alone or combined-modality radiation therapy and chemotherapy. More than 25% of patients were alive at 5 years in the group that received combined-modality therapy; none of the patients who

received radiation therapy alone were alive at 5 years. The median survival was 14 months for combined-modality therapy versus 9 months for radiation therapy alone.[20] Based on these data, radiation therapy alone is now reserved for palliative local–regional treatment. The results of the Herskovic study led to a series of trials designed to examine the role of chemoradiotherapy when combined with surgery (e.g., trimodality therapy) or when used instead of surgery (e.g., definitive therapy). The chemotherapy agents historically administered with radiation were fluorouracil (5-FU), a platinum drug (cisplatin or carboplatin), and/or mitomycin C.[21] With these combinations, the pathologic complete response (pCR) rate was approximately 20 to 25%.

Given the modest pCR rate with chemoradiation, definitive chemoradiotherapy is considered a standard option for patients with localized esophageal cancer who are not considered appropriate surgical candidates. Decisions regarding surgical appropriateness involve several factors, including, but not limited to, age, comorbidities, performance status, and need for laryngectomy (e.g., particularly for cancers located in the cervical esophagus). In addition, squamous cell cancers (mainly found in the middle and upper esophagus) are more sensitive to chemoradiation than adenocarcinomas and exhibit different tumor biology. Definitive chemoradiotherapy may therefore also be considered a viable option for squamous cell carcinoma of the esophagus.[22]

Preoperative chemotherapy prior to resection is not generally an accepted approach for patients with localized esophageal cancer, although this issue is controversial because of conflicting results from two large studies performed in the United Kingdom[23] and by the U.S. Intergroup.[24] Subsequently, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial—which compared perioperative chemotherapy using epirubicin/cisplatin/continuously infused 5-FU (ECF) with surgery alone for patients with gastric, gastroesophageal, and esophageal cancers—yielded a significant improvement in overall survival for patients who received perioperative chemotherapy (see “Gastric Cancer” section for more on gastric and gastroesophageal junction cancers).[25] A total of 26% of the patients in this trial had esophageal and gastroesophageal junction cancers, and multivariate subgroup analyses indicated a survival benefit from perioperative chemotherapy for gastroesophageal junction cancers. The OE05 study compared four cycles of preoperative ECF to two cycles of preoperative cisplatin/continuously infused 5-FU (CF) in patients with localized esophageal cancer and demonstrated no difference in outcome, thereby putting into question the role of epirubicin in esophageal cancer.[26] Thus, based on these data, perioperative chemotherapy with a combination platinum/5-FU regimen may be considered for patients with gastroesophageal junction cancers who are not optimal candidates for chemoradiation. Trials comparing optimized perioperative chemotherapy with neoadjuvant chemoradiation are highly warranted.

Various randomized trials have been conducted to compare preoperative chemoradiation therapy with surgery alone, but results were conflicting. A meta-analysis, which included 18 randomized controlled trials with approximately 3000 patients, found that trimodality therapy significantly improved 2-year survival (hazard ratio [HR], 0.81; p = 0.002; 13% absolute difference) and reduced locoregional recurrence when compared with surgery alone.[27] In the absence of medical contraindications, most patients in the United States with localized esophageal cancers receive neoadjuvant combined-modality therapy followed by surgery. Data from a Dutch phase III trial confirmed the superiority of a neoadjuvant radiochemotherapy approach compared with surgery alone for patients with localized esophageal cancer.[28] In this study, 368 patients were randomly assigned to receive radiochemotherapy with weekly carboplatin/paclitaxel and a relatively low radiation dose of 41.4 Gy followed by surgery or surgery alone. The neoadjuvant treatment led to a pCR rate of 29%. The overall survival was

significantly better (p = 0.003) in the group of patients treated with chemoradiation (HR, 0.66; 95% CI; 0.50, 0.87). Median survival was 49 months in the neoadjuvant arm versus 24 months in the surgery-alone arm. Interestingly, patients with squamous cell carcinoma had a pCR rate of 49% with neoadjuvant chemoradiotherapy compared with 23% for patients with adenocarcinomas (p = 0.008). In a cross-trial comparison, the toxicity of the carboplatin/paclitaxel regimen was mild and appeared less severe than the toxicity seen with the 5-FU/platinum combination used in CALGB 9781.[29] These results add further support for the use of trimodality therapy as standard of care for patients with localized esophageal cancers. The ongoing RTOG 1010 study is evaluating the role of adding trastuzumab to carboplatin/paclitaxel combined with radiation therapy for patients as neoadjuvant treatment for locally advanced HER2-positive esophageal adenocarcinoma (NCT01196390).[30]

No convincing data justify the routine use of adjuvant chemotherapy following surgery.[32] Similarly, radiation therapy has no role as the sole postoperative modality. Finally, patients who have a pCR following chemoradiotherapy may choose not to proceed to resection immediately, opting to wait for local recurrence and progression in the hope of avoiding an esophagectomy altogether. This approach, of salvage esophagectomy, is associated with similar survival to proceeding directly to esophagectomy as planned, but possibly with higher surgical morbidity, including anastomotic leak of 25% (for salvage esophagectomy) versus 3% if performed shortly after completion of combined modality therapy.[33]

Treatment of Metastatic Disease

The intent of treatment for metastatic esophageal cancer is to control the disease and provide palliation. Many agents have demonstrated some activity in esophageal cancer, including fluoropyrimidines (fluorouracil and capecitabine), platinum agents, taxanes, irinotecan, mitomycin C, anthracyclines, and, to a lesser extent, methotrexate, vinorelbine, and gemcitabine.[34] Treatment commonly is administered as a combination of two or three drugs or, less frequently, as single-agent therapy, depending on the patient's performance status. The utility of treatment regimens is similar to the experience with gastric cancer, especially with regard to adenocarcinomas of the gastroesophageal junction. In most clinical trials of single-agent therapy, the response rate has ranged from 10 to 20%. Combination regimens have yielded response rates as high as 40 to 50%. Palliation of dysphagia and bleeding is important and is difficult to achieve. The liberal use of esophageal stents and local therapies, such as laser therapy and brachytherapy, as well as palliative radiation with or without chemotherapy can be very useful in this setting.

The activity of novel targeted agents has also been investigated in clinical trials. A phase III trial that investigated the role of bevacizumab in advanced gastroesophageal and gastric cancers failed to improve overall survival.[35] Epidermal growth factor receptor (EGFR) monoclonal antibodies added to chemotherapy do not improve patient survival.[36,79] In contrast, the vascular endothelial growth factor receptor 2 (VEGFR2) monoclonal antibody ramucirumab led to survival benefits when combined with paclitaxel versus paclitaxel alone and when used as a single agent versus best supportive care for patients with advanced gastroesophageal cancers who received first-line chemotherapy with a fluoropyrimidine and a platinum agent.[37,38] Trastuzumab added to standard chemotherapy in HER2-overexpressing gastric and gastroesophageal cancers also improved overall and progression-free survival (PFS) as well as response rates compared with chemotherapy alone.[39] These data on novel biologic agents are discussed in detail later in the section on "Gastric Cancer."

KEY POINTS

- In the United States, the incidence of esophageal squamous cell carcinoma is decreasing, and the incidence of adenocarcinomas is rising rapidly, likely as an effect of lifestyle changes.
- Combined-modality chemotherapy and radiation are standard neoadjuvant approaches to the treatment of esophageal cancer.
- Definitive chemoradiation (without surgery) can be a valid treatment option, in particular for patients with squamous cell cancers of the esophagus.
- After trimodality therapy (radiochemotherapy followed by surgery), adjuvant therapy is not the standard of care.

GASTRIC CANCER

EPIDEMIOLOGY AND ETIOLOGY

The incidence of gastric cancer has varied considerably during the past century. In the United States, where the incidence of gastric cancer has decreased approximately 75% during the past few decades, the incidence of gastroesophageal tumors has concomitantly increased.[6] Although gastric cancer rates have experienced a significant decline in incidence worldwide, it is still prevalent in regions of the world where the storage of fresh foods and the quality of water are poor and in some industrialized nations as well (e.g., Japan). Gastric cancer is a major health issue in both Japan and Korea, and both countries have nationwide screening programs. In both Japan and Korea, gastric cancer is associated with a better prognosis than in Western cultures. When controlling for baseline tumor characteristics, patient demographics, and surgical factors, there remains a difference in survival that remains unexplained.[40]

The lowest incidences for gastric cancer are in Western cultures and among people of higher socioeconomic status. Studies of migrant populations have supported evidence for the effect of environmental influences on the development of gastric cancer.[41] Together, these data support the concept that gastric cancer is strongly influenced by nutritional, socioeconomic, and medical factors rather than dominated by genetic predisposition. In the United States, gastric cancer is seen twice as often in men as in women and more frequently in black men as in white men, and its incidence increases with age starting at age 50.[42] The mortality rate associated with gastric cancer has decreased for white men, paralleling the overall decline in the incidence of gastric cancer in this population. As mentioned previously, determining the reason for the considerable rise in the incidence of adenocarcinoma of the proximal stomach and distal esophagus remains a challenge for epidemiologists. Possible reasons for this rise include the prevalence of obesity, elevated BMI with increased incidence of GERD, and increased calorie consumption.[43] The use of aspirin and other nonsteroidal anti-inflammatory agents has been associated with a lower risk of cancer of the gastroesophageal junction and other gastrointestinal tumors.[44]

Factors associated with an increased risk of gastric cancer include nutritional factors such as high salt and nitrate intake, a diet low in vitamins A and C, the consumption of large amounts of smoked or cured foods, lack of refrigerated foods, and poor-quality drinking water.[45] Occupational exposure to rubber and coal also increases the risk. Cigarette smoking, *H. pylori* infection, Epstein–Barr virus, radiation exposure, and prior gastric surgery for benign ulcer

disease also have been implicated as risk factors. Genetic risk factors include type A blood, pernicious anemia, a family history of gastric cancer, hereditary nonpolyposis colon cancer (HNPCC), Li–Fraumeni syndrome, and hereditary diffuse gastric cancer (HDGC) caused by mutations in the E-cadherin gene, *CDH1*. HDGC is a genetic predisposition syndrome characterized by a family history of diffuse gastric cancer, often with early onset of disease (generally below age 40). The cumulative risk of the development of diffuse gastric cancer by the age of 80 years for *CDH1* mutation carriers is 70% for men and 56% for women. Women are also at higher risk for the development of lobular breast cancer, with a cumulative risk of 42% by age 80.[46] It is recommended that individuals with a germline mutation in *CDH1* undergo a risk-reducing prophylactic gastrectomy to prevent the future development of diffuse gastric cancer.[47] Gastric cancer precursor lesions include adenomatous gastric polyps, dysplasia, chronic atrophic gastritis, and intestinal metaplasia. Results from several studies have demonstrated an increased likelihood of *H. pylori* infection in patients with gastric cancer, particularly cancer of the distal stomach.[48,49] Although cancer does not develop in most people with *H. pylori* infections, the increased risk for patients who are infected has raised the issue of whether treatment of *H. pylori* might decrease the risk of gastric cancer. Although the role of *H. pylori* in gastric carcinogenesis is well defined, no definitive evidence shows that mass eradication could reduce the incidence of gastric cancer.[50] A large Chinese study showed no benefit in the prevention of gastric cancer with the eradication of *H. pylori.*[51] By contrast, a meta-analysis suggested that eradication could indeed reduce the risk of gastric cancer.[52] At present, treatment of patients with this infection should be reserved for those with demonstrated ulcers, gastritis, or other symptoms.

CLINICAL PRESENTATION AND DIAGNOSIS

Common presenting symptoms for gastric cancer include bleeding, hematemesis, pain, anorexia, early satiety, and dyspepsia. Clinical symptoms often arise from infiltration of the tumor within the stomach wall (causing anorexia, stomach pain, early satiety) and metastatic spread of disease inside the peritoneal cavity, resulting in the formation of ascites and abdominal pain. The disease is commonly diagnosed by upper endoscopy and direct biopsy. It is important that a biopsy be performed for samples from any gastric ulcer because it is difficult to distinguish benign from malignant ulcers endoscopically. Staging includes CT scan of the chest, abdomen and pelvis to rule out metastasis and to determine surgical resectability. Endoscopic ultrasound for tumor staging has less accuracy for stomach cancer than esophageal cancer; however, it may be used to distinguish early-stage cancer from locally advanced disease.[53] PET scans are able to identify occult disease in as many as 10% of patients.[54] Laparoscopy can identify up to 20% of occult peritoneal metastases as well, and is considered a standard staging procedure as well.[54]

TREATMENT

The only potentially curative treatment approach for patients with gastric cancer is surgical resection. The type of surgery performed in Asia differs from the type of resection most commonly performed in the United States. D2 resection, the standard surgery in Japan, involves the meticulous resection of all regional lymph nodes, whereas in the United States, D1 resection (removal of only perigastric lymph nodes) has long been the standard. Retrospective data suggest that the outcome for D2 resection is better than that for D1; however, the disparity might well be caused by a fundamental difference in the disease process itself, rather

than the surgical technique. Randomized trials initially did not clearly demonstrate a survival benefit for patients undergoing a D2, versus a D1, dissection.[55,56] After 15-year follow-up of a randomized Dutch trial that included 1078 patients, however, D2 lymphadenectomy was associated with lower locoregional recurrence (12% vs. 22%) and gastric cancer–related death rates (37% vs. 48%) than D1 surgery.[57] Although D2 dissection was associated with higher operative morbidity, these data suggest that D2 lymphadenectomy should be considered the surgical standard of care.

Localized Disease

Patients with early-stage operable gastric cancer have a reasonable chance of being cured with surgery alone. Surgery cures early-stage node-negative disease in 75 to 80% of patients. However, for patients with stage III disease, the reported 5-year survival rates are 25% or less. Adjuvant therapy for resected gastric cancer became a standard approach following the report of the INT-0116 randomized, phase III trial, which examined adjuvant chemotherapy combined with radiation therapy.[58] Patients with stage I to III gastroesophageal or gastric cancer were randomly assigned to receive either surgery alone or surgery followed by bolus 5-FU/leucovorin (LV)–based chemotherapy (Mayo Clinic regimen) with sandwiched chemoradiation therapy (45 Gy) and bolus 5-FU/LV as a radiosensitizer. The results showed an approximate 20% improvement in survival for the group receiving the combined-modality therapy. The median overall survival in the surgery-only group was 27 months, as compared with 36 months in the chemoradiation group; the HR for death in the surgery-only arm was 1.35 (95% CI; 1.09, 1.66; $p = 0.005$); the HR for relapse was 1.52 (95% CI; 1.23, 1.86; $p < 0.001$). The study has been criticized for the very low rate of D1 (or D2) lymph node dissections. In fact, less than 50% of patients underwent a D1 or D2 resection, which was mandated per protocol. In addition, only the rate of local recurrence, not the rate of distant metastasis, was reduced in the adjuvant chemoradiation group, suggesting that the adjuvant therapy could have mainly compensated for inferior surgery. On the other hand, the survival benefit observed with postoperative therapy was maintained in all (preplanned) subgroup analyses. Although these trial results were met with skepticism elsewhere, they established a new standard of care for patients with this disease in the United States. A large CALGB-led Intergroup trial (C80101) demonstrated that the addition of ECF, a combination regimen of infusional 5-FU/cisplatin/epirubicin to 5-FU sensitized radiation did not improve patient survival.[59] These data suggest that more aggressive chemotherapy does not add benefit to chemoradiotherapy in the adjuvant setting in this disease.

Perioperative chemotherapy with the ECF regimen administered before and after surgery for resectable gastric cancer also has shown a significant overall survival benefit compared with surgery alone in the MAGIC trial.[25] As compared with the surgery group, the perioperative chemotherapy group had a higher likelihood of overall survival (HR for death, 0.75; 95% CI; 0.60, 0.93; $p = 0.009$; 5-year survival rate, 36% vs. 23%) and of PFS (HR for progression, 0.66; 95% CI; 0.53, 0.81; $p < 0.001$). At the 2017 ASCO Annual meeting, the FLOT regimen (fluorouracil/leucovorin/oxaliplatin/docetaxel (T)), was examined in the peri-operative treatment setting compared with perioperative ECX.[31] This phase III study enrolled 716 patients, and demonstrated a significant improvement in median overall survival (35 mo with ECF/ECX versus 50 months with FLOT), HR 0.77 ($p = 0.012$). The study demonstrated approximately equal toxicity in both arms, suggesting that FLOT may be a more effective three-drug chemotherapy regimen in the perioperative setting.

There are two large, well-performed studies that also suggest a benefit of postoperative chemotherapy. The Japanese phase III trial of tegafur/gimeracil/oteracil (also known as S-1), an oral fluoropyrimidine approved for use in Japan and Europe, as adjuvant therapy after D2 resection of stage II or III gastric cancer demonstrated an overall survival benefit, with a 3-year overall survival rate of 80.1% in the S-1 group and 70.1% in the surgery-only group (HR, 0.68; 95% CI; 0.52, 0.87; p = 0.003).[60] The improvement in overall survival was confirmed after 5-year follow-up.[61] The Korean phase III trial CLASSIC, which included 1035 patients with D2-resected stage II/III gastric cancer, identified adjuvant therapy with capecitabine plus oxaliplatin as superior to surgery alone, with significant improvement in 3-year disease-free survival (DFS; 73% vs. 61%; HR, 0.58; p < 0.0001). The 5-year overall survival was 78% in the chemotherapy arm compared with 69% in the observation arm (HR for death, 0.66; 95% CI; 0.51, 0.85).[62] In addition to these individual trials, a meta-analysis of 17 trials with 3838 patients confirmed that adjuvant chemotherapy without radiation after gastric cancer resection was associated with a significant survival benefit with an HR of 0.82 (95% CI; 0.79, 0.90, p < 0.001).[63]

Several trials are attempting to definitively establish the benefits of adjuvant radiation combined with chemotherapy after D2 resection. The Korean Adjuvant Chemoradiotherapy in Stomach Tumors (ARTIST) trial evaluated the addition of radiation therapy to adjuvant chemotherapy in patients who underwent gastrectomy with D2 lymph node dissection.[64] Patients were randomly assigned to one of two arms: (1) six cycles of chemotherapy with capecitabine/cisplatin (XP), or (2) two cycles of XP followed by chemoradiation (with capecitabine), followed by two more cycles of XP. Neither DFS nor overall survival was different between the two arms, but subsets of patients with node-positive disease and intestinal-type gastric cancer did have a significantly improved DFS with the addition of radiation therapy. The ongoing ARTIST2 trial will try to determine whether the addition of radiation therapy to adjuvant chemotherapy improves DFS in these subsets of patients at higher risk for recurrent disease (NCT01761461). The Dutch Trial of Neo-adjuvant Chemotherapy Followed by Surgery and Chemotherapy or by Surgery and Chemoradiotherapy in Resectable Gastric Cancer (CRITICS Study) attempted to answer the question of whether adjuvant chemoradiation therapy is superior to chemotherapy alone. In this large randomized study, 788 patients were randomly assigned to receive perioperative chemotherapy (either epirubicin, cisplatin, capecitabine or epirubicin, oxaliplatin, capecitabine) or preoperative chemotherapy and postoperative chemoradiotherapy (as per the MacDonald study[58]).[65] There was no difference in patient outcomes, suggesting that postoperative chemoradiotherapy does not improve patient survival compared to chemotherapy. The TOPGEAR study will evaluate whether chemoradiation therapy in addition to perioperative chemotherapy (via the MAGIC approach) will be superior to the MAGIC approach alone (NCT01924819).

Based on the aforementioned trials and meta-analyses, three different approaches to the management of localized gastric cancer are considered standard of care and are used with varying frequency based on regional preferences: postoperative chemoradiotherapy (United States), pre- and postoperative chemotherapy (United Kingdom, United States, and much of Europe), or adjuvant chemotherapy alone after D2 resection (Asia).

Advanced Disease

The medical treatment of metastatic gastric cancer is primarily palliative, but it is associated with improved survival and an improved quality of life over best supportive care. Multiple agents are active, including fluoropyrimidines (fluorouracil, capecitabine, and S-1), anthracyclines,

platinum agents, taxanes (paclitaxel and docetaxel), irinotecan, and targeted therapies, including trastuzumab for HER2-overexpressing gastric cancers and, most recently, ramucirumab, a VEGFR2 antibody.[37,38] Combination regimens are associated with higher response rates and, according to a meta-analysis, also are associated with increased overall survival when compared with single-agent therapies.[66] Combinations including cisplatin/fluorouracil in various schedules were long considered the standard of care, with epirubicin commonly added to form a triple-drug regimen, which was pioneered mainly in the United Kingdom.[67] However, based on cumulative evidence, and most recently, the OE05 study comparing ECF to CF in the preoperative setting for localized esophageal cancer,[26] epirubicin is not believed to add significant efficacy and may be omitted.[68] A phase III trial involving 445 patients with gastric cancer demonstrated superiority of the addition of docetaxel to cisplatin and fluorouracil (DCF) compared with cisplatin and fluorouracil alone, in terms of response rate (37% vs. 25%, $p = 0.01$), time to tumor progression (5.6 months vs. 3.7 months, $p < 0.001$), and overall survival (9.2 months vs. 8.6 months, $p = 0.02$).[69] However, the addition of docetaxel is associated with significant toxicities, most notably, a high rate of febrile neutropenia (30%); therefore, this regimen is not advisable for patients with gastric cancer who have a poor performance status. Modifications to the DCF have been examined, and one randomized, phase II study demonstrated that a reduced intensity schedule of 5-FU/LV given over 48 hours, along with docetaxel 40 mg/m^2 and cisplatin 40 mg/m^2 (mDCF) administered every other week was at least as effective as DCF but with reduced toxicity.[70] Another large randomized phase III trial including 1002 patients tried to improve the ECF regimen by substituting oral capecitabine (X) for continuous-infusion fluorouracil and by using the nonnephrotoxic compound oxaliplatin (O) instead of cisplatin (C).[71] The combination of epirubicin/oxaliplatin/capecitabine (EOX) was found to be less toxic and at least as active as the ECF combination, with all efficacy parameters trending toward superiority. Median survival times in the ECF (control arm), ECX, EOF, and EOX groups were 9.9 months, 9.9 months, 9.3 months, and 11.2 months, respectively; survival rates at 1 year were 37.7%, 40.8%, 40.4%, and 46.8%. In a secondary analysis, overall survival was longer with EOX than with ECF, with an HR for death of 0.80 in the EOX group (95% CI; 0.66, 0.97; $p = 0.02$). PFS and response rates did not differ significantly between the regimens.

A third phase III trial compared cisplatin/5-FU with irinotecan/5-FU in 333 patients with advanced gastric cancer. No difference in outcome measures (response rate, PFS, and overall survival) could be found, but the irinotecan-based regimen was found to be less toxic and thus could be an alternative for patients who are not considered candidates for a platinum-based treatment regimen.[72] Based on these trial data, a combination regimen with a platinum agent (cisplatin or oxaliplatin) plus fluoropyrimidine as a backbone, with or without the addition of docetaxel, can be considered first-line standard of care in the palliative treatment of advanced gastric cancer. Irinotecan has clearly demonstrated activity and could be integrated in a sequential treatment approach.

The role of targeted agents, in particular drugs targeting the VEGF and EGFR/HER2 system, has been investigated in several clinical trials. The first targeted agent with documented efficacy in advanced gastric and gastroesophageal junction cancer was trastuzumab, the humanized monoclonal antibody against HER2. Based on the preclinical observations that about 20% of gastric cancers (and about 30% of gastroesophageal adenocarcinomas) overexpress HER2,[73] the phase III ToGA (Trastuzumab in GAstric cancer) trial investigated whether the addition of trastuzumab to standard chemotherapy would extend survival of patients with advanced adenocarcinoma of the stomach or gastroesophageal

junction.[39] Of the 3807 tumors from patients with gastric cancer tested, 810 (22.1%) were positive for HER2 overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) analysis. Eventually, 584 patients were randomly assigned to receive a fluoropyrimidine (5-FU 800 mg/m^2/day on days 1 to 5 or capecitabine 1000 mg/m^2 twice daily on days 1 to 14 based on physician choice) plus cisplatin 80 mg/m^2 on day 1 with or without trastuzumab (8 mg/kg loading dose followed by 6 mg/kg) on day 1. Cycles were repeated every 3 weeks for six cycles, and trastuzumab was subsequently continued every 3 weeks until disease progression. In the study, 55% of patients were from Asia and 18% of patients had tumors originating in the gastroesophageal junction. The addition of trastuzumab to cisplatin/fluoropyrimidine increased median overall survival from 11.1 months to 13.8 months (HR, 0.74; 95% CI; 0.60, 0.91; p = 0.0046). In addition, secondary endpoints such as PFS (6.7 months vs. 5.5 months, p = 0.0002) and overall response rate (47.3% vs. 34.5%, p = 0.0017) were also improved in the trastuzumab arm. There were no significant differences in toxicity between the two treatment arms. An asymptomatic decrease in ejection fraction occurred in 4.6% and 1.1% in the trastuzumab and chemotherapy-alone arms, respectively. As a result of the ToGA trial, trastuzumab added to standard chemotherapy is the standard of care in patients with metastatic, HER2-overexpressing gastric and gastroesophageal cancers. The HELOISE study examined the dose of trastuzumab in gastric cancer by randomly assigning 248 patients to receive cisplatin/capecitabine chemotherapy with either standard-dose or high-dose trastuzumab (8 mg/kg load followed by 10 mg/kg every 3 weeks).[74] Although a higher dose of trastuzumab did successfully increase trastuzumab trough concentrations, there was no improvement in survival when compared to standard trastuzumab dosing combined with chemotherapy (median overall survival, 12.5 months with standard trastuzumab vs. 10.6 months with high-dose trastuzumab).[74] These data firmly establish the standard dose of trastuzumab in gastric cancer.

In contrast with the positive results for trastuzumab in HER2-overexpressing gastric cancers, two phase III trials of lapatinib, an oral HER2/EGFR kinase inhibitor, added to chemotherapy in first-line (LOGIC) and second-line (TyTAN) treatment failed to meet their primary endpoints.[75,76] In the second-line treatment trial, however, the subgroup of patients with high HER2 expression (3+ on IHC testing) exhibited a survival benefit with the addition of lapatinib to paclitaxel versus placebo. It is unclear though whether lapatinib will be further developed in gastric cancer given the fact that trastuzumab has become the standard of care for HER2-positive gastroesophageal cancers. Finally, TDM-1, a novel antibody-drug conjugate combining trastuzumab with the drug emtansine, which acts on microtubules was examined in a phase III study in second-line gastric cancer and failed to show an improved survival compared with taxane therapy.[77] Together, the results of these studies demonstrate no evidence to support continuing HER2 blockade beyond progression in gastric cancer, providing yet another distinction among HER2-positive diseases.

Antibodies targeting the EGFR, a member of the HER family of receptor tyrosine kinases, such as cetuximab and panitumumab, have also been tested in randomized, phase III trials; unfortunately, the results were negative. The EXPAND trial randomly assigned over 900 patients with advanced gastroesophageal adenocarcinoma to receive capecitabine/cisplatin with or without cetuximab.[78] Although the toxicity was increased in the cetuximab arm, no benefit in any outcome parameter was noted. The REAL-3 trial investigated the addition of panitumumab to EOX in 553 patients.[79] The dose of EOX had to be reduced after an interim toxicity analysis, and the trial was eventually stopped when an interim efficacy analysis documented a detrimental effect in overall survival for the panitumumab-containing combination

compared with the standard arm. The consistently negative data from these two large phase III trials confirm that there is no role for the use of EGFR monoclonal antibodies in advanced gastroesophageal adenocarcinoma.

Results of a trial investigating angiogenesis inhibitors in gastric and esophageal cancers have been inconsistent. In the first phase III trial (AVAGAST), bevacizumab failed to demonstrate an overall survival benefit when added to cisplatin/fluoropyrimidine in patients with gastroesophageal junction and gastric adenocarcinomas.[35] Both median PFS (6.7 vs. 5.3 months; HR, 0.80; 95% CI; 0.68, 0.93; p = 0.0037) and overall response rate (46.0% vs. 37.4%; p = 0.0315) were significantly improved with bevacizumab versus placebo. However, the study failed to meet its primary endpoint of improving overall survival: median overall survival was 12.1 months with bevacizumab plus cisplatin/fluoropyrimidine and 10.1 months with placebo plus cisplatin/fluoropyrimidine (HR, 0.87; 95% CI; 0.73, 1.03; p = 0.10). Preplanned subgroup analyses revealed regional differences in efficacy outcomes with a survival benefit for Pan-American patients but not for patients from Asia, who, as expected, constituted the largest regional group. It has long been speculated that the biology of gastric cancers and the treatment approach to these tumors differs greatly between Asian and non-Asian countries. Thus, one would have to be careful with the interpretation of global trials in this disease, which will invariably include a substantial number of patients from Asia.

A second set of trials investigated ramucirumab, a VEGFR2 monoclonal antibody, in the second-line treatment setting of advanced gastroesophageal cancer. The REGARD trial randomly assigned 472 patients after first-line fluoropyrimidine/platinum therapy in a 2:1 ratio to receive single-agent ramucirumab or placebo.[37] Median overall survival was 5.2 months for the ramucirumab group and 3.8 months for the placebo group (HR, 0.776; 95% CI; 0.603, 0.998; p = 0.047). Aside from a higher rate of hypertension, no relevant differences were seen in recorded side effects between ramucirumab and placebo. In comparison with the AVAGAST bevacizumab trial, REGARD enrolled fewer patients from Asian countries (15% vs. 49%) and included a higher percentage of gastroesophageal junction cancers (25% vs. 14%). Concerns have been raised regarding the placebo control arm in the REGARD study, given the convincing documentation of a survival benefit associated with second-line chemotherapy. The RAINBOW trial was an international phase III study including 665 patients that compared paclitaxel plus placebo to paclitaxel plus ramucirumab as second-line therapy for those in whom disease progressed after exposure to a platinum/fluoropyrimidine–based regimen.[38] Overall survival was 9.6 months in the ramucirumab arm compared with 7.4 months with paclitaxel alone (HR, 0.807; 95% CI; 0.678, 0.962; p = 0.017). Patients in the ramucirumab arm had a significantly higher response rate (28% vs. 16%, p = 0.001) and improved PFS (4.4 months vs. 2.9 months, p < 0.0001) than patients in the paclitaxel alone arm. In the RAINBOW trial, overall survival was not significantly increased among Asian patients compared with non-Asian patients. Despite the activity of ramucirumab seen in the above second-line trials, a randomized phase II study did not show benefit to adding ramucirumab to mFOLFOX6 as first-line treatment for advanced gastroesophageal tumors.[80]

The usefulness of second-line chemotherapy in the palliative management of gastric cancer had long been questioned. Eventually, three randomized trials of chemotherapy versus best supportive care clearly demonstrated improvement in overall survival with the use of second-line chemotherapy with either irinotecan or taxane after failure of first-line fluoropyrimidine/platinum therapy.[81-83] A head-to-head comparison between two commonly used second-line therapies, paclitaxel and irinotecan, demonstrated similar efficacy for these approaches.[84]

Radiation therapy can be effective for metastatic disease (e.g., metastasis to bony

structures for symptom control) and perhaps for unresectable, bleeding tumors in conjunction with chemotherapy, but it is rarely used to treat primary advanced unresectable gastric cancer.

Several novel agents are currently being investigated in advanced gastric cancer. One of the most promising of these is the anti–programmed death 1 (PD-1) monoclonal antibody pembrolizumab. The KEYNOTE-012 trial evaluated pembrolizumab in patients with programmed death ligand 1 (PD-L1)–positive tumors.[85] Two-thirds of patients had undergone two or more prior systemic therapies. This 39-patient trial demonstrated impressive activity in this heavily pretreated population. The overall response rate was 22%, and the median overall survival was 11.4 months, which compares very favorably to the 5.2-month overall survival seen in the second-line REGARD study. In addition, a subset of patients had prolonged response to pembrolizumab, with a median response duration of 40 weeks (range, 20 to 48). In one phase III study of 493 patients with advanced gastric or gastroesophageal junction cancer whose disease has progressed on two or more lines of therapy, nivolumab, an anti–PD-1 monoclonal antibody, demonstrated significant efficacy over best supportive care, with a median OS of 5.3 months versus 4.14 months with best supportive care (HR, 0.63; 95% CI; 0.5, 0.78).[86] These studies suggest that immuno-oncology agents do have modest activity in gastric cancer, and studies to define their role are ongoing.

Antibody inhibitors of the mesenchymal-epithelial transition (MET) pathway also initially showed promise for advanced gastric cancers, particularly in patients whose tumors express the MET receptor (e.g., hepatocyte-growth factor receptor). A randomized, phase II trial, however, did not show an improvement in PFS with onartuzumab, a MET antibody, when combined with 5-FU/oxaliplatin (mFOLFOX).[87] Subsequent phase III studies evaluating the MET antibody, onartuzumab,[88] as well as the antibody to the hepatocyte growth factor, rilotumumab (also targeting the MET pathway), were also negative, confirming lack of efficacy of this strategy in advanced gastric cancer.[89]

In contrast, the multikinase inhibitor regorafenib did show an improvement in PFS compared with placebo (2.6 months vs. 0.9 months; $p < 0.0001$) in a randomized, phase II study (INTEGRATE) for chemotherapy-refractory advanced metastatic gastric and gastroesophageal junction tumors, demonstrating promise as salvage therapy for this patient population.[90]

KEY POINTS

- The incidence of gastric cancer correlates with socioeconomic status and is clearly dependent on environmental factors. The worldwide incidence of gastric cancer is in decline; however, there is an increase in more proximal and gastroesophageal cancers.
- Controversy surrounds the question of the best operation for gastric cancer, with data from Japanese studies suggesting a better result using a more aggressive, extensive lymph node dissection.
- Individuals who carry a germline *CDH1* mutation are at significant lifetime risk for the development of gastric cancer and should undergo risk-reducing prophylactic gastrectomy as early as their 20s.
- Randomized trials have demonstrated a survival benefit from adjuvant chemoradiotherapy, pre-operative and postoperative chemotherapy, or adjuvant chemotherapy without radiation for stages I to III gastric cancer resulting in several

standard-of-care options.

- Combination chemotherapy regimens have become more widely used for advanced disease, with some evidence that supports its benefit over single-agent therapy.
- The addition of trastuzumab to chemotherapy is standard of care in HER2-overexpressing metastatic gastric and gastroesophageal cancers. The standard dose of trastuzumab in gastric and gastroesophageal junction cancer has been defined in phase III evaluation.
- The VEGFR antibody ramucirumab has shown efficacy in second-line phase III trials in advanced gastric cancer and is now a standard care option either alone or with paclitaxel therapy.

PANCREAS CANCER

EPIDEMIOLOGY AND ETIOLOGY

Cancer of the exocrine pancreas is a substantial health problem in the United States, with an annual incidence of 53,670 cases and an annual mortality of 43,090 patients in the United States, with virtually all of those patients dying within 2 years of diagnosis.[1] It is estimated that more than about 270,000 patients die of pancreas cancer each year worldwide.[3] The incidence of pancreas cancer increased until the late 1970s and then plateaued. The risk factors for pancreas cancer are largely unknown, although there is some suggestion of a link to tobacco exposure.[91,92] Data regarding coffee and excess alcohol consumption are conflicting; therefore, they cannot be considered true etiologic factors. There is an association between pancreas cancer and diabetes; however, it is more likely that diabetes is an early manifestation of cancer and not necessarily a predisposing factor.[91,93] Chronic pancreatitis also may be a predisposing factor. Selective mutations of *BRCA2,* and to a lesser degree, *BRCA1* have been associated with familial pancreas cancer. Other less common genetic syndromes have been linked to pancreas cancer (e.g., hereditary pancreatitis, HNPCC, *p16* mutations, Peutz–Jeghers syndrome, ataxia telangiectasia).[94]

Approximately 10 to 20% of patients are thought to have a familial predisposition. There is no standard surveillance or screening for this disease. Most pancreas cancers harbor activating genetic mutations of the oncogene *KRAS,* which is integrated in signaling pathways of various receptor kinases such as EGFR and the insulin-like growth factor receptor I (IGFR-I). In addition, most pancreas cancers show mutations in several tumor suppressor genes, such as *p53, DPC4, p16,* and *BRCA2.*[95,96] A whole-genome sequencing study in 24 pancreas cancers identified an average of 63 genetic alterations per cancer, the majority of which were point mutations.[97] Pancreatic adenocarcinomas arise from ductal epithelial cells. Pancreatic intraepithelial neoplasia, which are microscopic lesions of the pancreas, and intraductal papillary mucinous neoplasms and mucinous cystic neoplasms, which are both macroscopic lesions, are thought to be precursors of invasive pancreatic cancer.[95,96]

CLINICAL PRESENTATION AND DIAGNOSIS

Symptoms associated with pancreas cancer at the time of presentation commonly include abdominal pain, weight loss, and/or jaundice. The classic description is midepigastric abdominal pain with bandlike radiation to the back. The disease typically is not diagnosed for several

months after the initial presentation with vague abdominal symptoms or back pain. Ultimately, the diagnosis is most often made with a CT scan, magnetic resonance imaging (MRI), or ultrasound. When evaluating patients with adult-onset diabetes without other risk factors, physicians should consider pancreas cancer as a possible diagnosis.[98] The most common diagnostic tests used for pancreas cancer are CT scan, MRI, EUS, and endoscopic retrograde cholangiopancreatography. Other tests, such as PET/CT and EUS, may play a role in distinguishing cancer from other abnormalities and are used to adequately stage the disease but do not replace biopsy as a definitive diagnostic test.

TREATMENT

The treatment for resectable pancreas cancer is primarily surgery, although neoadjuvant treatment strategies with either radiochemotherapy or chemotherapy alone have made inroads into clinical practice. For patients with tumors that appear resectable, which includes only approximately 20% of all pancreas cancers, surgery remains the only potentially curative treatment option. Tools such as EUS, MRI, and PET have improved the ability to determine which patients are candidates for surgery. To determine the resectability of a pancreas mass, a detailed evaluation of its spatial relationship to critical vascular structures—in particular, the superior mesenteric artery and celiac axis—must be performed. Most patients with pancreas cancer are found to have unresectable disease either because of a locally advanced disease (involvement of critical vascular structures) or obvious metastatic disease (liver, peritoneal involvement) at the time of diagnosis. The 5-year survival rate for the minority of patients who are able to undergo resection is 5 to 25%.[99]

Adjuvant Therapy

The optimal adjuvant therapy after pancreas cancer resection is controversial, particularly with regard to the value of radiation therapy. A small randomized study (43 patients) conducted in the United States over 30 years ago showed that a significantly larger number of patients in the combined-modality group were alive at 1 year compared with the surgery-alone group. On the basis of these findings, postoperative radiochemotherapy with bolus fluorouracil became the standard of care in the United States.[100] Since then, the role of radiation in this context has been repeatedly challenged by European investigators,[101] culminating in a trial suggesting that the use of radiation conferred an adverse outcome compared with patients who received adjuvant chemotherapy alone (ESPAC-1).[102,103] The complex study design, concerns about the radiation protocol, and the questionable randomization strategy used in ESPAC-1 limited acceptance of chemotherapy alone as a standard of care in the United States.

More recently, clinical trials have set somewhat competing standards for the adjuvant medical therapy of pancreas cancer. A German phase III trial (CONKO-1) including 364 patients demonstrated the superiority of adjuvant chemotherapy with gemcitabine compared with surgery alone for patients with resected pancreas cancer, regardless of whether a tumor-free resection margin could be obtained.[104,105] An update of this study demonstrated a significant improvement in 5-year overall survival of 20.7% (95% CI; 14.7, 26.6) compared with 10.4% (95% CI; 5.9, 15.0), for gemcitabine compared with surgery alone, and 10-year overall survival of 12.2% (95% CI; 7.3, 17.2) compared with 7.7% (95% CI; 3.6, 11.8).[106]

A large phase III trial conducted mainly in the United Kingdom, the European Study Group for Pancreatic Cancer (ESPAC)-3 trial, compared weekly gemcitabine to bolus 5-FU/LV (Mayo Clinic regimen) as adjuvant therapy in 1088 patients with resected pancreas cancer.[107] Median

survival was almost identical in the two groups (5-FU/LV, 23.0 months; gemcitabine, 23.6 months; p = 0.39). More mucositis/stomatitis and diarrhea were seen with bolus 5-FU/LV; patients taking gemcitabine had more thrombocytopenia. Since survival was equivalent, but a significantly higher rate of grade 3 and greater adverse events occurred in the 5-FU/LV arm (14% vs. 7.5%; p < 0.001), gemcitabine is the preferred standard option for adjuvant chemotherapy for resected pancreatic cancer.

The ESPAC-4 study compared adjuvant gemcitabine to gemcitabine/capecitabine in a large phase III study of 732 patients.[108] This study did demonstrate a modest improvement in survival with the combination adjuvant therapy; the median survival was 28.0 months, versus 25.5 months with gemcitabine alone (HR, 0.82; 95% CI; 0.68, 0.98, p = 0.032).

The randomized, phase III comparison of gemcitabine with S-1 in 385 patients with resected pancreas cancer were reported.[109] Although S-1 and gemcitabine had previously shown similar results in the advanced setting,[110] adjuvant S-1 was found to be superior to gemcitabine (HR, 0.57; 95% CI; 0.44, 0.72, p < 0.0001), with a 5-year estimated survival with gemcitabine of 24.4%, versus 44.1% with S-1. In Japan, S-1 has since emerged as the standard of care in adjuvant therapy for pancreas cancer.

A meta-analysis of nine large phase III clinical trials, reported in 10 articles, mostly support the role of adjuvant chemotherapy in pancreatic cancer, with an HR for death of 0.65 with adjuvant fluorouracil and of 0.59 with adjuvant gemcitabine.[111] Based on these studies and the meta-analysis of them, the combination of gemcitabine/capecitabine, gemcitabine alone, or S-1 in Asia are appropriate adjuvant options in patients with resected pancreatic cancer.

To expand on the potential role of radiation therapy, a U.S. trial (RTOG 9704) involving 451 patients documented an improved outcome for patients with cancers of the pancreas head (but not with cancers of the pancreas body or tail) who received adjuvant gemcitabine followed by radiochemotherapy with continuous infusion of fluorouracil (50.4 Gy, 5-FU at 250 mg/m^2/day) and subsequent gemcitabine monotherapy compared with postoperative fluorouracil-based radiochemotherapy.[112] In this updated analysis, patients with pancreas head tumors (388 patients) had a median survival of 20.5 months and a 5-year overall survival of 22% in the gemcitabine group compared with a median survival of 17.1 months and a 5-year survival of 18% in the fluorouracil group (p = 0.08).[112] This trial was designed to verify the role of adjuvant radiation therapy in resected pancreas cancer. Thus, for the foreseeable future, the standards of care might differ between the United States and Europe, with adjuvant gemcitabine-based chemotherapy without radiation favored in Europe and combined-modality approaches favored in the United States. The ongoing RTOG Intergroup phase III trial 0848 is currently evaluating the value of radiation therapy as adjuvant therapy for resected pancreas cancer (NCT01013649).

Based on the convincing results in advanced pancreas cancer, a phase III trial investigating the efficacy of mFOLFIRINOX (see “Treatment of Metastatic Pancreas Cancer” section) compared with gemcitabine as adjuvant therapy has been activated in France and Canada (NCT01526135). Similarly, the ongoing Adjuvant Therapy for Patients with Resected Pancreatic Cancer (APACT) study is a phase III trial comparing gemcitabine to gemcitabine plus nab-paclitaxel in the adjuvant setting (NCT01964430).

Chemotherapy and Radiation for Locally Advanced Pancreas Cancers

Preoperative chemotherapy and radiation are used in some centers in a neoadjuvant fashion in up-front resectable pancreas cancers, and results of phase II trials regarding this treatment

approach have been published.[113] For patients with initially unresectable cancers, a “conversion approach” of chemotherapy with or without radiation is attempted, with occasional adequate tumor responses allowing subsequent surgical resection. No randomized trial has been conducted yet, so it is unclear whether this approach is associated with a survival advantage. In addition, no clear definition of “borderline resectable” pancreas cancer has been established yet, although most surgeons consider abutment of major upper abdominal blood vessels the main criterion.[114]

For patients with locally advanced, unresectable disease, the two treatment strategies include primary radiochemotherapy and systemic chemotherapy. Most patients in the United States are currently treated with a combination of radiation therapy and chemotherapy. The standard regimen is infusional fluorouracil and radiation therapy, but the role of contemporary chemotherapy agents, including low-dose gemcitabine, capecitabine (an oral fluorouracil substitute), and targeted agents in combination with radiation therapy is now being explored. This approach may improve pain and prevent gastric or biliary obstruction. A randomized trial (E4201) validated this approach with a better outcome for patients receiving gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with localized, unresectable pancreas cancer.[115] The primary endpoint of the trial was survival, which was 11.1 months (95% CI; 7.6, 15.5) and 9.2 months (95% CI; 7.9, 11.4) for chemoradiation and gemcitabine alone, respectively (one-sided $p = 0.017$). However, this trial enrolled only 74 of the planned 316 patients with unresectable pancreas cancer, so the results are not necessarily definitive.

The other feasible strategy is to initiate systemic chemotherapy as primary therapy because the clinical benefit of gemcitabine-based therapy in this setting is well documented, even in the absence of significant tumor shrinkage. This approach has been found to be superior in a European phase III trial including 119 patients, which compared induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreas cancer.[116] Interestingly, median overall survival was shorter in the chemoradiation arm compared with gemcitabine-alone arm (8.6 months vs. 13 months, $p = 0.03$).

The role of radiation therapy as a component of the management of locally advanced pancreas cancers was further investigated by the international LAP07 phase III trial.[117] In this trial, patients with locally advanced, unresectable pancreatic cancer were initially randomly assigned to gemcitabine with or without erlotinib. Patients with at least stable disease after 4 months underwent a second randomization to either continue with the same chemotherapy as in the first phase or to proceed to chemoradiation with capecitabine as a radiation sensitizer. This study closed at the first planned interim analysis because of lack of efficacy. A total of 449 patients were randomly selected up front, 269 patients (61% of the initial study cohort) were eligible for the second randomization. One of the key findings of this study was that the addition of erlotinib to gemcitabine in this setting did not provide any benefit in overall survival. In fact, the overall survival trended toward a detrimental effect in the erlotinib arm. Secondly, no survival benefit was observed with the switch from chemotherapy to consolidating radiochemotherapy; the arms showed no difference in PFS and OS. A subsequent analysis to evaluate the effect of radiation therapy on locoregional tumor control found that patients in the radiation arm had significantly less local tumor progression (34% vs. 65%, $p < 0.0001$) and a longer time prior to reintroduction of chemotherapy (159 vs. 96 days, $p = 0.05$).[118] In conclusion, there appears to be no role for erlotinib in the management of locally advanced pancreas cancers. Chemoradiation after an induction chemotherapy phase can be considered

in select patients. Even though no survival benefit could be documented with this approach, it may provide local tumor control and allow patients a longer break from treatment of their advanced disease.

Based on the available data, radiochemotherapy or chemotherapy alone can be used as initial treatment for patients with unresectable pancreas cancer without distant metastases. Chemoradiation might be preferred for patients with poorly controlled pain from local tumor invasion in view of the well-documented analgesic effect of radiation therapy. Whether the high antitumor activity of FOLFIRINOX (see "Treatment of Metastatic Pancreas Cancer" section) with documented response rates above 30%[119] or gemcitabine plus nab-paclitaxel can emerge as the preferred neoadjuvant treatment for select patients is the focus of ongoing studies.

Other palliative means to treat patients in this setting include biliary stenting, intraoperative or external-beam radiation therapy, and celiac axis nerve blocks. Aggressive management of symptoms such as pain, anorexia, and obstruction should be the primary focus. Some patients require the placement of a duodenal stent for relieving gastric-outlet obstruction.[120] It is noteworthy in this context that the routine preoperative placement of biliary stents in patients with biliary obstruction and operable pancreas head cancers was associated with an increase in surgical complications when compared with up-front surgery without prior biliary drainage.[121] Thus, routine preoperative biliary drainage in patients undergoing subsequent surgery for cancer of the pancreas head should be considered only after close consultation with the surgeon and if it can be performed by an experienced interventional gastrointestinal team familiar with the placement of preoperative biliary stents.

Treatment of Metastatic Pancreas Cancer

Regarding advanced metastatic disease, several agents, such as fluoropyrimidines, gemcitabine, irinotecan, platinum compounds, and taxanes, have minor to moderate single-agent activity in pancreas cancer. In the mid-1990s, gemcitabine was tested in a randomized clinical trial with 126 patients against single-agent intravenous fluorouracil (administered without LV as short-term infusion, and thus not optimally administered).[122] Gemcitabine was found to be superior to fluorouracil with regard to clinical benefit, with more patients (24% vs. 5%) experiencing a reduction of pain as well as improvements in appetite and weight. There were few clinical responses in either arm (less than 10%), but the median survival (5.65 months vs. 4.4 months, $p = 0.0025$) and the 1-year survival rate (18% vs. 2%) were better for patients treated with gemcitabine. Subsequently, a plethora of clinical trials have tried to outperform gemcitabine monotherapy, with all studying gemcitabine compared with gemcitabine plus another agent. In phase III trials, agents added to gemcitabine consisted of several conventional chemotherapy drugs, such as fluorouracil, cisplatin, oxaliplatin, irinotecan, or pemetrexed. Novel biologic agents also were used, such as matrix metalloproteinase inhibitors, farnesyl-transferase inhibitors, or the VEGF-inhibitor bevacizumab and the EGFR antibody cetuximab. All of these trials failed to lead to improvements in overall survival.[123]

Subsequently, two phase III trials showed modest survival benefits of similar magnitude when another agent was used in combination with gemcitabine. In the first trial, the combination of gemcitabine with erlotinib, an EGFR tyrosine kinase inhibitor, was found to significantly increase PFS (HR, 0.77; 95% CI; 0.64, 0.92; $p = 0.004$) and overall survival (HR, 0.82; 95% CI; 0.69, 0.99; $p = 0.038$), albeit with a median overall survival improvement of only roughly 2 weeks.[124] No increase in response rate was noted. Nevertheless, based on these data, erlotinib obtained approval from the U.S. Food and Drug Administration (FDA) for the treatment of

advanced pancreas cancer in conjunction with gemcitabine. The second trial, a phase III trial comparing gemcitabine with or without capecitabine, initially demonstrated moderate benefits regarding response rates as well as PFS and overall survival.[125] However, in a combined analysis of two similar trials, the addition of capecitabine to gemcitabine was found to be associated with improved overall survival (HR, 0.86; 95% CI; 0.75, 0.98; p = 0.02).[125] A meta-analysis of 15 randomized trials involving 4465 patients that compared gemcitabine alone with gemcitabine plus either a platinum compound or fluoropyrimidine demonstrated a survival benefit for patients with good performance status who received combination chemotherapy (HR, 0.76; 95% CI; 0.67, 0.87; p < 0.0001). By contrast, application of combination chemotherapy to patients with an initially poor performance status appeared to be ineffective (HR, 1.08; 95% CI; 0.90, 1.29; p = 0.40).[126]

A new standard of care in the palliative therapy of pancreas cancer was defined by the results of a French study of 342 patients comparing gemcitabine with FOLFIRINOX, a combination of standard modified FOLFOX6—a well-known regimen established in colorectal cancer—with full-dose irinotecan (180 mg/m^2) in an every-2-week schedule.[119] The median overall survival was an unprecedented 11.1 months in the FOLFIRINOX group as compared with 6.8 months in the gemcitabine group (HR, 0.57; 95% CI; 0.45, 0.73; p < 0.001). Median PFS was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group (HR, 0.47; 95% CI; 0.37, 0.59; p < 0.001). The objective response rate was 31.6% for FOLFIRINOX compared with 9.4% for the gemcitabine group (p < 0.001). More adverse events were noted in the FOLFIRINOX group; 5.4% of patients in this group had febrile neutropenia. These results established FOLFIRINOX as the new standard of care for patients with advanced pancreas cancer, age less than 75, with good performance status, absence of biliary obstruction, and no infectious complications. The usefulness of FOLFIRINOX as adjuvant and neoadjuvant therapy as well as a backbone for the addition of targeted agents is currently being investigated in clinical trials.

Another standard first-line therapy for advanced pancreatic cancer was established when the addition of nab-paclitaxel to gemcitabine was found to be superior to gemcitabine alone in a phase III trial.[127] This study included 861 patients with metastatic pancreas cancer. The median OS was 8.5 months in the nab-paclitaxel/gemcitabine group, compared with 6.7 months in the gemcitabine-alone group (HR, 0.72; 95% CI; 0.62,0.83; p < 0.001). The median PFS was 5.5 months in the nab-paclitaxel/gemcitabine group, compared with 3.7 months in the gemcitabine-alone group (HR, 0.69; 95% CI; 0.58, 0.82; p < 0.001); the response rate according to independent review was 23% compared with 7% (p < 0.001). Neutropenia, febrile neutropenia (3% vs. 1%), neuropathy, and fatigue were significantly higher in the nab-paclitaxel arm. Subsequently, nab-paclitaxel received regulatory approval as a component of the gemcitabine-based first-line therapy of pancreas cancer.

Based on these studies, several first-line regimens can be considered appropriate treatment options for patients with metastatic pancreas cancer. With all caveats surrounding cross-trial comparisons, the outcomes data associated with FOLFIRINOX appear to be stronger than the nab-paclitaxel/gemcitabine results. On the other hand, the side-effect profile seems to favor the nab-paclitaxel/gemcitabine combination. It is unlikely that a direct head-to-head comparison between these two regimens will ever be performed, so that the available data will need to suffice to inform clinical practice. It could be reasonable to establish a three-tier approach toward metastatic pancreas cancer: otherwise healthy, younger patients in good performance status could preferentially be treated with FOLFIRINOX as first-line therapy and potentially nab-paclitaxel/gemcitabine as second-line therapy. Patients with poor performance status,

advanced age, and significant comorbidities could still be considered candidates for single-agent gemcitabine therapy. In between these extremes lies a group of patients who could be considered for nab-paclitaxel/gemcitabine as first-line therapy. It will be interesting to see how these treatment standards will be adopted into clinical practice in the future.

Second-line treatment options should be considered for patients with good performance status after progression on first-line therapy. In view of the commonly rapid progression of disease and deterioration of patients' performance status, randomized trials in second-line therapy are difficult to conduct. A German phase III trial randomly assigned 46 patients with advanced pancreas cancer who had received first-line gemcitabine to weekly infusional 5-FU/LV with biweekly oxaliplatin or best supportive care. The oxaliplatin-based therapy was able to confer a significant overall survival benefit (4.8 months vs. 2.3 months; HR, 0.45; p = 0.008).[128]

The recently reported NAnoliPOsomaL Irinotecan (NAPOLI)-1 trial evaluated nanoliposomal irinotecan (MM-398; nal-IRI) in patients with metastatic pancreatic cancer refractory to gemcitabine.[129] This trial randomly assigned 417 patients in a 1:1:1 fashion to receive nal-IRI alone, 5-FU/LV, or combination nal-IRI plus 5-FU/LV. Patients in the combination nal-IRI plus 5-FU/LV arm had a significantly improved overall survival compared with the 5-FU/LV arm—6.1 months compared with 4.2 months (HR, 0.67; p = 0.012) in the intention-to-treat population and 8.9 months compared with 5.1 months (HR, 0.57; p = 0.011) in the per-protocol population.[130] PFS was also improved (3.1 months vs. 1.5 months; HR, 0.56; p < 0.001). nal-IRI alone provided no survival benefit over 5-FU/LV. nal-IRI plus 5-FU/LV may provide another second-line treatment option for those in whom disease progressed on gemcitabine-based therapy but are not candidates for FOLFIRINOX. In October 2015, nanoliposomal irinotecan obtained FDA approval for use in combination with fluorouracil and LV in patients with metastatic pancreas cancer who have previously received gemcitabine-based therapy.

So far, agents targeting the VEGF system (bevacizumab) and the EGFR system (cetuximab) have failed to demonstrate activity in metastatic pancreas cancer.[131-133] Studies utilizing other targeted agents, including hedgehog inhibitors and IGFR inhibitors, have also not lived up to their initial promise. Other agents of interest currently undergoing investigation in clinical trials include *JAK2* inhibitors, *PI3K*, *MEK*, and *BRAF* inhibitors, as well as immune modulators and vaccines. In a randomized phase II study comparing the *JAK1/2* inhibitor ruxolitinib plus capecitabine with placebo plus capecitabine, a nonsignificant improvement was seen in median OS (137 vs. 130 days, p = 0.25).[134] However, in a subset of patients with very high levels of circulating inflammation (C-reactive protein > 13 mg/L), the survival advantage was 2.7 months (83 days) in the ruxolitinib plus capecitabine group compared with 1.8 months (55 days) in the placebo group (HR, 0.47; 95% CI; 0.26, 0.85; p = 0.011). Two phase III trials investigating the combination of ruxolitinib/capecitabine versus placebo with capecitabine in second-line treatment have been reported, having failed to show an improvement in survival.[135] Results of the combination of GVAX, an irradiated granulocyte macrophage colony-stimulating factor–secreting vaccine and CRS-207, a live-attenuated, mesothelin-expressing *Listeria monocytogenes* vaccine, also show promise in advanced pancreas cancer.[136] This trial included patients who received one or more prior lines of therapy and demonstrated an overall survival of 6.1 months for the combination GVAX/CRS-207 compared with 3.9 months for those who received GVAX alone (HR, 0.54; p = 0.011). Ongoing studies are evaluating this combination further in patients with advanced pancreatic cancer (NCT02004262).

AMPULLARY CARCINOMA

Ampullary cancers (also known as periampullary cancers) arise from the area known as the ampulla of Vater, which is a junction located adjacent to the pancreas, common bile duct, and duodenum. As such, tumors from this area are histologically divided into intestinal and pancreatobiliary subtypes. Genomic analyses suggest that *WNT* pathway alterations are more common in intestinal-type ampullary cancer, whereas *RAS* pathway alterations are more prevalent in the pancreatobiliary subtype.[137,138] Both studies identified *ELF3*, a member of the ETS transcription factor family, as a potential driver for ampullary carcinoma. Historically, these tumors have been thought to carry a relatively favorable prognosis, known for their high rates of resectability and good prognosis following pancreatoduodenectomy. In one series of 152 patients, the 5-year disease-free survival rate was 47.1%,[139] highlighting the better survival than true pancreatic cancers. Because ampullary cancers are rare, and difficult to isolate, there are few studies that specifically enroll ampullary cancers alone. Treatment of ampullary cancers generally follows the histology type; for example, intestinal-type ampullary cancers are preferentially treated as cancers of the small and large bowel, whereas pancreatobiliary ampullary cancers adopt a pancreatic or bile duct treatment paradigm.[140]

KEY POINTS

- Diagnostic tests, such as PET and EUS, do not replace the need for a biopsy to prove the diagnosis of pancreatic and ampullary cancers.
- The best approach to adjuvant therapy (especially the role of radiation) is controversial; however, it is clear that additional therapy beyond surgery alone is appropriate for most patients with stage I–III resected disease. Options include adjuvant gemcitabine, gemcitabine plus capecitabine, S-1, and possibly the inclusion of postoperative combined chemoradiotherapy.
- Both FOLFIRINOX and nab-paclitaxel with gemcitabine are superior combination regimens compared to gemcitabine monotherapy for patients with advanced pancreatic cancer who are considered candidates for more aggressive therapy.
- Ampullary carcinomas are tumors arising around and/or involving the ampulla of Vater; they can be of either the intestinal or the pancreatobiliary type, and they commonly carry a more favorable prognosis than pancreatic or bile duct cancers.
- Although there is no consensus, treatment of ampullary cancers generally follow the treatment of their histologic subtype.

CANCERS OF THE LIVER AND BILIARY TREE

EPIDEMIOLOGY AND ETIOLOGY

Primary hepatobiliary cancers, which include hepatocellular cancers, cholangiocarcinomas, and gallbladder cancers, represent the highest global incidence of solid organ tumors and are responsible for about 1 million deaths annually, although they are uncommon in Western cultures (particularly hepatocellular cancers).[3] The risk factors for hepatocellular cancer are well known (Table 10-1). Hepatitis B virus infection accounts for about 60% of the total liver cancer in developing countries and for about 23% of liver cancer in developed countries; the

corresponding percentages for hepatitis C virus infection are 33% in developing countries and 20% in developed countries.[141] In the United States and several other low-risk Western countries, alcohol-related cirrhosis and possibly nonalcoholic fatty liver disease, associated with obesity, are thought to account for the majority of liver cancers.[142]

Table 10-1 **Risk Factors for Hepatocellular Cancer**
Hepatitis B and C
Excessive alcohol consumption
Autoimmune hepatitis
Primary biliary cirrhosis
Androgenic steroids
Aflatoxins
Tobacco
Nitrosylated compounds
Thorotrast
Hemochromatosis
Alpha-1 antitrypsin deficiency
Wilson disease
Porphyria
Glycogen storage disease

HEPATOCELLULAR CANCER

Clinical Presentation and Diagnosis

Hepatocellular carcinoma is graded as well differentiated, moderately well differentiated, and poorly differentiated. The most important pathologic issue is the distinction between the fibrolamellar variant and the more traditional hepatocellular cancer. Fibrolamellar cancer is generally seen in younger patients, is much more likely to be resectable, and is less commonly associated with infection or cirrhosis.[143] In contrast, traditional hepatocellular cancer is found more often in men older than age 65. Less than 25% of the tumors are resectable, often because of underlying liver disease and inadequate hepatic reserve.[144] The predominant reason for nonresectability is the multifocal nature of the disease in the liver and detection late in the disease course, the latter of which is because of the long asymptomatic latency until diagnosis. Patients at high risk for the disease, such as patients with chronic hepatitis, are often monitored with imaging tests, which are often not very useful because of the similarity in appearance between cirrhotic and cancerous livers. Frequently, biopsies are required to distinguish cancer from cirrhosis. Likewise, the alpha-fetoprotein (AFP) tumor marker is not always helpful in distinguishing between the two diseases. Data suggest that an elevated subfraction of AFP, the lens culinaris agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3%), is a more reliable indicator of the presence of a hepatocellular carcinoma in patients with hepatitis C–related cirrhosis than is the total AFP.[145]

Treatment

The treatment of choice for patients with hepatocellular cancer is surgical resection or transplantation. However, resection is not possible in most cases, and transplantation is limited by organ availability. Attempts at administration of systemic chemotherapy have been unsuccessful in generating radiographic responses, with virtually no suggestion of improvement in survival in patients with localized disease. Nonetheless, hepatic arterial infusions of chemotherapy as well as chemoembolization (transcatheter arterial chemoembolization) have proved to be useful and have been associated with improved outcome in randomized trials.[146] Local ablative treatments are generally reserved for unresectable, localized disease. These approaches include alcohol injection and radiofrequency ablation. Percutaneous ablation achieves complete remission (CR) in more than 80% of tumors smaller than 3 cm in diameter, but in only 50% of tumors of 3 to 5 cm in size.[147] Although these response rates are high, it is unclear whether these techniques result in a survival benefit. A pooled analysis of eight comparative studies suggested that radiofrequency ablation was superior to other locally percutaneous ablative techniques.[148]

For the subset of patients who are able to undergo surgical resection or ablation with curative intent, there is currently no benefit to adjuvant systemic therapy. Based on the benefits of sorafenib, an oral inhibitor of VEGFR and *Raf*, in the advanced setting, the STORM trial tested whether patients would benefit from sorafenib after resection or ablation. A total of 1114 patients were randomly assigned to receive sorafenib 400 mg twice daily or placebo. There were no differences in recurrence-free or overall survival.[149]

Liver transplantation represents the ultimate local therapy for unresectable hepatocellular cancer. For patients with substantial cirrhosis, liver transplantation provides an excellent option for early-stage tumors because the procedure is therapeutic for both the cancer and for the underlying pathology. Once patients have passed the high-risk peritransplantation phase, the prognosis is similar to that for patients who have had resection of more localized disease.[150] Patients with known extrahepatic disease are not candidates for liver transplantation.

Repeated unfavorable outcomes have resulted in no standard systemic chemotherapy for advanced unresectable disease. Single-agent anthracyclines and fluoropyrimidines have been most widely used in clinical trials and clinical practice, but reported response rates and times to tumor progression vary considerably.[151] Combination regimens are associated with higher response rates but do not necessarily translate into better overall outcomes. A Chinese phase III trial that compared standard doxorubicin to FOLFOX4 noted a benefit in PFS and a trend toward improved outcome in overall survival with FOLFOX4 (median OS, 6.40 months vs. 4.97 months; HR, 0.80; 95% CI; 4.23, 6.03; p = 0.07), but the overall results were disappointing.[152]

Current trials are focusing on targeted therapies, such as angiogenesis and signal transduction inhibitors, either as single agents or in combination with chemotherapy or with other biologic agents, in particular, since sorafenib was established as standard first-line therapy. Sorafenib was compared with placebo in a phase III trial (SHARP) of 602 patients with unresectable hepatocellular cancer.[153] In this trial, the use of sorafenib was associated with significant prolongation of time to radiologic tumor progression (5.5 months vs. 2.8 months, p = 0.000007) and of OS (10.7 months vs. 7.9 months, p = 0.00058). Based on these data, sorafenib has emerged as new standard therapy for advanced, unresectable hepatocellular carcinoma and has received approval by regulatory agencies. It is unclear at this point whether the observed efficacy of sorafenib is more related to its VEGFR- or its *Raf*-inhibitory capacity. Interestingly, in a large phase III trial comparing sunitinib, another oral multikinase inhibitor with significant antiangiogenic activity, clearly demonstrated the superiority of sorafenib over

sunitinib.[154] The superiority was especially pronounced in patients with hepatitis C–associated hepatocellular carcinoma. Since the SHARP trial included only patients with Child–Pugh A (Table 10-2), questions regarding the activity and tolerability of sorafenib in patients with more severe liver dysfunction have been raised. In clinical practice, only patients with Child–Pugh A and perhaps B7 scores should be routinely considered for sorafenib therapy.

Clinical trials using VEGF and other kinase inhibitors (e.g., hepatocyte growth factor [HGF]/c-Met targeting agents) for hepatocellular cancer with or without other targeted agents or chemotherapy are underway, even though several studies with initially promising agents such as the bFGF/VEGF inhibitor brivanib have already showed negative results. The REACH study evaluated the efficacy of ramucirumab in patients with hepatocellular carcinoma that progressed on prior sorafenib therapy.[155] In the intention-to-treat population, the median overall survival was improved with ramucirumab compared with placebo, but the difference was not statistically significant (9.2 months vs. 7.6 months, p = 0.1391).[156] However, a prespecified subset analysis demonstrated a significant median OS benefit for patients with an AFP level of 400 ng/mL or greater of 7.8 months for ramucirumab compared with 4.2 months for placebo (HR, 0.67; 95% CI; 0.51, 0.90; p = 0.0059). Thus, the AFP level may serve as a marker for the benefit of ramucirumab in second-line treatment for advanced hepatocellular carcinoma. Regorafenib was examined against best supportive care in second-line treatment for patients with advanced hepatocellular carcinoma that progressed or were intolerant to sorafenib.[157] In this study, 573 patients were randomly assigned (2:1) to receive regorafenib 160 mg or placebo daily. Patients who received regorafenib experienced a median survival of 10.6 months, versus 7.8 months with placebo (HR, 0.63; 95% CI; 0.5, 0.79; p < 0.0001).[157]

Table 10-2 Child–Pugh Scoring System

The score employs five clinical measures of liver disease.
Each measure is scored 1 to 3, with 3 indicating the most severe derangement.

Measure	1 point	2 points	3 points
Total bilirubin, pmol/l (mg/dL)	< 34 (< 2)	34–50 (2-3)	> 50 (> 3)
Serum albumin, g/dL	> 3.5	2.8–3.5	< 2.8
PT INR	< 1.7	1.71–2.30	> 2.30
Ascites	None	Mild	Moderate to severe
Hepatic encephalopathy	None	Grades I to II (or suppressed with medication)	Grades III to IV (or refractory)

Chronic liver disease is classified into Child–Pugh class A to C, by adding the points: A = 5 to 6, B = 7 to 9, C = 10 to 15. Abbreviation: PT INR, prothrombin time international normalized ratio.

A potential treatment algorithm for hepatocellular carcinoma is outlined in Fig. 10-1.[144]

BILIARY CANCERS

Cancers of the extrahepatic bile duct and gallbladder are relatively rare, with only 11,740 cases diagnosed annually in the United States, resulting in approximately 3830 deaths annually.[1] The low mortality for biliary cancers overall can be explained by the fact that about 50% of gallbladder cancers are incidental findings on cholecystectomy, which—commonly diagnosed in an early stage—can have an excellent prognosis (3-year OS, 70 to 100%). It is important to note, though, that when a gallbladder cancer is found after laparoscopic cholecystectomy, re-resection of the adjacent liver segment and lymphadenectomy are indicated for all disease

stages except stage I.[158,159]

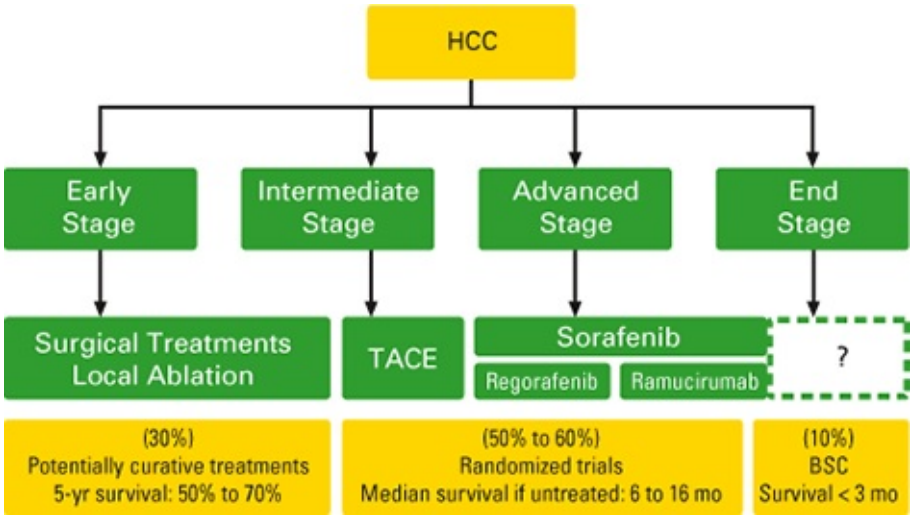

Fig. 10-1 Hepatocellular cancer (HCC) treatment algorithm.

Abbreviations: TACE, transcatheter arterial chemoembolization; yr, year; mo, months; BSC, best supportive care.

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Unfortunately, American statistics do not give specific numbers for intrahepatic cholangiocarcinomas but subcategorize them under “hepatobiliary tumors,” so that the actual incidence of biliary cancers is definitely higher, perhaps approaching the incidence of esophageal cancers, with about 15,000 cases per year.[160] Because of the location of these tumors, they are frequently difficult to resect; therefore, specialized surgical intervention should always be sought. Cholangiocarcinoma is most common in female patients older than age 50, and long-term survival is highly dependent on the effectiveness of surgical therapy. Conditions that are associated with an increased risk include primary sclerosing cholangitis (with an increased incidence among patients with inflammatory bowel disease), choledochal cysts, and other hepatic infections.[161] Gallstones also increase the risk of cancers of the gallbladder.

Clinical Presentation, Diagnosis, and Treatment

Cholangiocarcinomas typically present with jaundice or with a mass evident on CT or ultrasound or are visualized endoscopically. The primary treatment is surgical resection, if possible. The cure rate for patients with early-stage disease ranges from 60 to 70%; however, for patients with more advanced disease, the 5-year survival rate is only 10 to 25%.[162,163] Thus, the role of either preoperative or postoperative radiation and chemotherapy may be important. Although the role of radiation therapy—either alone or in combination with chemotherapy—has been evaluated in several studies, no substantial benefit has been seen.[164,165] Adjuvant therapy is often used for patients with positive margins (chemoradiation) or for patients with positive lymph nodes (chemoradiation and/or chemotherapy). This practice is supported by a meta-analysis, which demonstrated that the greatest benefit for adjuvant therapy was in patients with biliary cancers who had lymph node–positive disease (odds ratio [OR], 0.49; $p = 0.004$) and in those who had a positive microscopic resection margin (OR, 0.36; $p = 0.002$).[166] Based on Surveillance, Epidemiology, and End Results data for patients with resected gallbladder cancer between 1995 and 2005, a web-based nomogram predicting the benefit of adjuvant chemoradiation was developed for this patient group, which can serve as a guideline in the

absence of definitive phase III data in this setting.[167]

The effectiveness of systemic chemotherapy alone in advanced cancers is poor, with response rates ranging from 10 to 40% for both single-agent and combination chemotherapy regimens.[162] Although the surgical approaches for intra- and extrahepatic cholangiocarcinomas and gallbladder cancers differ, systemic chemotherapy does not currently distinguish between these cancers. Most of the regimens used are gemcitabine- or fluoropyrimidine-based and follow treatment strategies established in pancreas cancer. A pooled analysis of clinical trials in biliary cancers documented higher response rates and longer time to tumor progression for gemcitabine-based combination regimens with fluoropyrimidines and with platinum agents than for gemcitabine alone.[162]

The results of this pooled analysis were confirmed by a standard-setting phase III trial that randomly assigned 410 patients with advanced biliary tract cancers to receive gemcitabine 1000 mg/m^2 on days 1, 8, and 15 every 4 weeks for six cycles or gemcitabine 1000 mg/m^2 plus cisplatin 25 mg/m^2 on days 1 and 8 every 3 weeks for eight cycles.[168] The addition of low-dose cisplatin did not result in significant differences in grade 3 or 4 toxicities. The PFS was 8.4 months in the gemcitabine/cisplatin arm and 6.5 months in the gemcitabine-only arm (HR, 0.72; 95% CI; 0.57, 0.90; p = 0.003). This translated into an overall survival benefit of 11.7 months in the gemcitabine/cisplatin arm compared with 8.3 months in the gemcitabine-only arm (HR, 0.70; 95% CI; 0.54, 0.89; p = 0.002). This trial established a new standard of care in the treatment of advanced biliary cancers, gemcitabine/cisplatin, which can now serve as the backbone for the addition of targeted agents in future trials.

The role of photodynamic therapy for superficial, hilar cholangiocarcinomas is not well defined, but sustained palliation of biliary drainage has been reported.[169] Chemoembolization or radioembolization techniques have been used for unresectable cholangiocarcinomas with dominating liver involvement, but they should not yet be considered standard of care because of the paucity of available data.[170]

KEY POINTS

- Hepatocellular carcinoma is an important cancer whose global incidence can be reduced by vaccination against hepatitis B.
- Resection, when feasible, is the mainstay of treatment for this family of tumors.
- Locally ablative procedures and chemoembolization are components of a standard treatment algorithm for hepatocellular carcinomas without distant metastasis.
- Sorafenib has emerged as standard systemic palliative therapy for advanced hepatocellular carcinoma.
- Regorafenib is a standard second-line option in patients whose disease has progressed or who are intolerant of sorafenib.
- The combination of gemcitabine/cisplatin is a standard of care treatment option for patients with advanced biliary tree cancers.

COLORECTAL CANCER

EPIDEMIOLOGY AND ETIOLOGY

Colorectal cancer affects approximately 135,430 patients in the United States every year. Among all cancers, it is the second leading cause of death in the United States, with about 50,260 deaths, affecting both men and women equally (second only to lung cancer, which results in 155,870 deaths annually).[1] Colorectal cancer is both sporadic and familial. The incidence of colorectal cancer is higher in developed countries than in developing countries. In the past decade, there has been a decrease in the incidence and mortality of colorectal cancer in the United States.[1] Findings from epidemiologic studies indicate that during the past 2 decades, the anatomic distribution of colorectal cancer may have shifted from the distal to the proximal colon. These results indicate strong environmental associations for colorectal cancer. The amount of fat intake relative to dietary fiber has long been believed to have an effect on colorectal cancer. Findings from case–control studies demonstrate that intake of fiber-rich foods (at least 13 g per day of dietary fiber) is strongly associated with a low risk of colorectal cancer. Other etiologic factors include the content and quality of bile acids, as well as vitamin and mineral intake, with calcium appearing to play a critical role. Folate has long been thought to work as a chemoprotectant against colorectal cancer, but data from a prospective study failed to demonstrate a protective effect against the development of colorectal adenomas.[171] In general, however, data from prospective, interventional studies indicate that the association among dietary fiber, calcium, fat intake, and colorectal cancer is not clear.[172,173] Additional environmental factors include the intake of alcohol and tobacco, hormone replacement in women (protective), total calorie consumption, and physical activity as it relates to obesity.[174-177] Interestingly, there has been an increased recognition that the regular use of nonsteroidal anti-inflammatory agents, including aspirin and cyclooxygenase-2 inhibitors such as celecoxib, may have a protective effect against colorectal adenomas and colorectal cancer.[44,178-181] Initial studies on the chemoprotective effect of aspirin in the context of nonpolyposis familial predisposition, such as Lynch syndrome, were negative,[182] but a prospective, randomized trial in 861 carriers of Lynch syndrome taking aspirin compared with placebo demonstrated that 600 mg of aspirin per day for a mean of 25 months substantially reduced cancer incidence after 55.7 months (HR, 0.56; 95% CI; 0.32, 0.99; p = 0.05).[183]

FAMILIAL SYNDROMES:

The two most common inherited forms of colorectal cancer are HNPCC and the familial adenomatous polyposis (FAP) syndrome (Table 10-3). These two recognized genetic syndromes are distinct in molecular biology and in clinical characteristics.

The first syndrome to be recognized was FAP, which is caused by an inherited mutation in the adenomatous polyposis coli (*APC*) gene, a key regulator of the Wnt-signaling pathway. Mutations of the *APC* gene lead to the formation of a dysfunctional protein, which prevents it from binding beta-catenin so that beta-catenin can then activate the transcription of various oncogenes. Patients with mutated *APC* have hundreds to thousands of colonic polyps, predisposing them to malignant tumors at a young age. Although FAP represents a small percentage (approximately 0.5 to 1%) of the overall number of cases of colorectal cancer, *APC* (or beta-catenin) mutations activating the Wnt-signaling pathway have been found in the vast majority (80 to 85%) of sporadic colorectal cancers. Further gene expression studies along the adenoma–carcinoma sequence have provided an important genetic model in which specific genetic mutations, leading to invasive colorectal cancers, have been clearly elucidated (Fig. 10-2).[184]

Table 10-3 **Factors That Increase the Risk of Colon Cancer**
Polyposis Syndromes
■ Familial polyposis
■ Peutz–Jeghers syndrome
■ MUTYH-associated polyposis
■ Serrated polyposis syndrome
■ Juvenile polyposis
Nonpolyposis Syndromes
■ Hereditary nonpolyposis colorectal cancer
Other
■ Inflammatory bowel disease
■ Prior colon cancer
■ Prior polyps
■ First-degree relative diagnosed when younger than age 50
■ Western diet
■ Alcohol
■ Sedentary lifestyle
■ Obesity
■ Diabetes

Abbreviation: MUTYH, mutY Homolog (*E. coli*).

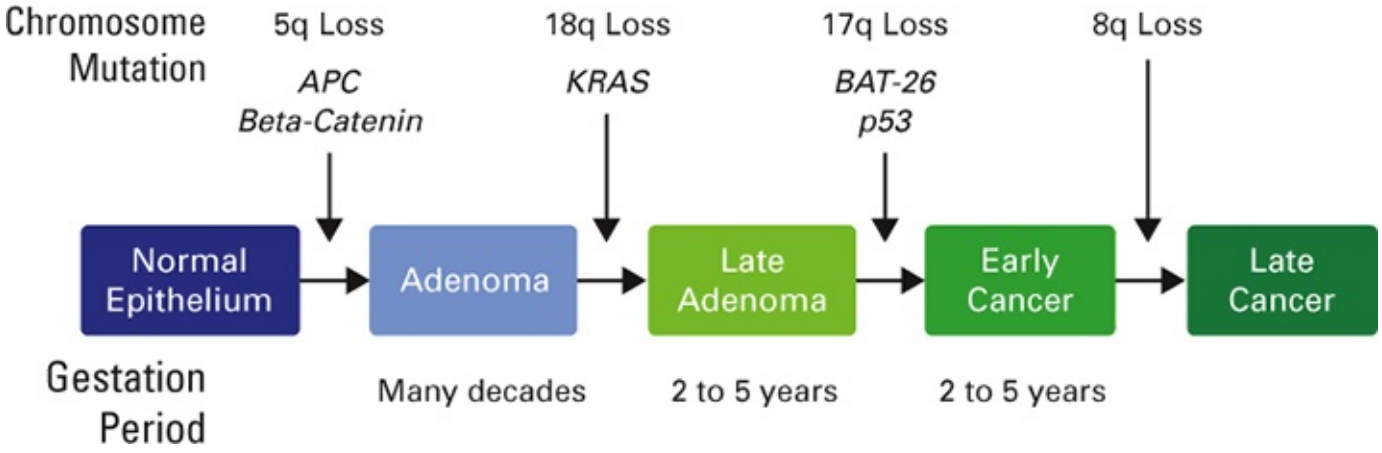

Fig. 10-2 A genetic model showing specific genetic mutations that lead to invasive colorectal cancers.

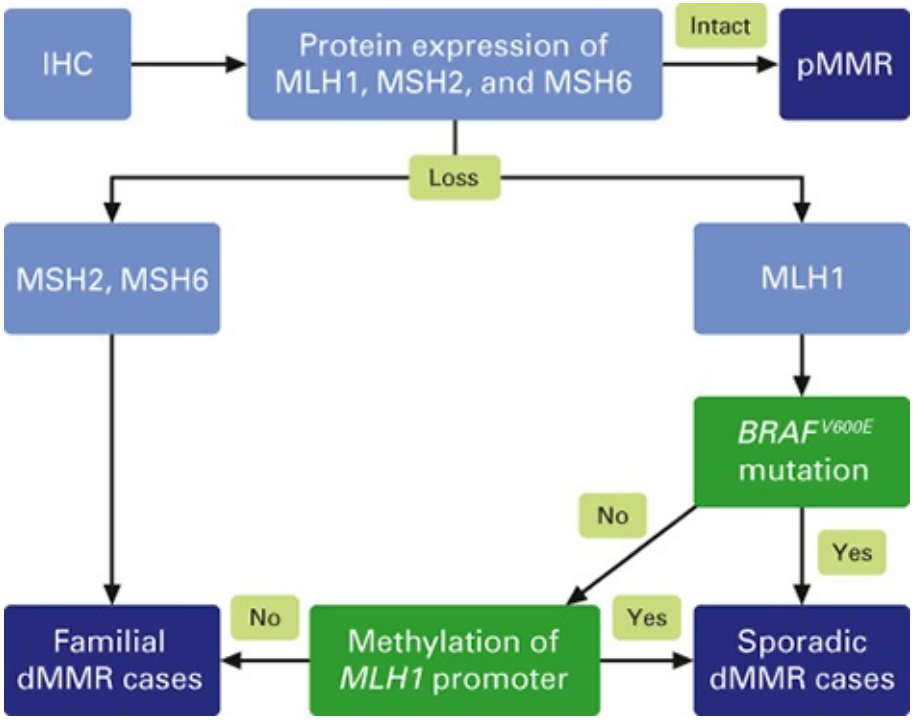

Fig. 10-3 Flow diagram to distinguish between patients with sporadic and familial mismatch repair–deficient (dMMR) colorectal cancers.[189]

Abbreviation: pMMR, proficient mismatch repair.

HNPCC is an inherited autosomal-dominant disease with high penetrance; it is the most common hereditary colorectal syndrome, accounting for approximately 5% of colorectal cancers. Colorectal cancer generally develops at an early age in these patients (median age, 45), commonly located in the proximal colon. Other associated malignancies with the genetic syndrome include ovarian, pancreas, breast, biliary, endometrial, gastric, genitourinary, and small bowel primary cancers. The Amsterdam Criteria and Bethesda Criteria are used to identify patients who should be considered for genetic testing (Table 10-4). The genetic abnormality of microsatellite instability (MSI) is common in HNPCC cancers and is caused by mutations in a group of genes that code for DNA mismatch repair enzymes, including *MSH-2, MLH-1, PMS-2,* and *MSH-6.*[185] The defect in mismatch repair allows spontaneous genetic mutations to accumulate in the colonic mucosa, which predisposes for the development of dysplasia and, eventually, for invasive cancers. MSI denotes that with reduced or absent DNA repair activity, the length of repetitive DNA sequences varies (becomes unstable) upon DNA replication. Approximately 10 to 15% of sporadic colon cancers also have aberrations in the mismatch repair enzymes,[186] generally caused by epigenetic silencing of MLH1,[187] and are thus characterized as having MSI. A panel of microsatellite markers is used to test for microsatellite instability, and tissue is classified as MSI-high (MSI-H) if two or more of five core markers show instability. The prevalence of MSI-H is about 15% in stage II, 8% in stage III, and 4 to 5% in stage IV colorectal cancers. Depending on how much the DNA repair capacity is affected in standardized polymerase chain reaction tests, MSI-high or MSI-low (as well as microsatellite-stable [MSS] tumors) are distinguished. IHC for protein products hMLH1 and hMSH2 provides a rapid, cost-effective, sensitive (92.3%), and specific (100%) method for screening for DNA mismatch repair defects. In a comparative study, the predictive value of normal IHC for an MSS (e.g., MSI-low, MSI-L) phenotype was 96.7%, and the predictive value of abnormal IHC was 100% for an MSI-H phenotype.[188] In terms of nomenclature, MSI-H is synonymous with deficient mismatch repair (dMMR), MSS is synonymous with proficient mismatch repair

(pMMR). Figure 10-3 shows a flow diagram to distinguish between patients with sporadic and familial mismatch repair deficient (dMMR) colorectal cancers.[189] HNPCC is clinically associated with an early age at onset, a proximal tumor location, a mucinous histology, and a higher grade at the time of diagnosis. Interestingly, the prognosis for patients with this type of cancer is better in stage II colon cancer, when compared with that for patients with MSS tumors. The improvement is seen despite an apparent lower responsiveness to fluorouracil-based chemotherapy.[186,190-194] MSI-H tumors are also characterized by strong lymphocytic infiltration and have recently been characterized as “hypermutated” with the potential for the generation of a large number of neoantigens, which could lead to an activation of the immune system.[195] This fact could make these tumors a target for the treatment with immune checkpoint inhibitors.[196] Other polyposis and colorectal cancer syndromes also exist (Table 10-5). The identification of Lynch syndrome in patients with colorectal cancer has significant implications for the choice of therapy and for screening recommendation for family members; therefore, universal testing of all patients with colorectal cancer using MSI analysis of IHC for mismatch repair enzyme expression in tumor tissue has been recommended.[195] Current guidelines published by the National Comprehensive Cancer Network (NCCN; www.nccn.org, Colon 2016.v1) suggest that Lynch syndrome screening should be considered for patients with colorectal cancer at age 70 or younger and also those older than 70 who meet the Bethesda guidelines. The Ohio Collaborative study showed that 16% of patients with newly diagnosed colorectal cancer who were under age 50 had identifiable germline mutations, suggesting that genetic counseling for all patients under age 50 who have colorectal cancers is also reasonable.[197]

Table 10-4 **Clinical Criteria to Determine Likelihood of Hereditary Nonpolyposis Colorectal Cancer (HNPCC)**
Amsterdam II Criteria (All criteria must be met.)
■ At least three relatives with an HNPCC-associated cancer (colorectal, cancer of the endometrium, small bowel, ureter, or renal pelvis).
■ One relative should be a first-degree relative of the other two.
■ Malignancies should include at least two successive generations.
■ At least one family member should be diagnosed before age 50.
■ Familial adenomatous polyposis is excluded.
■ Tumors should be verified by pathologic examination.
Revised Bethesda Criteria to identify colorectal cancer patients who should undergo pathologic examination for HNPCC (Any criterion is sufficient.)
■ Colorectal cancer in a patient under age 50.
■ Synchronous or metachronous colorectal cancer, or associated with another HNPCC-associated tumor (i.e., endometrial, stomach, small intestine, ovarian, pancreatic, biliary tract, ureter or renal pelvis, brain, sebaceous gland adenoma, or keratoacanthoma)
■ Pathologic features of a MSI-high cancer (e.g., tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, medullary growth pattern) in a patient under age 60
■ Development of colorectal cancer in an individual who has a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or colorectal adenoma, with one of the cancers diagnosed before age 50 or an adenoma diagnosed before age 40
■ Colorectal cancer in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

Inflammatory bowel disease, particularly ulcerative colitis, is associated with an increased risk for colon cancer, estimated to be 5 to 10% by 20 years after the time of diagnosis; it also is associated with a high incidence of synchronous cancers, affecting 10 to 20% of cases.[198] Crohn's disease also may have a role in the increasing risk for colorectal cancer, particularly cancer in the ileocolic region. However, in the absence of colonic involvement by Crohn's disease, there is no increased risk of colon cancer. The risk for the development of a subsequent cancer is 3% for patients with a history of adenomatous polyps.

COLORECTAL CANCER GENETIC ABERRATIONS

In 2012, the Cancer Genome Atlas published their analysis of genomic alterations in 224 tumor

and normal pairs, revealing the most prevalent genomic alterations in colorectal cancer. Hypermutated tumors (defined as > 12 mutations/10^6 base-pairs [bp]), representing ~15% of cases were separated from the ~85% nonhypermutated tumors (those with < 8 mutations/10^6 bp). Among the nonhypermutated tumors, there were 17 somatic recurrently mutated genes, the most common being *APC, TP53, KRAS, PIK3CA, FBXW7, SMAD4, TCF7L2,* and *NRAS.*[195] Another prevalent colorectal cancer subtype involves aberrant CpG methylation.[200] Characterized by global hypomethylation with regional hypermethylation commonly at CpG islands, the CpG island methylator phenotype (CIMP) represents ~20% of colorectal cancer. CIMP-positive tumors are associated with right-sided tumors, female sex, and *BRAF* V600E mutations.[200-202] Table 10-6 provides the frequencies of the most prevalent colorectal cancer molecular alterations.

Table 10-5 Polyposis and Colorectal Cancer Syndromes

Syndrome	Characteristic Polyp Features	Inheritance Pattern	Extracolonic Manifestations
Familial adenomatous polyposis	> 100, diffuse polyposis	Autosomal dominant	Small-bowel adenoma and adenocarcinoma, gastric adenoma and cancer, fundic gland polyps, adrenal adenomas and cancers, thyroid cancer, and desmoid tumor
Gardner syndrome	> 100, diffuse polyposis	Autosomal dominant (phenotypic variant of FAP)	Epidermoid cysts, desmoid tumors, osteomas, and fibromas
Turcot syndrome	> 100, diffuse polyposis	Autosomal dominant (phenotypic variant of FAP)	Brain tumors
Flat adenoma syndrome	1 to 100, right-sided polyps		Fundic gland polyps and periampullary cancer
MUTYH-associated polyposis	Includes conventional adenomas, serrated adenomas, and hyperplastic polyps.	Autosomal recessive	? others
Hereditary nonpolyposis colon cancer	1 to 10 polyps	Autosomal recessive	Cancers of the endometrium, stomach, biliary tree, and small bowel; transitional cell cancer of the ureter and renal pelvis
Peutz–Jeghers syndrome	1 to hundreds, diffuse	Autosomal dominant	Ovarian and testicular tumors

Abbreviation: MUTYH, mutY Homolog (*E. coli*).

SCREENING

The screening tests for colorectal cancer include digital rectal examination, fecal occult blood testing (FOBT), fecal immunochemical test (FIT), sigmoidoscopy, colonoscopy, and air-contrast barium enema. The FIT is performed essentially the same way as the traditional guaiac FOBT, but it does not require drug or dietary restrictions. The newest technique, virtual CT colonography, is a tool to reliably visualize polyps and cancer in a nonendoscopic way, which still requires a standard bowel preparation.[204] Each of these tools, with the exceptions of digital rectal examinations and virtual CT colonography (for paucity of prospective data), has been shown to have a positive effect on colorectal cancer–related mortality. However, there is still a poor compliance rate with these tests, with less than 50% of patients ever undergoing any screening procedures. For many years, the guidelines for standard screening options varied according to different medical societies, with a general shift away from emphasizing

sigmoidoscopy in favor of colonoscopy, particularly in light of the observed shift toward more proximal colon cancers. The obvious advantages of colonoscopic screening are that the entire large bowel and distal ileum can be assessed and that immediate intervention, such as biopsy and polypectomy, is possible. The results of studies have demonstrated that although sigmoidoscopy in conjunction with annual FOBT[205] is an effective means of reducing the mortality related to colon cancer, approximately 8% of distal cancers and all proximal cancers (approximately 40 to 50% of all colorectal cancers) will be missed. Therefore, the most common recommendation from various organizations is for colonoscopy to be performed every 5 to 10 years for a patient with average risk, starting at age 50. (See Chapter 1: "Epidemiology and Prevention" for more information.) In March 2008, the American Cancer Society, the American College of Radiology, and the U.S. Multi-Society Task Force on Colorectal Cancer (a group that comprises representatives from the American College of Gastroenterology, American Gastroenterological Association, and American Society for Gastrointestinal Endoscopy) released the first-ever joint consensus guidelines for colorectal cancer screening.[206] The guidelines added two new tests to the list of recommended options—stool DNA and CT colonography and, for the first time, included a preference for screening tests that can not only detect cancer early but also detect precancerous polyps; these tests provide a greater potential for cancer prevention through polyp removal. Two studies confirmed the long-term reduction in colorectal cancer mortality by population screening with either FOBT or endoscopy.[207,208] The first DNA-based stool test received FDA approval in 2014 based on a prospective, randomized study that compared a multitarget DNA stool test including quantitative molecular assays for *KRAS* mutations, aberrant *NDRG4* and *BMP3* methylation, and beta-actin, plus a hemoglobin immunoassay against standard FIT in 9989 participants from a population cohort.[209] The sensitivity for detecting colorectal cancer was 92.3% with DNA testing and 73.8% with FIT ($p = 0.002$). The sensitivity for detecting advanced precancerous lesions was 42.4% with DNA testing and 23.8% with FIT ($p < 0.001$). The Centers for Disease Control and Prevention includes the stool DNA test as part of their screening recommendations (http://www.cdc.gov/cancer/colorectal/basic_info/screening/tests.htm). Table 10-7 lists the recommendations of the joint task forces.

Table 10-6 **Selected Common Genetic Aberrations in Colorectal Cancer**

Gene	Function	Molecular Lesion	Frequency
APC	Regulates WNT signaling pathway	Inactivating mutations	40–70%
TP53	Regulates cell-cycle progression, DNA repair, and apoptosis	Inactivating mutation	~50%
KRAS	Regulates intracellular signaling via MAPK	Activating mutations (codons 12, 13, 61, 117, 146)	40%
NRAS	Regulates intracellular signaling via MAPK	Activating mutations	~10%
BRAF	Regulates MAPK pathway	Activating mutation (V600E)	8–20%
PIK3CA	Regulates PI3–AKT pathway	Mutation (exon 20 and 9)	~20%
SMAD4	Regulates the TGFβ and BMP pathways	Inactivating mutations and deletions	25%
TGFBR2	Regulates the TGFβ pathway	Inactivating mutations	20%
PTEN	Regulates PI3–AKT pathway	Mutation or loss of expression	10% mutation / 30% loss
Other Molecular Alterations			
Chromosome instability		Aneuploidy	70%
CpG island methylator phenotype		Methylation > 40% of loci	20%
Microsatellite instability		Unstable microsatellite repeats	15%

Abbreviations: MAPK, mitogen-activated protein kinase; PI3/AKT, phophatidylinositol-3 kinase/serine-threonine kinase.
Modified from Kuipers et al.[203]

Screening should be more regular for patients at high risk, including those with inherited syndromes, inflammatory bowel disease, and previous adenomatous polyps or colorectal cancer. Individuals with HNPCC should have screening by total colonoscopy every 1 to 3 years beginning between ages 20 and 25 because of the lack of a visible premalignant lesion in this population and the higher risk for right-sided colon cancers.[210] Individuals with FAP should start screening colonoscopies as early as age 10. If a colon cancer or severe dysplasia is found in patients with inflammatory bowel disease, the general recommendation is for a near-total or a subtotal colectomy because of the high incidence of synchronous and metachronous cancers in this population.[211] Surgery can be less extensive for patients with sporadic cancers. For patients with type II HNPCC, a more extensive surgery can be recommended, particularly for women beyond childbearing age, for whom hysterectomy and oophorectomy should be considered.

TREATMENT FOR COLORECTAL CANCER

Early-Stage Colon Cancer (Stages 0, I, II, and III)

Nearly all patients with stage 0 disease (carcinoma in situ or intramucosal cancer) are cured by endoscopic resection alone, recognizing that the lymph nodes are not adequately assessed by this technique. The primary treatment for virtually all invasive nonmetastatic colorectal cancers is surgery. Studies indicate that laparoscopic-assisted surgery for colon cancer provides the same outcomes for overall survival and rate of recurrence as open laparotomy.[212] Studies prospectively evaluating the role of laparoscopic-assisted surgery in rectal cancer are ongoing. Early outcome parameters of a large, 1103-patient European study did not demonstrate a difference between open and laparoscopic surgery for rectal cancer.[213]

Surgery alone is curative for more than 85% of patients who have stage I or early stage II disease. For patients with more advanced stage II disease, the 5-year survival rate is

approximately 80% for T4aN0 cancers but drops to around 60% for T4bN0 tumors.[214] For stage III disease (positive lymph nodes), the 5-year survival rate is 30 to 50% with surgical resection alone.

Prognostic and Predictive Factors. Factors other than stage (Table 10-8) that adversely affect outcome include male sex, extent of local invasion (T4), undifferentiated histology (outside of the context of MSI-H tumors), mucinous features, signet-ring features, lymphovascular and perineural invasion, and elevated levels of carcinoembryonic antigen (preoperatively).[216] Another important prognostic factor is the number of lymph nodes identified in the resected specimen; a minimum of 12 lymph nodes is necessary for adequate staging. The prognosis for colon cancer for patients with HNPCC (and cancers with the defective mismatch repair phenotype in general) in stage II is better than the prognosis for patients with sporadic tumors (or a proficient mismatch repair phenotype), perhaps because the accumulation of genetic mutations in tumor cells do not allow for metastatic spread and potentially because of an activation of the host's immune system. Interestingly, though, the prognosis of patients with MSI-H and MSS cancers in stage III is quite similar. Mutations in *KRAS* and *BRAF* have been shown to have a negative prognostic impact on recurrence-free survival and postrecurrence overall survival in patients with stage III colon cancers, although the prognostic implication of *KRAS* mutations has not been confirmed in all studies.[217,218] Following a genomewide or a candidate-gene screening approach, gene signatures for colorectal cancer are currently being developed that could identify prognostic and predictive markers for the usefulness of adjuvant chemotherapy in patients with borderline indications.[219,220]

Table 10-7 Screening Guidelines for Colon and Rectal Cancer[132]

Beginning at age 50, both men and women at average risk for the development of colorectal cancer should use one of the screening tests below. The tests that are designed to find both early cancer and polyps are preferred if these tests are available and the person is willing to have one of these more invasive tests.
Tests that find polyps and cancer
■ Flexible sigmoidoscopy every 5 years*
■ Colonoscopy every 10 years
■ Double-contrast barium enema every 5 years*
■ CT colonography (virtual colonoscopy) every 5 years*
Tests that mainly find cancer
■ Fecal occult blood test (FOBT) every year*†
■ Fecal immunochemical test (FIT) every year*†
■ Stool DNA test (sDNA), interval uncertain*
People should talk to their doctor about starting colorectal cancer screening earlier and/or being screened more often if they have any of the following colorectal cancer risk factors:
■ A personal history of colorectal cancer or adenomatous polyps
■ A personal history of chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis)
■ A strong family history of colorectal cancer or polyps (cancer or polyps in a first-degree relative [parent, sibling, or child] younger than age 60 or in two or more first-degree relatives of any age)
■ A known family history of hereditary colorectal cancer syndromes such as familial adenomatous polyposis (FAP) or hereditary nonpolyposis colon cancer (HNPCC)

*Colonoscopy should be done if test results are positive.
†For FOBT or FIT used as a screening test, the take-home multiple sample method should be used. A FOBT or FIT done during a digital rectal exam in the doctor's office is not adequate for screening.

Adjuvant Chemotherapy. The initial trial presented in the early 1990s that established adjuvant chemotherapy as standard of care in stage III colon cancer used a combination of fluorouracil and levamisole administered for 12 months.[221] A 10 to 20% absolute improvement in 5-year survival was documented for patients receiving postoperative adjuvant fluorouracil-based chemotherapy. Evidence from subsequent trials demonstrated that fluorouracil combined with LV provides a superior outcome, with 6 months of therapy being adequate to achieve this survival benefit.[222] For more than a decade, the standard in adjuvant therapy remained unchanged because of the lack of novel agents with relevant activity in colorectal cancer. This changed when oxaliplatin, irinotecan, and the oral fluorouracil prodrug capecitabine were utilized for the treatment of advanced colorectal cancer, with combination regimens of infusional fluorouracil plus either irinotecan or oxaliplatin demonstrating high antitumor efficacy.

Worldwide, six phase III trials were conducted to evaluate the value of these three novel chemotherapeutic agents in the adjuvant setting. To set the stage for the conduct and interpretation of these trials and their results, a large retrospective meta-analysis confirmed that, for adjuvant colon cancer, 3-year DFS can serve as an definitive surrogate marker for 5-year overall survival.[223] This finding had a major effect on clinical trial design and endpoint definition in subsequent studies of adjuvant colon cancer. Based on these findings, the FDA recognized 3-year DFS as an appropriate endpoint for full approval of a regimen for adjuvant colon cancer. Oxaliplatin was approved as part of adjuvant treatment for stage III colon cancer in 2004 on the basis of this endpoint. One trial established 6 months of oral capecitabine as a safe and at least equally effective alternative to conventional intravenous bolus fluorouracil with LV (Mayo Clinic regimen) for stage III colon cancer.[224] Two other trials confirmed the value of oxaliplatin as a component of adjuvant chemotherapy for stages II and III colon cancer.[225,226] The results of the pivotal Multicenter International Study of Oxaliplatin/5-FU/Leucovorin in the Adjuvant Treatment of Colon Cancer trial clearly demonstrated that oxaliplatin plus infusional fluorouracil and LV (FOLFOX) is superior to fluorouracil with LV in terms of 3-year DFS.[225] In a subgroup analysis, only the increase in DFS for patients with stage III disease was statistically significant, providing an absolute benefit of approximately 8 to 10% (HR, 0.76; 95% CI; 0.62, 0.92). In unselected patients with stage II disease, the DFS benefit for FOLFOX compared with fluorouracil and LV alone was approximately 3.5%, but it exceeded 5% for patients with stage II tumors with clinical high-risk features (undifferentiated tumors, T4, perforation, obstruction, fewer than 10 lymph nodes identified, and angiolymphatic invasion). An update demonstrated a significant improvement in 6-year (not 5-year) overall survival for patients with stage III, but not for patients with stage II, colon cancer when an oxaliplatin-based regimen was used as adjuvant therapy.[227] Results of the National Surgical Adjuvant Breast and Bowel Project C-07 trial further strengthened the role of oxaliplatin plus fluorouracil-based regimens in the adjuvant therapy of colon cancer.[226,228]

The third phase III trial in the sequence of studies comparing 5-FU/LV to a fluoropyrimidine/oxaliplatin combination as adjuvant therapy, the XELOXA trial (oxaliplatin/capecitabine [XELOX] vs. bolus 5-FU/LV), confirmed the role of oxaliplatin as a component of adjuvant therapy in stage III colon cancer with significant improvements in DFS (HR, 0.80; 95% CI; 0.69; 0.93; p = 0.0045) and a trend toward improved overall survival at 5 years.[229] As in the MOSAIC trial, longer follow-up is likely needed to demonstrate improved overall survival because of the available active treatment options upon tumor recurrence, which shift overall survival differences to a later time point.

Although irinotecan- and oxaliplatin-based regimens are thought to be equally effective as palliative therapy for advanced colorectal cancer, for unknown reasons, none of the three phase III trials using combination regimens of irinotecan/fluorouracil/LV demonstrated significantly superior efficacy regarding 3-year DFS when compared with fluorouracil and LV alone.[230-232]

Table 10-8 **Staging, Incidence per Stage, and Treatment Recommendations for Invasive Colon Cancer**

	Stage I	Stage II	Stage III	Stage IV
Staging	T1, N0, M0	A: T3, N0, M0	A: T1-2, N1/N1c, M0; T1, N2a, M0	A: Any T, Any N, M1a
	T2, N0, M0	B: T4a, N0, M0	B: T3-4a, N1/N1c, M0; T2/3, N2a, M0; T1-2, N2b, M0	B: Any T, Any N, M1b
		C: T4b, N0, M0	C: T4a, N2a, M0; T3-4a, N2b, M0; T4b, N1-2, M0	
Definition	Invades submucosa (T1) or muscular propria (T2)	Invades subserosa, nonperitonealized pericolic/perirectal tissues (T3) or penetrates to the surface of the visceral peritoneum (T4a) or directly invades into or is adherent to other organs or structures (T4b)	Involves 1-3 (N1-N1a: 1, N1b: 2 to 3) or more (N2-N2a: 4-6, N2b: > 6) lymph nodes; N1c for tumor deposits in subserosa, mesentery, or pericolic/perirectal tissue without lymph node metastasis	M1a: distant metastasis confined to one organ or site M1b: distant metastasis in more than one organ or site
Incidence	15%	25%	35%	25%
Usual treatment	Surgery	Surgery with or without chemotherapy	Surgery with chemotherapy	Chemotherapy with or without surgery

Used with the permission of the American Joint Committee on Cancer (AJCC). Chicago, Illinois. *AJCC Cancer Staging Manual, 7th Edition.* New York, NY: Springer.[215]

Based on these results, the standard adjuvant chemotherapy for stage III colon cancer is an oxaliplatin-containing regimen (FOLFOX, XELOX, or bolus fluorouracil/folinic acid/oxaliplatin [FLOX]) administered for 6 months. Capecitabine or fluorouracil and LV should be reserved for patients who are not considered optimal candidates for oxaliplatin.

To mitigate the long-term neurotoxic side effects of oxaliplatin-based adjuvant therapy, the International Duration Evaluation of Adjuvant chemotherapy (IDEA) collaboration was established to prospectively combine and analyze data from six randomized trials conducted around the world to answer the question of whether a 3-month course of oxaliplatin-based adjuvant therapy is noninferior to the current standard 6-month treatment for patients with stage III colon cancer. The final analysis, reported at the ASCO meeting in 2017, included 12,834 patients from 12 countries. There was significant heterogeneity, including varying treatments (FOLFOX and XELOX), tumor heterogeneity (pT4 varied from 12 to 29% across studies), and varying follow-up (35–62 months).[233] The primary analysis suggests that 3 months of oxaliplatin-based chemotherapy is not noninferior to 6 months with disease-free survival (HR, 1.07; 95% CI; 1.0, 1.15) because the upper bound of the 95% CI crossed the prespecified threshold of 1.12. Subgroup analyses suggest that 3 months may be noninferior for lower-risk patients (e.g., pT1–3N1), where the DFS HR was 1.01 (95% CI; 0.9, 1.12). However, for higher risk patients (T4 or N2+), the DFS HR was 1.12 (95% CI; 1.03, 1.24). Thus, for high-risk stage III colorectal cancer, the standard of care remains 6 months of adjuvant oxaliplatin-based therapy. However, for low-risk stage III patients, there is a suggestion that 3 months of oxaliplatin-based adjuvant therapy may be acceptable because of the complexity of the study and the heterogeneity of the study population; this recommendation remains controversial.

For patients with stage II disease, the role of adjuvant chemotherapy remains controversial; the results from a series of clinical trials demonstrated a trend toward improved recurrence-free survival and overall survival (HR, 0.80; 95% CI; 0.56, 1.15). Findings from two pooled retrospective analyses showed conflicting results.[234,235] One analysis suggested a 30% risk reduction, translating into an approximate 8% absolute reduction in mortality, whereas a similar

pooled data set showed no benefit from adjuvant chemotherapy. An analysis of Medicare data revealed that more than 50% of patients in the United States with stage II colon cancer receive postoperative adjuvant chemotherapy.[236] In view of these data, and the UK QUick And Simple And Reliable (QUASAR) trial, it appears that unselected patients with stage II colon cancer (i.e., not distinguished between high-risk and low-risk stage II) will have a 3% benefit in 3-year DFS and overall survival with fluorouracil and LV as adjuvant chemotherapy.[237] It has to be kept in mind, though, that the quality of lymph node assessment in the QUASAR trial did not meet our current standards, with more than 60% of patients having less than 12 lymph nodes identified in resected specimens; so the inclusion of a certain percentage of stage III cancers in this analysis seems likely.[238] Current ASCO recommendations dating back to 2004 suggest that not all patients with stage II tumors should receive adjuvant chemotherapy, but that a discussion should be led with patients about their individual benefit/risk ratio when utilizing adjuvant chemotherapy in stage II colon cancer.[239] Efforts have been made to individualize the baseline prognosis and to predict the benefits of chemotherapy for patients with resected colon cancer.[240] As a result, two web-based tools are now available to provide data of this type (an adjuvant therapy calculator developed by the Mayo Clinic[241] and Adjuvant! Online[242]). These tools can provide helpful information for clinical decision-making.[243,244]

The identification of prognostic factors might help distinguish patients at high risk for relapse and identify high-risk stage II patients who may more likely benefit from adjuvant treatment. Apart from the clinical risk factors listed previously, molecular determinants of poor prognosis, such as microsatellite stability and *LOH18q,* are being evaluated in prospective clinical trials. Remarkably consistent results from retrospective analyses of large adjuvant trials and pooled data sets have confirmed that patients with stage II colon cancer and MSI-high tumors, which represent tumors of the deficient mismatch repair phenotype (MMR-D), have excellent prognosis and do not need to be treated with adjuvant chemotherapy.[223,238,245,246] Efforts are underway to develop a molecular profile of prognostic variables that could potentially guide adjuvant treatment decisions in stage II colon cancer.[238,247,248] These tests include gene expression signatures such as the Oncotype DX Colon[238] and ColoPrint,[248] as well as molecular detection assays of micrometastasis in morphologically unaffected lymph nodes.[247] At this time, none of these assays is routinely recommended for use in clinical practice as a decision tool for adjuvant therapy in stage II colon cancer.

The role of novel targeted agents with clear efficacy in advanced colorectal cancer, such as bevacizumab (an antibody against VEGF) and cetuximab (an antibody against EGFR) have been investigated in the adjuvant setting in ongoing large phase II trials. The first trial in a human malignancy to test bevacizumab in the adjuvant setting, NSABP C-08 randomly assigned 2710 patients with stage II (25%) and stage III (75%) colon cancer to receive modified FOLFOX6 every 2 weeks for 12 cycles, or mFOLFOX6 using the same schedule plus bevacizumab given every 2 weeks on day 1 for a total of 1 year, meaning bevacizumab was continued for 6 months beyond the planned completion of chemotherapy.[249] After a median follow-up of 35.6 months, 3-year DFS, the primary endpoint, was 77.4% for mFOLFOX6 alone and 75.5% in the bevacizumab arm. These results were not statistically significant (HR, 0.89; $p = 0.15$). A transient reduction in the rate of tumor recurrences was observed at 1 year, coinciding with the extended duration of bevacizumab in the experimental arm, but this effect was lost after discontinuation of the VEGF inhibitor. Almost identical observations were made in the international three-arm phase III AVANT trial, which included a capecitabine/oxaliplatin plus bevacizumab experimental arm.[250] At this time, bevacizumab plays no role in the adjuvant therapy of colon cancer outside of clinical trials.

The EGFR antibody cetuximab has also been tested as a component of adjuvant therapy in stage III colon cancer added to a modified FOLFOX 6 backbone.[251] Initially conceived as a phase III trial of FOLFOX with or without cetuximab in all patients with resected stage III colon cancer, the trial was eventually amended to enroll only patients with *KRAS* wild-type cancers.[252] Unfortunately, even in this preselected patient group, which has shown to benefit from EGFR antibodies in the palliative setting, cetuximab failed to improve outcome measures. Indeed, it even showed a trend toward a detrimental effect, particularly in patients with *KRAS*-mutated cancers.[249] A similar European adjuvant study with cetuximab (PETACC-8) confirmed the lack of efficacy of cetuximab in the adjuvant setting when added to FOLFOX in *KRAS* wild-type colon cancers, although this trial did not suggest a detrimental effect.[253] The body of evidence confirms that EGFR antibodies do not enhance the efficacy of FOLFOX in the adjuvant setting.

After completion of adjuvant therapy, lifestyle changes should be discussed with the patient, as there is growing evidence that certain interventions can improve outcomes in patients with resected early-stage colorectal cancer.[254] Increased exercise after diagnosis and avoidance of a Western pattern diet are associated with a reduced risk of cancer recurrence and improved overall survival. Patients with classes II and III obesity (BMI > 35) have a modestly increased risk of recurrence. Regular use of aspirin or cyclooxygenase-2 inhibitors decreases recurrence rates. Lower serum vitamin D levels have been associated with an increased risk of recurrence, but prospective studies are lacking to show that increasing vitamin D to normal levels can improve outcomes. In contrast, change of weight after diagnosis or smoking status (never, past, or current) are not associated with outcomes after diagnosis. The role of aspirin in this setting deserves particular attention. Data from a large population cohort study[255] and an analysis of a prospective trial[256] demonstrated a profound effect of aspirin as secondary prophylaxis in patients with resected colorectal cancer harboring *PIK3CA* mutations (exons 9 and 20). *PIK3CA* mutations are found in about 12% of colorectal cancers, and aspirin could emerge as a key component of postresection therapy in these patients. Randomized trials are underway to evaluate aspirin (in Asia and the United Kingdom) and celecoxib (in the United States and Canada) as adjunctive therapy with standard surgery and adjuvant therapy for early-stage colon cancer.

Advanced Colorectal Cancer (Stage IV)

The prognosis for patients with stage IV disease without specific therapy is poor, with a median survival of 5 to 6 months. However, a subset of patients with isolated sites of metastases is potentially curable with surgery (see “Limited Hepatic or Pulmonary Metastasis” section). Nevertheless, for the majority of patients with metastatic disease, the goal of therapy is palliation using systemic medical therapy. For decades, standard first-line therapy consisted of fluorouracil/LV, with response rates of approximately 20% and a median survival of approximately 1 year. In the late 1990s and early 2000s, the addition of oxaliplatin/irinotecan to the backbone of fluorouracil/LV resulted in an improvement in median survival to nearly 24 months when patients received active first-line and second-line therapy. The introduction of biologic agents, such as bevacizumab, cetuximab, and panitumumab, have further enhanced the efficacy of systemic medical therapy.[257] The emphasis of current advances in medical therapy is on the development of predictive biomarker signatures, which can help guide treatment decisions for specific patient subpopulations.

The availability of various active agents for the treatment of metastatic colorectal cancer has resulted in an abundance of therapeutic options that now demand a goal-oriented, strategic

approach to therapy in order to maximize patient benefit. When treating a patient with metastatic colon cancer, the first determination is whether stage IV disease is potentially curable by a surgical resection of metastases either at the time of diagnosis or after downsizing initially unresectable metastases by neoadjuvant chemotherapy.[257] This will guide the choice and timing of chemotherapy because, in this scenario, the most appropriate treatment is conceivably the one that generates the highest response rates and carries the greatest potential to downsize metastases. If the patient's disease does not appear curable, the main goals of systemic chemotherapy are to extend the duration of a patient's life and to maintain quality of life for as long as possible. In this scenario, treatment regimens that offer the longest PFS and overall survival, as well as a favorable toxicity profile, are preferred.

Fluorouracil. Until 2000, standard first-line therapy for metastatic colon cancer was the fluoropyrimidine analog fluorouracil plus LV as biomodulator and activator. LV forms a complex with fluorouracil that permits prolonged inhibition of the enzyme thymidylate synthase, a key factor in DNA synthesis. Response rates of fluorouracil/LV are in the range of 15 to 25%. Over time, fluorouracil has been given with LV in varying schedules and doses. The most commonly used regimens in the United States included the Mayo Clinic regimen (425 mg/m^2 of fluorouracil and 20 mg/m^2 for LV on days 1 to 5 every 4 to 5 weeks)[258] and the Roswell Park regimen (500 mg/m^2 of fluorouracil and 500 mg/m^2 of LV administered weekly for 6 out of 8 weeks).[259] Although these regimens used fluorouracil exclusively as bolus administration, European protocols preferred to use fluorouracil in the form of protracted infusions (e.g., for 2 days in the French biweekly LV5FU2 regimen or for 24 hours in the German weekly Arbeitsgemeinschaft Internistische Onkologie regimen).[260,261] The incorporation of the novel cytotoxic agents irinotecan and oxaliplatin into fluorouracil-based regimens has resulted in significantly improved efficacy. This has shifted the paradigm for front-line treatment from fluorouracil and LV alone to combination regimens incorporating these newer cytotoxic agents.

Capecitabine. Capecitabine is an oral fluoropyrimidine, a prodrug of fluorouracil, which is metabolized to its active form in three enzymatic steps. Its efficacy is similar to that of bolus fluorouracil and LV, with slightly higher response rates.[262] Common side effects of this drug include diarrhea and hand–foot syndrome. Capecitabine has been used as a backbone of combination regimens with both oxaliplatin and irinotecan, but overlapping toxicities (diarrhea) make a combination with irinotecan more difficult to tolerate than oxaliplatin. Other oral fluoropyrimidines, which have not been approved in the United States, include tegafur/uracil, S-1 (a prodrug of 5-FU), gimeracil (5-chloro-2,4-dihydropyridine), which inhibits dihydropyrimidine dehydrogenase enzyme activity, and oteracil (potassium oxonate). Although capecitabine has never been directly compared with infusional 5-FU/LV, oxaliplatin-based combination regimens with either capecitabine (CAPOX or XELOX) versus infusional 5-FU/LV (FOLFOX) have been shown to have similar efficacy in the treatment of advanced colorectal cancer.[263-265] It is notable, though, that patients in the United States do not tolerate the capecitabine doses used in European or Asian trials, presumably because of the higher nutritional folate intake in the United States.[266,267] Reducing the dose of capecitabine by about 20% in combination regimens with oxaliplatin, however, does not appear to decrease the treatment efficacy, but it greatly improves the side-effect profile of the treatment.[268]

Irinotecan. The first chemotherapy agent other than fluorouracil that improved survival for metastatic colon cancer—initially in second-line and later in first-line therapy—was irinotecan.[269-272] This compound has single-agent activity, which yields approximately a 15% response rate for patients with metastatic colon cancer refractory to fluorouracil.[269,271,272] In a

landmark clinical trial, patients with fluorouracil-refractory metastatic colon cancer were randomly selected to receive either best supportive care or single-agent irinotecan. The results of the trial demonstrated that irinotecan offers an approximate 3-month survival advantage as well as an improvement in quality of life.[269] A second trial in the same second-line patient population found irinotecan superior to infusional 5-FU.[271] Following this, three key trials were conducted to test the role of irinotecan in first-line treatment. In the United States, a three-arm trial was conducted to compare three treatment regimens: weekly bolus 5-FU/LV (Roswell Park regimen); weekly bolus 5-FU/LV plus irinotecan (IFL); and irinotecan alone.[272] The results of the trial revealed a survival advantage of longer than 2 months (14.8 months vs. 12.6 months, $p = 0.04$) and an almost doubling of the response rate (39% vs. 21%, $p < 0.001$) for patients receiving the three-drug regimen compared with those receiving the bolus 5-FU/LV regimen. This study established the three-drug regimen as the standard of care in the United States at that time.

In Europe, two phase III trials were conducted, in which fluorouracil was given as an infusion in combination with irinotecan, to form the FOLFIRI regimen. The results demonstrated a similar significant increase in response rate and time to disease progression for the three-drug regimen.[270-274] However, only the trial reported by Douillard et al.[270] demonstrated significant prolongation of overall survival (17.4 months vs. 14.1 months, $p = 0.031$), likely because of the limited availability of active second-line and third-line treatment options compared with the second European trial conducted later.[274] The main side effects of irinotecan are diarrhea, myelosuppression, and alopecia.

Oxaliplatin. Although oxaliplatin has very limited activity in colorectal cancer as a single agent (single-agent response rate, 24.1%[275]), it shows enhanced clinical efficacy in combination with fluoropyrimidines, in particular with infusional fluorouracil and LV. In three European phase III trials, combination protocols of infusional fluorouracil/LV/oxaliplatin (biweekly FOLFOX or weekly FUFOX) were compared with 5-FU/LV as first-line therapy for patients with advanced colorectal cancer.[276-278] In all three studies, a higher antitumor activity was noted for the combination regimens, with response rates of approximately 50% and PFS in the range of 8 to 9 months. However, this higher efficacy did not translate into a significantly improved overall survival, most likely because of the availability of active salvage therapies for both treatment arms, which blurred the effects of the first-line chemotherapy on overall survival in the trials. Of note, the median overall survival achieved with fluorouracil/LV/oxaliplatin was in the range of 17.5 to 20 months—the longest overall survival reported in phase III trials for advanced colorectal cancer at that time. Because no overall survival benefit was achieved in these first-line trials, in 2000 the FDA did not approve oxaliplatin for colorectal cancer. The FDA approval of oxaliplatin in combination with fluorouracil/LV in 2002 was based on the results of a second-line study that showed prolonged PFS and increased response rates compared with infusional fluorouracil/LV for patients who experienced disease progression while receiving IFL as first-line therapy.[279] It is notable that, in this trial, the arm with oxaliplatin as single agent, without 5-FU, did not show any relevant tumor activity, which highlights that oxaliplatin needs to be combined with another agent, preferably a fluoropyrimidine. The key side effect and dose-limiting toxicity of oxaliplatin is neurotoxicity, which comes in two distinct forms: an acute, cold-triggered sensory neuropathy, which is temporary, rapidly reversible, and does not appear to cause structural nerve damage; and a chronic cumulative sensory neurotoxicity, which is related to the cumulative dose of oxaliplatin administered over time and constitutes the dose-limiting side effect of oxaliplatin.[280] Preliminary data initially suggested that the infusion of calcium/magnesium salts before and after oxaliplatin can potentially reduce the incidence and

severity of chronic neurotoxicity,[281] but a larger, definitive trial unfortunately showed no neuroprotective effect of intravenous calcium/magnesium.[282]

Comparing Irinotecan- and Oxaliplatin-Based Regimens. With its FDA approval in 2000, the combination regimen IFL had emerged as standard first-line therapy for patients with advanced colorectal cancer in the United States. The encouraging results of trials conducted in Europe using oxaliplatin formed the rationale for the North Central Cancer Treatment Group (NCCTG)/Intergroup trial N9741.[283] This pivotal and practice-changing trial compared FOLFOX with the non–fluorouracil-containing combination of irinotecan/oxaliplatin (IROX), as well as with standard combination IFL. The results of N9741 clearly demonstrated the superiority of FOLFOX compared with IFL as first-line therapy for colorectal cancer with regard to response rate (45% vs. 31%, p = 0.002), PFS (8.7 months vs. 6.9 months, p = 0.0014), and overall survival (19.5 months vs. 15.0 months, p = 0.0001). The toxicity profile likewise favored FOLFOX compared with IFL, with only neurotoxicity being more prevalent for patients receiving the oxaliplatin-based combination. Results for IROX were in between the two other arms (response rate, 35%; PFS, 6.5 months; overall survival, 17.4 months), and, as such, FOLFOX emerged as new standard first-line therapy, with rapid and widespread adaptation in the United States. It should be emphasized that N9741 did not directly compare oxaliplatin and irinotecan; rather, it compared two different combination regimens with different fluorouracil and LV backbones. The higher efficacy and better tolerability observed with infusional fluorouracil and LV may have contributed to the differences in efficacy between IFL and FOLFOX. Two smaller trials comparing FOLFOX and FOLFIRI with the same fluorouracil and LV backbone failed to show significant differences in activity.[284,285] Although the small sample size of these trials might preclude wide-reaching conclusions, the choice between FOLFOX and FOLFIRI in the clinic should be based mainly on the expected side-effect pattern. Because the benefit of second-line therapy in colorectal cancer has been well established, patients should receive all active cytotoxic drugs in the course of their therapy in order to optimize outcome.[286] Combinations of 5-FU/LV/irinotecan/oxaliplatin (FOLFOXIRI) show high activity but also increased toxicity.[287] The use of this triplet combination should be reserved for specific situations, for instance, when substantial tumor shrinkage, as a prerequisite for a surgical approach toward borderline resectable liver metastases, is required.

Bevacizumab. Bevacizumab, a recombinant humanized monoclonal antibody to VEGF-A, has demonstrated clinical efficacy for the treatment of metastatic colorectal cancer. In a large phase III, placebo-controlled trial with 813 patients, irinotecan/bolus fluorouracil/LV (IFL protocol) was compared with IFL plus bevacizumab (5 mg/kg every 2 weeks) as first-line therapy for advanced colorectal cancer.[288] The addition of the anti-VEGF antibody led to a significantly increased response rate (45% vs. 35%, p = 0.0036), PFS (10.6 months vs. 6.2 months; HR, 0.54; p < 0.00001), and median overall survival (20.3 months vs. 15.6 months; HR, 0.66; p = 0.00004). This trial was the first phase III validation of an antiangiogenic agent as an effective treatment option in a human malignancy. Subsequently, bevacizumab also has been shown to enhance the efficacy of oxaliplatin-based regimens in first- and second-line treatments, as well as in combination with fluorouracil and LV alone or with irinotecan.[289-292] It is important to note that bevacizumab does not appear to have significant single-agent activity in metastatic colorectal cancer.[289] The main side effects observed with bevacizumab consist of hypertension (a class-effect of all agents targeting VEGF signaling), bleeding, gastrointestinal perforations (in 1.5 to 2% of patients), as well as arterial thrombotic events in approximately 4 to 5% of patients.[293] In addition to arterial thrombotic events, a meta-analysis identified a 33% higher incidence of venous thrombotic events in patients receiving bevacizumab compared with

the non-bevacizumab control arm in randomized trials,[294] although another, more recent analysis refuted this claim.[295] Based on its well-documented efficacy and relative moderate toxicity, bevacizumab has emerged as a standard component of first-line chemotherapy for advanced colorectal cancer.

Although most patients with metastatic colorectal cancer will tolerate and receive bevacizumab in the context of an irinotecan- or oxaliplatin-based combination regimen, it is unclear whether specific subgroups, in particular elderly patients, could benefit from a bevacizumab/fluoropyrimidine combination alone. This question was addressed in the pivotal and practice-informing AVEX phase III trial.[296] In this study, 280 patients age 70 or older (median age, 76), who were not deemed to be candidates for oxaliplatin- or irinotecan-based chemotherapy first-line regimens, were randomly selected to receive capecitabine (1000 mg/m^2 orally twice a day on days 1 to 14) alone or with bevacizumab (7.5 mg/kg intravenously on day 1), given every 3 weeks. PFS, the primary endpoint, was significantly longer with bevacizumab/capecitabine than with capecitabine alone (median, 9.1 months vs. 5.1 months; HR, 0.53; 95% CI; 0.41, 0.69; $p < 0.0001$). Although the study was underpowered to demonstrate a statistically significant improvement in overall survival, the median survival in the bevacizumab arm of 20.7 months (compared with 16.8 months for capecitabine alone) is remarkable given the age of the patient population and the limited postprogression therapies patients received. The combination of a fluoropyrimidine/bevacizumab can be considered as an acceptable standard of care for elderly patients who are not eligible for irinotecan or oxaliplatin but have no contraindication to receiving bevacizumab.

Initial reports suggested an over-additive activity when bevacizumab was combined with cetuximab in salvage therapy.[297] Subsequent larger, randomized first-line trials, however, suggested an antagonistic effect of the combination of EGFR antibodies with bevacizumab in the context of concurrent chemotherapy.[298,299] Thus, combinations of bevacizumab and EGFR antibodies should not be used in clinical practice outside of a clinical trial at this time.

It has been suggested that prolonged inhibition of the VEGF-mediated proangiogenic system is required to maximize treatment benefit for patients who are receiving anti-VEGF therapy, particularly since the mechanism and onset of secondary resistance could differ between chemotherapy and bevacizumab.[300] The efficacy of prolonged VEGF inhibition with bevacizumab added to chemotherapy was highlighted by several randomized trials. A prespecified analysis of a large phase III trial (NO16966) adding bevacizumab to an oxaliplatin-based first-line regimen demonstrated that improvements in PFS were much more profound in patients who received treatment until progression than in those who stopped therapy for other reasons.[297] Since the treatment-limiting toxicity of oxaliplatin-based first-line therapy is cumulative neurotoxicity, proactive strategies have to be employed to maximize treatment duration for patients who start palliative therapy with FOLFOX plus bevacizumab, the most commonly used first-line regimen in the United States. Therefore, induction-maintenance approaches with a limited number of oxaliplatin-containing treatment cycles up front and maintenance therapy with a fluoropyrimidine/bevacizumab combination can be considered a standard of care. This concept is supported by several prospective trials, most prominently by the recently presented Dutch CAIRO3 study.[301] In this trial, 558 patients who had achieved at least stable disease after an 18-week (six cycles) induction therapy of XELOX plus bevacizumab were randomly assigned to a complete chemotherapy-free interval or maintenance therapy with low-dose continuous capecitabine (625 mg/m^2 twice daily) plus bevacizumab (7.5 mg/kg every 3 weeks). All prospectively defined outcome parameters in this strategy trial were in favor of the maintenance therapy arm, even with a strong trend toward

improvement in overall survival. Toxicity associated with maintenance was mild and manageable. Thus, an induction-maintenance approach with a limited duration of oxaliplatin-based therapy and prolonged fluoropyrimidine/bevacizumab therapy may be considered an option to minimize toxicity in patients with advanced colorectal cancer.

Further evidence supporting the concept of prolonged VEGF inhibition as an optimized treatment approach in colorectal cancer comes from the so-called ML18147 (TML) phase III trial, which tested the efficacy of bevacizumab beyond progression (BBP) added to chemotherapy in metastatic colorectal cancer.[298] A total of 820 patients who had received first-line palliative therapy with a bevacizumab-based combination were randomly assigned at progression to either continue bevacizumab with another standard chemotherapy backbone or stop bevacizumab. The primary endpoint of the study, improvement in overall survival, was reached with an HR of 0.81 (95% CI; 0.69, 0.94) and a median improvement of 1.4 months (11.2 vs. 9.8 months, $p = 0.0062$). This effect was confirmed in all evaluated subgroups and supported by the results of PFS, which demonstrated superiority for the BBP arm (HR, 0.68; median 5.7 vs. 4.1 months, $p < 0.0001$). No increase in response rate was seen in the BBP group, and the response rates seen in both arms in second-line therapy were low, around 4 to 5%. No new or unexpected safety issues emerged for bevacizumab.

Ziv-aflibercept (VEGF-Trap) is a VEGF receptor decoy fusion protein that consists of extracellular-domain components of VEGFR1 and VEGFR2 fused with the Fc region of IgG1. VEGF-Trap binds to the VEGF-A, VEGF-B, and PGF (placental growth factor) ligands and prevents their interaction with VEGF receptors.[303] Aflibercept was tested in a second-line treatment trial among patients who had all failed oxaliplatin-based first-line chemotherapy.[304] About 1200 patients were randomly selected to receive FOLFIRI with aflibercept or placebo. The primary endpoint of improvement in overall survival was reached (13.5 vs. 12.1 months; HR, 0.82; $p = 0.0032$) and was mirrored by improvements in PFS (6.9 vs. 4.7 months; HR, 0.758; $p = 0.00007$) and response rate (19.8% vs. 11.1%, $p = 0.0001$). It is of note, though, that only 30% of patients in this trial had access to front-line bevacizumab, so the data are largely based on a VEGF inhibitor–naive population. The toxicity analysis demonstrated a surprisingly high rate of adverse events in the aflibercept arm, including side effects such as infections, asthenia, mucositis, and diarrhea not thought to be associated with a pure VEGF-inhibition mechanism. The FDA approved aflibercept in 2012 as a component of second-line therapy in combination with FOLFIRI.

Ramucirumab is a human monoclonal antibody directed against the VEGFR-2, the main mediator of VEGF-A signaling, located on the surface of endothelial cells. In a phase III, placebo-controlled trial of 1072 patients, the addition of ramucirumab to FOLFIRI as second-line therapy for patients pretreated with a fluoropyrimidine plus oxaliplatin and bevacizumab improved overall survival (median overall survival, 13.3 months vs. 11.7 months; HR, 0.8; 95% CI; 0.73, 0.98; $p = 0.022$) and PFS.[305] Observed adverse events fell within the range of expectations for a VEGF inhibitor, as discussed for bevacizumab. Ramucirumab, already approved for gastric cancer and non-small cell lung cancer, received FDA approval as a component of second-line therapy for advanced colorectal cancer in 2015. It is of note for clinical practice that single-agent use of the large-molecule VEGF inhibitors (bevacizumab, ziv-aflibercept, and ramucirumab) are not recommended in clinical practice.

Anti-EGFR Antibodies: Cetuximab and Panitumumab. Both monoclonal antibodies against the EGFR, cetuximab and panitumumab, have single-agent efficacy in advanced colorectal cancer. Two U.S. phase II trials confirmed the activity of cetuximab for the treatment of patients who had experienced disease progression on prior irinotecan-based therapy.[306] The single-agent

response rate of approximately 10% noted with cetuximab alone was in the same range as previously noted with FOLFOX in the same setting. A large international randomized, phase III trial comparing cetuximab with cetuximab/irinotecan confirmed the findings with almost identical results.[307] For patients who experienced progressive disease while receiving irinotecan-based therapy (with approximately two-thirds of their diseases also refractory to oxaliplatin), cetuximab monotherapy induced responses for approximately 11% of patients. When irinotecan was added, response rate and time to progression were significantly increased (HR, 0.54; 95% CI; 0.42, 0.71; $p < 0.001$). These data served as the basis for the initial approval of cetuximab as a treatment option for patients with metastatic colorectal cancer who were pretreated with irinotecan-based regimens. Single-agent panitumumab was tested against best supportive care in a large international phase III trial in an extensively pretreated population; crossover upon progression was optional.[308]

Panitumumab demonstrated similar single-agent activity to cetuximab, with an approximate 10% response rate when used as salvage therapy after failure of standard chemotherapy. In comparison with best supportive care, it significantly prolonged PFS (HR, 0.54; 95% CI; 0.44, 0.66; $p < 0.0001$). Overall survival was not increased, presumably because 75% of patients crossed over from best supportive care to the panitumumab arm. Based on these data, panitumumab was approved by the FDA as a single-agent salvage therapy option in the United States in 2006. A similar last-line trial comparing cetuximab with best supportive care (without crossover) showed almost identical results in terms of response rate and PFS but also with survival benefit for the cetuximab arm.[309] Both antibodies have been tested as components of first-line therapy in combination with modern chemotherapy regimens, such as FOLFOX and FOLFIRI, the results of which will be discussed further.[310-313] A phase III head-to-head comparison of both antibodies in salvage therapy for 999 patients recently confirmed the equivalent efficacy of both agents.[314] There are no data to support a switch from one EGFR antibody to the other in the case of tumor progression, but panitumumab can be considered for patients with allergic reactions to cetuximab.

The main toxic effects of anti-EGFR antibodies are skin rash, hypomagnesemia, diarrhea, and hypersensitivity reactions, which is particularly relevant for the chimeric antibody cetuximab.[293] Anaphylactic reactions to cetuximab have been correlated with the presence of preexisting serum immunoglobulin E antibodies to an oligosaccharide, galactose-alpha-1,3-galactose, which is present on the Fab portion of the cetuximab heavy chain.[315] These antibodies have been found in up to 21% of individuals from Tennessee who had never been exposed to cetuximab, compared with only 0.6% of individuals from the Boston metropolitan region.[315] The reason for these geographic differences are not known, but it is conceivable that environmental influences with exposure to sensitizing antigens play a role.

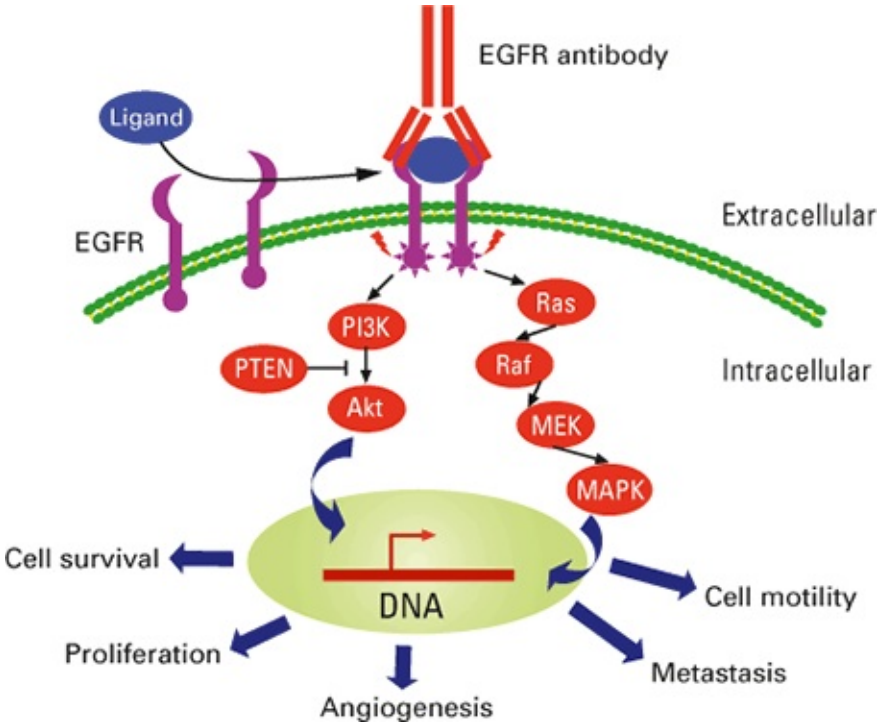

Fig. 10-4 EGFR-signaling pathway and predictive biomarkers for the efficacy of EGFR antibodies.

Data from various clinical trials and translational studies now have opened the door to individualized treatment approaches in colorectal cancer by identifying patients who are most likely to benefit from antibodies against EGFR, cetuximab, and panitumumab. It increasingly appears that patients with advanced colorectal cancer must have a tumor wild-type for both *KRAS* and *NRAS* for EGFR antibodies to be effective (Fig. 10-4).[311,313,316-321] *KRAS* is a phosphorylated signal transducer that self-inactivates via intrinsic guanosine triphosphatase (GTPase) activity.[322] It is a homolog of the transforming gene Kirsten rat sarcoma-2 virus. Several *KRAS* oncogene mutations—in colorectal cancer mainly in codons 12 and 13 (exon 2)—that result in the production of proteins with reduced guanosine triphosphatase (GTPase) activity have been identified. These *KRAS* mutations are among the most common oncogenic alterations in cancer. Four points are important to note with regard to *KRAS* mutations in colorectal cancer:

- *KRAS* mutations occur early in the adenoma–carcinoma sequence, leading to colorectal cancer and implying that the mutation can be found in all tumor cells derived from the initial malignant clone, in metastases as well as the primary tumor.[184,317]
- The determination of *KRAS* mutations is a yes/no binary decision; a tumor harbors either wild-type or mutated *KRAS.* No cutoff levels or subjective grades of expression levels have to be considered.
- The tests for *KRAS* mutation, whether mutation-specific polymerase chain reaction or next-generation gene sequencing is being used, are very robust, are high sensitivity and specificity, and can be obtained from formalin-fixed, paraffin-embedded tissue.
- The frequency of *KRAS* exon 2 mutations in colorectal cancer is about 40%.

In 2013, data emerged that beyond the currently routinely tested *KRAS* exon 2 mutations (codons 12 and 13), lower-frequency mutations in *KRAS* exons 3 and 4 and in *NRAS* also lead to resistance to EGFR monoclonal antibodies.[323,324] Thus, these mutations identify another 10 to 15% of patients beyond the 40% of patients identified with the conventional *KRAS* exon 2

mutations who have no benefit from cetuximab and panitumumab. In fact, results of the pivotal PRIME phase III trial in which patients were randomly assigned to first-line FOLFOX with or without panitumumab suggest that patients with tumors carrying these additional *RAS* mutations might actually experience a detrimental effect when treated with panitumumab.[323] A similar trend was observed for cetuximab added to FOLFIRI in the FIRE-3 trial, which will be discussed in detail in the following section.[324] NCCN guidelines now demand expanded *RAS* mutation testing before EGFR monoclonal antibodies are used for patients with colorectal cancer.

Further predictive biomarkers for the activity of EGFR antibodies in colorectal cancer have been identified in retrospective studies, in which the activity of cetuximab was correlated with the maintained expression of phosphatase and tensin (PTEN) homolog and higher levels of the EGFR ligands amphiregulin and epiregulin.[325-328] At this time, these biomarkers should not be used to exclude EGFR antibody therapy.

BRAF encodes a protein GTPase downstream of *RAS*. *BRAF* V600E mutations can be found in about 5 to 10% of patients with advanced colorectal cancer. They are mutually exclusive with *RAS* mutations[321] and have been consistently found to be associated with a very poor prognosis.[312,317,325] Even in the era of modern combination therapy, the median survival of patients with *BRAF*-mutated stage IV colorectal cancer is only 12 to 14 months.[312] More recent data, however, suggest that an aggressive first-line treatment approach using a triplet chemotherapy combination (FOLFOXIRI) plus bevacizumab might at least partially counteract the poor prognosis of patients with *BRAF*-mutated colorectal cancers.[330,331] More recently, in a random assignment phase II study including 106 patients, those with *BRAF* mutant colorectal cancer that had progressed on at least one line of therapy were randomly assigned to treatment with irinotecan/cetuximab with or without the *BRAF* V600E inhibitor vemurafenib.[328] Patients assigned to the three-drug regimen had significantly improved PFS, with median of 4.4 months versus 2.0 months with irinotecan and cetuximab alone (HR, 0.42; 95% CI; 0.26, 0.66; $p < 0.001$).[332] Thus, FOLFOXIRI/bevacizumab is recommended as first-line treatment for patients with *BRAF* mutations, and the combination of irinotecan/cetuximab/vemurafenib could emerge as the preferred second-line treatment option.

Whether activating *BRAF* mutations can be considered negative predictive markers for the activity of EGFR antibodies has long been unclear because of their strong negative prognostic effect and their low prevalence. Initial data suggested that cetuximab and panitumumab might still have some, albeit attenuated, activity in *BRAF*-mutated colorectal cancers.[312] A meta-analysis of nine phase III trials and one phase II trial, which all randomly assigned patients to treatment with or without an EGFR antibody, showed no benefit for the use of these antibodies with regard to PFS, overall survival, or response rate.[333] Thus, the use of EGFR antibodies for patients with tumors containing activating *BRAF* mutations should not be considered as first choice, if at all. Patients with *BRAF* mutations should preferably be enrolled in clinical trials using a rational combination of targeted agents with or without conventional chemotherapy. A subgroup of *BRAF* mutant colorectal cancer will be dMMR and, therefore, candidates for immunotherapy. Identification of this subset may be very important for patient care (discussed later).

With the proof of efficacy of two biologic therapeutic approaches in colorectal cancer—bevacizumab as VEGF-targeting agents and cetuximab/panitumumab as EGFR antibodies—it appears logical to try to further enhance the efficacy of therapy by combining the two approaches. Initial data for the combination of bevacizumab and cetuximab with or without irinotecan in salvage therapy were promising,[297] so that several subsequent clinical trials

investigated the combination of standard chemotherapy (FOLFOX, CAPOX, or FOLFIRI) plus bevacizumab with or without either cetuximab or panitumumab. The addition of an EGFR antibody to the bevacizumab-based combination therapy reduced PFS in the intention-to-treat populations, and not even the *KRAS* wild-type tumor population benefited from the intensified therapy.[298,299] In view of these findings, the combination of bevacizumab with EGFR antibodies should not be used outside of clinical trials.

Head-to-Head Comparison between EGFR Monoclonal Antibodies and Bevacizumab. Since EGFR antibodies and bevacizumab should not be combined in first-line therapy, a head-to-head comparison of these two biologic agents added to standard chemotherapy had been eagerly awaited. The FIRE-3 trial randomly selected 592 patients with conventionally assessed *KRAS* exon 2 wild-type colorectal cancer to receive FOLFIRI plus cetuximab or FOLFIRI plus bevacizumab.[334] The primary endpoint of the trial was investigator-assessed response rate, with an expected difference in the intention-to-treat analysis of 12%. The primary endpoint was not reached in the intention-to-treat analysis (cetuximab, 62%; bevacizumab, 58%; p = 0.18). In addition, no difference in PFS was noted (10.0 months vs. 10.3 months); in fact, the PFS curves were almost completely superimposable. Surprisingly, however, a statistically significant difference was found in overall survival, with a difference in median overall survival of 3.7 months (28.7 months vs. 25.0 months; HR, 0.77; p = 0.017) in favor of FOLFIRI/cetuximab. The survival curves appeared to split at 24 months—more than 12 months after the median PFS had been reached. An updated analysis, which accounted for additional mutations in *KRAS* exons 3 and 4 as well as *NRAS* mutations in exons 2, 3, and 4, demonstrated an even larger difference in median overall survival (33.1 months vs. 25.6 months; HR, 0.70; p = 0.011), again without a statistically significant difference in response rate and PFS.[324] As outlined above, for patients with tumors harboring the additional *KRAS* and *NRAS* mutations, cetuximab might have introduced a detrimental effect.

Data from the larger U.S. Intergroup study, CALGB/South-west Oncology Group (SWOG) 80405, were released in 2014.[335] This study compared chemotherapy (FOLFOX or FOLFIRI) with cetuximab with chemotherapy with bevacizumab as first-line therapy for 1137 patients with *KRAS* exon 2 wild-type metastatic colorectal cancer. In contrast to the FIRE-3 trial, no difference in overall survival was noted between the two treatment arms, not even when any *RAS*-mutated cancers were excluded. Both treatment arms showed long median overall survival —31.2 months for chemotherapy plus bevacizumab and 32.0 months for chemotherapy plus cetuximab (HR, 0.9; p = 0.40). Note that the outcome parameters of FIRE-3 and CALGB/SWOG 80405 were more alike than different, with the exception of the poor performance of the bevacizumab arm in FIRE-3. Table 10-9 details pertinent results of the two studies.

Table 10-9 **Comparison of Outcome Parameters of FIRE-3 and CALGB/SWOG 80405**

	FIRE 3 CT + Bev vs. CT + Cetux	CALGB/SWOG 80405 CT + Bev vs. CT + Cetux
Primary endpoint	Response rate	Overall survival
CT backbone	All FOLFIRI	FOLFOX 74%/FOLFIRI 26%
ITT (*KRAS* WT exon 2)	n = 295 vs. 297	n = 559 vs. 578
RR, %	58 vs. 62 (p = 0.183)	57.2 vs. 65.6 (p = 0.02)
PFS, months	10.3 vs. 10.0; HR, 1.06 (p = 0.547)	10.8 vs. 10.4; HR, 1.04 (p = 0.55)
Median OS, months	25.0 vs. 28.7 HR, 0.77 (p = 0.017)	29.0 vs. 29.9 HR, 0.92 (p = 0.34)
RAS WT	n = 201 vs. 199	n = 256 vs. 270
RR, %	58.7 vs. 65.3; OR, 1.33 (p = 0.18)	53.8 vs. 68.6; (p < 0.01)
PFS, months	10.2 vs. 10.3; HR, 0.97 (p = 0.77)	11.3 vs. 11.4; HR, 1.1 (p = 0.31)
OS, months	25.0 vs. 33.1 HR, 0.70 (p = 0.006)	31.2 vs. 32.0 HR, 0.9 (p = 0.40)

Abbreviations: Bev, bevacizumab; Cetux, cetuximab; CT, chemotherapy HR, hazard ratio; ITT, intention-to-treat; OR, odds ratio; OS, overall survival; PFS, progression-free survival; RR, recurrence rate; WT, wild-type.

Further analyses regarding duration of therapies and subsequent lines of treatment are underway to potentially discover reasons for the difference in overall survival outcomes, although an initial analysis of tumor location has been enlightening. Colon tumors present with substantial heterogeneity in molecular features, which is strongly associated with tumor location. Left-sided tumors often present with wild-type *BRAF* (*BRAF*-WT), *KRAS* point mutations (codons 12, 13, and 61; *KRAS*-mut), and extensive copy number alterations, as well as other structural genomic aberrations, including chromosomal instability and loss of heterozygosity (LOH). In contrast, right-sided tumors are enriched for *BRAF* V600E point mutations (*BRAF*-mut); are wild-type for *KRAS*; and have a diploid copy number, MSI, DNA hypermutation, and extensive DNA hypermethylation associated with CIMP. Based on these molecular differences, left- and right-sided colon tumors are now becoming increasingly recognized as two unique cancer types that may benefit from different therapeutic strategies. It appears that the difference in outcome between FIRE-3 and CALGB 80405 may have been the proportion of patients with left- and right-sided tumors in each study. Right-sided colorectal tumors are not sensitive to EGFR-antibody therapy,[336] and an imbalance of right- and left-sided

colon cancers likely explain the discordant results in these two studies.[337]

At this time, there does not appear to be a difference in outcome between first-line chemotherapy with bevacizumab or cetuximab, so the treatment approach can be adjusted based on patient and physician preference, goal of therapy, the side-effect profile associated with each regimen, and financial implications. Tumor sidedness (right or left), while intriguing, and potentially prognostic, has not yet been accepted as standard of care for choosing between a VEGF and EGFR antibody inhibitor.

Oral Agents in Salvage Therapy of Colorectal Cancer. Regorafenib, a small-molecule inhibitor of multiple cell-signaling kinases, has documented efficacy in salvage therapy in advanced colorectal cancer.[338] After preliminary data suggested a high disease control rate for patients with treatment-refractory colorectal cancer, regorafenib was investigated in a placebo-controlled, randomized, phase III trial in a salvage therapy setting. Efficacy results of the trial demonstrated a benefit in overall survival for patients receiving regorafenib compared with placebo (6.4 months vs. 5.0 months; HR, 0.77; $p = 0.0052$).[339] The activity of regorafenib was also reflected in an improvement of PFS (1.9 months vs. 1.7 months; HR, 0.49; $p < 0.000001$). The most common severe toxicities observed with regorafenib were hand–foot skin reaction, fatigue, diarrhea, and hypertension. Regorafenib is FDA-approved as a salvage therapy option in patients with advanced colorectal cancer who have previously been treated with a fluoropyrimidine, oxaliplatin, irinotecan, a VEGF inhibitor and, if *KRAS* wild-type, an EGFR monoclonal antibody

TAS-102 is a novel oral anticancer agent consisting of trifluorothymidine (FTD), as the antitumor component, and tipiracil hydrochloride, which prevents the degradation of FTD, at a molar ratio of 1:0.5. FTD, a thymidine analog, in its triphosphate form is incorporated and retained in the DNA of cancer cells.[340] This incorporation and its subsequent effects on DNA dysfunction appear to be the primary mechanism of sustained antitumor activity. Coadministration of tipiracil hydrochloride enables adequate and sustained serum levels of FTD, which would otherwise be immediately eliminated by thymidine phosphorylase in the human liver. After a randomized, phase II trial conducted in Japan showed promising activity of TAS-102 compared with best supportive care as salvage therapy for patients with metastatic colorectal cancer,[341] an international phase III study of 800 patients was launched in the same setting with a 2:1 randomization favoring TAS-102.[343] The primary endpoint of the trial was met, with an improvement of overall survival (median overall survival, 7.1 months vs. 5.3 months; HR, 0.68; 95% CI; 0.58, 0.81; $p < 0.001$). PFS was also improved, with an HR of 0.48. The most common grade 3/4 adverse event was neutropenia in about 40% of patients, with 4% having febrile neutropenia. TAS-102 received FDA approval in September 2015 for the treatment of patients with metastatic colorectal cancer who have previously been treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biologic product, and an anti-EGFR monoclonal antibody, if *RAS* wild-type. This puts TAS-102 in the same clinical setting as regorafenib. It remains to be seen how these two agents will be sequenced in clinical practice. The two agents have distinctly different side-effect profiles (TAS-102: neutropenia; regorafenib: hand–foot skin reaction, fatigue) but very similar efficacy data.

An evidence–based treatment algorithm in the palliative management of colorectal cancer including biologic agents based on molecular testing for *RAS* and *BRAF* is outlined in Fig. 10-5. It highlights that in the salvage setting, regorafenib and TAS-102 can both be considered and could be sequenced in patients whose disease is considered appropriate for continued antitumor therapy.

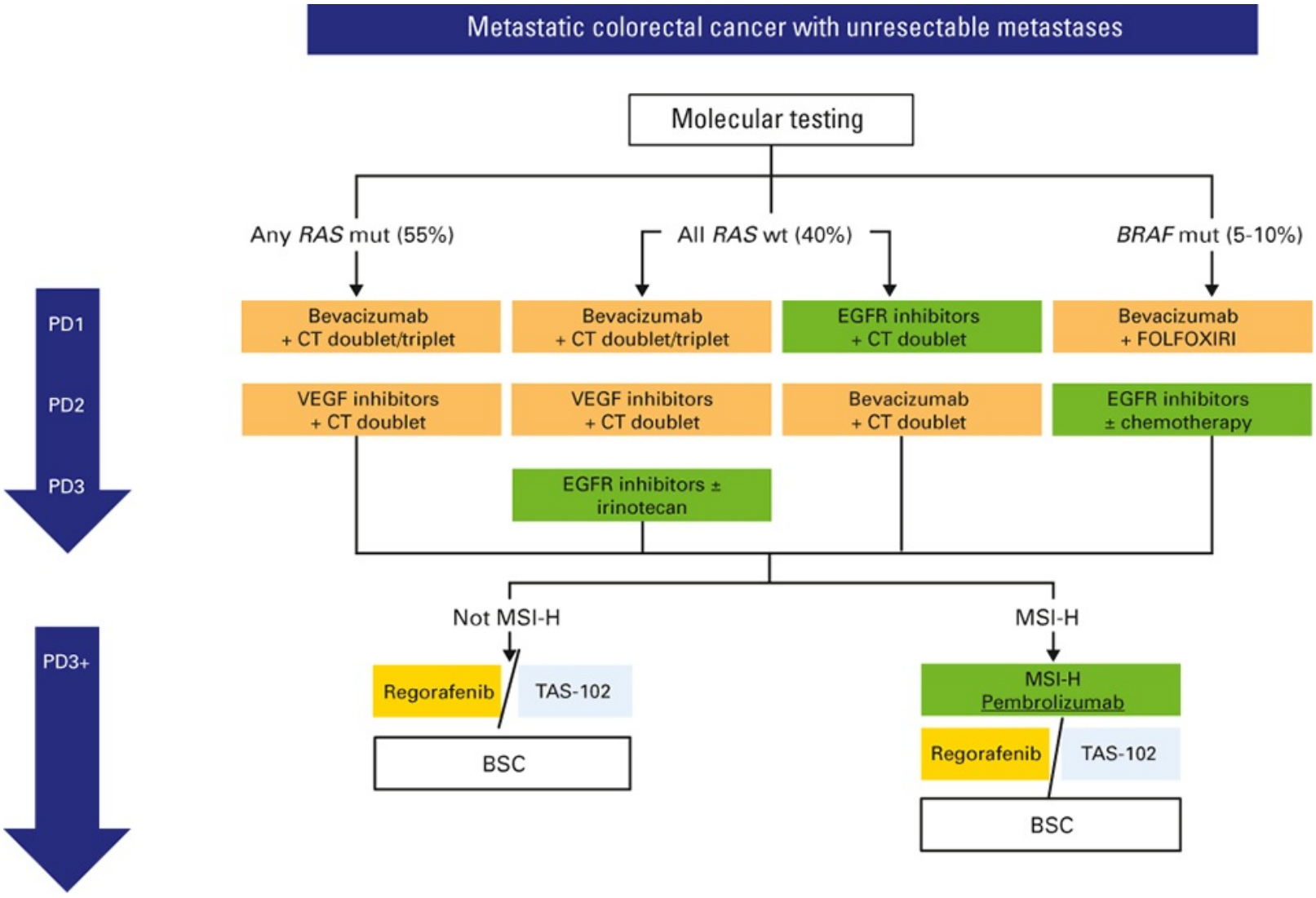

Fig. 10-5 Evidence-based treatment algorithm in the palliative management of colorectal cancer including biologic agents based on molecular testing for *RAS* and *BRAF*.

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PD-1/PD-L1 Immune Checkpoint Inhibitors in Colorectal Cancer

Immune checkpoint inhibitors targeting the PD-1 pathway by binding to PD-1 or its ligand(s) (PD-L1/L2) have shown proof of efficacy in various malignancies since 2014, and several antibodies targeting this system have already received FDA approval in noncolorectal malignancies such as melanoma and non-small cell lung cancer.[343] PD-1/PD-L1 inhibitors allow the patient's immune system to recognize cancer cells by blocking immunosuppressive mechanisms generated by tumor cells, in particular, when these tumor cells carry a high DNA mutation burden with consecutive expression of a large number of neoantigens. It has long been known that MSI-H/dMMR colorectal cancers carry 10 to 100 times as many somatic mutations as MSS/pMMR tumors.[195] In addition, MSI-H/dMMR colon cancers are commonly characterized by dense lymphocytic infiltrates indicating a potential activation of the host's immune system.[344] Based on these observations, a pivotal pilot study was initiated that investigated the role of pembrolizumab, an antibody against PD-1, in heavily pretreated patients with advanced colorectal cancer with cohorts identified by their MSI status (MSI-H/dMMR vs. MSS/pMMR).[196] In addition, a cohort of MSI-H/dMMR noncolorectal cancer was included in the study. Single-agent pembrolizumab showed a remarkable activity only among patients with MSI-H/dMMR cancers independent of their histologic origin. In MSI-H/dMMR colorectal

cancers, patients experienced a more than 60% response rate and a more than 90% disease control rate with some experiencing durable response for more than a year. These findings have led to the initiation of several studies with PD-1/PD-L1 antibodies, which target the about 4 to 5% of patients with metastatic colorectal cancers characterized as MSI-H/dMMR. Furthermore, for the first time, the FDA granted approval of pembrolizumab for any dMMR solid tumor. For colorectal cancer, pembrolizumab is approved for MSI-H/dMMR tumors following prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Limited Hepatic or Pulmonary Metastasis

For the subgroup of patients with recurrent metastatic colon cancer confined to the liver, the roles of hepatic-directed chemotherapy and hepatic resection have become better defined. There is only one multicenter evaluation of potentially resectable liver metastases; the results showed an improved survival for patients undergoing resection compared with those who either had unresectable disease or noncurative resection.[345] The survival advantage is clinically significant, with a near doubling of survival, to almost 37 months.[346] When pooling data for all patients who have a hepatic resection, the average 5-year survival rate is approximately 30%, with a less favorable prognosis for patients with multiple lesions, a short interval between the diagnosis of the primary tumor and recurrence, and the presence of stage III disease at the time of initial diagnosis.[347-349]

Preoperative chemotherapy can be used to downsize initially unresectable metastases to make them amenable for a surgical approach. It has been shown that the overall survival of patients who undergo successful neoadjuvant therapy with subsequent R0 resection of liver metastases approaches the survival of patients with initially resectable metastases.[346,347] Thus, the initial therapeutic approach for a patient with limited metastatic disease should always include consideration of a potentially curative option.

The role of chemotherapy in the potentially curative management of metastatic colorectal cancer can be classified in three different categories:

- **Neoadjuvant therapy**—For initially resectable metastases, mainly to obtain prognostic information, to treat potentially disseminated micrometastases as early as possible, and to test the chemosensitivity of the tumor;
- **Conversion therapy**—For initially unresectable or for borderline resectable metastases to allow for metastasectomy after tumor shrinkage; and
- **Adjuvant therapy**—After curative resection of metastases.

To date, no studies have been conducted to establish the value of neoadjuvant therapy (versus surgery alone or surgery plus postoperative therapy) for patients with resectable liver metastases. A European phase III trial in resectable, liver-limited metastatic colorectal cancer randomly assigned 364 patients to either proceed directly to surgery or to receive FOLFOX chemotherapy for 3 months followed by resection and then followed by 3 additional months of FOLFOX.[350] Patients meeting the eligibility criteria of the trial who received perioperative chemotherapy had a significant improvement in 3-year PFS compared with patients in the surgery-alone arm (36.2% vs. 28.1%; HR, 0.77; p = 0.041). The study was not able to determine whether all patients with resectable liver metastasis should receive neoadjuvant chemotherapy. Any beneficial effects of chemotherapy in this situation will have to be balanced against potential side effects of therapy and, in particular, against the observed higher surgical morbidity after neoadjuvant therapy.[350] After a median follow-up of 8.5 years, no difference in

overall survival was seen in this study; although it is important to realize that the trial was powered for PFS and not overall survival.[351]

The likelihood of conversion therapy to eventually lead to liver resection has been correlated with the overall response rate observed with a specific treatment regimen.[287,352]

The data on adjuvant therapy following resection of hepatic or pulmonary metastasis are limited. In one randomized clinical trial, half of the patients who had successful hepatic resection received both systemic and intrahepatic chemotherapy with floxuridine (FUDR); the other half received only systemic chemotherapy.[353] The results demonstrated a survival advantage at 2 years for patients who received the intrahepatic chemotherapy combination. This approach has not gained widespread use worldwide because of its difficult drug-delivery process and its associated hepatic toxicities and in view of the high activity of modern systemic combination chemotherapy. A pooled analysis of two small trials, with a combined 278 patients, that utilized adjuvant therapy after liver resection and a 5-FU/LV regimen demonstrated a strong trend toward improved outcome with systemic adjuvant chemotherapy in this setting (PFS, 27.9 months vs. 18.8 months; HR, 1.32; $p = 0.058$).[353]

The role of biologic agents (EGFR antibodies and VEGF inhibitors) in the context of pre- or perioperative therapy for potentially resectable liver metastases is unclear. Initial data suggest some benefit for the addition of cetuximab to chemotherapy (FOLFOX or FOLFIRI) in this setting,[354] but more recent results from a randomized trial conducted in the United Kingdom suggested an unexplained detrimental effect when cetuximab was added to chemotherapy in the perioperative setting.[355] No randomized trial exists that tests the role of bevacizumab in the context of liver resection. If bevacizumab is used in the preoperative setting, it needs to be discontinued about 6 weeks before planned surgery to reduce the risk of wound healing complications.[356]

It is important to note that there are substantial data to support disease resection outside of the liver, with the lung being the next most common site for secondary resection. In contrast, the role of aggressive surgical approaches toward peritoneal carcinomatosis, commonly conducted in the context of hyperthermic intraperitoneal chemotherapy, is controversial.[357]

KEY POINTS

- Screening for colorectal cancer, which can conceivably reduce the mortality of this disease, is underutilized. Screening endoscopy and FOBT/FIT testing have been shown to reduce colorectal cancer mortality long term.
- All individuals under age 70 should have their tumors evaluated for mismatch repair proteins or for MSI status. Patients younger than age 50 with colorectal cancer should be considered for formal genetic counseling.
- Adjuvant chemotherapy with an oxaliplatin-based regimen is the standard of care for stage III colon cancer; the role of adjuvant therapy in stage II colon cancer should involve shared decision-making given the marginal benefit in some subgroups.
- Patients with stage II colon cancer and MMR-D/MSI-H have an excellent prognosis and do not require adjuvant therapy.
- After completion of adjuvant therapy, lifestyle changes should be discussed with the patient, including diet, exercise, and use of anti-inflammatory agents.

- Patients with stage IV disease have a chance at cure if their metastases are amenable to complete surgical resection.
- Various conventional cytotoxic drugs (fluoropyrimidines, oxaliplatin, and irinotecan), as well as targeted agents (bevacizumab, aflibercept, regorafenib, as well as cetuximab and panitumumab in *RAS* wild-type cancers) have shown proof of efficacy for metastatic colorectal cancer.
- Expanded *RAS* mutation testing for mutations in *KRAS* and *NRAS* exons 2, 3, and 4 can be considered mandatory before the use of EGFR monoclonal antibodies.
- There is no single standard of care first-line regimen for the management of advanced colon cancer. The decision will involve molecular and histologic assessment of the tumor, goals of treatment, and shared decision-making based on anticipated toxicity.

NEOADJUVANT AND ADJUVANT THERAPY FOR RECTAL CANCER

Cancers arising in the rectum are associated with a higher overall risk of recurrence than that associated with similar stages of colon cancer. The reason for local recurrence in rectal cancer is believed to be the anatomic location of the rectum and the challenge this presents to the surgeon, particularly surgeons practicing in low-volume hospitals. However, pre- and postoperative therapy can help decrease differences in local recurrence rates between hospitals.[358] There is increasing evidence to suggest that local excision should be restricted to patients with T1 stage rectal cancer without high-risk factors.[359] For all other stages, total mesorectal excision (TME) has emerged as the preferred surgical technique. This technique honors natural tissue planes and decreases the chance for local seeding and for subsequent recurrence.[360] In combination with preoperative or postoperative chemoradiation, 5-year local recurrence rates of less than 10% can be achieved.[358,361-363]

The recognition of the significant morbidity and the potential mortality associated with local relapse led to the use of both preoperative and postoperative radiation therapy as additional regional treatment options designed to reduce local recurrence. Two different approaches have been used in this regard: short-term, high-dose radiation commonly delivered as 5 Gy daily for 5 days (5 × 5) immediately before surgery, or prolonged combined-modality therapy with radiosensitizing chemotherapy administered concurrently with radiation to a total dose of 50.4 Gy (45 + 5.4 Gy local boost) over 5 to 6 weeks, followed by a 3- to 4-week interval before curative surgery.[361,363,364] It is important to note that only the longer chemoradiation approach has repeatedly been demonstrated to be able to downstage tumors and cause tumor shrinkage, which might allow sphincter-preserving surgery. Both treatment approaches, however, have been associated with a decrease in local–regional failure. Prevention of local recurrence has not uniformly been associated with improved overall survival. However, the results of one Swedish trial, in which 1168 patients were randomly assigned to either 5 days of high-dose radiation therapy (to 25 Gy) in the week before surgery or to surgery alone, demonstrated a reduction in local recurrences (11% vs. 27%, $p < 0.001$) and a survival advantage at 5 years (58% vs. 48%, $p = 0.004$) for preoperative radiation therapy.[364] A subsequent Dutch trial, using the same radiation technique in combination with quality-controlled TME surgery, confirmed a low rate of local recurrence (at 2 years 2.4% vs. 8.4%, $p < 0.001$) but failed to demonstrate a survival benefit.[361] It is of note, however, that the local recurrence rate of tumors more than 10 cm from the anal verge was not significantly affected. Although the

shorter, high-dose preoperative radiation strategy is most commonly used in Scandinavia and other European countries, U.S. oncologists have historically preferred combined-modality therapy as preoperative or postoperative chemoradiation. Findings from two studies of postoperative adjuvant chemoradiation demonstrated that fluorouracil-based chemotherapy plus radiation was more effective than radiation or surgery alone in preventing both local and distant recurrence.[365,366] Results from another trial showed that prolonged infusion of fluorouracil was superior to bolus administration during radiation therapy, providing a 3-year DFS advantage.[367] This finding confirms that protracted delivery of chemosensitizing agents concomitantly with radiation is the best option for combined-modality therapy. In clinical practice, capecitabine administered twice daily parallel to radiation (common dose, 825 mg/m^2 twice daily on days of radiation) has become a widely used substitute for the continuous infusion of fluorouracil. Two phase III studies confirmed the noninferiority of capecitabine as a radiosensitizer compared with protracted infusion of 5-FU as neoadjuvant therapy in rectal cancer.[368,369]

The long-standing question about whether preoperative or postoperative chemoradiation results in improved outcomes was definitively answered by the results of a large German randomized trial that compared standard continuously infused fluorouracil plus radiation either before or after quality-controlled TME surgery.[363] Patients undergoing preoperative combined-modality therapy had a lower rate of local recurrence (6% vs. 13% at 5 years), a lower rate of acute and chronic toxicities, and a significantly higher rate of sphincter preservation compared with postoperative chemoradiation ($p = 0.006$). This trial established preoperative neoadjuvant radiochemotherapy with fluorouracil as a radiosensitizer as a new standard of care for stages II and III rectal cancers. Subsequent studies have tried to further improve the local control rate by incorporating additional radiosensitizing agents, such as oxaliplatin, and biologic agents into the preoperative treatment phase.[370-373] Data call into question the potential role of oxaliplatin as a radiosensitizer when added to fluoropyrimidines in the neoadjuvant radiochemotherapy of rectal cancer.[374-376] Consistent results from Italian, French, and U.S. phase III trials, found that the addition of oxaliplatin to fluoropyrimidine (5-FU or capecitabine) as a component of neoadjuvant radiochemotherapy did not increase the rate of pCR with the use of oxaliplatin, but it significantly increased toxic effects, mainly diarrhea. Only a German trial, which used a slightly different schedule of oxaliplatin administration, showed superiority of the oxaliplatin arm in terms of pathologic response.[377] However, the overwhelming body of evidence suggests that at this time, oxaliplatin should not be used as part of neoadjuvant radiochemotherapy for rectal cancer outside of clinical trials even if the results of long-term efficacy parameters, such as local recurrence rate, DFS, and overall survival, are still pending.

Two smaller phase III trials compared neoadjuvant chemoradiation therapy following the Sauer protocol to short-course radiation therapy (5 × 5 Gy) as neoadjuvant treatment for localized rectal cancer.[378,379] The two trials demonstrated that both treatment approaches are valid options in the preoperative setting of rectal cancer, with similar rates of local recurrence and overall survival.

The role of adjuvant therapy, particularly after neoadjuvant treatment, has been disputed by individual trials and by a meta-analysis of four studies.[380] The meta-analysis included subgroups of patients from trials, two of which were completed a decade ago. The trials utilized 5-FU-based adjuvant chemotherapies administered according to outdated regimens that are no longer considered standards of care, such as the Mayo Clinic regimen and its variations. Neoadjuvant therapy was heterogeneous and included chemoradiation therapy and radiation alone. The authors found no difference in distant relapse and overall survival associated with the use of adjuvant therapy. However, these results should not change the standard of care that

models the adjuvant approach in rectal cancer to strategies established in colon cancer. This concept has been validated by three randomized trials that used an adjuvant oxaliplatin-based treatment and that consistently found a DFS advantage mirroring the same findings in adjuvant colon cancer.[381-383] The design of these more current studies did not allow them to be included in meta-analyses. The similarity of treatment approaches between colon and rectal cancer is further supported by the results of the Cancer Genome Atlas project, which did not find major differences in the mutational and gene expression profile between rectal and colon cancers.[195] Thus, in agreement with current guidelines (NCCN, European Society for Medical Oncology), patients with rectal cancers should receive adjuvant therapy after resection, with the treatment intensity based on the initial clinical stage before neoadjuvant therapy.

Current studies seek to enhance the efficacy of preoperative therapy by adding biologic agents to a fluoropyrimidine backbone. In addition, studies are underway to compare systemic chemotherapy without radiation against standard chemoradiation for patients with cancers of the mid and upper rectum to spare them the short- and long-term toxicity of radiation therapy. Some studies have also examined the approach of increasing treatment, or even completing all treatment (e.g., total neoadjuvant treatment), prior to surgical resection. In this multicenter, randomized trial, 292 patients were randomly assigned to neoadjuvant fluorouracil-sensitized radiotherapy followed by zero, two, four, or six cycles of FOLFOX therapy prior to total mesorectal excision. Patients who received six cycles of FOLFOX therapy prior to surgery (e.g., total neoadjuvant therapy) experienced 38% pCR, significantly greater than the 18 to 25% pCR experienced with zero or twocycles of FOLFOX prior to resection ($p = 0.0036$).[384]

KEY POINTS

- Neoadjuvant chemoradiotherapy followed by total mesorectal excision is the standard treatment approach for stages II and III rectal cancer.
- Both a protracted course of radiotherapy (45 cGy in 25 fractions plus a 5.4-cGy boost) with chemosensitization or a short course of radiotherapy are acceptable neoadjuvant radiotherapy approaches.
- Capecitabine may be substituted for infusional 5-FU during a protracted course of radiotherapy.
- Adjuvant therapy (to a total course of approximately 4 months) is standard, based on the clinical stage prior to initiation of neoadjuvant chemoradiotherapy.

ANAL CANCERS

EPIDEMIOLOGY AND ETIOLOGY

Cancers of the anus are relatively uncommon in the United States; however, there is an increased incidence in certain populations, such as young men in whom genital viral infections have been implicated. The male-to-female ratio is approximately 2 to 3.5. The most clear causal relationship for anal cancer is infection with human papillomavirus (HPV) (mainly HPV-16). One large study found a strong positive correlation between the amount of sexual activity and the risk of anal cancer.[385] In addition, an association with venereal infection was noted in both men and women. Infection with HPV was presumed to be the etiologic cause. Although

earlier studies suggested that anal-receptive intercourse was directly linked to an increased risk of anal cancer, this finding has not been confirmed in more recent larger-scale trials. Cancers of the anal canal also have been associated with condylomata in both the general population and in gay men. In women with a history of genital warts, anal cancer was associated with seropositivity for herpes simplex virus type 1 and *Chlamydia trachomatis.* For men with no history of genital warts, there was an association with gonorrhea. The association between AIDS and anal cancer has been known for some time, but the exact etiologic relationship has not been elucidated. The incidence of anal cancer in patients infected with HIV is increased more than 40 times compared with the general population.[386] Further risk factors for anal cancers are smoking and chronic inflammation/fistulas in the context of inflammatory bowel disease.

The efficacy of a quadrivalent HPV vaccine (HPV-6, 11, 16, and 18) against anal intraepithelial neoplasia was prospectively investigated in a double-blind, randomized study of 602 healthy homosexual men, ages 16 to 26.[387] The rate of grade 2 or 3 anal intraepithelial neoplasia related to infection with HPV-6, 11, 16, or 18 was reduced by 54.2% (95% CI; 18.0, 75.3) in the intention-to-treat population and by 74.9% (95% CI; 8.8, 95.4) in the per-protocol efficacy population. These intriguing findings, which could lead to a decrease in the incidence of anal cancers through HPV vaccination, prompted the Advisory Committee on Immunization Practices to recommend, in October 2011, the routine use of the quadrivalent HPV vaccine in males ages 11 to 12.[388]

Most anal cancers are squamous cell cancers or cloacogenic cancers, with a few adenocarcinomas. In addition, melanoma accounts for a small percentage of cancers found in the anal canal. Tumors tend to spread by local extension but have the potential to metastasize. Involvement of the inguinal lymph nodes is found in as many as 63% of cases. The most important prognostic factors are the T stage (T1, < 2 cm; T2, 2–5 cm; T3, > 5 cm; T4, invasion into adjacent organs) and the lymph node status. In a pooled analysis of four randomized trials with a total of 644 patients, tumor diameter greater than 5 cm and lymph node involvement were associated with poorer 5-year DFS ($p < 0.0001$) and 5-year overall survival ($p = 0.0001$). In stratified analyses, lymph node involvement had more adverse influence on DFS and overall survival than did tumor diameter. Patients with greater than 5-cm tumor and lymph node metastases had the worst DFS (only 30% at 3 years compared with 74% for the best group; < 5 cm primary and N0) and overall survival (only 48% at 4 years compared with 81% for the best group; < 5 cm primary and N0). Men had worse DFS ($p = 0.02$) and overall survival ($p = 0.016$).[389]

TREATMENT

In the distant past, treatment for patients with anal cancers was surgical resection using an anterior–posterior approach. This treatment option was curative for only approximately 50% of patients and was associated with a high morbidity rate. Today, the standard approach to treatment of anal squamous cell cancers is combined-modality chemotherapy and radiation. Local excision is reserved for patients with small tumors that are well differentiated or are removed incidentally at the time of hemorrhoidectomy.

In initial chemoradiation trials, combinations of fluorouracil and mitomycin C with radiation yielded a high rate of response, including pCR.[386,390] Eventually, it was recognized that surgical resection was not necessary, and it is used today only as salvage therapy for patients with local recurrences following radiation. The expectation is that the CR rate with combined-

modality therapy will be between 70 and 80%, with an overall 5-year survival rate of more than 65%. However, a substantial number of patients will still experience either local relapse or metastatic disease. Treatment of disease in such patients is much more difficult. The addition of mitomycin C to fluorouracil as a radiation sensitizer improved colostomy-free and DFS compared with fluorouracil alone.[391] A phase III RTOG trial involving 682 patients with anal cancer, which compared the role of mitomycin C and fluorouracil with an intensified treatment approach consisting of induction chemotherapy with cisplatin/fluorouracil followed by cisplatin/fluorouracil during radiation therapy, did not show superiority of the experimental arm.[392] In fact, both the 5-year local–regional recurrence rate (25% vs. 33%) and the distant metastasis rates (15% vs. 19%) trended in favor of the mitomycin-based treatment. The cumulative rate of colostomy was significantly better for mitomycin-based than for cisplatin-based therapy (10% vs. 19%; p = 0.02). An updated analysis with long-term follow-up identified the standard mitomycin-based arm as significantly superior in overall survival.[393] Results of a more recent phase III comparison between fluorouracil combined with either mitomycin or cisplatin parallel to up-front radiation therapy did not find a significant difference in outcome,[394] so the inferior results of the RTOG trial for the cisplatin arm could be related to the delay in radiation because of its initial induction chemotherapy component.

Thus, in clinical practice, the well-established combined-modality approach using fluorouracil and mitomycin C plus radiation remains the standard of care. Cisplatin/fluorouracil can be used for patients with contraindications against mitomycin.

Intensity-modulated radiation therapy for anal cancer is currently being evaluated in an effort to reduce short- and long-term toxicity from radiotherapy.[395] Further trials are evaluating the role of cetuximab and bevacizumab as a component of multimodality therapy in local and also metastatic anal cancers. It is of note in this context that anal cancers have a very low rate of *KRAS* mutations.[396]

For patients in whom disease is present in the inguinal lymph nodes at the time of diagnosis or in whom disease develops in those nodes metachronously, additional radiation therapy or node dissection may be beneficial, although the latter is used less frequently. Salvage radiation therapy may result in a cure for up to 50% of patients who have an incomplete response to initial combined-modality therapy or for those who have a local relapse.[397] For patients who have metastatic disease, chemotherapy regimens used for other squamous cell cancers, such as fluorouracil, mitomycin C, cisplatin, paclitaxel, and others (e.g., EGFR antibodies) should be considered, but such treatment is palliative at best.

The treatment of anal cancer for patients with HIV is somewhat more complex. Standard aggressive combined-modality therapies should be used for patients with a CD4 count of more than 200×10^9 mm^3/L who have no signs or symptoms of other HIV-related diseases. For patients with more severe HIV-related problems, reduced doses of radiation, chemotherapy, or both should be considered to maintain local disease control.[398]

KEY POINTS

- Anal cancers are often cured by chemoradiotherapy.
- A quadrivalent HPV vaccine has shown to reduce the incidence of anal intraepithelial neoplasia.
- Mitomycin C plus fluorouracil with radiation remains the standard approach for localized

anal squamous cell cancers.

- At this time there is no role for induction chemotherapy which has not demonstrated benefit and may be associated with worse patient outcomes.

PANCREATIC ENDOCRINE TUMORS AND NEUROENDOCRINE TUMORS, INCLUDING CARCINOIDS

Pancreatic endocrine tumors are a group of uncommon neoplasms that histologically share several key cytochemical features with melanoma, pheochromocytoma, carcinoid tumors, and medullary thyroid cancers. All amine precursor uptake and decarboxylation neoplasms have the capacity to synthesize and secrete polypeptide products that have specific endocrine hormone activity. Most behave in a malignant fashion. The types of tumors are characterized by the hormones they secrete, including gastrinomas, insulinomas, vasoactive intestinal peptide tumors, glucagonomas, somatostatinomas, growth hormone–releasing factor tumors, and adrenocorticotropic hormone tumors. Pancreatic endocrine tumors and carcinoids are considered either functional (if associated with a clinical syndrome because of the production of hormones) or nonfunctional (if hormones are not a substantial element of the presentation). Thus, it is important to note that the absence of detectable hormone production does not rule out the presence of a neuroendocrine tumor. The nomenclature and classification of neuroendocrine tumors are summarized in Table 10-10.[399]

PANCREATIC NEUROENDOCRINE TUMORS

The diverse clinical presentation of pancreatic neuroendocrine (or islet cell) tumors and their frequently silent and relatively benign pathologic presence makes it difficult to accurately determine their true incidence. Many pancreatic neuroendocrine tumors remain asymptomatic and undiagnosed. Most of these tumors appear in sporadic cases without substantial personal or family history. However, certain patient groups have clear evidence of an inherited predisposition to multiple neoplasias of the endocrine system that is manifested in an autosomal-dominant fashion with mutations in the tumor suppressor gene *MEN1* that encodes the protein menin.[400] The syndrome first described (MEN1, Wermer syndrome) is characterized by the presence of tumors of the pituitary gland and parathyroid gland, as well as neuroendocrine tumors of the pancreas.[401] Multiple endocrine neoplasia type 2, associated with mutations in the *RET* gene, typically does not involve pancreatic neuroendocrine tumors; rather, it expresses tumors of the parathyroid, pheochromocytoma, and medullary thyroid cancer.[402] Table 10-11 lists common clinical, hormone-related symptoms associated with functional pancreatic neuroendocrine tumors.

CARCINOID TUMORS

About two-thirds of carcinoid tumors arise within the gastrointestinal system, with the appendix being the most common primary location.[403] However, carcinoid tumors may arise throughout the body, including in the chest. Carcinoid tumors are members of the neuroendocrine tumor family and share cytochemical features with melanomas, pheochromocytomas, medullary thyroid cancers, and pancreatic endocrine tumors. Some undifferentiated, and often nonfunctional, neuroendocrine tumors are characterized by a high mitotic rate (e.g., > 20/10 high-power fields [HPF]) and a high Ki-67 index (e.g., >20%). These high-grade tumors behave

like small cell cancers, have a much more aggressive clinical behavior than common carcinoids, and share characteristics with small cell lung cancers, including their chemo- and radiosensitivity.[404] The determination of cancer can be made only if invasion or distant metastasis is found. The disease is most commonly diagnosed during routine appendectomy. Carcinoid tumors synthesize bioactive amine and peptides, including neuron-specific enolase, 5-hydroxytryptamine, synaptophysin, chromogranin A, and other peptides such as insulin, growth hormone, neurotensin, corticotropin, gastrin, pancreatic polypeptide, and calcitonin. More than 80% of patients with resectable primary tumors are disease-free at 20 years, with similar overall survival rates for an age- and sex-matched cohort. Of those tumors with regional node metastasis, as many as 50% will recur more than 10 years after diagnosis. Typically, the prognosis for patients with resectable carcinoid tumors is favorable.[405] It is important to recognize the long disease-free interval that can occur, which requires patients to have a longer period of follow-up than patients with other tumor types. It is also important to note that appendectomy is inadequate if the carcinoid tumor is larger than 2 cm and/or if lymphovascular invasion or involvement of the mesoappendix is present. In these cases, right hemicolectomy is indicated as definitive oncologic surgery.[406]

Table 10-10 Nomenclature and Classification of Neuroendocrine Tumors

Differentiation and Grade	Mitotic Count (per 10 HPF)	Ki-67 Index (%)*	Traditional Classification	ENETS/WHO Classification
Well differentiated				
Low grade (grade 1)	< 2	< 2	Carcinoid, islet cell, pancreatic (neuro) endocrine tumor	Neuroendocrine tumor, grade 1
Intermediate grade (grade 2)	2–20	3–20	Carcinoid, atypical carcinoid,† islet cell, pancreatic (neuro) endocrine tumor	Neuroendocrine tumor, grade 2
Poorly differentiated				
High grade (grade 3)	> 20	> 20	Small-cell carcinoma	Neuroendocrine carcinoma, grade 3 small cell
			Large-cell neuroendocrine carcinoma	Neuroendocrine carcinoma, grade 3 large cell

Abbreviations: ENETS, European Neuroendocrine Tumor Society; HPF, high-power field (×40 magnification); WHO, World Health Organization.
*MIB1 antibody
†The term *atypical carcinoid* applies only to intermediate-grade neuroendocrine tumors of the lung.

Table 10-11 **Clinical Features of the Most Common Functional Pancreatic Neuroendocrine Tumors**

Tumor Type	Secreted Hormone	Clinical Symptoms	Comments
Gastrinoma	Gastrin	Peptic ulcers	Zollinger-Ellison syndrome (ZES)
		Diarrhea	
Insulinoma	Insulin, proinsulin, peptide C	Hypoglycemia	
Glucagonoma	Glucagon	Rash	
		Mucositis	
		Venous thrombosis	
		Hyperglycemia	
VIPoma	Vasoactive intestinal peptide (VIP)	Watery diarrhea	Watery diarrhea, hypokalemia, and achlorhydria (WDHA) syndrome
		Dehydration	
		Hypokalemia	
		Achlorhydria	
Somatostatinoma	Somatostatin	Hyperglycemia	
		Achlorhydria	
		Cholelithiasis	
		Diarrhea	

Carcinoid Syndrome

As with pancreatic neuroendocrine tumors, carcinoid tumors can manifest with signs and symptoms of abnormal hormone production—namely, the malignant carcinoid syndrome. Flushing is the most common sign, followed by diarrhea, heart disease (valvular abnormalities), and bronchoconstriction. Diarrhea is not necessarily related to the flushing but appears to be caused by increased gastrointestinal motility as a direct consequence of hormone secretion. For intestinal carcinoids, the characteristic carcinoid syndrome appears only when liver metastases have been established and the biogenic amines can bypass the hepatic metabolic activity. When carcinoid syndrome is suspected, serologic testing should be done to measure 24-hour urine levels of 5-hydroxyindoleacetic acid (5-HIAA), serum serotonin levels, and/or serum chromogranin A. The cardiac disease associated with this condition typically involves abnormalities of the valves on the right side of the heart. Therefore, an echocardiogram is an important element in the evaluation of patients with prolonged disease courses. Novel imaging techniques, including octreotide scanning—a nuclear medicine test specifically designed for the detection of carcinoid tumors—have become more common. Individuals with positive findings on an octreotide scan are more likely to benefit from therapy with octreotide. The most common imaging techniques are CT and MRI, with the latter showing the greatest sensitivity for detection of intrahepatic metastases. PET scans commonly are ineffective because of the low proliferative and metabolic activity of differentiated carcinoids. Selective sampling of blood through venous catheterization sometimes can be helpful, but this technique is rarely used.

TREATMENT OF PANCREATIC NEUROENDOCRINE TUMORS AND CARCINOID TUMORS

Surgery is the main treatment for these tumors. Most tumors are easily resectable or are found

incidentally during surgery for other indications. Even when lymph nodes are involved, patients may live for long periods of time without apparent recurrence, but long-term follow-up typically shows continuing disease relapse over many years. In contrast to the situation for other tumor types, cytoreductive surgery (debulking) for palliative purposes (decreasing the amount of hormone-producing tissue) should be considered for these tumors. Such surgery includes hepatic resection or resection of other intra-abdominal and thoracic metastases. Surgical palliation of bowel obstruction from tumor masses or mesenteric fibrosis associated with carcinoid tumors may substantially improve quality of life. Hepatic surgery for liver metastasis may allow patients to remain disease-free for prolonged periods and may reduce hormone production.

Liver-directed therapy, such as (chemo)embolization, high-frequency radioablation, or surgical resection, commonly is used for these tumor types.[405] These techniques are particularly useful for reducing symptoms caused by local growth of the tumor or by hormone production and should be regarded as nonsurgical debulking. These procedures also are associated with a greater likelihood of prolonged tumor regression.

Octreotide and its analogs have been used for some time to control the secretion of 5-HIAA and other peptides.[407,408] More recently, the analogs have been assessed for their antitumor activity, despite their poor tumoricidal effect resulting in few regressions. There is substantial evidence from small phase II clinical studies that these agents have cytostatic effects and may prolong survival.[408] In a prospective, placebo-controlled, randomized trial of 85 patients with midgut neuroendocrine tumors (classic carcinoids) the PROMID study, the use of long-acting octreotide (30 mg IM monthly) was associated with significant delay in tumor progression and a trend toward improvement in overall survival.[409] Patients with carcinoid syndrome symptoms refractory to standard therapy with somatostatin analogs may benefit from telotristat etiprate, which targets an enzyme involved in excess serotonin production, tryptophan hydroxylase. In a phase III trial, patients with carcinoid syndrome uncontrolled on somatostatin analogs experienced a 35% reduction in the number of bowel movements with telotristat etiprate compared with placebo (17%; $p < 0.001$).[410] Patients in the telotristat etiprate arm also had a lower frequency of flushing episodes and less intense abdominal pain compared with placebo, although these differences were not statistically significant.

Another biologic agent that may have clinical benefit is interferon-alfa, which has been shown to decrease the tumor size for a few patients with metastatic disease. Similar to octreotide, interferon appears to have a tumoristatic effect rather than a tumoricidal one. Interferon has been investigated in combination with octreotide for patients with advanced carcinoid.[411] The addition of interferon did not improve PFS over octreotide alone. Given the apparent lack of substantial activity over octreotide, the role of interferon for the treatment of differentiated carcinoid tumors is still under debate.

An alternative long-acting somatostatin analog, lanreotide, was evaluated in advanced neuroendocrine tumors in the CLARINET trial.[412] In contrast to the aforementioned PROMID study, which included mainly patients with low-grade, midgut neuroendocrine tumors, CLARINET enrolled patients with neuroendocrine tumors from the pancreas, midgut, or hindgut or of an unknown origin that were well or moderately differentiated and had a Ki-67 index of less than 10%. A total of 204 patients were randomly assigned to lanreotide or placebo. PFS was not reached in the lanreotide arm compared with a PFS of 18 months in the placebo arm (HR, 0.47; 95% CI; 0.30, 0.73; $p < 0.001$). The 2-year PFS rates were 65.1% and 33.0% for the lanreotide and placebo arms, respectively. Overall survival was not different between the arms, likely because crossover was allowed on the study as well as potential differences in

subsequent treatments. Lanreotide was approved by the FDA in December 2014. Lanreotide's role in the management of advanced neuroendocrine tumors, in which another long-acting somatostatin analog (octreotide) is well established is uncertain, but given its broader indication, lanreotide may play a more of a role in the management of pancreatic neuroendocrine tumors (PNETs) and low-grade hindgut neuroendocrine tumors.

^{177}Lu-DOTA^{0}-Tyr^{3}-octreotate is a peptide receptor radionuclide therapy that has been available in Europe since 2000. This therapy was tested in the randomized, phase III trial NETTER-1, which randomly assigned patients with progressive, somatostatin receptor-positive midgut neuroendocrine tumors to receive four doses of ^{177}Lu-DOTA^{0}-Tyr^{3}-octreotate over 8 weeks along with 30 mg of octreotide every 28 days compared with octreotide alone 60 mg every 28 days.[413] The median PFS was not reached in the ^{177}Lu-DOTA^{0}-Tyr^{3}-octreotate plus octreotide arms and was 8.4 months in the octreotide arm (HR, 0.21; 95% CI; 0.13, 0.34; $p < 0.0001$). The promising results of the NETTER-1 trial will likely lead to an additional treatment option for patients with carcinoid tumors.

Traditional chemotherapy has been tested extensively for the treatment of patients with carcinoid cancers. Agents commonly used include fluorouracil and its oral analog capecitabine, streptozocin, and anthracyclines, such as doxorubicin and liposomal doxorubicin. Unfortunately, response rates for chemotherapeutic agents in combination regimens have been poor (typically < 20%). Therefore, for most patients, the use of systemic chemotherapy is either reserved for end-of-life care or should not be considered at all. It is important to recognize that the slow-growing nature of carcinoid tumors may allow patients to be followed for a long period of time without any considerable intervention. Patients should be monitored closely to determine whether the disease is slow-growing. If so, simple observation often is sufficient.

The outcome with systemic chemotherapy may be better for patients with noncarcinoid pancreas neuroendocrine tumors. One trial, in which streptozocin plus doxorubicin was compared with streptozocin plus fluorouracil, demonstrated that the doxorubicin-containing regimen was superior (response rate, 69% vs. 45%; $p = 0.05$; and overall survival, 2.2 years vs. 1.4 years; $p = 0.004$).[414] Several retrospective trials have evaluated the combination of capecitabine and temozolomide in advanced PNETs with encouraging results.[415] The observed overall response rate was 55% and the observed median PFS was more than 14 months. Thus, there is evidence that a combination temozolomide/capecitabine regimen has activity in this patient population.

For patients who have poorly differentiated gut neuroendocrine tumors, the selection of chemotherapy is similar to that for small cell lung cancer, with the most consistent regression observed using combination etoposide and cisplatin. This distinction is important and emphasizes the need for pathologic evaluation to distinguish between the small cell variant and the more slow-growing pancreatic neuroendocrine/carcinoid tumors.

Novel biologics—including VEGF inhibitors such as sunitinib and signal transduction inhibitors such as mammalian target of rapamycin (mTOR) inhibitors—have shown efficacy in PNETs.[416] Data from a placebo-controlled phase III trial with sunitinib (37.5 mg/day) versus best supportive care for 169 patients with advanced pancreatic neuroendocrine cancer, all of which had progressed in the past 12 months, have been released.[416] PFS increased from 5.5 months with placebo to 11.4 months in the sunitinib group (HR, 0.42; 95% CI; 0.26, 0.66; $p < 0.001$). Data on overall survival were not mature at the time of presentation, but a reduced death rate was noted in the sunitinib arm at the time of data cutoff (10% vs. 25%, $p = 0.02$). The most commonly reported grade 3/4 adverse events in the sunitinib group were neutropenia (12%),

hypertension (9%), abdominal pain (7%), diarrhea (97%), hypoglycemia (7%), and hand–foot syndrome (7%). In a parallel, placebo-controlled, phase III trial of 410 patients with advanced low- to intermediate-grade pancreatic neuroendocrine tumors, the mTOR inhibitor everolimus (10 mg daily) likewise improved median PFS from 4.6 months to 11.0 months (HR, 0.35; 95% CI; 0.27, 0.45; $p < 0.001$).[417] Overall survival data have been presented and they show a median overall survival of 44.0 months in the everolimus arm and 37.7 months in the placebo arm (HR, 0.94; 95% CI; 0.73, 1.20; $p = 0.300$).[418] Although the 6.3-month difference was clinically significant, it did not reach statistical significance, most likely because of the high (85%) crossover rate in the trial. Most common side effects of everolimus were (all grades) stomatitis (64%), rash (49%), diarrhea (34%), fatigue (31%), and infections (23%). Based on these positive trial results, in 2011 sunitinib and everolimus gained FDA approval for the treatment of pancreatic neuroendocrine tumors.

Although these positive results established a new medical standard of care in PNETs, the same treatment appears to be less effective in carcinoids. Everolimus added to octreotide initially demonstrated only modest activity for patients with carcinoids with only a borderline statistically significant improvement in PFS.[419] The RADIANT-4 study was a randomized, phase III trial of everolimus versus placebo for patients with advanced, progressive, well-differentiated, nonfunctional lung and gastrointestinal neuroendocrine tumors.[420] Patients in the everolimus arm had a median PFS of 11.0 months compared with 3.9 months with placebo ($p < 0.001$). There were very few partial responses (2% and 1% for everolimus and placebo, respectively). An interim analysis did show a trend for overall survival benefit with everolimus (HR, 0.64; 95% CI; 0.40, 1.05; $p = 0.037$). This study demonstrated that the activity of everolimus extends to well-differentiated neuroendocrine tumors regardless of origin.

A phase II study of everolimus plus bevacizumab versus everolimus alone for metastatic PNETs showed an improved response rate (31% vs. 12%; $p = 0.005$) but no significant difference in PFS or overall survival.[421]

In summary, though, these results can be regarded as proof of principle for the role of multitargeted kinase inhibitors in neuroendocrine cancers. Ongoing studies are currently investigating the activity of combinations of targeted agents (e.g., VEGF plus mTOR inhibition) in neuroendocrine malignancies.[215]

KEY POINTS

- Pancreatic neuroendocrine tumors are a heterogeneous group of rare tumors that have a variable course of illness depending on the histologic grade, mitosis rate, and Ki-67 index.
- Surgery is the primary treatment for tumors amenable to resection, and there is a role for cytoreductive surgery as well.
- Octreotide and its analogues (e.g., lanreotide) are standard options for most well or moderately differentiated neuroendocrine cancers with a low Ki-67 index.
- Everolimus and sunitinib are standard of care options in pancreatic neuroendocrine tumors following progression on hormonal therapy.

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GENITOURINARY CANCERS

Matthew I. Milowsky, MD

Recent Updates

Bladder Cancer

- Checkpoint inhibitors including anti-PD-1 and anti-PD-L1 antibodies have changed the landscape for the management of patients with locally advanced or metastatic urothelial cancer with an improvement in survival for patients who have progressed after platinum-based chemotherapy and promising activity in those unfit for cisplatin in the first-line setting. (Rosenberg JE, *Lancet* 2016; Massard C, *J Clin Oncol* 2016; Balar AV, *Lancet* 2017; Sharma P, *Lancet Oncol* 2017; Bellmunt J, *N Engl J Med* 2017; Apolo AB, *J Clin Oncol* 2017; Balar AV, *Lancet Oncol* 2017)

Renal Cancer

- Cabozantinib, an oral small molecule inhibitor of VEGFRs, MET, and AXL, improves survival as compared to everolimus in patients with metastatic clear cell renal cell carcinoma (RCC) who have received prior antiangiogenic therapy and improves progression-free survival (PFS) as initial targeted therapy compared to sunitinib in patients with intermediate/poor risk disease. (Choueiri TK, *Lancet Oncol* 2016; Choueiri TK, *J Clin Oncol* 2017)
- In treatment-naïve patients with advanced or metastatic clear cell RCC, the combination of nivolumab plus ipilimumab demonstrated an improvement in overall response rate (ORR), PFS, and overall survival (OS) as compared to sunitinib in patients with intermediate/poor risk disease. (Escudier B, ESMO, 2017)
- The S-TRAC trial of adjuvant sunitinib compared with placebo in patients with high-risk RCC after nephrectomy demonstrated a diesase-free survival (DFS) benefit for sunitinib; however, in another adjuvant trial, ASSURE, no significant differences in DFS or OS were seen with either sunitinib or sorafenib, and in both studies sunitinib-related toxicity was significant. (Ravaud A, *N Engl J Med* 2016; Haas NB, *Lancet* 2016)

Prostate Cancer

- There is a high frequency of DNA damage repair germline mutations in men with metastatic prostate cancer. DNA repair gene mutations are associated with responses to PARP inhibitors in men with metastatic prostate cancer. (Pritchard CC, *N Engl J Med* 2016; Mateo J, *N Engl J Med* 2015)
- Two prospective randomized clinical trials, LATITUDE and STAMPEDE, have shown an OS benefit for the addition of abiraterone (with prednisone or prednisolone) to androgen deprivation therapy in men with noncastrate metastatic prostate cancer. (Fizazi K, *N Engl J Med* 2017; James ND, *N Engl J Med* 2017)

OVERVIEW

Genitourinary cancers accounted for 20% of new cancer cases and 10% of cancer-related deaths, with an estimated 335,000 cases and 58,000 deaths in the United States for the year 2016.[1] Aside from arising in genitourinary organs and requiring a multidisciplinary approach to management, each cancer type is unique with respect to its biology, natural history, and treatment options. The medical oncologist must understand the following: the use of a risk-

adapted approach including surveillance, surgery, radiation therapy, and chemotherapy in patients with germ cell tumors; the integration of chemotherapy and immunotherapy in the treatment of muscle-invasive and metastatic urothelial cancer; the use of targeted therapy and immunotherapy in advanced kidney cancer; and the role for androgen-deprivation therapy, chemotherapy, immunotherapy, radiopharmaceuticals, and antiresorptive bone therapies in the treatment of localized and advanced prostate cancer. The medical oncologist also has a key role in survivorship issues that accompany each disease. Although recent advances have led to novel treatment options that are associated with an improvement in outcome, a cure remains elusive for the majority of patients with advanced genitourinary cancers, and continued research is needed.

GERM CELL TUMORS

Germ cell tumors are the most common malignancies among men between ages 15 and 35. It is estimated that 8720 cases and 380 deaths occurred in the United States in 2016.[1] Germ cell tumors most frequently originate in the gonads (testis or ovary) and less commonly in the retroperitoneum and mediastinum. (For a discussion of germ cell tumors in women, see Chapter 12: Gynecologic Cancers.) Retroperitoneal tumors are often associated with an invasive tumor or carcinoma in situ within the testis, even in the absence of a palpable testicular mass. Primary mediastinal germ cell tumors are not associated with testicular involvement. Primary extragonadal germ cell neoplasms also arise rarely in the sacrum, pineal gland, paranasal sinuses, and liver. Regardless of the stage or extent of disease, the therapeutic objective is cure, which requires an integrated multidisciplinary approach.

EPIDEMIOLOGY

Germ cell tumors are primarily seen in white patients. Risk factors include both abdominal and inguinal cryptorchidism, spermatic or testicular dysgenesis, and a family history that confers a 4- to 10-fold increase in risk.[2] Orchiopexy or surgical correction of abdominal cryptorchidism results in an improved ability to monitor the testis; and treatment of an undescended testis before puberty decreases the risk of testicular cancer as compared to correction after puberty.[3] Factors associated with increased testicular cancer mortality include age older than 40, nonwhite race, and lower socioeconomic status.[4] Testicular seminoma occurs more frequently in men with HIV, and the treatment by stage is the same as for the HIV-negative population.[5] Klinefelter syndrome is a risk factor for the development of mediastinal germ cell tumors. Carcinoma in situ (intratubular germ cell neoplasia) is found in virtually all cases of testicular germ cell tumors. Men in whom in situ disease is identified during a testicular biopsy as part of an infertility evaluation have a 50% risk of an invasive tumor within a 5-year period. A metachronous or synchronous testicular primary germ cell tumor occurs in 2% of patients, with seminoma as the most common histology.[6] Regular self-examination of the remaining testis is recommended.

BIOLOGY

Germ cell tumors are derived from the malignant transformation of premeiotic germ cells. To create a pluripotential tumor, these transformed germ cells must be able to differentiate in a manner similar to the totipotential zygote without the reciprocal genetic information that results from fertilization.[7] An isochromosome of the short arm of chromosome 12—i(12p)—is present

in 80% of all histologic subtypes, including carcinoma in situ and extragonadal tumors. The remaining 20% of cases have excess 12p genetic material as an increase in copy number, tandem duplication, or transposition, which indicates that one or more genes on 12p are involved in malignant transformation. Although the 12p target genes have not been clearly defined, several candidate genes include *CCND2* at 12p13, as well as *SOX5, JAW1,* and *KRAS* mapped to an amplified region at 12p11.2-12.1.[8] Most germ cell tumors are hyperdiploid, often triploid or tetraploid, implying that endoreduplication is important in the early steps of malignant transformation. Based on several studies identifying genetic loci associated with a predisposition to testicular cancer, aberrant KITLG-KIT signaling may be involved in the development of intratubular germ cell neoplasia.[9] Epigenetic regulation including DNA methylation may then have a role in the development of the different histologic subtypes.[10] An integrated analysis of genomewide messenger (mRNA) and micro RNA (miRNA) expression profiles in testicular cancer demonstrated alterations in gene sets implicated in processes related to male reproductive function.[11] Several single-nucleotide polymorphisms (SNPs) within genes involved in gonocyte development have been identified that increase the risk of a germ cell tumor diagnosis.

DIAGNOSIS

A painless testicular mass is highly suggestive of a testicular tumor; however, the majority of patients present with diffuse testicular swelling, hardness, pain, or some combination of these findings. For patients who present with pain, the initial therapy prescribed is often antibiotics for presumed infectious epididymitis or orchitis. Scrotal ultrasonography should be performed when there is any concern about the possibility of a testicular tumor. If the ultrasound is abnormal and a testicular tumor is suspected, a radical inguinal orchiectomy with removal of the testis and ligation of the spermatic cord at the level of the internal ring is performed. Because the testes originate in the genital ridge and migrate through the abdomen and inguinal canal into the scrotum, the vascular and lymphatic drainage of the testes is to the renal or great vessels and the retroperitoneal nodes, respectively. A testicular biopsy or transscrotal orchiectomy is contraindicated because the normal vascular and lymphatic drainage is disturbed. Levels of alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH) also should be determined. Less common presentations include gynecomastia (as a result of elevated levels of HCG), back pain related to retroperitoneal nodal disease, superior vena cava syndrome from primary mediastinal tumors, and hemoptysis from extensive pulmonary metastases.

PATHOLOGY

Germ cell tumors are classified histologically into seminomas and nonseminomas. Seminomas, which account for approximately half of testicular germ cell tumors, retain totipotentiality and are exquisitely sensitive to radiation and chemotherapy. Nonseminomas are composed of the following cell types: embryonal carcinoma, teratoma, choriocarcinoma, and yolk sac tumors.[12,13]

Table 11-1 shows the World Health Organization (WHO) Classification for Germ Cell Tumors.[14] Embryonal carcinoma is the most undifferentiated, with totipotential capacity to differentiate into extraembryonic malignant cell types, such as yolk sac tumors and choriocarcinoma, and somatic cell types, such as teratoma. Teratoma is composed of somatic cells from two or more germ cell layers (i.e., ectoderm, mesoderm, or endoderm), and thus can differentiate into tissue types such as cartilage, muscle, mucinous glandular epithelium, and

others. The presence of any component of nonseminoma with seminoma is treated as a nonseminomatous germ cell tumor. In addition, an abnormal serum AFP level is not seen in seminoma and indicates a nonseminomatous germ cell tumor. Most nonseminomas show mixed histologies, including embryonal carcinoma, yolk sac tumors, teratoma, and choriocarcinoma. When reporting histology, all subtypes present must be noted, starting with the most prevalent and ending with the least common component.

Table 11-1 Classification of Germ Cell Tumors

Germ cell tumors derived from germ cell neoplasia in situ
Noninvasive germ cell neoplasia
• Germ cell neoplasia in situ
• Specific forms of intratubular germ cell neoplasia
Tumors of a single histologic type (pure forms)
• Seminoma
• Seminoma with synctiotrophoblast cells
• Nonseminomatous germ cell tumours
• Embryonal carcinoma
• Yolk sac tumor, postpubertal-type
• Trophoblastic tumours
◦ Choriocarcinoma
◦ Nonchoriocarcinomatous trophoblastic tumours
◦ Placental site trophoblastic tumour
◦ Epithelioid trophoblastic tumour
◦ Cystic trophoblastic tumour
• Teratoma, postpubertal-type
• Teratoma with somatic-type malignancy
Nonseminomatous germ cell tumors of more than one histologic type
• Mixed germ cell tumours
Germ cell tumors of unknown type
• Regressed germ cell tumours
Germ cell tumors unrelated to germ cell neoplasia in situ
• Spermatocytic tumor
• Teratoma, prepubertal-type
◦ Dermoid cyst
◦ Epidermoid cyst
◦ Well-differentiated neuroendocrine tumour (monodermal teratoma)
• Mixed teratoma and yolk sac tumor, prepubertal-type
• Yolk sac tumor, prepubertal-type

Adapted from 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. Eur Urol. 2016 Jul; 70(1): 93-105 with permission from Elsevier.

Seminomas are positive for placental alkaline phosphatase (PLAP), CD117 (c-kit), OCT-4, and SALL-4. They are negative for cytokeratins and CD30. Embryonal carcinoma, however, almost universally expresses cytokeratins, epithelial membrane antigen (EMA), CD30, OCT-4, and SALL-4; approximately 50% express PLAP. Yolk sac tumors are positive for cytokeratins,

AFP, and SALL-4, but negative for CD117 and CD30. Immunohistochemical analysis and testing for i(12p) may be useful in the evaluation of patients with midline tumors of uncertain histogenesis.

PATTERNS OF SPREAD

The primary lymphatic drainage for testicular germ cell tumors is to the retroperitoneal lymph nodes (primary landing zones). The right testicular artery originates from the aorta, and the right testicular vein drains into the inferior vena cava. The left testicular artery originates near the left renal artery, and the left testicular vein terminates in the left renal vein. Right-sided tumors spread to the interaortocaval lymph nodes immediately below the renal blood vessels, and left-sided tumors spread to the para-aortic lymph nodes immediately below the left renal artery and vein. Cross-metastases are more commonly seen from right to left. Invasion of the epididymis or spermatic cord may be associated with iliac nodal involvement, and inguinal metastases may be seen with scrotal invasion or if there has been disturbance of the normal lymphatic drainage related to prior surgery. Additional metastatic sites include retrocrural, mediastinal, and supraclavicular lymph nodes; the lungs; and, less commonly, the liver, central nervous system, and bone.

STAGING

Pretreatment Evaluation

The extent of disease evaluation for patients with newly diagnosed germ cell tumors includes a chest x-ray, computed tomography (CT) of the abdomen and pelvis, and tumor markers. Indications for a CT scan of the chest include an abnormal chest x-ray, known mediastinal disease, and risk for pulmonary metastases. A bone scan and magnetic resonance imaging (MRI) of the brain are indicated only if related symptoms are present. Measurement of tumor markers, including AFP, HCG, and LDH, is used to establish the diagnosis and may assist in determining histologic subtype. Sperm banking should be performed before treatment is pursued.

Stage Groupings

A tumor–node–metastasis (TNM) staging classification system was developed by the American Joint Committee on Cancer (AJCC) and incorporates serum tumor markers, including AFP, HCG, and LDH (Table 11-2).[15] Adverse factors include mediastinal primary site; degree of elevation of AFP, HCG, and LDH; and presence of nonpulmonary visceral metastases. Based on these findings, advanced germ cell tumors are risk-stratified as follows: good risk, accounting for 60% of germ cell tumors and resulting in a 5-year survival rate of 91%; intermediate risk, accounting for 26% of germ cell tumors and a 5-year survival rate of 79%; and poor risk, accounting for 14% of germ cell tumors and a 5-year survival rate of 48%. All seminomas are either good or intermediate risk (Table 11-3).[16] Regardless of the initial risk stratification, patients with advanced germ cell tumors who survive and remain without disease more than 2 years after their diagnosis have an excellent chance of remaining disease-free in subsequent years.[17]

TUMOR MARKERS

Tumor markers are measured before, during, and after treatment. An initial rise in tumor

markers may occur with chemotherapy, particularly in the setting of bulky advanced disease. The serum half-lives of AFP and HCG are 5 to 7 days and 30 hours, respectively, and a slow marker decline after orchiectomy or during chemotherapy implies residual active disease. Elevated or rising AFP and/or HCG levels that occur without radiologic or clinical findings imply active disease and must be managed accordingly. Other conditions associated with elevated AFP levels include hepatocellular carcinoma, liver damage, and other gastrointestinal malignancies. HCG elevations may occur as a result of treatment-related hypogonadism or cross-reactivity with pituitary hormones, including luteinizing hormone. This cross-reactivity is generally less of an issue with current assays specific for the beta subunit of HCG. Hyperthyroidism may be associated with elevated levels of HCG related to cross-reactivity of HCG with the thyroid-stimulating (TSH) receptor. A spurious elevation in HCG also has been associated with marijuana use.[18] With these exceptions, increased levels of AFP are pathognomonic of a nonseminoma and not seen in seminoma, whereas elevated levels of HCG may be seen in both seminoma and nonseminoma. LDH levels can increase for patients with advanced seminoma or nonseminoma and are used for staging and assessment of outcome. Elevations in any one marker or combination are found in approximately 20% of patients with stage I disease, 40% of patients with stage II disease, and 60% or more of patients with stage III disease.

SEMINOMA

Approximately 70% of patients with seminoma have stage I disease. After radical inguinal orchiectomy, standard treatment options include surveillance, adjuvant infradiaphragmatic radiotherapy to include the para-aortic nodes, and single-agent carboplatin, recognizing that approximately 80% of these patients will not have required treatment and that the long-term survival is nearly 100% regardless of the initial option chosen. Observational studies of patients with clinical stage I seminoma indicate a 15 to 20% likelihood of disease relapse, mostly in the retroperitoneum; however, the median time to relapse is 14 months, which is twice as long as for clinical stage I nonseminomatous tumors, and late relapses at greater than 5 years may occur.[19] Based on the excellent outcome for patients with stage I seminoma and the potential for long-term radiation-related toxicity, including secondary malignancies, surveillance represents a preferred strategy for the management of patients with clinical stage I disease.[20-23] Radiation therapy is to be avoided in the setting of inflammatory bowel disease or a horseshoe kidney. Radiotherapy using a para-aortic field as compared with a dogleg field is associated with reduced toxicity and a low rate of recurrence.[24] A randomized trial comparing radiotherapy with single-dose carboplatin in the adjuvant treatment of stage I seminoma has shown a noninferior relapse-free rate for single-dose carboplatin (AUC 7), with a reduced risk of a second primary germ cell tumor in the carboplatin arm.[25,26] Although chemotherapy represents a potential strategy for the management of clinical stage I disease, concerns have been raised based on the relatively short follow-up period (median, 6.5 years) to evaluate for late relapse and late toxicity.[27,28] In a retrospective report on patients who experienced a relapse after adjuvant carboplatin, 15% of the relapses occurred > 3 years after adjuvant treatment.[29]

Patients with stage IIA and nonbulky IIB disease are treated with 30 to 36 Gy of radiation to the para-aortic and ipsilateral iliac lymph nodes. Chemotherapy is preferred for patients with clinical stage IIB seminoma with bulkier disease. Chemotherapy will cure more than 90% of the patients who experience disease relapse after radiotherapy; approximately 99% of patients

with early-stage seminoma are cured.

Advanced Seminoma

Approximately 10% of patients with seminoma require chemotherapy. Fifteen to 20% of patients with advanced seminoma present with an elevated HCG. An elevated AFP indicates a nonseminomatous tumor, and the patient should be treated accordingly. Patients with retroperitoneal masses larger than 5 cm (stage IIC), supradiaphragmatic lymphadenopathy, visceral disease, bulky retroperitoneal tumors, tumor-related back pain, and mediastinal extragonadal presentations are treated with primary chemotherapy. Approximately 90% of patients with advanced seminoma will be classified as having a good prognosis and receive treatment with good-risk chemotherapy, with an 86% 5-year survival, whereas only 10% of patients have intermediate risk disease. Pure seminomas are never classified as poor risk (see section on Management of Advanced Germ Cell Tumors by Risk Classification).[16]

Table 11-2 **Staging of Testicular Germ Cell Tumors**	
Primary Tumor (T)	
Clinical T (cT)	Note: Except for Tis confirmed by biopsy and T4, the extent of the primary tumor is classified by radical orchiectomy
cTX	Primary tumor cannot be assessed
cT0	No evidence of primary tumor
cTis	Germ cell neoplasia *in situ*
cT4	Tumor invades scrotum with or without vascular/lymphatic invasion
Pathological T (pT)	
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pTis	Germ cell neoplasia in situ
pT1	Tumor limited to testis (including rete testis invasion) without lymphovascular invasion (subclassification only applies to pure seminoma)
pT1a	Tumor < 3 cm
pT1b	Tumor ≥ 3 cm
pT2	Tumor limited to testis (including rete tesis invasion) with lymphovascular invasion;
	OR Tumor invading hilar soft tissue or epididymis or penetrating visceral mesothelial layer covering the external surface of tunica albuginea with or without lymphovascular invasion
pT3	Tumor invades the spermatic cord with or without lymphovascular invasion
pT4	Tumor invades the scrotum with or without lymphovascular invasion
Regional Lymph Nodes (N) Clinical	
cNX	Regional lymph nodes cannot be assessed
cN0	No regional lymph node metastasis
cN1	Metastasis with a lymph node mass ≤ 2 cm in greatest dimension;
	OR Multiple lymph nodes, none > 2 cm in greatest dimension
cN2	Metastasis with a lymph node mass > 2 cm but not > 5 cm in greatest dimension;
	OR Multiple lymph nodes, any one mass > 2 cm but not > 5 cm in greatest dimension
cN3	Metastasis with a lymph node mass > 5 cm in greatest dimension
Pathologic (pN)	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass ≤ 2 cm in greatest dimension and ≤ 5 nodes positive, none > 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass > 2 cm but not > 5 cm in greatest dimension;
	OR > 5 nodes positive, none > 5 cm in greatest dimension; or evidence of extranodal extension of tumor

Pathologic (pN)	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass ≤ 2 cm in greatest dimension and ≤ 5 nodes positive, none > 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass > 2 cm but not > 5 cm in greatest dimension;
	OR > 5 nodes positive, none > 5 cm in greatest dimension; or evidence of extranodal extension of tumor
pN3	Metastasis with a lymph node mass > 5 cm in greatest dimension
Distant Metastases (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonretroperitoneal nodal or pulmonary metastasis
M1b	Nonpulmonary visceral metastases
Serum Tumor Markers (S)	
SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH is < 1.5 times the upper limit of normal (ULN) **and** HCG (mIU/mL) is < 5000 **and** AFP (ng/mL) is < 1000
S2	LDH is 1.5 to 10 times ULN **or** HCG is 5000 to 50,000 **or** AFP is 1000 to 10,000
S3	LDH is > 10 times ULN **or** HCG is > 50,000 **or** AFP is > 10,000
Anatomic Stage/Prognostic Groupings	
Stage 0	pTis N0 M0 S0
Stage I	pT1-4 N0 M0 SX
Stage IA	pT1 N0 M0 S0
Stage IB	pT2 N0 M0 S0
Stage IB	pT3 N0 M0 S0
	pT4 N0 M0 S0
Stage IS	Any pT/TX N0 M0 S1-3
Stage II	Any pT/TX N1-3 M0 SX
Stage IIA	Any pT/TX N1 M0 S0
	Any pT/TX N1 M0 S1
Stage IIB	Any pT/TX N2 M0 S0
	Any pT/TX N2 M0 S1
Stage IIC	Any pT/TX N3 M0 S0
	Any pT/TX N3 M0 S1
Stage III	Any N M1 SX
Stage IIIA	Any N M1a S0
	Any N M1a S1
Stage IIIB	Any pT/TX N1-3 M0 S2
	Any pT/TX Any N M1a S2
Stage IIIC	Any pT/TX N1-3 M0 S3
	Any N M1a S3
	Any N M1b Any S

Abbreviations: AFP, alpha-fetoprotein; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; ULN, upper level of normal.

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Surgery after chemotherapy is technically more difficult for patients with seminomas due to a dense desmoplastic reaction than for patients with nonseminomas. Postchemotherapy residual masses usually represent fibrosis rather than persistent seminoma. Options have included surgery for postchemotherapy masses larger than 3 cm or close observation with CT imaging and intervention if there is evidence of disease progression. 18-fluorodeoxyglucose positron-emission tomography (FDG-PET) has been shown to be a predictor for viable tumors in postchemotherapy seminoma.[30] The specificity, sensitivity, and negative predictive value of FDG-PET are improved if performed 6 weeks after the end of the last chemotherapy cycle compared with before 6 weeks.[31] In summary, FDG-PET is recommended in patients with a residual mass greater than 3 cm and normal tumor markers. A positive FDG-PET scan indicates viable seminoma, for which surgery is indicated.

Table 11-3 Risk Stratification According to the International Germ Cell Consensus Classification

Seminoma	**Good risk**
	Any primary and any markers and no nonpulmonary visceral metastases
	Intermediate risk
	Any primary and any markers and nonpulmonary visceral metastases
Nonseminoma	**Good risk**
	Testis or retroperitoneal primary and good-risk markers and no nonpulmonary visceral metastases
	Intermediate risk
	Testis/retroperitoneal primary and intermediate-risk markers and no nonpulmonary visceral metastases
	Poor risk
	Mediastinal primary site or testis or retroperitoneal primary with either nonpulmonary visceral metastases or poor-risk markers

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NONSEMINOMATOUS GERM CELL TUMORS

Stage I Disease

Approximately 30 to 40% of patients with nonseminomatous germ cell tumors present with stage I disease. Management options include surveillance, retroperitoneal lymph node dissection, or primary chemotherapy.

Surveillance is a preferred option for compliant patients with stage IA (pT1 tumors; i.e., those with no vascular/lymphatic invasion or with invasion into the tunica vaginalis, spermatic cord, or scrotum) who have a low risk for recurrence. Absence of a predominant embryonal carcinoma component in the primary tumor is also favorable. Approximately 20% of patients will experience a recurrence of the disease (most commonly in the retroperitoneum) and will need chemotherapy. Most recurrences of nonseminomatous germ cell tumors will occur within 2 years of orchiectomy, and these patients must have meticulous follow-up that includes a history, physical examination, and measurement of serum tumor markers every 2 months, as well as a chest x-ray at months 4 and 12 and an abdominal/pelvic CT scan every 4 to 6 months during the first year. Although the intervals for follow-up increase during subsequent years, it is important to remember that late recurrences can occur.[32] Compliance with this surveillance schedule, and with salvage therapy as indicated, produces cure rates of 98 to 99% and spares the 75 to 80% of patients without micrometastatic disease from additional therapy. The potential long-term risk of secondary cancers associated with exposure to low-dose ionizing radiation with medical imaging procedures has generated particular concern for young patients with germ cell tumors.[33] Although one report suggested that the risk of secondary cancers was not associated with the amount of diagnostic radiation, the observation period was relatively short at only 11 years.[21,34]

Patients with stage I disease for whom the risk of disease recurrence is high (> 50%) based on pathologic features—including embryonal carcinoma predominance (> 50%), and/or the presence of lymphatic, vascular, scrotal, or spermatic-cord invasion (stage IB)—may be considered for a nerve-sparing retroperitoneal lymph node dissection by a surgeon experienced in the procedure. Surveillance in a compliant patient with stage IB is an accepted option and is preferred by some experts in the field. Low recurrence rates have been demonstrated in studies evaluating the use of short-course adjuvant chemotherapy with one or two cycles of combination bleomycin/etoposide/cisplatin (BEP) in patients with clinical stage I nonseminomatous germ cell tumors; however, some experts have concerns regarding the many men exposed to unnecessary chemotherapy, resulting in a potential for long-term adverse effects.[35-38] The decision to recommend adjuvant chemotherapy after a retroperitoneal lymph node dissection is made on the basis of pathologic findings, as described for patients with pathologic stage II disease. Patients without evidence of clinical disease and persistently elevated tumor markers, including HCG, AFP, or both after orchiectomy (stage IS), should receive standard chemotherapy for advanced disease rather than surgery.

Stage II Disease

The standard treatment for a patient with stage IIA disease (nodes ≤ 2 cm in diameter) is a modified, bilateral retroperitoneal lymph node dissection. In this procedure, the dissection becomes unilateral at the level of the inferior mesenteric artery. Experience with the technique is essential because, depending on the location of the tumor, a nerve-sparing procedure can be performed.

Approximately 20 to 25% of patients who have undergone a primary retroperitoneal lymph node dissection will have pathologic N1 (metastases with node diameter of ≤ 2 cm or ≤ 5 involved nodes) with an approximate 20% risk of relapse such that surveillance is preferred in a compliant patient. The likelihood of micrometastatic disease is 50% or more for patients with an involved node diameter of more than 2 cm, more than five involved nodes, or any extranodal extension (pathologic N2). Assuming that serum tumor marker levels return to normal after

surgery, these patients should receive two cycles of adjuvant chemotherapy, which results in a 98 to 99% likelihood of cure.[39,40] In patients with pathologic N3 (node diameter > 5 cm), three to four cycles of chemotherapy are administered. In circumstances wherein disease relapses or if the serum tumor markers do not normalize, indicating residual active disease, then three to four cycles of chemotherapy and subsequent surgical excision of residual macroscopically documented disease, if present, are indicated, as is required for any patient with disseminated disease.

The majority of patients with clinical stage IIB disease (nodes > 2 cm but not > 5 cm in diameter) are generally advised to receive primary chemotherapy. In addition, patients with back pain related to psoas invasion, bilateral retroperitoneal involvement, suprahilar or retrocrural adenopathy, or other signs that the disease may be unresectable should undergo primary chemotherapy. Clinical stage IIC disease (nodes > 5 cm in diameter) should also be treated with chemotherapy.

Stage III Disease

Approximately 70 to 80% of patients with metastatic disease will be cured with cisplatin-based chemotherapy combined with surgery to resect residual disease as an integral part of management. The therapeutic objective is cure, with distinct approaches for disease deemed good risk (i.e., high probability of cure) and poor risk (i.e., lower probability of cure).[41] For patients with good-risk disease, the goal is to minimize toxicity without compromising cure, whereas management of poor-risk disease focuses less on minimizing toxicity and more on increasing the probability of cure.

MANAGEMENT OF ADVANCED GERM CELL TUMORS BY RISK CLASSIFICATION

The treatment of germ cell tumors is based on the International Germ Cell Consensus Classification, developed in 1996 (Table 11-3).[16]

Good Risk

Approximately 60% of patients with nonseminomatous germ cell tumors present with good-risk disease. Patients with good risk include those with stage II or III disease with testis/retroperitoneal primary tumors, no nonpulmonary visceral metastases, and good-risk tumor markers. The majority of patients with advanced seminoma have good-risk disease. Based on the results of clinical trials, more than 90% of these patients will be cured with the use of combination chemotherapy, including cisplatin and etoposide with or without bleomycin.[42-47] Summaries of the trials are as follows:

- Four cycles of etoposide plus cisplatin and three cycles of BEP achieve a durable complete response in approximately 90% of patients with good-risk disease.
- The elimination of bleomycin can compromise cure if only three cycles of therapy with etoposide and cisplatin are given or adequate doses of etoposide are not administered.[47,48]
- Although carboplatin has less toxicity, it cannot be substituted for cisplatin because it is less effective.[49,50]

A trial from the Genito-Urinary Group of the French Federation of Cancer Centers randomly assigned patients with good-risk nonseminomatous germ cell tumors to three cycles of BEP or

to four cycles of etoposide plus cisplatin.[46] In 257 assessable patients, there was no significant difference among the BEP or etoposide plus cisplatin arms in response (94.7% vs. 96.8%; p = 0.34), 4-year event-free survival (91% vs. 86%; p = 0.135) and 4-year overall survival (96% vs. 92%; p = 0.096). One additional cycle of treatment is required with the regimen of etoposide plus cisplatin, but the nine bleomycin treatments are avoided. Bleomycin is associated with Raynaud phenomenon and pulmonary toxicity, although clinically significant pulmonary toxicity is rare.[51] Risk factors for bleomycin-induced lung toxicity include older age, a history of smoking, and impaired renal function. Three cycles of BEP or four cycles of etoposide/cisplatin are the standard regimens for the treatment of patients with good-risk germ cell tumors.

The lower limit of dose for bleomycin and etoposide was addressed in a trial that compared three cycles of standard BEP (20 mg/m^2 of cisplatin on days 1 to 5; 100 mg/m^2 of etoposide on days 1 to 5; and 30 kU of bleomycin on days 1, 8, and 15, repeated every 21 days) with four cycles of the same combination at different dosages (100 mg/m^2 of cisplatin on day 1; 120 mg/m^2 of etoposide on days 1 to 3; and 30 kU of bleomycin on day 1, repeated every 21 days). The trial was stopped when an interim analysis attributed a higher cancer death rate with the alternative regimen, which was thought to be related to the lower total dose and dose intensity of bleomycin and to the lower dose intensity of etoposide.[52]

In an attempt to decrease toxicity, the substitution of carboplatin for cisplatin was addressed in a randomized trial in which etoposide plus cisplatin was compared with etoposide plus carboplatin (500 mg/m^2 on day 1 of each cycle) for four cycles.[49] There were significantly inferior event-free and relapse-free survival rates for patients who received etoposide plus carboplatin. Therefore, carboplatin should not be substituted for cisplatin in the treatment of patients with germ cell tumors.

Intermediate Risk

The intermediate-risk group includes patients with nonseminomatous tumors with intermediate-risk tumor markers, as well as patients with seminoma who have nonpulmonary visceral metastases. These patients comprise 20 to 30% of those with germ cell tumors and have a 5-year survival rate of approximately 80%. A regimen that includes four cycles of BEP is the standard treatment.

Poor Risk

Patients with poor-risk disease include those with nonseminomatous germ cell tumors with nonpulmonary visceral metastases, poor-risk tumor markers, or primary mediastinal site. These patients comprise 10 to 20% of those with nonseminomas and have a 5-year survival of approximately 50%. For patients with poor-risk disease, the standard of care remains four cycles of conventional-dose BEP. A randomized trial showed that the substitution of ifosfamide for bleomycin has similar efficacy but significantly greater toxicity.[53] Additionally, the use of high-dose cisplatin (200 mg/m^2) is not superior to standard-dose cisplatin (100 mg/m^2) when administered in combination with etoposide and bleomycin.[54] A randomized, phase III trial of 219 patients with intermediate- or poor-risk germ cell tumors compared two cycles of standard BEP followed by two cycles of high-dose chemotherapy (cyclophosphamide/etoposide/carboplatin) plus stem cell rescue to four cycles of conventional-dose BEP.[55] The primary endpoint was the percentage of patients with complete response at 1 year. Final analysis showed that there was not a significant difference, with a complete

response at 1 year of 52% for BEP plus high-dose chemotherapy and 48% for BEP alone (p = 0.53). A second randomized, phase III study comparing standard-dose BEP with sequential high-dose cisplatin/etoposide/ifosfamide (VIP) plus stem cell support in patients with poor-prognosis germ cell cancer did not demonstrate a benefit for high-dose chemotherapy given as part of first-line therapy.[56] In a population-based study of treatment guided by tumor marker decline in patients with metastatic nonseminomatous germ cell tumors, intensification of therapy based on prolonged marker decline was associated with improved outcome such that the survival rate for intermediate-risk patients approached that of good-risk patients.[57] A phase III trial in poor-prognosis germ cell tumors of personalized chemotherapy based on serum tumor marker decline demonstrated that treatment intensification determined by the rate of early marker decline reduces the risk of progression or death; however, the dose-dense intensification used in the study is not a standard regimen.[58] In patients with primary mediastinal nonseminomatous germ cell tumors, a recent report from Indiana University demonstrated a high rate of postoperative pulmonary failure and mortality after BEP with a suggestion to substitute ifosfamide for bleomycin in the treatment of these patients who will undergo a major thoracic surgery.[59]

SALVAGE THERAPY FOR GERM CELL TUMORS

In 20 to 30% of patients with advanced germ cell tumors, the disease will fail to achieve a durable response to chemotherapy regimens, including cisplatin and etoposide with or without bleomycin. Approximately 25% of these patients will experience a durable complete response using vinblastine/ifosfamide/cisplatin as salvage therapy.[60] Patients whose disease does not achieve a durable complete response to induction chemotherapy have a particularly poor prognosis.[61] In addition, patients with a mediastinal primary tumor site rarely experience a durable complete response to cisplatin plus ifosfamide-based salvage chemotherapy. The timing of relapse is also important, with late relapse beyond 2 years associated with a high degree of resistance to standard salvage chemotherapy and with an overall poor prognosis.[32] Paclitaxel/ifosfamide/cisplatin (TIP) was evaluated as second-line therapy for patients with favorable prognostic features for response, including testis primary tumor site and a prior complete response to a first-line chemotherapy program.[62] Four cycles of TIP as second-line therapy resulted in a 70% complete response rate to treatment, with a 63% durable complete response rate and a 2-year progression-free survival (PFS) rate of 65%. The high level of activity with TIP as salvage therapy is, in part, related to the criteria used to select patients who are more likely to benefit from conventional-dose second-line therapy. A retrospective study demonstrated that the TIP regimen followed by surgery may be effective for patients with late-relapse germ cell tumors who are not candidates for primary surgery.[63] Ifosfamide-based therapy has been associated with significant hematologic, renal, and neurologic toxicities, and the use of hematopoietic growth factors is considered standard. A phase II study of cisplatin plus epirubicin has also demonstrated activity in the salvage setting.[64] Additional regimens, such as those incorporating gemcitabine and oxaliplatin, have demonstrated antitumor activity in patients who have been heavily pretreated.[65] Clinical trials should be considered in the salvage setting. In patients experiencing treatment failure with cisplatin-based first-line chemotherapy, prognostic variables including histology, primary tumor location, response, progression-free interval after first-line treatment, AFP, and HCG, as well as the presence of liver, bone, or brain metastases, have been used to develop a prognostic model to guide salvage therapies.[66]

HIGH-DOSE CHEMOTHERAPY WITH PERIPHERAL STEM CELL RESCUE FOR GERM CELL TUMORS

The use of high-dose chemotherapy with peripheral stem cell rescue may be considered for patients who do not have an initial complete response to induction chemotherapy and should be considered in those who experience a relapse after first-line salvage therapy. The use of high-dose carboplatin and etoposide followed by peripheral-blood stem cell transplantation or autologous bone marrow transplantation rescue with a repeat course of therapy given after hematopoietic reconstitution was evaluated as initial salvage therapy in 65 patients with testicular cancer.[67] Postchemotherapy resection of residual disease was performed in selected patients. At a median follow-up of 39 months, 37 (57%) of the 65 patients were continuously disease-free, and 3 additional patients were disease-free with surgery. The use of sequential, dose-intensive paclitaxel/ifosfamide/carboplatin/etoposide (TI-CE) with stem cell rescue was evaluated in 107 patients with germ cell tumors whose disease was resistant to cisplatin and who had unfavorable prognostic features for response to conventional-dose salvage therapy, including extragonadal primary site, incomplete response to first-line therapy, or relapse/incomplete response to ifosfamide/cisplatin-based conventional-dose salvage therapy.[68] A total of 54 patients (50%) achieved a complete response, and 8 (8%) achieved a partial response with negative tumor markers. With a median follow-up of 61 months, the 5-year disease-free survival (DFS) was 47%; overall survival (OS) was 52% with no relapses occurring after 2 years. In a retrospective review from Indiana University of 184 consecutive patients with metastatic testicular cancer who had disease progression after receiving cisplatin-containing combination chemotherapy and who were treated with high-dose chemotherapy and stem cell rescue, 116 had a complete remission of disease without relapse with a median follow-up of 48 months (range, 14 to 118).[69] Durable remissions were seen in patients receiving high-dose chemotherapy plus stem cell rescue as second-line therapy, as third-line (or later) therapy, and in patients with platinum-refractory disease.[70] An update of the Indiana University experience in 364 consecutive patients with metastatic germ cell tumors who progressed after cisplatin-based combination chemotherapy and were subsequently treated with high-dose chemotherapy and peripheral-blood stem cell rescue reported a 2-year PFS of 60% (95% CI; 55, 65) and a 2-year OS of 66% (95% CI; 60, 70).[71] Three hundred three patients were treated in the second-line setting with a 2-year PFS of 63% (95% CI, 57, 68), and 61 patients received treatment in the third-line or later setting with a 2-year PFS of 49% (95% CI; 36, 61). Patients with primary mediastinal germ cell tumors treated with high-dose chemotherapy and with stem cell rescue demonstrated worse outcomes, and these patients should be enrolled in clinical trials at specialized centers. Treatment-related morbidity following high-dose therapy can be substantial, and all patients should be referred to major treatment centers specializing in this approach.[72] An important unanswered question relates to the selection of patients for standard salvage versus high-dose chemotherapy, as two prospective, phase III trials that evaluated the role of high-dose chemotherapy versus standard-dose salvage therapy demonstrated mixed results. An important ongoing phase III trial of initial salvage chemotherapy for patients with germ cell tumors (TIGER) randomly assigns patients with relapsed disease to TIP for four cycles or ifosfamide plus paclitaxel for two cycles followed by high-dose carboplatin and etoposide for three cycles.

SURGERY AFTER CHEMOTHERAPY FOR NONSEMINOMATOUS TUMORS

Surgery after chemotherapy is an integral part of the treatment of patients with germ cell

tumors and should be considered for individuals with residual radiographic abnormalities but with normal serum tumor markers after treatment. Retroperitoneal lymph node dissection is the standard surgery for patients with evidence of disease in the retroperitoneum. All residual masses at all sites should be excised, as the histology at one site does not adequately predict the histology at other sites. Approximately 45% of residual masses will consist of necrotic debris or fibrosis, 40% will consist of mature teratoma, and 15% will harbor viable germ cell tumor. If viable germ cell tumor has been completely resected, two additional cycles of chemotherapy are administered. Although histologically benign, teratoma arises from malignant germ cells and may grow over time; surgical removal is needed. Additionally, a minority of resected teratomas will have malignant transformation to cell types including rhabdomyosarcoma, adenocarcinoma, and others. Surgical resection is the mainstay of treatment; however, chemotherapy for metastases of a particular cell type may result in major responses and long-term survival in select patients.[73]

The role for surgery in all patients who initially present with visible disease on imaging and have normalization or minimal residual disease on repeat imaging after chemotherapy is controversial. In 87 patients with minimal residual tumor masses (largest diameter of the residual mass on transaxial plane, ≤ 20 mm) after chemotherapy, 58 patients (67%) had complete fibrosis or necrosis, 23 (26%) had teratoma, and 6 (7%) had viable malignant germ cell tumor. Thus, approximately one-third of patients had vital tumor tissue with teratoma at risk for growth and/or malignant transformation and viable germ cell tumor at risk for progression.[74] Many experts advocate for no surgery if retroperitoneal lymph nodes have normalized (residual mass < 1 cm) on CT scan with a reported 15-year recurrence-free and cancer-specific survival of 90% and 97%, respectively, for a nonsurgical approach.[75] Additional concerns with a nonsurgical approach include the poor outcome associated with late relapses and the finding that a lack of prior retroperitoneal surgery is a major predisposing factor.[32,76] Patients with a late relapse who are symptomatic at presentation, as well as those with multifocal disease, have a significantly decreased survival.[77] With nonseminomatous germ cell tumors, FDG-PET scans are unable to distinguish fibrosis from teratoma, thereby limiting the utility of PET imaging in determining the histology of residual masses after chemotherapy.

An exception to the requirement for normal tumor markers is the patient with elevated serum tumor markers whose disease did not respond to salvage chemotherapy. This clinical scenario is rare because fewer than 5% of patients who do not have normal marker status are candidates for surgical excision of a solitary residual mass. Surgery in the setting of elevated markers should be considered only by specialists with experience in the management of these cases.

ASSOCIATED MALIGNANT DISEASE

Malignant transformation of a somatic teratomatous component of a nonseminoma to somatic malignancies, including rhabdomyosarcoma, adenocarcinoma, primitive neuroectodermal tumor, and leukemia, as well as others, has been well described.[73] The presence of i(12p) or excess 12p copy number in these tumors establishes the clonal germ cell tumor origin. The finding of i(12p) or excess 12p genetic material by either molecular or cytogenetic studies correlates with response to cisplatin therapy.[78] Mediastinal nonseminomatous germ cell tumors also are associated with the presence of myeloproliferative disorders, including acute nonlymphocytic leukemia and acute megakaryocytic leukemia. A minority of patients with poorly differentiated carcinomas of unknown primary origin have a complete response to cisplatin-based

chemotherapy. The presence of additional clinical features, including male sex, predominant midline tumor, relatively young age, and elevated serum tumor markers, has suggested that the minority of patients with poorly differentiated carcinomas of unknown primary origin may have germ cell tumors. Clinical features as well as molecular and cytogenetic studies are important in the management of carcinomas of unknown primary or midline tumors of uncertain histogenesis.

SURVIVORSHIP AND LATE EFFECTS

An evaluation of the long-term risk of cardiovascular disease in survivors of testicular cancer demonstrated a moderately increased risk of myocardial infarction at young ages for patients with nonseminomatous germ cell tumors.[79] Increased risk was associated with prior chemotherapy regimens including cisplatin/vinblastine/bleomycin, as well as BEP, and with previous mediastinal irradiation and recent tobacco use. In a 20-year follow-up study of 990 men treated for unilateral testicular cancer, treatment with infradiaphragmatic radiation therapy and/or cisplatin-based chemotherapy increased the long-term risk for cardiovascular disease.[80] Patients who were treated with BEP alone had a 5.7-fold higher risk (95% CI; 1.9, 17.1) for coronary artery disease compared with surgery only and a 3.1-fold higher risk (95% CI; 1.2, 7.7) for myocardial infarction compared with age-matched controls from the general population. Acute chemotherapy-induced cardiovascular changes have been observed in patients treated with cisplatin-based chemotherapy, including an increase in plasma von Willebrand factor levels and an increased intima-media thickness of the carotid artery.[81] In addition to chemotherapy-induced endothelial damage, cardiovascular toxicity also is likely related to metabolic syndrome and gonadal dysfunction.[82]

There is an increased risk of secondary malignancies in patients with testicular cancer that is related to prior radiotherapy or chemotherapy for at least 35 years after treatment.[23] Increased risks have been seen for cancers of the stomach, gallbladder, bile ducts, pancreas, bladder, kidney, and thyroid, as well as for soft-tissue sarcoma, nonmelanoma skin cancer, and myeloid leukemia.[83] The long-term risks of second malignant neoplasms and cardiovascular disease were evaluated in a cohort from the Netherlands of 2707 men with testicular cancer who were 5-year survivors.[84] Radiotherapy and chemotherapy increased the risk of second malignant neoplasms or cardiovascular disease to a similar extent as smoking. Subdiaphragmatic radiation strongly increased the risk of secondary malignancies but not of cardiac disease, whereas chemotherapy increased the risks for both. Median survival was 1.4 years after a secondary malignancy and 4.7 years after cardiovascular disease. In a population-based study evaluating the risk for solid tumors after chemotherapy or surgery for testicular nonseminoma, a significantly increased risk for solid tumors was seen among patients treated in the modern era of cisplatin-based chemotherapy with no increase in risk following surgery (standardized incidence ratio for chemotherapy, 1.43; 95% CI; 1.18, 1.73, compared with 0.93 for surgery alone; 95% CI; 0.76, 1.14).[85]

Patients with newly diagnosed testicular cancer are at risk for decreased sperm counts or impaired sperm motility. With treatment, infertility can result from retrograde ejaculation after retroperitoneal lymph node dissection or as a result of radiation or chemotherapy. Some patients will have long-standing chemotherapy-induced oligospermia or azoospermia; however, in a survey study of patients treated with two to four cycles of standard cisplatin-based chemotherapy without additional treatment after surgery, the 15-year actuarial paternity rate was 85%, with decreased success with increasing number of cycles.[86] Patients who are scheduled to have a retroperitoneal lymph node dissection, radiation therapy, or chemotherapy

are advised to bank sperm. Other late effects of treatment include ototoxicity, chronic neurotoxicity, renal impairment, pulmonary toxicity, and anxiety disorder.[87,88] In light of a young age at diagnosis and high cure rates, patients with testicular cancer require specialized follow-up care with close attention to monitoring for late effects of cancer and cancer therapy.[89,90]

KEY POINTS

- Germ cell tumor staging includes serum tumor markers, and management of advanced disease requires the use of a risk-adapted classification system.
- The main histologic subtypes of germ cell tumors (i.e., seminoma and nonseminoma) have biologic significance and require different treatment strategies.
- Surveillance represents an important treatment option for patients with early-stage germ cell tumors.
- Combined-modality treatment approaches are used to achieve the highest probability of cure with the least morbidity.
- Potential management options for relapsed or refractory germ cell tumors include standard salvage chemotherapy, high-dose chemotherapy with peripheral stem cell rescue, and surgery.
- Survivorship issues are an important component of the treatment of patients with germ cell tumors.

BLADDER CANCER

EPIDEMIOLOGY

An estimated 76,960 (58,950 men and 18,010 women) new cases of bladder cancer and 16,390 (11,820 men and 4570 women) related deaths occurred in the United States in 2016.[1] The incidence of bladder cancer is 3 to 4 times higher in men than in women and the median age at diagnosis is 73. The approximate 5:1 ratio of incidence to mortality reflects the frequency of noninvasive tumors compared with muscle-invasive tumors and metastatic disease. Although white Americans have a 2-fold higher incidence of bladder cancer, black Americans have a higher mortality rate, with a higher incidence of high-grade and muscle-invasive tumors.[91,92] The difference in mortality does not appear to be related to the intensity and quality of care received.[93] Risk factors for bladder cancer include tobacco use, occupational exposures, urinary tract diseases, and pharmaceutical drug use.[94] Cigarette smoking is strongly associated with an increased risk of bladder cancer among men and women. In the United States, the risk of bladder cancer in former smokers (hazard ratio [HR], 2.22; 95% CI; 2.03, 2.44) and current smokers (HR, 4.06; 95% CI; 3.66, 4.50) compared with the risk in never-smokers has increased over time.[95] Although smoking cessation is associated with a reduced risk of bladder cancer, the risk as compared with that in never-smokers remains elevated for those who have quit even after 10 years or more of smoking. This risk increases in proportion to the amount and duration of cigarette exposure with heavy smokers (more than 20 cigarettes per day and/or more than 40 years), resulting in up to a 5-fold higher relative risk compared with nonsmokers. Occupational exposure to aromatic amines (particularly 2-

naphthylamine, benzidine, and polycyclic aromatic hydrocarbons) is associated with an increased incidence of bladder cancer (e.g., workers in dyestuff manufacturing and rubber and aluminum industries). Infection with the trematode *Schistosoma haematobium* leads to chronic irritation of the urothelium and to an increased risk of both squamous and urothelial carcinomas. Other chronic urinary tract infections, including stones and cystitis, also may lead to chronic inflammation and to an increased risk of bladder cancer. Heavy use of phenacetin-containing analgesics is associated with tumors of the renal pelvis and ureter, and cyclophosphamide also has been associated with an increased risk of urothelial carcinoma. These myriad risk factors lead to field changes within the urothelium that predispose individuals to the development of recurrent tumors, as well as to the involvement of new locations in the urothelial tract (polychronotropism). Hereditary nonpolyposis colon cancer (HNPCC) syndrome, also known as Lynch syndrome, is associated with an increased risk for the development of bladder and other urothelial cancers, most notably upper tract tumors.[96]

The three general categories of disease—non–muscle-invasive, muscle-invasive, and metastatic—differ in tumor biology, clinical phenotype, management, and prognosis. For non–muscle-invasive tumors, the goal is to prevent recurrence and progression to an incurable state. For muscle-invasive disease, the goal is to maximize the chance for cure using a multimodality approach incorporating chemotherapy with surgery or radiation therapy. The management of metastatic disease requires the use of established prognostic and predictive factors to determine the therapeutic objectives and potential for treatment-related toxicity. The main goals are prolongation of survival and palliation of symptoms. Bladder preservation may be considered in select patients using a trimodality approach: a maximal transurethral resection followed by concurrent chemotherapy and radiation therapy.

PATHOLOGY

Urothelial carcinoma may occur throughout the urinary tract (i.e., in any structure lined by the urothelium), with more than 90% of tumors originating in the bladder. Upper urinary tract tumors, including the renal pelvis and ureter, account for 5 to 7% of urothelial carcinomas, with renal pelvis tumors comprising the majority. In the United States, 92% of lower urinary tract tumors are urothelial carcinomas, 5% are squamous cell cancers, 2% are adenocarcinomas, and 1% are small cell carcinomas. Lesions of mixed histology generally are variants of urothelial carcinoma. Adenocarcinomas may be of urachal origin, occurring at the junction of the urachal ligament and bladder dome. In Northern Africa and other parts of the world where there is a high prevalence of infection with *S. haematobium,* up to 75% of tumors are pure squamous cell carcinomas.

BIOLOGY

Molecular profiling has demonstrated that urothelial tumors evolve through divergent pathways corresponding to the clinical phenotypes of nonlethal, recurrent non–muscle-invasive lesions and lethal, muscle-invasive, and metastatic disease.[97] Deletions of both arms of chromosome 9 are seen during the earliest stages of urothelial tumorigenesis. Overexpression of *HRAS,* the first human oncogene identified in urothelial carcinoma, is seen in the majority of human urothelial cancers. The RAS signaling pathway appears to have a major role in the development of low-grade, noninvasive lesions; 30 to 40% are characterized by activating mutations in the *HRAS* gene and 70% have mutations in *FGFR3,* an upstream tyrosine kinase receptor involved in cellular proliferation and angiogenesis. Although approximately 70% of these low-grade lesions

will recur, only 10 to 15% will progress to invasive lesions. Progression of low-grade lesions to invasive disease is characterized by structural and functional alterations in the tumor suppressors p53 and Rb, in addition to chromosome aberrations, including deletions in chromosome 8p, 11p, 13q, and 14q. Approximately 20 to 30% of patients will present with high-grade muscle-invasive tumors, with greater than 50% of these tumors containing alterations in p53 and Rb. Despite radical cystectomy and the use of perioperative chemotherapy, up to 50% of muscle-invasive tumors will progress to local and distant metastases. This ability to invade and metastasize is not only a function of alterations in the tumor cells, but also involves the interactions of the tumor cells with the local micro-environment. The following are seen in urothelial carcinoma: defects in cell–cell adhesion with loss or reduced expression of E-cadherin; increased levels of matrix metalloproteinases, such as MMP9 and MMP2, which lead to degradation of the extracellular matrix; and increased angiogenic factors, such as vascular endothelial growth factor (VEGF).

Retrospective studies have suggested that p53 nuclear overexpression is an independent predictor of progression and decreased survival.[98] Immunohistochemical staining for p53, p21, pRB, and p16 in a series of patients with bladder cancer who underwent radical cystectomy and bilateral pelvic lymphadenectomy demonstrated that altered expression of each of the four cell cycle regulators was associated with bladder cancer outcome, with p53 as the strongest predictor.[99] A phase III study of molecularly targeted adjuvant therapy in locally advanced bladder cancer based on p53 status failed to confirm both the prognostic value of p53 and the benefit of chemotherapy in p53-positive tumors.[100] Using oligonucleotide microarrays, a genetic profile consisting of 174 probes has identified patients with lymph node metastases and poor survival.[101]

In an attempt to identify actionable genomic alterations in high-grade bladder cancer, an integrative genomic analysis including mutational profiling and DNA copy number alterations was performed on 97 high-grade tumors.[102] Core pathway alterations included the RTK/RAS/RAF pathway (e.g., *ERBB2* amplification and *FGFR3* mutation), *TP53* (e.g., *TP53* mutation and *MDM2* amplification), *RB1/E2F3* (e.g., *RB1* mutation and *E2F3* amplification), and phosphoinositide 3-kinase *(PI3K)/AKT* (e.g., *PIK3CA* mutation and *TSC1* mutation). Overall, 61% of the tumors harbored genetic alterations representing potential drug targets. The Cancer Genome Atlas Research Network comprehensive molecular characterization of urothelial bladder carcinoma revealed recurrent mutations in genes involved in cell-cycle regulation, chromatin regulation, and kinase signaling with potential therapeutic targets identified in 69% of tumors including targets in the PI3K/AKT/mTOR pathway and the RTK/MAPK pathway.[103] In addition to novel targets, data suggests that mutations in DNA damage repair (DDR) genes in urothelial cancers including *ERCC2*, *ATM*, *FANCC*, *RB1* as well as others may predict response to platinum-based chemotherapy.[104,105] In addition to DNA sequencing, whole-genome mRNA expression profiling has resulted in the identification of intrinsic subtypes of muscle-invasive bladder cancer including luminal and basal subtypes that resemble the hallmarks of breast cancer biology.[106-108] In the recently published updated Cancer Genome Atlas Research Network comprehensive molecular characterization of 412 muscle-invasive bladder cancers, 58 genes were significantly mutated and the high mutational load was driven mainly by APOBEC-mediated mutagenesis. In addition, mRNA expression clustering analyses identified a “neuronal” subtype lacking small cell or neuroendocrine histology and associated with a poor survival.[109] Bladder cancer has the fourth highest mutational burden after melanoma, lung squamous, and lung adenocarcinoma.[110] Recent positive results from clinical trials of immune checkpoint inhibitors including anti-programmed death-1 (anti-PD-1) and anti-programmed death ligand 1

(PD-L1) antibodies in patients with metastatic bladder cancer suggest that this high mutational burden may enhance the ability of the immune system to recognize tumor cells and also emphasizes the importance of immune surveillance in urothelial cancer.[111]

DIAGNOSIS AND STAGING

The most common presenting symptom is hematuria. Irritative voiding symptoms including dysuria in a patient with risk factors such as tobacco use may be related to carcinoma in situ or a bladder tumor. Less frequently, patients present with symptoms related to distant metastases. The diagnosis is established by cystoscopy and biopsy. The T staging for bladder cancer is listed below:

- Ta tumors are noninvasive papillary lesions that tend to recur but not invade.
- Tis, or carcinoma in situ (CIS), is the precursor of a more aggressive and potentially lethal invasive variant.
- T1 tumors invade the subepithelial connective tissue, including lamina propria or muscularis mucosa.
- T2 tumors invade the muscle.
- pT2a tumors invade superficial muscle.
- pT2b tumors invade deep muscle.
- T3 tumors invade perivesical tissue.
- pT3a are evident microscopically.
- pT3b are evident macroscopically (extravesical mass).
- T4 tumors invade the prostate, seminal vesicles, uterus, vagina, pelvic, and/or abdominal wall.

The major problem with staging is that the correlation of depth of invasion determined by cystoscopy and biopsy with the results of cystectomy is only 50 to 60%. Noninvasive imaging with CT or MRI can identify extravesical or nodal disease and is more reliable if done prior to the transurethral resection with a distended bladder. FDG-PET/CT may have a role in the staging of muscle-invasive disease and in the detection of metastatic bladder cancer.[112,113] The histologic grading system of low-grade and high-grade is more relevant for noninvasive tumors, because virtually all invasive neoplasms are high grade.

THERAPY FOR BLADDER CANCER BY DISEASE STAGE

Non–Muscle-Invasive Disease

Up to 80% of patients with newly diagnosed bladder cancer present with non–muscle-invasive disease (includes papillary urothelial neoplasm of low malignant potential [PUNLMP], CIS, and low- and high-grade urothelial cancers), with 70% confined to the mucosa (Ta or Tis) and 30% involving the submucosa (T1). The treatment involves complete removal of the lesion by transurethral resection followed by rigorous surveillance with cystoscopy and urine cytology at 3-month intervals for recurrence and/or progression to a more advanced stage. The sensitivity of urine cytology ranges from 13 to 75%, and the limitations of cystoscopy include impaired visualization related to bleeding and difficulty distinguishing flat carcinoma in situ from benign lesions; however, urine markers, such as nuclear matrix protein (NMP22) and fluorescence in situ hybridization to detect chromosomal alterations might complement cystoscopy and urine

cytology in the detection of recurrence.[114-116] Approximately 70% of patients with non–muscle-invasive bladder cancer will have a recurrence or a new occurrence within 5 years, and approximately 15% will progress to a more advanced stage. When urinary cytology is positive but cystoscopy reveals no visible lesions in the bladder or urethra, selective catheterization and visualization of the upper urinary tracts is warranted. The management of non–muscle invasive bladder cancer involves a complete transurethral resection with or without intravesical therapy.[117] Intravesical therapy has two uses: as prophylaxis—to prevent or delay tumor recurrence and/or progression—and as therapy for carcinoma in situ. A single dose of intravesical mitomycin after transurethral resection in patients with non–muscle-invasive bladder cancer is associated with a significant reduction in tumor recurrence.[118] Although the indications for prophylaxis vary, intravesical therapy generally is recommended for multifocal or recurrent Ta lesions, carcinoma in situ, and T1 disease. Randomized trials have established bacille Calmette-Guérin (BCG) with six weekly installations, including a maintenance schedule, as the intravesical treatment of choice to limit recurrence and reduce the incidence of progression.[119] Salvage intravesical therapy with BCG and interferon (IFN)-alpha-2b may be effective for patients whose disease does not respond to BCG alone. Alternative intravesical agents include mitomycin C, gemcitabine, docetaxel, doxorubicin, and valrubicin, which have been shown to prevent recurrence with minimal effect on progression. For disease that does not respond to BCG, these alternative agents may be considered. In some cases, cystectomy is indicated, with a delay in cystectomy leading to worse outcome.[120-122] A meta-analysis of outcomes and prognostic factors in 15,215 patients with high-grade T1 bladder cancer aimed at improving selection criteria for early cystectomy demonstrated that depth of invasion (T1b/c) into lamina propria as well as several other previously described factors including lymphovascular invasion, associated carcinoma in situ, nonuse of BCG, tumor size greater than 3 cm, and older age predicted progression and cancer-specific survival.[123]

Muscle-Invasive Disease

Although the majority of patients present with non–muscle-invasive disease, approximately 20 to 40% of patients either present with more advanced disease or experience disease progression after therapy for non–muscle-invasive disease. Staging for patients with muscle-invasive disease includes a CT scan of the abdomen and pelvis, chest imaging, and, if clinically indicated, a bone scan. The standard treatment for a muscle-invasive tumor is a radical cystectomy with bilateral pelvic lymphadenectomy that includes removal of the bladder, prostate, seminal vesicles, and proximal urethra for men, and removal of the bladder, urethra, and uterus (including bilateral salpingo-oophorectomy), as well as excision of a portion of the anterior vaginal wall, for women. The pelvic lymph node dissection is a necessary part of the radical cystectomy surgery, with a more extended lymph node dissection associated with an improvement in outcome.[124,125] The three main types of urinary diversions include an ileal conduit that drains to an appliance on the anterior abdominal wall, a continent cutaneous reservoir constructed from detubularized bowel segments, and an orthotopic neobladder. More men are candidates for continent urethral reservoirs than women because of anatomic considerations. It is not clear that continent reconstruction after radical cystectomy is associated with an improvement in quality of life as compared with conduit diversion.[126] In fact, most patients report a favorable quality of life regardless of the type of diversion used.

Prognosis varies inversely with higher T stage, lymphatic or vascular invasion in the primary tumor, and lymph node involvement. In addition, extracapsular extension of lymph node

metastases is associated with a worse outcome.[127] In a series of 1054 patients undergoing radical cystectomy and pelvic lymphadenectomy, the overall recurrence-free survival rates at 5 and 10 years were 68% and 66%, respectively.[128] Patients with non–organ-confined, lymph node–negative tumors had a significantly higher ($p < 0.001$) probability of recurrence compared with patients who had organ-confined bladder cancers (Table 11-4). The 5- and 10-year recurrence-free survival rates for the 246 patients with lymph node involvement were 35% and 34%, respectively. Patients with organ-confined tumors and fewer than five involved lymph nodes had improved survival rates. The median time to recurrence among the 311 patients in whom the cancer recurred was 12 months (range, approximately 5 months to 11 years). Multivariate nomograms have been developed to predict outcome after radical cystectomy.[129,130] A partial cystectomy can provide adequate local control of invasive bladder cancer in select patients.[131] Less invasive surgical techniques, including laparoscopic and robotic radical cystectomy, have been evaluated and robot-assisted techniques may be similar to standard open surgery in terms of operative, pathologic, oncologic, complication, and most functional outcomes.[132-134] The use of bladder-sparing protocols as alternatives to surgery in the management of muscle invasive bladder cancer will be reviewed in the Bladder Preservation section.

Table 11-4 Survival Rates for Bladder Cancer According to Stage

	5-Year Survival (%)	10-Year Survival (%)
Node-Negative Disease		
pT2	77	57
pT3a	64	44
pT3b	49	29
pT4a	44	23
Lymph Node Involvement		
	31	23

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Metastatic Disease

Urothelial tumors are sensitive to several chemotherapy agents with different mechanisms of action, including methotrexate, vinblastine, doxorubicin, cisplatin, the taxanes, ifosfamide, pemetrexed, and gemcitabine. Two-, three-, and four-drug combinations have been used with the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) and gemcitabine plus cisplatin (GC) representing the standard regimens.[135-137] Randomized trials comparing MVAC with single-agent cisplatin and with the three-drug combination of doxorubicin, cyclophosphamide, and cisplatin demonstrated superior response rates, prolongation of time to progression, and improved OS for patients treated with MVAC. Increasing the dose intensity of MVAC in a 2-week schedule with growth factor support compared with classic MVAC on a 4-week schedule led to a borderline statistically significant relative reduction in the risk of

progression and death compared with MVAC. The median survival was 15.1 months with high-dose intensity MVAC and 14.9 months with MVAC.[138]

MVAC was compared with GC in patients with locally advanced or metastatic urothelial carcinoma.[136] Although this trial was not designed as a noninferiority study, the results demonstrated a similar response rate (GC, 49% vs. MVAC, 46%; p = 0.51), PFS (GC, 7.7 months vs. MVAC, 8.3 months; p = 0.63), and median survival (GC, 14 months vs. MVAC, 15.2 months; p = 0.66), as well as less toxicity for GC compared with MVAC. Specifically, treatment with GC produced less neutropenia, neutropenic fever, sepsis, and mucositis, but more anemia and thrombocytopenia compared with MVAC. The combination of docetaxel and cisplatin plus granulocyte colony-stimulating factor (G-CSF) has been compared with MVAC plus G-CSF in advanced urothelial carcinoma.[139] Treatment with MVAC resulted in a superior response rate (54.2% vs. 37.4%; p = 0.17), median time to progression (9.4 months vs. 6.1 months; p = 0.003), and median survival (14.2 months vs. 9.3 months; p = 0.026).

Several trials using taxanes have demonstrated promising results with ifosfamide plus paclitaxel and cisplatin, gemcitabine plus paclitaxel and cisplatin, and gemcitabine plus paclitaxel and carboplatin.[140] The superiority of triplet regimens has not been established. A randomized, international trial in patients with advanced urothelial cancer without prior systemic therapy comparing GC with paclitaxel/cisplatin/gemcitabine (PCG) demonstrated a higher overall response rate (ORR) for PCG that did not translate into a higher PFS or median survival for the triplet.[141] A sequential regimen using gemcitabine and doxorubicin followed by the combination of ifosfamide, paclitaxel, and cisplatin demonstrated a high ORR; however, the regimen was associated with toxicity without a clear benefit compared with other nonsequential, cisplatin-based regimens.[142]

As a disease of older individuals with coexisting medical problems, including impaired performance status and renal insufficiency, approximately 40 to 50% of patients with advanced bladder cancer are not eligible for cisplatin-based chemotherapy. Suggested criteria to determine ineligibility for cisplatin-based chemotherapy include at least one of the following: Eastern Cooperative Oncology Group (ECOG) performance status of 2 or higher, creatinine clearance less than 60 mL/min, grade 2 or greater hearing loss, grade 2 or greater neuropathy, and/or New York Heart Association Class III heart failure.[143] For patients with renal insufficiency who are not candidates for cisplatin, alternative regimens such as gemcitabine or paclitaxel with carboplatin have been used. Multiple phase II trials have suggested an improvement in outcome with cisplatin compared with carboplatin-based chemotherapy.[144] A phase II/III trial of gemcitabine and carboplatin compared with methotrexate and vinblastine plus carboplatin (M-CAVI) in patients with metastatic urothelial cancer ineligible for cisplatin-based chemotherapy (WHO performance status of 2 and/or creatinine clearance of 30 to 60 mL/min) demonstrated no difference in outcome and improved tolerability for gemcitabine and carboplatin as compared with M-CAVI.[145] Single-agent chemotherapy or supportive care alone may be most appropriate for some patients who are ineligible for cisplatin-based chemotherapy and have other significant medical issues and/or poor risk disease as defined below. That being said, results from the IMvigor 210 study, a multicenter, single-arm, two-cohort, phase II trial evaluated the anti-PD-L1 antibody, atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma (cohort 1).[146] At a median follow-up of 17.2 months in 119 patients who received atezolizumab, the objective response rate was 23% (95% CI; 16, 31) with 11 (9%) complete responses seen and 19 of the 27 responses ongoing. The median overall survival was 15.9 months (10.4 to not estimable). Tumor mutational load was associated with response. Atezolizumab was well tolerated, with immune-mediated adverse events

occurring in 14 (12%) patients. In a similar patient population including elderly patients and those with a poor performance status, the KEYNOTE-052 trial evaluated the anti-PD-1 antibody, pembrolizumab in 370 patients and demonstrated promising activity, with an ORR of 24%.[147] The median duration of response was not reached, with 83% of responses ongoing. Pembrolizumab was generally well tolerated. Based on these studies, both atezolizumab and pembrolizumab have received accelerated approval from the U.S. Food and Drug Administration (FDA) as first-line treatment for cisplatin-ineligible patients with locally advanced or metastatic urothelial carcinoma.

The prognostic factors predicting long-term survival of patients with metastatic urothelial carcinoma receiving MVAC chemotherapy include Karnofsky Performance Status (< 80%) and presence or absence of visceral metastases (lung, liver, or bone).[148] Median survival times for patients who had zero, one, or two risk factors were 33 months, 13.4 months, and 9.3 months, respectively. Two nomograms for predicting survival in patients with metastatic urothelial cancer have been published.[149,150] The pretreatment variables used to predict OS in the models include the presence and number of visceral metastases, albumin, performance status, hemoglobin, site of the primary tumor, lymph node metastases, and leukocyte count. Toxicity varies as a function of risk group. For patients with poor-risk disease, treatment-related mortality has been reported in 3 to 4% of cases. Although the frequency of these events may be reduced with the use of hematopoietic growth factors, MVAC is generally avoided in patients with poor-risk disease.

Until recently, there was no accepted standard of care for second-line chemotherapy in advanced bladder cancer.[151] Evaluations of single agents, such as ifosfamide, docetaxel, gemcitabine, paclitaxel, and pemetrexed, have demonstrated response rates between 9 and 27%, with a PFS in the range of 2 to 3 months and no documented improvement in OS. In a randomized phase III trial of vinflunine (a microtubule inhibitor) plus best supportive care compared with best supportive care alone as second-line therapy after a platinum-containing regimen, vinflunine did not demonstrate a significant survival benefit.[152] Although multidrug regimens have been associated with higher response rates, this does not appear to translate into an improvement in survival. In patients with metastatic disease who experience treatment failure after a platinum-based regimen, three adverse risk factors, including ECOG performance status greater than 0, hemoglobin level less than 10 g/dL, and the presence of liver metastasis, have been shown to predict OS.[153] The median OS times for patients with zero, one, two, or three risk factors are 14.2, 7.3, 3.8, and 1.7 months, respectively. A nomogram including baseline prognostic factors has been developed to estimate the activity of second-line therapy.[154]

In cohort 2 of the IMvigor 210 study, 315 patients with locally advanced or metastatic urothelial carcinoma whose disease progressed after prior platinum-based chemotherapy were enrolled, with 310 receiving atezolizumab at 1200 mg intravenously every 3 weeks.[155] PD-L1 expression on tumor-infiltrating immune cells (ICs) was prospectively assessed by immunohistochemistry by the percentage of PD-L1 positive immune cells present (IC0, < 1%; IC1, ≥ 1% but < 5%; and IC2/3, ≥5%). Compared with a historical response rate of 10%, treatment with atezolizumab resulted in a significantly improved RECIST v1.1 response rate for each immune cell group (IC2/3, 27%; 95% CI; 19, 37, $p < 0.0001$; IC1/2/3, 18%; 95% CI; 13, 24; $p = 0.0004$) and in all patients (15%; 95% CI; 11, 20; $p = 0.0058$). With a median follow-up of 11.7 months, ongoing responses were recorded in 38 (84%) of 45 responders. The median overall survival was 11.4 months (95% CI; 9.0, not estimable) in patients in the IC2/3 group. Exploratory analyses showed that responses were significantly higher in the TCGA luminal

cluster II RNA subtype than in other subtypes and that the median mutational load was significantly increased in responders. Atezolizumab demonstrated good tolerability with grade 3–4 immune-mediated adverse events occurring in 15 (5%) of 310 treated patients. Based on this study, atezolizumab received FDA accelerated approval for patients with locally advanced or metastatic disease who progress during or following platinum-containing chemotherapy. A more recently reported phase III study, KEYNOTE-045 compared the anti-PD-1 antibody, pembrolizumab, to investigator's choice of paclitaxel, docetaxel, or vinflunine for previously treated advanced urothelial cancer. Pembrolizumab was associated with a 27% reduction in the risk of death compared with chemotherapy (median OS, 10.3 months [95% CI; 8, 11.8] with pembrolizumab, vs. 7.4 months [95% CI; 6.1, 8.3] with chemotherapy [HR, 0.73, p = 0.0022]), leading to FDA approval of pembrolizumab in patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.[156] There was no significant difference in PFS in the total population or among patients who had a tumor PD-L1 combined positive score (percentage of PD-L1–expressing tumor and infiltrating immune cells relative to the total number of tumor cells) of 10% or more. The response rate was 21.1% in the pembrolizumab group as compared to 11.4% in the chemotherapy group (p = 0.001). Pembrolizumab was well tolerated, with fewer treatment-related adverse events in the pembrolizumab arm as compared to chemotherapy. Rare serious immune-related adverse events with pembrolizumab including pneumonitis, colitis, and nephritis were seen. Three additional checkpoint inhibitors including nivolumab, durvalumab, and avelumab, have received FDA accelerated approval for patients with metastatic urothelial carcinoma that progressed after platinum-containing chemotherapy.[157-159] Additional studies evaluating immune checkpoint inhibitors alone and in combination with other therapies in patients with different clinical stages of urothelial cancer are being actively pursued.

Other treatments under investigation in metastatic urothelial cancer also include molecularly targeted agents such as those targeting fibroblast growth factor receptor 3 (FGFR3) as well as the vascular endothelial growth factor (VEGF) pathway.[160] A phase I study of the FGFR 1-3 kinase inhibitor, BGJ398, demonstrated promising activity in *FGFR3*-mutant urothelial cancers.[161] The RANGE trial, a phase III study of docetaxel with or without the VEGF receptor 2 antibody, ramucirumab, in platinum-refractory advanced or metastatic urothelial carcinoma randomly assigned 530 patients with locally advanced or unresectable or metastatic urothelial carcinoma whose disease progressed on or after platinum-based chemotherapy to docetaxel plus either ramucirumab or placebo with a primary endpoint of investigator-assessed PFS.[162] PFS was significantly prolonged in patients who received ramucirumab plus docetaxel as compared to placebo plus docetaxel (median 4.07 months; 95% CI; 2.96, 4.47; vs. 2.76 months; 95% CI; 2.60, 2.96; hazard ratio [HR], 0.757, 95% CI; 0.607, 0.943; p = 0.0118). The ORR was higher in the ramucirumab plus docetaxel arm (24.5% vs. 14.0%). The combination did not result in significant additive toxicity. A phase III study, Cancer and Leukemia Group B (CALGB) 90601, that randomly assigned patients with advanced urothelial cancer to gemcitabine and cisplatin with or without bevacizumab, has completed accrual with results awaited.

In highly selected patients with metastatic urothelial carcinoma, resection of metastatic disease can result in long-term disease control.[163,164]

PERIOPERATIVE CHEMOTHERAPY FOR MUSCLE-INVASIVE AND LOCALLY ADVANCED BLADDER CANCER

The use of perioperative chemotherapy in the management of invasive and locally advanced bladder cancer has been studied in the neoadjuvant and adjuvant settings. The potential advantages for neoadjuvant chemotherapy include evaluation of response to therapy in vivo with assessment of the pathologic response in the cystectomy specimen, tumor downstaging to allow for a less complicated surgery, and the delivery of full-dose chemotherapy without the potential problems associated with postoperative recovery. The major advantages for the use of adjuvant chemotherapy include treatment based on pathologic criteria with the ability to select those patients at higher risk who are most likely to benefit from chemotherapy and to avoid the unnecessary treatment of patients with lower-risk disease.

Adjuvant Chemotherapy for Bladder Cancer

Although many physicians favor the use of adjuvant chemotherapy for patients with nodal involvement and extravesical tumor extension, definitive trials are lacking. Unfortunately, most of the adjuvant studies that have been performed have major limitations, including flawed statistical methodology with underpowered trials and early termination, as well as the use of suboptimal chemotherapy with non–cisplatin-containing regimens. For example, in one study, 91 patients with pT3, pT4, or node-positive disease were randomly assigned to receive either four cycles of adjuvant cisplatin, cyclophosphamide, and doxorubicin or observation. Although the trial demonstrated a significant delay in time to disease progression in patients who received chemotherapy, with 70% of patients disease-free at 3 years compared with 46% of untreated patients, the 5-year OS was not significantly different.[165] Several methodologic problems with this trial include the small sample size, the premature closure, and that 25% of patients assigned to chemotherapy never received it. A German study randomly assigned patients with pT3b, pT4a, and/or lymph node involvement to observation after cystectomy or to three cycles of adjuvant MVAC or combination methotrexate, vinblastine, epirubicin, and cisplatin.[166] The trial was terminated early when an interim analysis indicated an inferior DFS rate and a significantly higher relapse rate (18 of 22 patients, 82%) among untreated patients compared with patients who received chemotherapy (3 of 18 patients, 17%; $p = 0.0012$). For patients with nodal involvement, disease progressed in 92% of patients undergoing observation compared with 73% of patients who received adjuvant chemotherapy ($p < 0.002$). A survival difference was subsequently shown; however, patients did not receive chemotherapy at the time of relapse.[167] An Italian multicenter, randomized phase III trial comparing adjuvant GC chemotherapy with chemotherapy at relapse for patients with muscle-invasive bladder cancer after radical cystectomy did not demonstrate a significant difference in DFS and OS between the groups; however, the study was underpowered, having not met its accrual goal.[168] A randomized phase III trial that compared adjuvant PGC to observation in patients with resected high-risk bladder cancer (pT3-4 and/or pN+) by the Spanish Oncology Genitourinary Group demonstrated an improvement in DFS and OS; however, this trial was prematurely closed and underpowered, limiting the conclusions.[169] The largest adjuvant phase III study published to date, EORTC 30994, randomly assigned patients with pT3-pT4 or N+ M0 bladder cancer after radical cystectomy to immediate (4 cycles of GC, high-dose MVAC, or MVAC) compared with 6 cycles of chemotherapy at relapse.[170] The trial was closed after recruitment of only 284 of 660 planned patients. Although no significant improvement in OS with immediate treatment compared with deferred treatment was observed, the 5-year PFS was 47.6% compared with 31.8%, respectively, and median PFS was 3.11 years compared with 0.99 years, respectively (HR, 0.54; 95% CI; 0.4, 0.73; $p < 0.0001$). A systematic review and meta-analysis of 491

patients with bladder cancer from six randomized, controlled trials that compared local treatment plus adjuvant chemotherapy with local treatment alone revealed an overall HR for survival of 0.75 (95% CI; 0.60, 0.96; p = 0.019) suggesting a 25% relative reduction in the risk of death associated with adjuvant chemotherapy.[171] The power of the meta-analysis is clearly limited by the sample size, as well as by the flawed trials from which the analysis was derived. A 2013 updated systematic review and meta-analysis of randomized trials of adjuvant chemotherapy that included 945 patients from nine trials revealed a pooled HR of 0.77 (95% CI; 0.59, 0.99; p = 0.049) for OS and 0.66 (95% CI; 0.45, 0.91; p = 0.014) for DFS.[172] A comparative effectiveness study utilizing the National Cancer Database comparing cystectomy alone to cystectomy followed by adjuvant chemotherapy in patients with ≥ pT3 and/or pN+ bladder cancer has also demonstrated an improvement in overall survival with adjuvant chemotherapy (HR, 0.70; 95% CI, 0.64, 0.76).[173] The American Society of Clinical Oncology (ASCO) guideline endorsement on muscle-invasive and metastatic bladder cancer states that adjuvant chemotherapy may be offered to high-risk patients who have not received neoadjuvant chemotherapy.[174]

Neoadjuvant Chemotherapy for Bladder Cancer

Several of the initial prospective randomized trials of neoadjuvant chemotherapy using single agents and combination chemotherapy failed to demonstrate a benefit. The largest phase III neoadjuvant chemotherapy trial performed to date randomly assigned 976 patients with T2 G3, T3, or T4a and N0/X, M0 bladder cancer undergoing cystectomy or radiotherapy or both to three cycles of neoadjuvant chemotherapy with cisplatin, methotrexate, and vinblastine or no chemotherapy. Chemotherapy-associated mortality was 1% and cystectomy-associated mortality was 3.7%. At a median follow-up of 8 years, a significant 16% reduction in the risk of death (HR, 0.84; 95% CI; 0.72, 0.99; p = 0.037) corresponding to an increase in 10-year survival from 30 to 36% was seen in the chemotherapy arm.[175] The chemotherapy regimen was associated with a higher pathologic complete response rate.[176] A U.S. phase III Intergroup trial randomly assigned patients with T2-4aN0M0 bladder cancer to neoadjuvant MVAC plus cystectomy (153 patients) or to cystectomy alone (154 patients).[177] At a median follow-up of 8.7 years, the estimated risk of death was reduced by 25% for the patients who received MVAC and cystectomy. Median survival of patients assigned to surgery alone was 46 months compared with 77 months among patients assigned to MVAC plus cystectomy. The survival benefit of neoadjuvant MVAC was associated with tumor downstaging to pT0 (38% in those patients who received MVAC compared with 15% of those who received cystectomy), with an 85% 5-year survival for patients who experienced a pathologic complete response to neoadjuvant chemotherapy. A meta-analysis of neoadjuvant chemotherapy of 3005 patients with invasive bladder cancer enrolled in 11 randomized trials showed a significant OS benefit for platinum-based combination chemotherapy, with a 14% reduction in the risk of death and 5% absolute survival benefit at 5 years, with OS increasing from 45 to 50%.[178] This effect did not vary between subgroups of patients or type of local treatment. Based on these data, neoadjuvant cisplatin combination chemotherapy represents a standard of care in the management of muscle-invasive bladder cancer (Table 11-5). Although not formally evaluated in a randomized trial in the neoadjuvant setting, the most widely used regimen is gemcitabine/cisplatin.[179] Two phase II studies utilizing dose-dense MVAC with pegfilgrastim support demonstrated promising pathologic response rates in patients with cT2-cT4a, N0-1, M0 muscle-invasive bladder cancer.[180,181] Although perioperative chemotherapy has been grossly

underutilized, recent data suggest improved utilization of neoadjuvant chemotherapy.[182,183] There are insufficient data to support the use of noncisplatin chemotherapy regimens in the neoadjuvant setting. Thus, renal insufficiency or coexisting medical problems may limit the ability to use perioperative chemotherapy.

A recent comparative effectiveness study using the National Cancer Database of treatment strategies for bladder cancer with clinical evidence of regional lymph node involvement demonstrated that compared with cystectomy alone, preoperative chemotherapy was associated with a significant improvement in OS (HR, 0.80; 95% CI; 0.66-0.97).[184]

BLADDER PRESERVATION

A bladder-sparing approach is justified only when the treatment can completely eradicate the tumor in the bladder, the risk of recurrence is low, and there is not substantial compromise of bladder function.

Although neoadjuvant chemotherapy in combination with local therapy has been shown to improve OS, the role of chemotherapy alone in bladder preservation is problematic because of the inability to definitively determine which bladders are truly without residual tumor. In addition, pathologic complete response rates after neoadjuvant chemotherapy at the time of cystectomy are only 20 to 40%. At a minimum, chemotherapy alone cannot replace definitive treatment of the bladder by surgery or radiation.

In randomized trials, radiation therapy alone has been shown to be inferior to cystectomy with respect to survival, particularly for patients with T3 or T4 disease. Although radical cystectomy has not been formally compared with a multimodality bladder-sparing approach, multiple studies have evaluated trimodality treatment consisting of transurethral resection (as complete as safely possible) together with chemotherapy plus radiation therapy for select patients resulting in long-term DFS and OS rates approaching those seen in radical cystectomy series.[185] An analysis of long-term outcomes of selective bladder preservation in 348 patients at the Massachusetts General Hospital demonstrated 5-year disease-specific survival and OS rates of 64% and 52%, respectively, with preservation of the native bladder in greater than 70% of patients.[186] The majority of trimodality protocols have used cisplatin-based chemotherapy; however, other agents such as paclitaxel and gemcitabine have been used as well. In the largest randomized study to compare chemoradiotherapy using fluorouracil and mitomycin with radiotherapy alone in muscle-invasive bladder cancer, the chemoradiotherapy arm was associated with a 32% reduction in the risk of locoregional recurrence (HR, 0.68; 95% CI; 0.48, 0.96; p = 0.03) at a median follow-up of 69.9 months.[187] An important component of many bladder-sparing protocols has included an evaluation of early response of the primary tumor to treatment with less than a complete response requiring cystectomy. Approximately one-third of patients initiated on a bladder-sparing protocol will ultimately require cystectomy for a less-than-complete response or for recurrent muscle-invasive tumors.[188]

Quality of life is another important consideration. Radiation therapy can induce disturbances in the function of the bladder, anal sphincter, and large bowel. The morbidity of radiation therapy has decreased with the availability of better imaging, allowing for a boost to the primary tumor and a reduction in fraction size. An evaluation of late pelvic toxicity after bladder-sparing therapy in patients with invasive bladder cancer who received treatment in four prospective Radiation Therapy Oncology Group (RTOG) protocols showed low rates of substantial late pelvic toxicity (7% of patients with late grade 3 or greater pelvic toxicity: 5.7% genitourinary and 1.9% gastrointestinal) at a median follow-up of 5.4 years.[189] The main

disadvantage for bladder preservation is the requirement for lifelong surveillance as a result of the risk of recurrence or development of a new bladder cancer. However, many of these new or recurrent tumors are noninvasive and can be managed endoscopically. There is not a clear role for the use of neoadjuvant chemotherapy prior to combined modality therapy in bladder preservation.[190]

OTHER UROTHELIAL TRACT CANCERS

Cancers of the renal pelvis, ureter, and proximal urethra also are of urothelial origin and should be treated on the basis of primary histology. Upper urinary tract tumors may have a worse outcome as compared to urothelial carcinomas that arise in the bladder. Comprehensive genomic profiling of upper tract tumors has revealed novel mutations, differing mutational frequencies and expression subtypes with unique molecular profiles as compared to bladder cancer.[191] Unfortunately, unlike bladder cancer, there is great difficulty in the clinical staging of upper tract urothelial carcinomas and management decisions generally rely on tumor grade. Because bladder cancer will develop in approximately 20 to 50% of patients with urothelial carcinomas of the upper urinary tract, surveillance cystoscopy is necessary. The two theories for the multifocal nature of urothelial carcinoma include the field cancerization effect and monoclonality (i.e., tumor cells spreading from their origin to multiple sites). Thus, simultaneous or metachronous primary tumors of the urothelium at multiple sites may occur, and monitoring is required, including follow-up cystoscopies and imaging of the upper tracts.

Table 11-5 **Randomized Trials of Neoadjuvant Cisplatin-Based Combination Chemotherapy for Muscle-Invasive Bladder Cancer**

Clinical Trial	Eligible Disease	Comparison	Median Survival (years)	pT0 Rate (%)	Survival Rates (%)
Grossman et al.[177]	T2-4a, N0, M0	Three cycles of MVAC plus cystectomy	6.4	38	57 (5 years)*
		Cystectomy alone	3.8	15	42 (5 years)*
Hall[176]	T2(G3), T3-T4a, N0/NX, M0	Three cycles of CMV plus cystectomy or radiotherapy or both	NA	33	56, 49, 36† (3, 5, 10 years)
		Cystectomy or radiotherapy or both	NA	12	50, 43, 30† (3, 5, 10 years)

*p - 0.06 by a stratified log-rank test
†p = 0.037; HR, 0.84; 95% CI; 0.72, 0.99.
Abbreviations: CMV, cisplatin/methotrexate/vinblastine; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; NA, not available; pT0, pathologic complete response.
Adapted from Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med. *2003;349(9): 859-866; Adapted from Hall RR et al. The Intl Collaboration of Trialists of the MRC Advanced Bladder Cancer Group, MRC Clinical Trials Unit. ASCO Annual Meeting.* Proc Am Soc Clin Oncol. *2002:21:Abstract 710, No. 18S; and adapted from International Collaboration of Trialists, Medical Research Council Advanced Bladder Cancer Working Party (now the National Cancer Research Institute Bladder Cancer Clinical Studies Group), European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group, et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial.* J Clin Oncol. *2011;29:2171-2177.*

Regarding the management of noninvasive bladder cancer with intravesical BCG, it is not uncommon for relapse to occur at the ureteral orifices, ureter, or urethra—areas that are less accessible to intravesical treatment. As such, monitoring must include periodic evaluations of the remaining urothelium with cytology and imaging to ensure relapses or new primary tumors are identified and treated early.

The chemotherapy used for urothelial carcinoma has been considered to be less effective in nonurothelial histology tumors; however, a secondary analysis of the U.S. phase III Intergroup trial of neoadjuvant MVAC in patients with nonurothelial components in the tumor including squamous and glandular differentiation, demonstrated a survival benefit from chemotherapy in these mixed histology tumors.[192] For patients with pure small cell or adenocarcinoma, the use of chemotherapy regimens that have demonstrated activity in other sites with similar histology is generally used (e.g., etoposide and cisplatin for small cell carcinoma of the lung may be used for the management of small cell carcinoma of the bladder). Micropapillary bladder cancer, a rare variant of urothelial carcinoma, has been associated with a poor prognosis.[193] Intravesical therapy may be less effective, and early radical cystectomy is often recommended.

SURVIVORSHIP AND ELDERLY CONSIDERATIONS

Bladder cancer is predominantly a disease of older individuals with coexisting medical issues, which strongly affect management decisions. Although the majority of patients are diagnosed with non–muscle-invasive disease, lifelong surveillance including urine cytology, cystoscopy, and periodic imaging is required. For those with muscle-invasive disease, the requirement for a radical cystectomy in the majority of patients necessitates a urinary diversion procedure, and in patients receiving neoadjuvant cisplatin-based chemotherapy, the potential for both short- and long-term chemotherapy-related side effects including peripheral neuropathy, hearing loss, and renal dysfunction, as well as others exists. Although life expectancy is limited in patients with metastatic disease, chemotherapy-related side effects can have a substantial effect on quality of life. Many older patients are not candidates for perioperative chemotherapy secondary to the normal physiologic decline in renal function with aging, baseline hearing loss, and other comorbidities such as cardiac disease. Further advancements in immuno-oncology such as with checkpoint inhibitors may allow for the treatment of older patients who otherwise would be unable to receive standard chemotherapy. For example, 21% of the patients treated with atezolizumab in the first-line setting on IMvigor 210 were age ≥ 80. Although radical cystectomy is a major surgical procedure, there is evidence to support the ability to safely perform a radical cystectomy in older individuals, including octogenarians.[194]

KEY POINTS

- Urothelial tumorigenesis results in three general categories of urothelial tract tumors—non–muscle-invasive, muscle-invasive, and metastatic—that differ with respect to tumor biology, clinical phenotype, prognosis, and management. The staging of localized bladder cancer requires a transurethral resection specimen that includes muscle to ensure that a muscle-invasive tumor is not missed.
- Level 1 evidence supports the use of neoadjuvant cisplatin-based combination chemotherapy in patients with muscle-invasive bladder cancer. Although the data for adjuvant chemotherapy are less robust, it may be considered for patients with high-risk features after radical cystectomy.
- Bladder preservation may be considered in select patients using a trimodality approach: a maximal transurethral resection followed by concurrent chemotherapy and radiation therapy.

- Immune checkpoint inhibitors including anti-PD-1 and anti-PD-L1 antibodies have become the standard of care for patients with locally advanced and metastatic urothelial cancer after platinum-based chemotherapy and have also demonstrated promising activity in patients who are not fit enough for cisplatin in the first line setting in patients who are unable to receive cisplatin.

RENAL CANCER

Renal cell carcinomas (RCC) account for 90% of all malignant neoplasms of the kidney, with an estimated 62,700 newly diagnosed cases of kidney tumors (39,650 men and 23,050 women) and 14,240 deaths (9240 men and 5000 women) in 2016.[1] Renal cancers were historically called the “internist's tumor” based on its protean clinical presentations, including fatigue, weight loss, and anemia. Today, less than 10% of cases present with the classic triad of hematuria, abdominal pain, and a palpable mass. Between 1993 and 2004, the proportion of patients diagnosed with stage I RCC increased from 43.0 to 57.1%, whereas the proportion of patients diagnosed with stage IV disease decreased from 27.4 to 18.7%, as a result of the increased use of imaging for other diagnostic purposes.[195] Risk factors for RCC include smoking, obesity, hypertension, and acquired cystic kidney disease, which is associated with end-stage renal disease.[196,197] Tobacco use (longer duration and exposure) is associated with an increased risk of advanced RCC.[198] Approximately 2% of cases are associated with inherited syndromes.

CT scan with contrast medium is a reliable method for detecting and staging renal cancers. MRI is useful when renal function is poor, as well as to evaluate for local invasion or to assess the renal vein and inferior vena cava for thrombus. Although negative FDG-PET imaging does not reliably exclude renal cancer, it may be useful in evaluating for local recurrence and distant metastases.[199] Staging is performed using the AJCC staging classification (Table 11-6).[15]

Surgical excision by open or laparoscopic nephrectomy is the primary treatment for patients with localized disease, either by radical nephrectomy or nephron-sparing partial nephrectomy for small tumors. The management of small renal masses (defined as incidentally image-detected, contrast-enhancing renal tumors ≤ 4 cm in diameter) that are generally consistent with stage T1a RCC may include a biopsy when the results may alter management, active surveillance for patients with significant comorbidities and limited life expectancy, and a partial nephrectomy for patients in whom an intervention is indicated and with a tumor amenable to this approach.[200] Percutaneous thermal ablation may be considered in appropriately selected patients. In one prospective, randomized trial, a lymph node dissection did not prolong OS,[201] although the role for lymphadenectomy remains controversial.[202] Tumor extension into the renal vein or inferior vena cava, indicating stage III disease, does not preclude resection, and cardiopulmonary bypass may be required; approximately 50% of such patients have prolonged survival with a successful resection. There is no benefit to postoperative radiation therapy for patients with locally advanced disease. Signs and symptoms of hepatic dysfunction may occur in patients with localized renal cancer (i.e., without evidence of metastatic disease). This is a paraneoplastic phenomenon referred to as Stauffer syndrome. Although rare, patients with this syndrome should undergo resection, which leads to reversal of the hepatopathy.

Cytoreductive nephrectomy should be considered as an initial treatment for patients with metastatic disease or to relieve symptoms or control bleeding. Two prospective, randomized studies demonstrated improved survival for patients subsequently treated with IFN alpha-2b, with a combined analysis showing a median survival of 13.6 months for patients undergoing

nephrectomy plus IFN compared with 7.8 months for patients receiving IFN alone, despite similar low response rates to IFN.[203] The role for cytoreductive nephrectomy is less well defined in the newer era of novel agents targeting angiogenesis. A retrospective study of cytoreductive nephrectomy in patients with metastatic RCC who received VEGF-targeted therapy revealed a prolonged survival with nephrectomy.[204] A National Cancer Database study of patients with metastatic renal cancer treated with targeted therapy with or without cytoreductive nephrectomy demonstrated an improvement in survival for cytoreductive nephrectomy, with a median OS of 17.1 months (95% CI; 16.3,18.0) versus 7.7 months (95% CI; 7.4, 7.9; $p < 0.001$) as compared to no surgery.[205] The use of neoadjuvant antiangiogenic agents in patients with locally advanced RCC has demonstrated tumor downsizing as well as the use of partial nephrectomy in a subset of patients who would otherwise have required a radical nephrectomy.[206] Use of embolization is often recommended preoperatively for large primary tumors and for the resection of metastatic lesions because of the highly vascular nature of RCC. Surgical excision of oligometastatic disease at presentation or following prolonged disease-free intervals may be appropriate in select patients.

Table 11-6 **Staging of Kidney Cancer**[15]	
Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤ 4 cm in greatest dimension, limited to the kidney
T1b	Tumor > 4 cm but not ≥ 7 cm in greatest dimension, limited to the kidney
T2	Tumor > 7 cm in greatest dimension, limited to the kidney
T2a	Tumor > 7 cm but ≤ 10 cm in greatest dimension, limited to the kidney
T2b	Tumor > 10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor extends into the renal vein or its segmental branches, or invades the pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor extends into the vena cava below the diaphragm

T3c	Tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Anatomic Stage/Prognostic Groups	
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T1 N1 M0
	T2 N1 M0
	T3 N0 M0
	T3 N1 M0
Stage IV	T4 Any N M0
	Any T Any N M1

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PATHOLOGY AND MOLECULAR PATHOGENESIS

The Heidelberg classification of renal tumors introduced in 1997 correlated histopathologic features with genetic abnormalities.[207] The classification of adult epithelial kidney tumors has expanded to include less common histologies that are associated with distinct clinical outcomes.[208,209] The most common types of renal cancer in adults are clear cell (75% of cases) and papillary (10% of cases) renal cell carcinoma; and rarer types include chromophobe (≤ 5% of cases), collecting-duct and renal medullary (each in ≤ 1% of cases), and translocation (< 1% of cases) carcinoma.[210] Sarcomatoid differentiation, which is associated with a worse prognosis, can occur in any major histologic subtype. Specific cytogenetic and molecular abnormalities that frequently result in dysregulation of metabolic pathways are associated with

each major histologic subtype (Table 11-7).[211,212]

Von Hippel–Lindau (VHL) disease is an autosomal-dominant familial cancer syndrome that predisposes individuals to renal clear cell cancers, retinal angiomas, hemangioblastomas of the spinal cord and cerebellum, and pheochromocytomas, as well as to other rare neoplasms. Frequent loss of at least one allele on chromosome 3p in renal tumors from patients with VHL disease led to the identification of the *VHL* tumor-suppressor gene. This gene encodes a protein that promotes the ubiquitination and destruction of hypoxia-inducible factor (HIF-alpha) (Fig. 11-1).[213] Several proteins encoded by HIF-alpha are involved in angiogenesis, such as VEGF and platelet-derived growth factor B chain (PDGF-B). When the VHL protein is lost in renal cancers, VEGF, PDGF-B, and other proteins are overexpressed, promoting angiogenesis and tumor cell growth. Defects in the *VHL* gene, including mutation or gene silencing through methylation, also occur in the majority of tumors from patients with sporadic clear cell carcinomas. Tumor angiogenesis is also stimulated by other growth factors that activate AKT and mTOR (mammalian target of rapamycin) signaling, which also increases HIF-alpha expression.[214] Therapies that target VHL-regulated and AKT signaling pathways have demonstrated substantial antitumor activity. Several mutations in genes involved in histone modification have been identified in clear cell RCCs,[215] including the SWI/SNF chromatin remodeling complex gene *PBRM1,* which was mutated in 41% of sporadic clear cell carcinomas,[216] suggesting new potential targets for therapy.

Table 11-7 **Molecular Classification of Renal Epithelial Neoplasms**[482-484]

Type of Cancer	Cytogenetics	Molecular Alteration	Familial Syndrome
Clear cell (conventional)	-3p, +5q	*VHL* inactivating mutation or hypermethylation, *PBRM1, SETD2, BAP1,* and *TORC1* pathway mutations	von Hippel-Lindau
Type I papillary	+7, +17, -Y	c-met alterations	Hereditary papillary renal cell carcinoma
Type II papillary	Complex cytogenetics	Fumarate hydratase inactivating mutation	Hereditary leiomyomatosis and renal cell carcinoma
Chromophobe	-1, -2, -6, -10, -13, -17, -21	*TP53* mutations; *ND5* mutations; *FLCN* mutations	Birt-Hogg-Dubé syndrome (associated with *FLCN* mutation)
Oncocytoma	-1, -Y		Birt-Hogg-Dubé syndrome
Collecting-duct carcinoma	Not defined		
Medullary carcinoma	Not defined	*SMARCB1* inactivation	

Alterations in the MET receptor tyrosine kinase, whose gene is located on chromosome 7, occur in hereditary papillary renal carcinoma and in type I sporadic papillary tumors.[217] Germline mutations in tricarboxylic acid cycle enzymes that are part of mitochondrial oxidative phosphorylation result in an increased risk of type II papillary renal tumors. The syndrome of hereditary leiomyomatosis and renal cell cancer (HLRCC) is associated with loss-of-function mutations in the Krebs cycle enzyme fumarate hydratase leading to a risk for cutaneous and uterine leiomyomas and solitary papillary renal carcinomas.[218] Early-onset renal tumors also occur in patients with germline mutations of the succinate dehydrogenase gene *SDHB*.[211,212] Sporadic cases of papillary (or clear cell) renal carcinomas containing chromosomal translocations involving the *TFE3* gene at chromosome Xp11.2 are rare, more commonly

occurring in children and young adults.[219] The Birt–Hogg–Dubé syndrome is another rare autosomal-dominant disorder characterized by hair-follicle hamartomas of the face and neck, renal and pulmonary cysts, and, for some patients, multiple chromophobe or mixed chromophobe–oncocytoma renal tumors.[220] Collecting-duct carcinomas are more similar to transitional-cell carcinomas.[221] Medullary carcinoma, a variant of the collecting-duct subtype, is associated with sickle cell trait or disease and with inactivation of the tumor suppressor gene *SMARCB1*.[222]

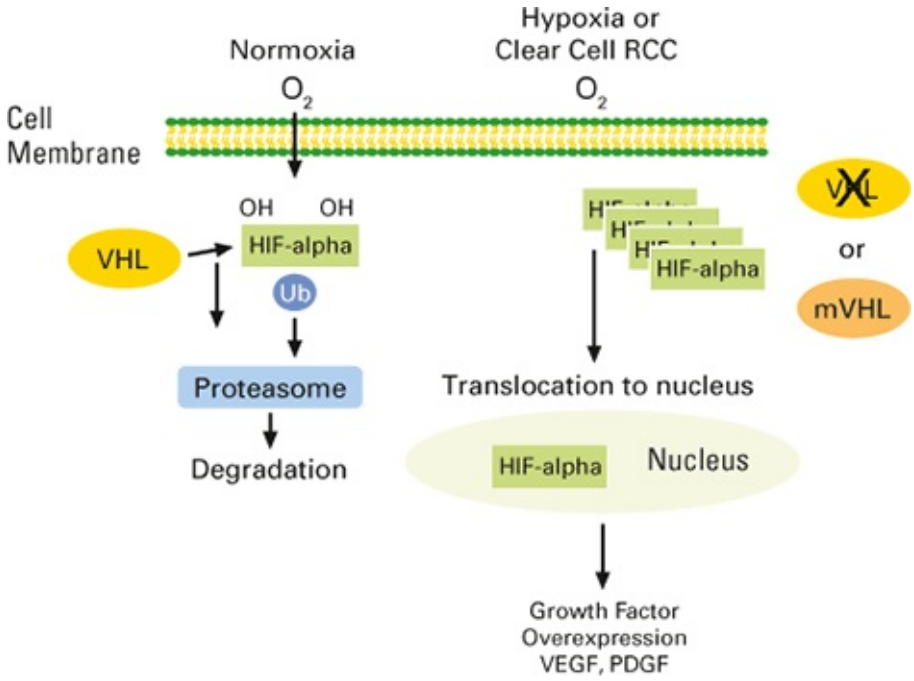

Fig. 11-1 Von Hippel–Lindau (VHL) pathway in clear cell renal cancer.

Under normoxic conditions, HIF-alpha is hydroxylated, allowing VHL to bind and target HIF-alpha for ubiquitination (Ub) and degradation via the 26S proteasome pathway. Under hypoxic conditions, HIF-alpha is not hydroxylated or marked by VHL for degradation, resulting in HIF-alpha accumulation and subsequent translocation to the nucleus to form a complex with HIF-beta. It then functions to induce transcription of growth stimulatory genes such as *VEGF, PDGF,* and *TGF-alpha,* as well as erythropoietin. Similarly, in clear cell carcinomas in which VHL is lost or mutated (mVHL), HIF-alpha accumulates and translocates to the nucleus, and stimulates growth factor expression that promotes angiogenesis and tumor cell growth.

Abbreviations: PDGF, platelet-derived growth factor; RCC, renal cell carcinoma; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

BIOLOGY

RCC can have a variable natural history that reflects the biology of the histologic tumor type. Oncocytomas are considered benign. Chromophobe carcinomas also are typically indolent and uncommonly result in metastases and cancer-related death,[223] although tumor necrosis and sarcomatoid differentiation predict a more aggressive phenotype.[224] The clinical course of clear cell carcinomas, which compromise the majority of renal tumors, is typically aggressive, although some patients can have an indolent course with stable metastases for years or metastases occurring decades after complete resection of a primary tumor. Molecular studies are attempting to identify markers that may predict prognosis. Papillary tumors are divided into type I and type II lesions according to architectural, cytologic, and genetic features. Type II papillary RCC is associated with more aggressive clinicopathologic features and a worse outcome.[225] Collecting-duct carcinomas have a very aggressive clinical course, with over half of patients presenting with metastases and a median survival of only a few months for patients with metastatic disease.[226]

SYSTEMIC THERAPIES

Patients with metastatic RCC may have a varied, unpredictable, and in some cases, protracted clinical course. One prospective, phase II study of patients with treatment-naive, asymptomatic, metastatic RCC with a primary endpoint of time to initiation of systemic therapy made at the discretion of the treating physician and patient reported a median time on surveillance of 14.9 months.[227] More adverse risk factors and an increased number of metastatic sites was associated with a shorter time on surveillance. Thus, a subset of patients with metastatic RCC can safely be on a surveillance program prior to systemic therapy. One nomogram used to predict survival based on patients treated in the cytokine era includes the following as poor prognostic variables: no prior nephrectomy, low Karnofsky Performance Status (< 80%), low hemoglobin level, high "corrected" serum calcium, and high serum LDH. The median survival was 24 months (good risk), 12 months (intermediate risk), and 5 months (poor risk) for patients with 0, 1 to 2, or 3 or more risk factors, respectively.[228,229] Newer prognostic models for patients with metastatic RCC treated with contemporary targeted therapies have generally included these prognostic factors in addition to others, such as platelet count, alkaline phosphatase, and number and sites of metastases. Although the International Metastatic Renal-Cell Carcinoma Database Consortium (IMDC) model (risk factors: anemia, thrombocytosis, neutrophilia, hypercalcemia, Karnofsky Performance Status < 80%, and < 1 year from diagnosis to treatment) has been externally validated in patients treated with first-line VEGF-targeted treatment, prospective validation has not yet been performed.[230-233]

VEGF Targeted Treatments

Bevacizumab. Increased expression of VEGF in clear cell renal carcinomas led to a phase II randomized trial of bevacizumab, a humanized VEGF-neutralizing antibody, in patients with cytokine-refractory disease that demonstrated a 10% response proportion and a prolonged PFS of 4.8 months compared with 2.5 months for patients who received placebo.[234] Hypertension and asymptomatic proteinuria were the most common adverse events. Two subsequent multicenter phase III studies compared bevacizumab plus IFN-alpha to IFN-alpha alone as first-line treatment in patients with metastatic RCC.[235-238] In the AVOREN study, the addition of bevacizumab significantly increased PFS (10.2 months vs. 5.4 months; HR, 0.63; $p < 0.001$) and objective tumor response rate (30.6% vs. 12.4%; $p < 0.0001$). In the Cancer and Leukemia Group B (CALGB) 90206 trial, the median PFS was 8.5 months for patients receiving bevacizumab plus IFN (95% CI; 7.5, 9.7) compared with 5.2 months (95% CI; 3.1, 5.6) for patients receiving IFN monotherapy (HR, 0.71; $p < 0.0001$), with a significant increase in objective tumor response rate (25.5% vs. 13.1%; $p < 0.0001$).

Sorafenib. Sorafenib is another multikinase inhibitor designed as a c-RAF and BRAF kinase inhibitor, but it also inhibits the VEGF receptor, PDGF receptor, FLT3, and c-KIT. Encouraging results from a phase II randomized discontinuation trial of sorafenib in patients with renal cancer led to the phase III randomized TARGET trial of sorafenib compared with placebo for second-line therapy in patients with cytokine-refractory disease.[239] Based on the results of this study, which showed that patients who received sorafenib had a significantly prolonged median PFS compared with placebo (24 weeks vs. 12 weeks), sorafenib was FDA-approved for second-line therapy.[240] Patients had clear cell histology, with the majority undergoing nephrectomy, an excellent performance status, and good- or intermediate-risk disease. A randomized, phase II trial of first-line treatment with sorafenib (400 mg twice daily) compared

with IFN for treatment-naive patients with clear cell RCC demonstrated a median PFS of 5.7 months and 5.6 months for sorafenib compared with IFN, respectively (HR, 0.88; p = 0.504).[241] Major response rates were less than 10% in both treatment arms.

Sunitinib. Sunitinib is an oral broad-spectrum receptor tyrosine kinase inhibitor that targets the VEGF receptor, PDGF receptor, the Fms-like tyrosine kinase (FLT3), and the c-KIT receptor tyrosine kinase. Phase II trials in patients with cytokine-refractory disease demonstrated a response rate of 41% and a PFS of 8.2 months,[242,243] which led to FDA approval of sunitinib for second-line therapy in 2006. A randomized, phase III trial that compared sunitinib with IFN in previously untreated patients with clear cell carcinoma demonstrated a 47% objective response rate, and a median PFS and OS of 11 months and 26.4 months, respectively, in the sunitinib arm compared with a 12% objective response rate, 5-month median PFS, and 21.8-month median OS in the IFN arm.[244,245] In this study, 90% of patients had undergone nephrectomy and 93% of patients had good- or intermediate-risk disease. The recommended dosing schedule for sunitinib is 50 mg daily, 4 weeks on and 2 weeks off. A randomized, phase II study that compared the intermittent schedule to low-dose (37.5 mg) continuous dosing did not demonstrate a benefit for continuous dosing in terms of quality of life or PFS, with a nonsignificant trend toward inferior time to progression and PFS with the continuous dosing regimen.[246] Alternative dosing schedules including 2 weeks on and 1 week off may be associated with improved tolerability and similar efficacy as standard dosing.

Pazopanib. Pazopanib is another oral, broad-spectrum receptor tyrosine kinase inhibitor with targets similar to those for sunitinib. In a phase III, 2:1 randomized clinical trial comparing pazopanib with placebo, PFS was significantly improved in both treatment-naive patients (11.1 months vs. 2.8 months; HR, 0.40; 95% CI; 0.27, 0.60; p < 0.0001) and patients pretreated with cytokines (7.4 months vs. 4.2 months; HR, 0.54; 95% CI; 0.35, 0.84; p < 0.001) with an ORR of 30% in patients who received pazopanib.[247] This study led to FDA approval of pazopanib for metastatic RCC. A randomized, phase III noninferiority trial compared the efficacy and safety of pazopanib and sunitinib as first-line therapy.[248] The PFS for pazopanib-treated patients was noninferior to sunitinib-treated patients (HR, 1.05; 95% CI; 0.90, 1.22) and the OS was similar (HR, 0.91; 95% CI; 0.76, 1.08). The safety profile favored pazopanib with less fatigue (55% vs. 63%), hand–foot syndrome (29% vs. 50%), and thrombocytopenia (41% vs. 78%). A higher incidence of increased alanine aminotransferase was seen with pazopanib (60% vs. 43%). Health-related quality of life measures favored pazopanib with less fatigue and soreness of the mouth, hands, and feet.

Axitinib. Previous phase II studies had shown that patients whose disease progressed while taking a VEGF-targeted therapy may experience a response to another targeted therapy.[249] A prospective, randomized trial compared the VEGF selective receptor tyrosine kinase inhibitor axitinib to sorafenib in patients whose disease had progressed during first-line therapy (AXIS trial). The overall median PFS was 6.7 months for patients who received axitinib compared with 4.7 months for patients treated with sorafenib (HR, 0.665; 95% CI; 0.544, 0.812; p < 0.0001).[250] Subgroup analysis showed that PFS was 12 months compared with 6.5 months (HR, 0.46; p < 0.0001) after prior cytokine therapy and 4.8 months compared with 3.4 months (HR, 0.74; p = 0.011) after prior sunitinib therapy for patients treated with axitinib and sorafenib, respectively.

Cabozantinib. A randomized, open-label, phase III trial (METEOR) compared cabozantinib, an oral, small-molecule tyrosine kinase inhibitor that targets VEGFR as well as MET and AXL, with everolimus in patients with advanced RCC that had progressed after VEGFR-targeted therapy and demonstrated a significant benefit in PFS for cabozantinib (HR 0.58; $p < 0.001$).[251] The final OS results based on an unplanned second interim analysis demonstrated a median survival of 21.4 months (95% CI; 18.7, not estimable) with cabozantinib and 16.5 months (95% CI; 14.7, 18.8) with everolimus (HR, 0.66; 95% CI; 0.53, 0.83; $p = 0.00026$).[252] Cabozantinib resulted in improved PFS (HR, 0.51; 95% CI; 0.41, 0.62; $p < 0.0001$) and objective response (17% vs 3%; $p<0.0001$). The most common grade 3/4 adverse events with cabozantinib were hypertension, diarrhea, fatigue, and palmar–plantar erythrodysesthesia. Dose reductions due to adverse events occurred more often in patients treated with cabozantinib than in those treated with everolimus (60% vs. 25%). A phase II, multicenter trial evaluated cabozantinib compared with sunitinib in 157 patients randomly assigned to first-line therapy in IMDC poor- or intermediate-risk metastatic RCC (The Alliance A031203 CABOSUN Trial).[253] Cabozantinib significantly increased median PFS (8.2 vs. 5.6 months) with a 34% reduction in rate of progression or death as compared to sunitinib (adjusted HR, 0.66; 95% CI; 0.46, 0.95; one-sided $p = 0.012$). ORR was 46% (95% CI; 34, 57) for cabozantinib versus 18% (95% CI; 10, 28) for sunitinib. Based on the CABOSUN trial, cabozantinib was FDA approved for first-line treatment of patients with advanced RCC.

Lenvatinib with Everolimus. A randomized, phase II study compared lenvatinib, a tyrosine kinase inhibitor against both VEGF and FGF receptors, to everolimus and the combination of lenvatinib and everolimus in patients with metastatic RCC who progressed after one previous VEGF-targeted therapy, and demonstrated an improvement in PFS with lenvatinib and with the combination as compared to everolimus alone.[254] Grade 3/4 events occurred in 71% of patients who received lenvatinib plus everolimus, with diarrhea as the most common.

VEGF-Targeted Therapy Toxicties. Toxicity from this class of drugs includes fatigue, hypertension, diarrhea, rash, hand–foot syndrome, myelosuppression including thrombocytopenia, hypothyroidism, and congestive heart failure.[255-259] Pazopanib therapy may also be associated with serious hepatotoxicity. Sunitinib-associated hypertension, defined as a maximum or mean systolic blood pressure of greater than 140 mmHg, was associated with an improvement in clinical outcome, suggesting that the development of hypertension during therapy may be a biomarker of response to sunitinib.[260]

mTOR Inhibitors

Temsirolimus. The mTOR protein is frequently activated in RCC, which can result in increased production of HIF-1-alpha and HIF-2-alpha. Consequently, agents that inhibit mTOR have been studied in patients with metastatic RCC. The mTOR inhibitor temsirolimus demonstrated an improvement in survival in a phase II study of patients with cytokine-refractory RCC,[261] resulting in a phase III, multicenter study in previously untreated patients with advanced RCC. Patients with three or more of six poor prognostic factors (a serum LDH > 1.5 times the upper limit of normal, a hemoglobin level below the lower limit of the normal range, a corrected serum calcium level of > 10 mg/dL [2.5 mmoL/L], a time from initial diagnosis of RCC to random assignment of < 1 year, a Karnofsky Performance Status score of 60 or 70, or metastases in multiple organs) were randomly assigned to 25 mg of temsirolimus weekly, IFN alone, or to the

combination of 15 mg of temsirolimus weekly plus IFN.[262] Single-agent temsirolimus was associated with an improvement in OS compared with IFN (HR, 0.73; 95% CI; 0.58, 0.92; p = 0.0078), with a median OS of 10.9 months compared with 7.3 months for patients receiving IFN alone. PFS was 5.5 months in the temsirolimus arm and 3.1 months in the IFN arm (HR, 0.66; 95% CI; 0.53, 0.81). The combination arm did not increase survival. This led to FDA approval of single-agent temsirolimus in 2007.

Everolimus. Everolimus is an orally administered mTOR inhibitor. A phase III, 2:1 randomized, double-blind trial compared everolimus with placebo for patients whose disease had progressed on sunitinib (46%), sorafenib (28%), or both agents (26%).[263] Median PFS for patients who received everolimus was 4.0 months, compared with 1.9 months for patients who received placebo (HR, 0.3; p < 0.0001). The probability of being progression-free at 6 months was 26% for the treatment arm compared with 2% for the placebo arm. Adverse reactions from mTOR inhibitors include rash, asthenia, mucositis, nausea, edema, myelosuppression, hyperlipidemia, hypercholesterolemia, hyperglycemia, and drug-induced pneumonitis. This study was the first phase III, randomized trial to demonstrate efficacy of second-line therapy for patients whose disease progressed while taking a VEGF inhibitor.

Sequential and Combination Targeted Therapy Strategies

The use of an mTOR inhibitor or a VEGFR tyrosine kinase inhibitor in the second-line setting was evaluated in the randomized, phase III INTORSECT trial of temsirolimus compared with sorafenib as second-line therapy after sunitinib in patients with metastatic RCC.[264] Although no significant difference between treatment arms was seen for the primary endpoint of PFS (HR, 0.87; p = 0.19), there was a significant OS difference in favor of sorafenib (HR, 1.31; p = 0.01) with a median survival in the temsirolimus arm of 12.3 months, compared with 16.6 months for sorafenib, suggesting that sequenced VEGFR inhibition may be beneficial.

The combination of two targeted agents may improve response rates, but may result in increased toxicity.[265,266] Combination studies have failed to demonstrate an improvement in PFS,[267,268] whereas sequential use of targeted agents does appear to improve both PFS and OS in patients with metastatic RCC.[269] A phase II, randomized trial (RECORD-3) comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic RCC did not demonstrate PFS noninferiority for everolimus compared with sunitinib as first-line therapy, thus supporting first-line sunitinib followed by everolimus upon progression.[270] Ongoing studies are evaluating novel combinations such as cabozantinib with immune checkpoint inhibitors.

Non–Clear Cell RCC

Sunitinib and sorafenib have also shown activity in patients with non–clear cell RCC, including patients with metastatic papillary RCC and chromophobe carcinoma.[271-273] Two phase II studies have demonstrated modest activity for sunitinib and everolimus in patients with non–clear cell RCC.[274,275] In one of the studies, sunitinib improved PFS in good/intermediate risk and papillary/unclassified patients while everolimus improved PFS in patients with poor risk and chromophobe. In a subset analysis of a randomized, phase III trial that compared temsirolimus, IFN, or the combination,[262] patients with non–clear cell histology who received temsirolimus had a significant improvement in PFS (7 months vs. 1.8 months) and OS (11.6 months vs. 4.3 months) compared with patients who received IFN, suggesting that temsirolimus has activity in

non–clear cell RCC.[276] Better therapies are needed for patients with non–clear cell RCC, and clinical trials are preferred when available.

Activation of the c-MET signaling pathway in papillary RCCs has led to early-phase trials with agents that target the c-MET tyrosine kinase receptor or its ligand, hepatocyte growth factor, in patients with metastatic papillary RCC.[277-279] A phase II and biomarker study of the dual MET/VEGFR2 inhibitor foretinib demonstrated activity in patients with advanced papillary RCC and a high response rate in patients with germline mutations.[241] In a single-arm, uncontrolled, multicenter phase II trial from the Southwest Oncology Group (SWOG; S0317), 45 patients with advanced papillary RCC were treated with the oral EGFR kinase inhibitor erlotinib.[280] An overall partial response rate of 11% and a disease control rate of 64% (five partial responses and 24 patients with stable disease) were observed. The 6-month PFS was 29% and the median OS was 27 months.

Targeted Therapy in the Adjuvant Setting

Several studies have been performed to evaluate the potential role for VEGFR tyrosine kinase inhibitor or mTOR inhibitor therapy in the adjuvant setting for patients with high-risk disease after nephrectomy. The ASSURE (E2805) randomized, phase III study evaluated adjuvant sorafenib, sunitinib, or placebo in 1943 patients with completely resected RCC (pT1b high grade to pT4 any grade, N any) for up to 1 year.[281] At a planned interim analysis, there were no significant differences in the primary endpoint of DFS or OS between either of the experimental arms and placebo, and both agents were associated with significant toxicity. A second adjuvant sunitinib study (S-TRAC) randomly assigned 615 patients with local-regional high-risk clear cell RCC (tumor stage 3 or higher, regional lymph node metastasis, or both) to adjuvant sunitinib or placebo for 1 year or until disease progression, with a primary endpoint of DFS.[282] There was an improvement in DFS with sunitinib compared to placebo (6.8 years vs. 5.6 years; HR, 0.76; 95% CI; 0.59, 0.98; p = 0.03) at a cost of a higher adverse event rate. Based on the results of S-TRAC, sunitnib was FDA approved for use as an adjuvant therapy in patients with RCC who have undergone nephrectomy and are at high risk for recurrence. A randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced RCC (PROTECT) did not demonstrate a DFS benefit for pazopanib over placebo in the adjuvant setting.[283] The results of additional adjuvant targeted therapy trials are awaited.

Immunotherapy

Until 2006, immunotherapy had represented the primary treatment for patients with advanced renal cancer. The most extensively studied agents were IFN-alpha and aldesleukin (human recombinant interleukin-2 [IL-2]). IFN-alpha demonstrated low but reproducible response rates of 10 to 20% with occasional durable responses. Response rates higher than 30% have been reported for patients with small-volume disease that is primarily limited to the lung. Two randomized trials showed that patients treated with IFN-alpha compared with those treated with vinblastine or medroxyprogesterone achieved a small survival advantage,[284,285] although other studies have not demonstrated a survival benefit.[286] A dose response to IFN-alpha is suggested, as few responses are associated with a dose of less than 3 million units per day, with maximal benefit seen in the dose range of 5 to 20 million units daily. In randomized trials, no consistent survival benefit has been demonstrated with the addition of vinblastine, IL-2, 13-*cis*-retinoic acid, or floxuridine to IFN therapy.

Therapy with IL-2 results in major responses in 10 to 15% of patients with clear cell

histology, with durable responses in 4 to 5% of cases. High-dose regimens appear to be more effective than low-dose regimens.[287] Prolonged and durable responses occur more commonly in patients with a good performance status and young age. One study demonstrated a higher response proportion with IL-2 compared with prior studies, but failed to confirm carbonic anhydrase IX expression as a predictor of response.[288] Toxicity associated with high-dose bolus IL-2 is related to increased vascular permeability and often necessitates treating patients in an intensive-care setting. IL-2 has been associated with a 4% incidence of treatment-related death. IL-2 in combination with autologous lymphokine-activated killer cells obtained by leukapheresis did not result in any added benefit.[289] IL-2 remains the only therapy that is associated with durable complete responses and may be most appropriate for young, good-risk patients. There is no proven role for adjuvant cytokine therapy for patients who undergo nephrectomy and who are at high risk of recurrence.

Promising data have emerged using anti-PD-1 and anti-PD-L1 therapies in advanced kidney cancer.[290] A randomized, phase II trial of nivolumab, a fully human immunoglobulin G4 PD-1 checkpoint inhibitor antibody, demonstrated antitumor activity and manageable toxicity in patients with metastatic RCC.[291] Nivolumab has subsequently received FDA approval for the treatment of advanced RCC in patients who have received prior antiangiogenic therapy based on the results of a randomized, open-label, phase III study that compared nivolumab with everolimus in previously treated (one or two previous regimens of antiangiogenic therapy) patients with RCC and demonstrated a significant OS benefit for nivolumab (HR, 0.73; p = 0.002). The median OS was 25.0 months (95% CI; 21.8, not estimable) with nivolumab and 19.6 months (95% CI; 17.6, 23.1) with everolimus.[292]

The recently reported CheckMate 214 phase 3 randomized trial comparing the efficacy and safety of nivolumab plus the anti-CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) antibody ipilimumab versus sunitinib for treatment-naive patients with advanced or metastatic clear cell RCC will change the landscape to include the use of immunotherapy in the first-line metastatic disease setting.[293] The co-primary endpoints for the study included ORR, PFS, and OS in IMDC intermediate- and poor-risk patients. In 847 patients with IMDC intermediate/poor-risk disease, a significant improvement in ORR (42% vs 27%; p<0.0001), PFS (11.6 vs 8.4 months, HR 0.82 [0.64-1.05]; p=0.0331), and OS (not reached vs 26.0 months, HR 0.63 [0.44-0.89]; p<0.0001) was seen with the combination. In 249 IMDC favorable risk patients, a higher ORR and improved PFS was seen with sunitinib. The safety profile of nivolumab and ipilimumab was manageable with less Grade 3-5 adverse events seen with the combination (46%) as compared to sunitinib (63%). Systemic corticosteroids were required in 60% of patients treated with nivolumab and ipilimumab.

Variability in trial design and eligibility criteria for the multiple studies makes it difficult to compare results and to determine whether one agent is superior as first- or second- or subsequent-line therapy. Figure 11-2 provides therapeutic options for metastatic RCC. These options will most certainly be revised as additional studies are completed and results reported.

Chemotherapy

RCC is, in general, highly resistant to single-agent and combination chemotherapy, except for patients with sarcomatoid or collecting-duct carcinomas.[294] The combination of weekly gemcitabine with continuous infusional 5-fluorouracil or oral capecitabine showed modest activity in clear cell renal cancers.[295] A phase II trial investigated doxorubicin and gemcitabine in patients with sarcomatoid features (ECOG 8802).[296] The objective response rate (complete

plus partial response) was 16% (one complete and five partial responses), and 10 patients (26%) had stable disease. The median PFS was 3.5 months and the median OS was 8.8 months. A prospective, phase II trial of patients with metastatic collecting-duct carcinoma treated with gemcitabine and cisplatin or carboplatin demonstrated antitumor activity.[297] VEGF-targeted agents have also shown activity in clear cell RCC with varying degrees of sarcomatoid differentiation, with a PFS in most studies of 4 to 5 months.[298]

Supportive Care

Approximately one-third of patients with advanced RCC have bone metastases and these are predominantly osteolytic. Treatment with bone-targeting agents, such as zoledronic acid or denosumab, has been shown to decrease the risk of skeletal-related events in patients with bone metastases.[299,300] Brain metastases are a frequent complication in patients with metastatic clear cell renal cancer. Surgical resection or stereotactic radiosurgery are feasible alternatives to whole-brain radiation and may result in long-term survival.[301] Patients with treated brain metastases may safely receive systemic therapy with a multikinase inhibitor.[302] Limited studies also suggest that patients with severe renal impairment or end-stage renal disease who are on hemodialysis may safely be treated with selected targeted therapies.[303]

SURVIVORSHIP AND ELDERLY CONSIDERATIONS

Radical nephrectomy is a significant risk factor for chronic kidney disease. With the normal physiologic decline in renal function attributed to aging, older patients have a greater decline in kidney function compared with younger patients. Nephron-sparing approaches should be considered in appropriately selected patients in an effort to preserve renal function; however, despite similar tumor sizes, fewer older patients are treated with a partial nephrectomy.[304] Although novel agents targeting the VEGF and mTOR pathways have substantially improved the outcome for patients with advanced kidney cancer, these drugs are associated with a new spectrum of side effects, including hypertension, hand–foot syndrome, thyroid dysfunction, hyperglycemia, hyperlipidemia, dysphonia, and pneumonitis, as well as others, as compared with conventional cytotoxic therapy. Monitoring for and management of these new toxicities is critical to ensure that patients tolerate treatment and derive the greatest benefit from these effective therapies. With the substantial improvement in survival associated with targeted therapies in RCC, special attention to long-term side effects, including cardiac disease, thyroid dysfunction, renal insufficiency, and infection risk, as well as others, is needed. Older patients with preexisting medical issues such as hypertension or heart disease must be monitored closely for worsening hypertension and left ventricular function decline during treatment. For example, patients with a history of hypertension and coronary artery disease are at an increased risk for cardiotoxicity related to sunitinib.[305] An analysis of age and efficacy and toxicity from phase III trials of sorafenib, sunitinib, temsirolimus, and bevacizumab, and from an expanded access experience with sunitinib and sorafenib, suggests that outcomes and major toxicities are similar for patients age 65 and older and younger patients.[306] Prospective studies of targeted agents in the elderly with advanced RCC with particular attention to side effects are most certainly needed. Further advancements with checkpoint inhibitors may allow for the treatment of older patients who otherwise would be unable to receive targeted therapies.

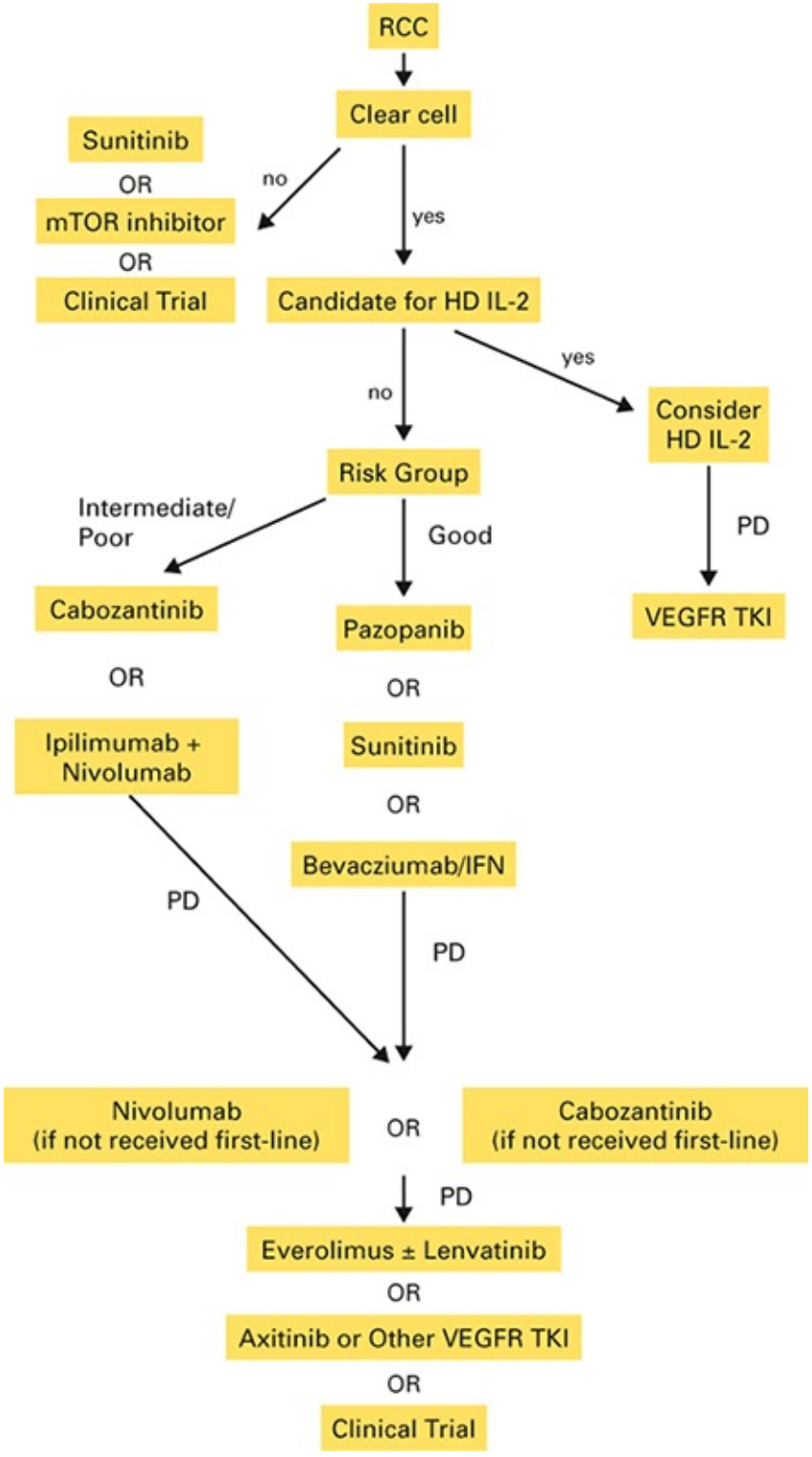

Fig. 11-2 Therapeutic options for patients with metastatic renal cell carcinoma.

Abbreviations: CR, complete response; HD IL-2, high-dose interleukin-2; IFN, interferon; PD, progressive disease; PR, partial response; RCC, renal cell carcinoma; SD, stable disease.

KEY POINTS

- Kidney cancer is not one disease and the classification of renal tumors is based on histology and genetic abnormalities.
- The role for surgery in the management of kidney cancer includes the use of nephron-sparing approaches, cytoreductive nephrectomy, and metastasectomy.

- Numerous angiogenesis-directed therapies targeting VEGF as well as mTOR inhibitors have led to a significant improvement in outcomes in patients with metastatic disease.
- Immune checkpoint inhibitors have demonstrated promising results in patients with metastatic renal cell cancer.

PROSTATE CANCER

Prostate cancer represents 21% of all newly diagnosed cancers in males and 8% of cancer-related deaths. In 2016, there were an estimated 180,890 new cases of prostate cancer and 26,120 deaths.[1] The 8:1 ratio of incidence to mortality demonstrates that although the disease is lethal for some men, the majority of men with prostate cancer die of other causes. Autopsy series show that nearly 70% of men older than age 80 have occult prostate cancer. These data highlight the variable biology and clinical course of prostate cancer. Many prostate cancers do not require immediate intervention, since the risk of death from non–cancer-related causes exceeds that of the cancer; other prostate cancers require multimodality approaches, both to eradicate the tumor locally and to eliminate micrometastases.

A risk-adapted approach for prostate cancer, initially proposed in 2000, categorizes prostate cancer into a series of clinical states for which the therapeutic objectives are distinct (Fig. 11-3). Each state represents a clinically important milestone for which an intervention may or may not be needed. For example, for patients with a new prostate cancer diagnosis, a management decision must incorporate an understanding of the individual's risk for metastases or death from prostate cancer in a given time frame. Using this model, it is clear that some patients may not be at risk for the development of metastases or symptoms for years (such that the risk of death from non–cancer-related causes exceeds that of prostate cancer), whereas other patients may require a more immediate intervention. Until a patient has progressive castration-resistant prostate cancer (CRPC; previously referred to as hormone-refractory or androgen-independent prostate cancer), he is unlikely to die of his illness. Examples of the distinct therapeutic objectives for each disease state are as follows:

- For men who do not have a diagnosis, but who may be at high risk for the disease (e.g., black males or those with a family history of prostate cancer), screening is the objective.
- For patients with localized disease, the objectives are to identify patients who can be cured by local modalities directed at the prostate only, patients who have indolent tumors who can be safely observed, and patients who have aggressive disease that will require combined-modality approaches aimed at eradicating the tumor locally and eliminating micrometastases.
- For patients with CRPC, the goal is to prevent or eliminate symptoms of disease and prolong life.

ANATOMY

The prostate is composed of branching tubuloalveolar glands that are arranged in lobules and surrounded by stroma. Prostatic fluid is secreted through ducts to the urethra and comprises the bulk of seminal emissions. Associated structures are the dorsal vein complex, which is responsible for passive urinary control, and the pelvic plexus, which provides innervation to the pelvic organs and corpora cavernosa through the neurovascular bundle and is responsible for

erectile function. Protection of these fibers is essential to preserve potency. The peripheral zone is palpable by digital rectal examination (DRE) and is the site of origin of 70% of cancers. The transition zone surrounds the urethra and cannot be assessed by DRE. Up to 20% of all cancers develop in the transition zone; however, benign prostatic hypertrophy is more common than prostate cancer in the transition zone.

Fig. 11-3 Clinical states of prostate cancer.

EPIDEMIOLOGY

In the United States, approximately one in seven men will be diagnosed with prostate cancer in his lifetime. Individuals with one first-degree relative diagnosed with prostate cancer have a 2-fold increased lifetime risk, which increases to 4-fold if two or more relatives are affected before age 70. Current estimates suggest that 5 to 10% of all cases of prostate cancer are hereditary. Identification of genes that result in hereditary prostate cancer have led to the elucidation of more than 30 SNPs that are consistently associated with prostate cancer, yet the magnitude of risk elevation attributed to an individual SNP is low. A rare, but recurrent mutation (G84E) in *HOXB13* (rs138213197), a homeobox transcription factor, is strongly associated with early-onset, familial prostate cancer, suggesting that rare genetic variants exist that contribute to familial clustering of prostate cancer.[307] A more recent study of 692 men with metastatic prostate cancer unselected for family history of cancer analyzed germline DNA for mutations in 20 DNA repair genes associated with autosomal dominant cancer predisposition syndromes.[308] Eighty-four germline DNA repair gene mutations presumed to be deleterious were identified in 82 men (11.8%). Mutations were found in 16 genes, including *BRCA2, ATM, CHEK2, BRCA1, RAD51D,* and *PALB2.* Mutation frequencies did not differ according to family history of prostate cancer or age at diagnosis. The overall frequency of DNA damage repair germline mutations in men with metastatic prostate cancer exceeded the prevalence in men with localized prostate cancer (4.6%). The authors suggest that these findings along with the activity of poly-ADP ribose polymerase (PARP) inhibitors and platinum-based chemotherapy in men with metastatic prostate cancer and DNA repair gene mutations provides an argument for considering the routine evaluation of men with metastatic prostate cancer for the presence of germline mutations in DNA repair genes.

Although the frequency of histologic cancers at autopsy is similar throughout the world, the clinical incidence is significantly higher in Western countries, suggesting a role for environmental factors. High consumption of dietary fats, in particular the fatty acid alpha-linoleic acid, is believed to increase risk by 2- to 3-fold. Several potential protective dietary factors for prostate cancer incidence have been proposed, including tomatoes (lycopenes), cruciferous vegetables, carotenoids, fish, long-chain marine omega-3 fatty acids, soy, and polyphenols.[309]

The biology of prostate cancer appears to differ in certain racial groups. For example, matched for age, black men have both a greater number of precursor prostatic intraepithelial neoplasia (PIN) lesions and larger tumors as compared with white men.

PATHOLOGY AND MOLECULAR PATHOGENESIS

Prostatic intraepithelial neoplasia is an epithelial cellular proliferation within benign-appearing glands and acini. Approximately 50% of men with PIN as demonstrated on prostate biopsy will have prostate cancer in 5 years.[310] More than 99% of prostate cancers are adenocarcinomas; less than 1% are pure ductal and mucinous variants. In atypical prostatic lesions, expression of alpha-methylacyl-coenzyme A racemase (AMACR) is useful to confirm adenocarcinoma. Other histologic subtypes include small-cell carcinoma and rare mesenchymal tumors (rhabdomyosarcomas in younger patients and leiomyosarcomas in older patients). Urothelial carcinomas of the prostate are confined to the periurethral ducts and are more common among patients who have been successfully treated for noninvasive bladder cancer. Lymphomas and leukemias may also occur in the prostate gland.

The Gleason grading system is used to describe the morphology of adenocarcinomas of the prostate. Using the original system, the morphology was described using a score of 1 to 5 for the primary and secondary growth patterns within the tumor. Pattern 1 tumors were the most differentiated, with discrete glandular formation, whereas pattern 5 lesions were the most undifferentiated, with virtually complete loss of the glandular architecture. In 2005, a consensus conference modified Gleason grading to include the use of immunohistochemistry.[311] This resulted in a more narrow definition of Gleason 3 pattern (discreet glandular units) and widened the scope of Gleason 4 pattern. The Gleason score is determined by adding the Gleason grade of the two most predominant histologies. A tertiary (third most prevalent) Gleason pattern 5 is associated with adverse pathologic features and biochemical recurrence in some series. A higher Gleason score is associated with more aggressive disease and a greater probability of extracapsular extension, nodal involvement, and the subsequent development of metastases. A new prostate cancer five-group grading system includes:

Group 1: Gleason score ≤ 6,
Group 2: Gleason score 3 + 4 = 7,
Group 3: Gleason score 4 + 3 = 7,
Group 4: Gleason score 8, and
Group 5: Gleason scores 9–10.

Androgens are the primary regulators of prostate cancer cell growth and proliferation. Prostate cancer rarely develops in castrated men or in those who have hypopituitarism before age 40. The androgen receptor, located on chromosome Xq11-13, is a member of a superfamily of ligand-dependent transcription factors that have a similar structure with different functional domains. The development of prostate cancer involves a multistep process in which androgen receptor signaling plays a key role. Specific genetic changes have been identified in tumors representing different clinical states. In early-stage cancers, loss of function of genes that detoxify carcinogens may contribute to hypermethylation, leading to loss of function of multiple genes including the PI-class glutathione *S*-transferase.[312] Gene fusions in prostate cancer, including the androgen-regulated gene *TMPRSS2* (21q22.3) and an ETS transcription factor family member, either *ERG* (21q22.2), *ETV1* (7p21.2), or *ETV4* (17q21), were first described in 2005.[313] Among these, the *TMPRSS2-ERG* fusion is the most prevalent, occurring in 40 to 70% of clinically localized prostate cancers. Subsequently, gene fusions involving additional ETS family members, *RAF* kinases and *SPINK-1,* have been identified. Some studies suggest that patients with *TMPRSS2-ERG* fusions have an inferior prognosis, but the clinical

and therapeutic implications of this and other molecular abnormalities are unclear and require further study.

Gene expression profiling has identified numerous molecular abnormalities that may differ among primary, metastatic, and CRPCs. As such, the targets relevant for the treatment of early-stage disease may not be the same as those for late-stage tumors. For example, the frequency of expression of HER2 and BCL-2 is higher in castration-resistant metastatic lesions than untreated localized tumors.[314,315] In contrast, the frequency of expression of prostate-specific membrane antigen (PSMA) is relatively constant across all clinical states, although the intensity of staining is higher in castration-resistant metastatic tumors.[316] Potential molecular targets that have undergone clinical investigation include HER2, BCL-2, VEGF, Src, the endothelin receptor, IL-6, and PSMA. Neuroendocrine prostate cancer is associated with amplification of the genes, aurora kinase A *(AURKA)* and N-myc (*MYCN*).[317]

TUMOR STAGING

The TNM system describes the extent of the primary tumor (T), status of the regional nodes (N), and presence or absence of distant metastases (M) (Table 11-8).[15] Tumors detected by biopsy on the basis of an elevated PSA level and no palpable disease detected by DRE are designated T1c. Staging for T2 tumors includes: T2a, tumor involving one-half of one lobe or less; T2b, tumor involving more than one-half of one lobe, but not both lobes; and T2c, tumor involving both lobes. In T3 disease, tumor extends through the prostate capsule (T3a) or invades the seminal vesicles (T3b), whereas tumors are considered T4 if they invade into adjacent structures or organs. With the widespread use of PSA testing, T1c is the most frequent classification at the time of diagnosis. T1c disease should be reclassified in the appropriate T category for nonpalpable disease if a tumor is reliably visible on an imaging study. Margin positivity, which is influenced by surgical technique and anatomic extent of disease, should be specified in the pathology report by an R1 descriptor (residual microscopic disease). Positive surgical margin status is not classified specifically in the pathologic T stage because the data were inconclusive regarding effect on disease outcomes when the TNM system was last revised.[318]

The clinical studies used to assess the primary tumor, including DRE, transrectal ultrasound (TRUS), CT, and MRI are not sufficiently accurate for determining whether a tumor is organ-confined. To improve diagnostic precision and to guide treatment selection, nomograms based on the DRE, PSA level, and Gleason score are frequently used to predict the probability of capsular penetration, seminal vesicle, and lymph node involvement.[319] There has been increased utilization of multiparametric MRI (mpMRI) which incorporates T2-weighted, diffusion-weighted, and dynamic contrast-enhanced MRI imaging for the detection, staging, and management of prostate cancer. The Prostate Imaging-Reporting and Data System (PI-RADS) assessment uses a 5-point scale based on the mpMRI findings to determine the likelihood of a clinically significant cancer in the prostate gland.

PREVENTION

A number of chemoprevention strategies have been studied in prostate cancer. The PCPT was a randomized, double-blind, multicenter study designed to investigate the use of finasteride, a 5-alpha reductase inhibitor, to prevent prostate cancer in men age 55 and older. Over 18,000 men were enrolled, of whom one-half received 5 mg of finasteride daily for 7 years and one-half received placebo. The results initially demonstrated a 24.8% reduction in prostate cancer

risk among men treated with finasteride, with a higher frequency of high-grade lesions for this same group,[320] although the clinical significance of the high-grade disease was uncertain.[321] In a PCPT update, prostate cancer was diagnosed in 989 of 9423 (10.5%; 3.5% high grade) in the finasteride group and 1412 of 9457 (14.9%; 3.0% high grade) in the placebo group (relative risk [RR], 0.70; 95% CI; 0.65, 0.76; $p < 0.001$ and for high-grade cancer [Gleason score, 7 to 10] RR, 1.17; 95% CI; 1.00, 1.37; $p = 0.05$).[322] With up to 18 years of follow-up, there was no significant difference in OS or survival after the diagnosis of prostate cancer between the finasteride and the placebo groups (10-year survival rates were 83.0% in the finasteride group and 80.9% in the placebo group for men with low-grade prostate cancer and 73.0% and 73.6%, respectively, for patients with high-grade prostate cancer). A complementary study of another 5-alpha reductase inhibitor, the REDUCE trial of high-risk men had PSA-based entry criteria: baseline values of 2.5 ng/mL to 10 ng/mL for men younger than age 60, and of 3.0 ng/mL to 10 ng/mL for older men.[323] Participants had a negative prostate biopsy in the 6 months prior to enrollment and no evidence of prostate cancer, PIN, or atypical small acinar proliferation. Men were randomly assigned to receive 0.5 mg per day of dutasteride or placebo for 4 years, with prostate biopsies performed after 2 years and at the end of the study. Prostate cancer was diagnosed in 857 patients who received placebo compared with 659 of patients who received dutasteride, representing a 23% risk reduction ($p < 0.0001$). Subgroup analyses consistently favored dutasteride regardless of patient age, family history of prostate cancer, or baseline prostate symptom score, prostate volume, or PSA level. As in the PCPT trial, there was a small increase in the number of high-grade cancers.

In 2011, an FDA advisory committee analysis of both trials confirmed a relative reduction of approximately 25% in the overall incidence of prostate cancer. The analysis noted, however, that this was limited to tumors with a modified Gleason score of 6 or lower, and that many of the detected cancers were diagnosed by prostate biopsy in response to an elevated PSA level or to an abnormal DRE.[324] The reassessment of the PCPT and REDUCE trials confirmed a significantly increased incidence of high-grade prostate cancers, and the committee estimated that use of a 5-alpha reductase inhibitor for prevention of prostate cancer would result in one additional high-grade cancer in order to avert three to four potentially clinically relevant lower-grade cancers. The advisory committee concluded that finasteride and dutasteride do not have a favorable risk-benefit profile for chemoprevention of prostate cancer in healthy men.

The Physicians' Health Study II randomized controlled trial evaluating vitamins E and C supplementation in 14,641 male physicians in the United States initially age 50 or older did not reduce the risk of prostate cancer.[325] The SELECT evaluated 35,553 men in a double-blind, 2 × 2 factorial study of selenium and vitamin E alone and in combination for men age 50 or older (black men) or age 55 or older (all other men), a serum PSA of 4 ng/mL or less, and a normal DRE.[326] The endpoint was clinical incidence of prostate cancer. With a median follow-up of 5.46 years, there were no significant differences in the development of prostate cancer in any cohort ($p > 0.15$). At a median follow-up of 7 years, there was a 17% increased risk of prostate cancer in the vitamin E group ($p = 0.008$), but not in the selenium plus vitamin E group ($p = 0.46$), suggesting that vitamin E supplementation at 400 IU daily significantly increases the risk of prostate cancer.[327] Of note, the recommended daily dietary allowance for vitamin E is 22.4 IU.

Table 11-8 **Staging of Prostate Cancer**[15]

Primary Tumor (T)	
Clinical T (cT)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy found in one or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one side but not both sides
T2c	Tumor involves both lobes
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Pathologic (pT) †*	
pT2	Organ-confined
pT3	Extraprostatic extension
pT3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
pT3b	Seminal vesicle invasion
pT4	Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Regional Lymph Nodes (N)	
Clinical	
NX	Regional lymph nodes were not assessed
N0	No positive regional nodes
N1	Metastasis in regional node(s)
Distant Metastasis (M) ‡	
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease; most advanced

*There is no pathologic T1 classification.
†Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).
‡When more than one site of metastasis is present, the most advanced category is used; M1c is most advanced.
The original source for this material is the AJCC Cancer Staging Manual, 8th Edition (2017) published by Springer Science and Business Media LLC, www.springerlink.com.

EARLY DECTECTION AND SCREENING

The rationale for prostate cancer screening is that early detection and treatment of early-stage, asymptomatic cancers compared with diagnosis and treatment at the time of clinical diagnosis (e.g., a palpable mass on DRE) may improve survival. Although case-controlled studies suggest an association between PSA screening and a decrease in mortality, prospective, randomized trials have not convincingly proven that PSA screening decreases mortality.[328] Consequently, there is substantial controversy regarding PSA screening for prostate cancer.[329] In 2012, the U.S. Preventive Services Task Force updated their 2008 recommendation statement on screening for prostate cancer and recommended against PSA-based screening for prostate cancer for men in the general U.S. population, regardless of age (grade D recommendation).[330] This recommendation generated substantial controversy, with some other organizations

concluding that PSA screening is warranted and should not be dismissed as nonbeneficial. A recent updated draft recommendation from the U.S. Preventive Services Task Force recommends against PSA-based screening for prostate cancer in men 70 years and older (grade D recommendation), but for men ages 55 to 69 they recommend individualized decision-making after discussion with a clinician to understand the potential benefits and harms of screening and to incorporate the patient's values and preferences into the decision (grade C recommendation).[331] The final U.S. Preventive Services Task Force recommendation is awaited.

The risk of prostate cancer overdetection and overtreatment with screening are substantial, and a large proportion of men are diagnosed with prostate cancer that would otherwise not progress to clinically significant disease during their lifetime. Serial PSA screening has at best a modest effect on prostate cancer mortality during the first decade of follow-up. With the recognition that no randomized trial has unquestionably indicated a benefit for screening in terms of reducing mortality from prostate cancer, several national groups, including the American College of Physicians and the American Academy of Family Physicians, modified their positions on screening and recommend that a patient be informed of the implications related to PSA screening prior to a PSA measurement. The American Urological Association now recommends shared decision-making for PSA-based screening for men ages 55 to 69 years; however, outside this age range, routine PSA-based screening is not recommended.[332] Recommendations for prostate cancer screening are summarized in Table 11-9.

Table 11-9 Prostate Cancer Screening Guidelines

Recommendation		American Urological Association[332]	American Cancer Society[328]	U.S. Preventive Services Task Force[331]
Shared decision-making between patient and clinician		Yes, for men ages 55 to 69	Yes (consider use of decision aid)	Yes (when patients request screening)
Average age to begin offering screening	Average-risk patients	55	50	Not applicable
	High-risk patients (black patients and patients with a first-degree relative with prostate cancer)	Not applicable	40 to 45	Not applicable
Discontinuation of screening		In men age 70+ or any man with less than a 10- to 15-year life expectancy	Life expectancy < 10 years	Not applicable
Screening tests	PSA, DRE	PSA, optional DRE	Not applicable	
Frequency of screening		To reduce the harms of screening, a routine screening interval of 2 years or more may be preferred over annual screening in those men who have participated in shared decision-making and decided on screening.	Annually (every other year when PSA < 2.5 ng/mL)	Not applicable
Criteria for biopsy referral		At this point, the use of DRE, PSA derivatives (PSA density and age-specific reference ranges) and PSA kinetics (velocity and doubling time), PSA molecular forms (percent free PSA and proPSA), novel urinary markers (PCA3), and prostate imaging should be considered secondary tests (not primary screening tests) with potential utility for determining the need for a prostate biopsy, but with unproven benefit as primary screening tests.	PSA > 4.0 ng/mL, abnormal DRE, individualized risk assessment if PSA is 2.5 ng/mL to 4.0 ng/mL	Not applicable

Abbreviations: DRE, digital rectal examination; PCA, prostate cancer antigen; PSA, prostate-specific antigen.

PSA is a single-chain glycoprotein with a molecular weight of 34 kD that functions as a kallikrein-like serine protease causing liquefaction of seminal coagulum. It is prostate-specific, but not prostate cancer–specific, and an elevated PSA may occur as a result of prostatitis, nonmalignant enlargement of the gland, biopsy of the prostate, ejaculation, and prostate cancer. A DRE does not alter PSA levels appreciably. The half-life of PSA is estimated to be 2 to 3 days, and levels should remain undetectable if the prostate has been removed. A PSA level greater than 4 ng/mL has predictive value for the diagnosis of prostate cancer, however, lower PSA values may also be associated with prostate cancer, as well as high-grade cancers, as demonstrated in an analysis of the prevalence of prostate cancer among men with a PSA level less than 4 ng/mL in the placebo group of the Prostate Cancer Prevention Trial.[333] The prevalence of prostate cancer was 6.6% with a PSA up to 0.5 ng/mL, 10.1% with a PSA between 0.6 ng/mL and 1.0 ng/mL, 17% with values of 1.1 ng/mL to 2.0 ng/mL, 23.9% with

values of 2.1 ng/mL to 3.0 ng/mL, and 26.9% with values of 3.1 ng/mL to 4.0 ng/mL. Of the prostate cancers diagnosed with a PSA less than 4.0 ng/mL, approximately 15% had a Gleason score of 7 or higher. This highlights the limitations of using a PSA cutoff value in the diagnosis of prostate cancer and specifically in detecting high-grade disease. For men with a PSA value between 4 ng/mL and 10 ng/mL, a PSA velocity of at least 0.75 ng/mL per year is suspicious for cancer. PSA measurement should be made on at least three consecutive occasions over at least 12 to 18 months because of variability. Because 5-alpha reductase inhibitors including finasteride and dutasteride are associated with a lowering of the PSA level, failure to have a substantial decrease in PSA (approximately 50%) or an increase in PSA while receiving these agents can be associated with prostate cancer.

An abnormal DRE necessitates a referral to a urologist for additional diagnostic testing. The sensitivity, specificity, and positive-predictive value have been determined for DRE and PSA (using a cutoff of 4 ng/mL).[334] The positive-predictive value of an abnormal DRE is 21%, whereas 25% of men with an elevated PSA level and abnormal DRE have cancer. Conditions that mimic prostate cancer on DRE include acute and granulomatous prostatitis and a prostatic calculus. When establishing a diagnosis, a TRUS is used to ensure that biopsy specimens encompass all portions of the gland. A TRUS has no role in screening. The diagnosis of prostate cancer is established with a TRUS-guided needle biopsy using a biopsy gun. An extended-pattern 12-core biopsy is recommended, and additional biopsies may be performed if clinically indicated. Ongoing studies are evaluating multiparametric MRI (mpMRI) of the prostate using the structured reporting system, PI-RADS, to detect and localize prostate cancer.

PSA testing has produced a shift in the frequency and proportion of men with early-stage disease. It remains controversial whether prostate cancer screening of the general population decreases prostate cancer mortality. Two large randomized trials of PSA screening for prostate cancer—the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial of the National Cancer Institute and the European Randomized Study of Screening for Prostate Cancer (ERSPC), both with the common endpoint of prostate cancer-specific mortality—were begun in the 1990s to assess the effectiveness of PSA screening.[335,336] In the ERSPC study, the initial mortality results were presented for 162,243 men between ages 55 and 69 randomly assigned to PSA screening every 4 years or to a control group with no PSA screening. During a median follow-up of 9 years, the cumulative incidence of prostate cancer was 8.2% in the screened group and 4.8% in the control group (71% increase in diagnosis). The rate ratio for death from prostate cancer in the screening group, as compared with the control group, was 0.80 (95% CI; 0.65, 0.98; adjusted $p = 0.04$)—a 20% lower mortality from prostate cancer in the screened group. The absolute risk difference was 0.71 deaths per 1000 men, indicating that 1410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent one death. An update after 11 years of follow-up indicated that 1055 men would need to be invited for screening and 37 cancers would need to be detected to prevent one death from prostate cancer.[337] In the PLCO study, 76,693 men were assigned to either annual screening for 6 years and DRE for 4 years, or to no screening with no reduction in mortality with screening. After 7 years of follow-up, the incidence of prostate cancer per 10,000 person-years was 116 (2820 cancers) in the screening group and 95 (2322 cancers) in the control group (rate ratio, 1.22; 95% CI; 1.16, 1.29). The incidence of death per 10,000 person-years was 2.0 (50 deaths) in the screening group and 1.7 (44 deaths) in the control group (rate ratio, 1.13; 95% CI; 0.75, 1.70). There are numerous criticisms of both of these studies, including a large proportion of men having undergone PSA screening prior to enrollment,

contamination with PSA screening in the control group, and the relatively short follow-up.[338,339] Subsequent analyses suggest a greater benefit to screening.[340] In a third screening trial from Sweden, which included ERSPC subjects and had a 14-year median follow-up, only 293 men needed to be screened and 12 diagnosed with prostate cancer in order to prevent one death from prostate cancer.[341]

Improving Specificity and Sensitivity of PSA Testing

PSA testing should be considered as a continuum, particularly as more men are diagnosed on the basis of a change in the measurement over time. A number of modifications to PSA testing have been proposed to increase its sensitivity, including PSA doubling time, PSA density (determined by dividing the serum PSA concentration by the volume of the prostate gland measured by TRUS), and PSA velocity (the change in serum PSA level over time)[342]; however, the utility of these modifications is disputed.[343] PSA exists in serum in a complexed form bound to either alpha l-antichymotrypsin or beta-2 macroglobulin, two extracellular protease inhibitors. When bound to these elements, the enzyme is inactive but still detectable using conventional immunoassays. For men with total PSA levels of 4 to 10 ng/mL, cancer is more likely if the percent free (the fraction not protein bound in the serum) is less than 25%.[344] Free PSA is not generally recommended to determine whether to perform a prostate biopsy. Elevation of prostate cancer antigen 3 (PCA3) in the urine following a DRE may suggest the presence of prostate cancer and may assist in determining whether a prostate biopsy is indicated in a patient with an elevated PSA.[345] PCA3 is FDA-approved to help determine the need for repeat prostate biopsies in men who have had a previous negative biopsy. A blood test based on PSA—the Prostate Health Index (PHI)—is a mathematic formula that combines total PSA, free PSA, and (-2)proPSA to produce a score to assist in prostate cancer detection.

MANAGEMENT OF PROSTATE CANCER BY DISEASE STAGE

Localized Disease

Localized prostate cancers are those confined to the prostate gland without nodal involvement or metastases. Treatment selection considers whether the disease can be eradicated by a treatment directed solely at the prostate, whether a combined local and systemic approach is necessary for cure, or whether therapy is not needed or can be deferred because of a low risk of progression. In general, therapy is aimed at complete local control to decrease the potential for recurrence while preserving optimal bowel, bladder, and sexual function.

Within each T category are tumors with a range of prognoses—especially for men with T1c disease—mandating the consideration of other factors to assess outcomes and select treatment. Many groups have developed prognostic models based on the combination of the initial T stage, Gleason score, and baseline PSA level. Some prognostic models use discrete cut points, and others are nomograms that use PSA level and Gleason score as continuous variables. These algorithms are used to predict disease extent (i.e., organ-confined vs. non–organ-confined), node status (negative or positive), and the probability of success using a PSA-based definition of failure specific to the local therapy under consideration. Specific nomograms have been developed for radical prostatectomy, external-beam radiation therapy, and brachytherapy (radioactive seed implantation). The eighth edition of the *AJCC Cancer Staging System* includes prognostic groupings that incorporate anatomic stage and PSA (Table 11-10).[15]

Table 11-10 **Anatomic Stage/Prognostic Groups***[15]

Group	T	N	M	PSA	Grade Group	Gleason Score
I	cT1a-c	N0	M0	<10	1	≤ 6
	cT2a	N0	M0	<10	1	≤ 6
	pT2	N0	M0	<10	1	≤ 6
IIA	cT1a-c	N0	M0	³10<20	1	≤ 6
	cT2a	N0	M0	³10<20	1	≤ 6
	cT2b-c	N0	M0	<20	1	≤ 6
IIB	T1-2	N0	M0	<20	2	7
IIC	T1-2	N0	M0	<20	3	7
	T1-2	N0	M0	<20	4	8
IIIA	T1-2	N0	M0	³20	1-4	≤ 8
IIIB	T3-4	N0	M0	Any PSA	1-4	≤ 8
IIIC	Any T	N0	M0	Any PSA	5	9 or 10
IV	Any T	N1	M0	Any PSA	Any	Any Gleason
	Any T	N0	M1	Any PSA	Any	Any Gleason

**Changes from AJCC Cancer Staging Manual: T4N0M0 is now stage III; WHO Grade should be used to record tumor grade*
The original source for this material is the AJCC Cancer Staging Manual,
8th Edition (2017) published by Springer Science and Business Media LLC, www.springerlink.com.

Pelvic Lymph Node Involvement

Pelvic CT or MRI scans are recommended if the tumor is T3, T4, or T1 to T2 and the nomogram indicates the probability of lymph node involvement is greater than 10%.[346] The FDA has approved the radioimmunoconjugate capromab pendetide that recognizes PSMA for the detection of prostate cancer nodal metastases; however, based on poor test characteristics, capromab pendetide is infrequently used.[347,348]

Distant Metastases

Prostate cancers spread by local extension through the capsule and seminal vesicles, the lymphatic system to regional nodes, or hematogenously to bone and visceral sites. Bone metastases are predominantly osteoblastic rather than osteolytic, although the two types may coexist. Radionuclide bone scans are used to detect metastases to the skeleton. The yield of a bone scan is low for patients with tumors that are T2 or less, with a Gleason score of 7 or less, and a PSA level of less than 10 ng/mL. Bone scans are recommended if the following criteria are met: tumor is T1 and the PSA is greater than 20 ng/mL; T2 and the PSA is greater than 10 ng/mL; the Gleason score is greater than or equal to 8; the tumor is T3 or T4; or the patient has symptoms of bone metastases.[346] CT may be helpful for evaluating focal areas of the skeleton, as well as for identifying healing fractures, arthritis, Paget disease, bone infections, and other inflammatory bone conditions that may mimic prostate cancer on a bone scan.

THERAPY FOR TUMORS CONFINED TO THE PROSTATE

Tumors that are confined to the prostate are generally managed by radical surgery, radiation therapy, or, in some cases, active surveillance. All are considered options by the American Urological Association Prostate Cancer Clinical Guidelines Update Panel.[349] An assessment of

the patient's life expectancy, overall health status, and tumor characteristics should be undertaken before a treatment decision is made. For patients with low-risk localized prostate cancer, active surveillance, interstitial prostate brachytherapy, external-beam radiation therapy, and radical prostatectomy are appropriate monotherapy treatment options. For patients with intermediate-risk or high-risk localized prostate cancer, combined-modality therapy may be indicated. With few randomized trials, comparisons among treatments have been limited by selection bias and differences in outcomes reporting, both with respect to cancer control and quality of life. Nomograms and other prognostic models have been developed to assist in decision-making, while quality-of-life assessments have become more standardized.

Reported complication rates for each modality vary widely in the literature. For radical prostatectomy, impotence rates range from 25 to 89%, and incontinence ranges from 2 to 47%. The differences are related to the different definitions used, whether the patient or physician is reporting, and the time from the treatment to the assessment of symptoms. Health-related quality-of-life studies (HRQOL) are more accurately defining the patient's satisfaction with the different treatments for localized prostate cancer. For example, in one study, adjuvant hormone therapy was associated with worse QOL outcomes among patients receiving brachytherapy or external radiotherapy, whereas urinary incontinence was observed after prostatectomy, but urinary irritation and obstruction improved, particularly in patients with large prostates.[350] In one large study of erectile function at 2 years after men underwent prostatectomy, external-beam radiotherapy, or brachytherapy for prostate cancer, the estimated 2-year function probabilities ranged from as low as 10% or less to as high as 70% or greater depending on the individual's pretreatment characteristics and treatment details (i.e., pretreatment sexual HRQOL score, age, serum PSA level, race/ethnicity, body mass index, and intended treatment details).[351] These analyses have led to the development of HRQOL nomograms that may help guide treatment choice in an individual patient with localized prostate cancer.

Watchful Waiting and Active Surveillance

Watchful waiting or deferred therapy is a policy of no therapeutic intervention after a diagnosis has been established until disease progression is evidenced by changes in the PSA level, local tumor growth, or the development of metastases. The approach evolved from studies of predominantly older men with well-differentiated tumors in whom tumor progression was found to occur over a protracted period of time, and in which, during the follow-up interval, a substantial proportion of men died of non–prostate cancer–related illnesses. In a structured literature review of patients treated with a deferred approach, radical prostatectomy, or external-beam radiation, the 10-year mean weighted survivals were 93% for patients who received radical prostatectomy, 84% for patients treated with a deferred approach, and 74% for patients who received external-beam radiation.[352] A retrospective, population-based cohort study using the Connecticut Tumor Registry indicated that the 20-year prostate cancer-specific survival for men with a Gleason score of 6 or less treated with watchful waiting was 80 to 90%.[353] A retrospective study of 44,630 men ages 65 to 80 who were diagnosed between 1991 and 1999 with organ-confined, well- or moderately-differentiated prostate cancer stratified by having received treatment or observation found a significant survival advantage associated with treatment (HR, 0.69; 95% CI; 0.66, 0.72).[354] A benefit associated with treatment was seen in all subgroups examined, including older men (ages 75 to 80 at diagnosis), black men, and men with low-risk disease.

Three randomized, controlled trials have compared treatment to watchful waiting or active monitoring for clinically localized prostate cancer. In the Scandinavian Prostate Cancer Group-4 (SPCG-4) trial of 695 men with early prostate cancer randomly assigned to watchful waiting or radical prostatectomy, death from prostate cancer after over 23.2 years of follow-up occurred in 99 men assigned to watchful waiting compared with 63 patients who had surgery (relative risk, 0.56; 95% CI; 0.41, 0.77; p = 0.001) with an absolute difference of 11.0 percentage points (95% CI; 4.5, 17.5).[355,356] At 18 years, 26.1% of men in the surgery group and 38.3% of men in the watchful waiting group had been diagnosed with distant metastases (difference, 12.2 percentage points; 95% CI; 5.1, 19.3), for a relative risk of 0.57 (95% CI; 0.44, 0.75; p < 0.001). Of note, the mean PSA value was 13 ng/mL, and only 12% of the patients had nonpalpable T1c tumors, making it unlikely that these results are applicable to the current U.S. population, in which nearly half of newly diagnosed patients are diagnosed with T1c prostate cancer. In the Prostate Cancer Intervention versus Observation Trial (PIVOT), 731 men with localized prostate cancer were randomly assigned to radical prostatectomy or to undergo observation.[357] After 19.5 years of follow-up, surgery was not associated with significantly lower all-cause (absolute difference in risk, 5.5 percentage points; 95% CI; -1.5, 12.4; HR, 0.84; 95% CI; 0.70,1.01; p = 0.06) or prostate-cancer (absolute difference in risk, 4.0 percentage points; 95% CI; -0.2, 8.3; HR, 0.63; 95% CI; 0.39, 1.02; p = 0.006) mortality than observation. Surgery was associated with more adverse events than observation but a lower frequency of treatment for disease progression (mostly for asymptomatic, local, or biochemical progression). As compared to the SPCG-4 study, PIVOT involved men during the early era of PSA testing. A third trial, the Prostate Testing for Cancer and Treatment (ProtecT) study included 2664 men (ages 50 to 69) who received a diagnosis of localized prostate cancer, and 1643 agreed to undergo randomization to active monitoring (545 men), surgery (553), or radiotherapy (545) with a primary outcome of prostate-cancer mortality.[358] At a median follow-up of 10 years, there were only 17 prostate cancer–specific deaths with no significant difference among the treatments and no significant difference in deaths from any cause. Active monitoring was associated with higher rates of disease progression and metastases. Overall, these trials suggest that long-term prostate cancer mortality is low in the majority of men with localized disease (particularly in those with low-risk disease) who undergo observation or active monitoring.

As a consequence of PSA screening resulting in overdiagnosis and overtreatment of men with indolent tumors, active surveillance or close monitoring of good-risk patients (defined as a Gleason score of 6 or less, PSA less than 10 ng/mL, and T1c-T2a disease) for delayed intervention has gained increased acceptance as an initial strategy for men diagnosed with prostate cancer. Men are actively monitored by serial PSA, DRE, and periodic prostate biopsies every 1 to 2 years. Emerging data suggest that the inclusion of mpMRI may be useful in active surveillance protocols. Therapy is offered based on various risk progression criteria that may include biochemical (change in PSA), histologic (increase in Gleason score or number of positive biopsies), and stage (by DRE or imaging) measures. This approach may also be considered in select men with intermediate-risk prostate cancer.[359] A genomic prostate cancer score (Oncotype DX) that measures disease biology through the expression of 17 genes across four important genetic pathways and, in conjunction with clinical risk factors may be used at the time of diagnosis in patients with clinical low-risk disease (Gleason score 3+3 and 3+4) to predict disease aggressiveness and may help men make more informed decisions between active surveillance and immediate treatment.[360]

Radical Retropubic Prostatectomy

The goal of radical retropubic prostatectomy is to completely excise the cancer while maintaining urinary control and preserving potency. After the prostate has been removed, PSA levels should decline to undetectable. Cancer control is assessed by PSA relapse-free survival, time to objective progression (local or systemic), cancer-specific survival, and OS. The procedure continues to evolve as clinicians use biopsy algorithms that include more extensive sampling and imaging such as mpMRI to determine both the extent and location of the tumor within the prostate. This approach has resulted in refined selection of cases and surgical planning, which, in turn, has led to more rapid recovery, higher rates of continence, and improved potency. In a large series, continence returned in 2 months, predicted by younger age and preservation of both neurovascular bundles. Overall, 6% of patients had mild stress urinary incontinence (requiring one pad daily), 2% had moderate incontinence (more than one pad daily), and 0.3% had severe incontinence that required an artificial urinary sphincter, with 92% having complete continence at 1 year. With preservation of both neurovascular bundles, erectile function returns in a median of 4 to 6 months. Sacrificing one nerve bundle decreases recovery by 50%. Minimally invasive surgery, including both conventional and robotic laparoscopic radical prostatectomy, has emerged as an alternative to open surgery for patients with clinically localized prostate cancer.[361]

Radiation Therapy

Radiation can be administered using external-beam techniques, an implant of radioactive seeds, or a combination of the two. Androgen-deprivation therapy (ADT) may or may not be administered. As is the case with surgery, the reported outcomes vary, but most trials measure the proportion of patients who have a decline in PSA level to less than 0.5 ng/mL or 1 ng/mL, the proportion with nonrising PSA, and/or the proportion with negative findings on biopsy of the prostate 2 years after the completion of treatment. The standard Phoenix definition for a biochemical failure after external-beam radiation therapy with or without hormonal therapy is PSA nadir plus 2 ng/mL.[362] Contemporary external-beam radiation therapy incorporates three-dimensional conformal treatment planning with intensity modulation to maximize the administered dose to the tumor while minimizing the exposure of surrounding normal structures. These techniques allow for the safe administration of higher doses, which in turn have resulted in improved outcomes. Compared with surgery, radiation therapy is associated with a higher frequency of bowel complications, mainly loose stools and diarrhea, and lower rates of urinary incontinence and sexual dysfunction.

The use of interstitial radiation or implantation of radioactive seeds is based on the principle that deposition of radiation energy in tissues decreases exponentially as a square function of the distance from the radiation source. Older techniques relied on digital placement of the seeds, whereas modern techniques use computer-generated templates to place the seeds more accurately under direct visualization. The result is better cancer control and reduced toxicity. An acute toxicity associated with implantation is irritative urinary symptoms including urinary frequency. Incontinence is rare, and potency may be better than that observed with radical surgery.[350,351,363-365]

Four prospective randomized trials have demonstrated that radiotherapy doses less than 70 Gy are inadequate for the curative treatment of clinically localized prostate cancer.[366] It is not clear whether doses exceeding 78 Gy to 79 Gy render additional benefit. Hypofractionated external-beam radiotherapy has been compared to standard fractionation in several trials

(including patients with low-, intermediate-, and high-risk disease) with relatively short follow-up and has demonstrated similar efficacy outcomes.[367-369] Another recent study, ASCENDE-RT, included patients with high- or intermediate-risk prostate cancer treated with 12 months of ADT and 46 Gy of external-beam radiation therapy followed by randomization to either a dose-escalated external-beam radiation therapy boost to 78 Gy or an experimental arm that substituted a low-dose-rate brachytherapy boost. At a median follow-up of 6.5 years, men randomized to the low-dose-rate brachytherapy were twice as likely to be free of biochemical failure as compared to those treated with a standard dose-escalated external-beam radiation therapy boost (multivariable analysis [MVA] HR, 2.04; p = 0.004).[370]

Focal Therapy

Cryosurgery is a minimally invasive procedure aimed at local control with low complication rates and favorable functional outcomes. This approach often is considered for patients whose disease is not suitable for radical surgery or who have local recurrences. Sufficient long-term follow-up is lacking to estimate efficacy in terms of prostate cancer-specific mortality. High-intensity focused ultrasound (HIFU), a hyperthermia therapy, is another minimally invasive treatment.

Neoadjuvant and Adjuvant ADT

Although neoadjuvant ADT before surgery leads to a reduction in the rate of positive surgical margins, it has not had an effect on overall outcome and is not recommended. The benefit of immediate adjuvant ADT following surgery in men with localized disease at high risk for relapse is not proven.

In contrast to surgery, the role of neoadjuvant and concurrent ADT for patients receiving radiation is well established. Results of numerous randomized trials suggest that neoadjuvant and concurrent androgen deprivation is beneficial for intermediate-risk patients receiving external-beam radiation therapy with an optimal duration of 3 to 6 months,[366,371-374] although 6 months of ADT was associated with a longer time to PSA recurrence and decreased mortality for men with a pretreatment PSA velocity more than 2 ng/mL per year.[375] Several randomized trials provide support for early ADT in conjunction with local therapy in patients with high-risk disease. In an early study conducted by Bolla et al., 415 patients with locally advanced prostate cancer were randomly assigned to receive radiotherapy alone or radiotherapy plus 3 years of androgen ablation. With a median follow-up of 66 months, 5-year OS was 62% (range, 52 to 72) in the radiotherapy alone group and 78% (range, 72 to 84) (p = 0.0002) in the combination group. The trial has been criticized for the poor outcomes in the control group.[376] Ten-year follow-up of RTOG 8531, which tested whether the use of lifelong ADT after radiation therapy improved outcomes, showed that patients treated with early ADT had superior local, biochemical, and distant disease control rates (all p < 0.0001), as well as improved disease-specific survival (83% vs. 78%; p = 0.0053) and OS (47% vs. 38%; p = 0.0043) compared with patients treated at relapse.[377,378] With radiation therapy, patients with high risk disease should receive long-term ADT for at least 2 years.[379,380] Use of early ADT is also supported by the trials previously described in which patients with pathologically confirmed lymph node involvement receiving immediate ADT had improved survival. In the SWOG 9921 study, 983 men with high-risk prostate cancer were randomly assigned postprostatectomy to adjuvant therapy with ADT alone (gonadotropin releasing hormone [GnRH] agonist plus bicalutamide for 2 years) or ADT with mitoxantrone chemotherapy. An early analysis of the 481 men treated on

the ADT-alone arm at a median follow-up of 4.4 years found a 5-year biochemical-free survival of 92.5% and an OS of 95.9%.[381] However, this trial was not designed specifically to address the role of adjuvant androgen ablation after prostatectomy, and it has many inherent problems (e.g., selection bias and PSA-driven stage migration).

In the Early Prostate Cancer Program, patients with localized disease were randomly assigned to receive 150 mg of bicalutamide or placebo. The primary endpoint was objective clinical progression that included detectable disease in soft tissue or the documentation of bone metastases at 2 years. Early combined results of three trials showed that the proportion of patients in whom osseous metastases developed within 2 years was 9% for patients who received bicalutamide and 14% for patients who received placebo. This finding represented an HR of 0.58 (95% CI; 0.51, 0.66; $p < 0.001$).[382] No effect on survival was demonstrated. Subgroup analysis showed the greatest benefit in patients with nodal disease.[383] An update, however, showed no benefit for early bicalutamide therapy for patients with localized disease at low risk for recurrence.[384]

Pelvic nodal radiation with concurrent androgen deprivation for patients at intermediate and high risk for nodal involvement remains controversial.[385]

The role for immediate long-term androgen suppression in patients with pathologically documented lymph node involvement is supported by subset analysis of lymph node-positive patients in RTOG 85-31. Patients randomly assigned to immediate androgen suppression in conjunction with standard external-beam radiation therapy demonstrated significantly improved outcomes compared with patients receiving radiation alone.[377] In a study of patients undergoing radical prostatectomy, patients with lymph node–positive disease at surgery were randomly assigned to undergo castration (surgically or medically) or observation. PSA testing was not in wide use during the conduct of this study, so that objective progression was defined as the development of metastases on imaging tests. At a median follow-up of 11.9 years, men assigned to immediate androgen suppression demonstrated a significant improvement in PFS, prostate cancer-specific survival, and OS.[386] Although there is evidence that early (adjuvant) androgen deprivation may benefit patients with node-positive disease after radical prostatectomy, it is based on only 98 men and a control arm with a lower than predicted cancer-specific survival.

THERAPY FOR PROGRESSIVE DISEASE

Local Failure

Adjuvant and Salvage Radiation Therapy. Adjuvant radiation is considered for patients with certain high-risk features at the time of radical prostatectomy, whereas salvage radiation therapy to the prostatic bed is administered in select patients who develop a biochemical recurrence following surgery.[387] There are no prospective data comparing adjuvant radiation to salvage radiation. In the setting of a biochemical recurrence, a local recurrence is more likely if the PSA first became detectable more than 1 year after surgery, the PSA doubling time is greater than 10 months, the radical prostatectomy specimen contained a cancer of low Gleason score (< 7), and there was no seminal vesicle invasion or lymph node metastases in the pathologic specimen. In a retrospective review of 1540 patients who received salvage radiotherapy, the 6-year progression-free probability was 32% (95% CI; 31%, 51%).[388] Of the patients treated with salvage radiotherapy alone at PSA levels of 0.50 ng/mL or lower, 48% (95% CI; 40, 56) were disease-free at 6 years, including 41% (95% CI; 31, 51) who also had a PSA doubling time of 10 months or less or poorly differentiated cancer (Gleason grade 8 to

10). A recent update to a multiinstitutional predictive nomogram for salvage radiation after radical prostatectomy emphasizes the importance of early salvage radiotherapy at low PSA levels.[389] The 5-year freedom from biochemical failure rate was 56% overall, 71% for those with a presalvage radiotherapy PSA level of 0.01 to 0.2 ng/mL compared to 43% for those with a PSA of 1.01 to 2.0 ng/mL (341 patients). Furthermore, another retrospective study demonstrated that salvage radiotherapy alone was associated with a significant 3-fold increase in prostate cancer-specific survival relative to those who received no salvage treatment (HR, 0.32; 95% CI; 0.19, 0.54; $p < 0.001$).[390] The increase in prostate cancer–specific survival associated with salvage radiotherapy was limited to men with a PSA doubling time of less than 6 months and remained after adjustment for pathologic stage and other established prognostic factors. Other studies suggest that PSA kinetics, and specifically a pretreatment PSA velocity greater than 2 ng/mL per year, an interval to PSA failure of less than 3 years, and a posttreatment PSA doubling time of less than 3 months, increase the risk of metastases and subsequent prostate cancer–specific mortality, and may indicate that these men are poor candidates for salvage radiation therapy.[391]

Three prospective, randomized trials suggested that immediate postoperative radiotherapy in men with advanced pathologic features (stage pT3a or pT3b) and/or positive surgical margins improves biochemical PFS.[392] In each of these studies, there was an improvement in biochemical PFS for patients receiving immediate postoperative radiotherapy, but no improvement in OS. At nearly 13 years of follow-up in the SWOG 8794 trial, in which men with pT3N0M0 or margin-positive disease were randomly assigned to immediate radiation to the prostatic fossa or to usual care, the metastasis-free survival rate was 43% in the radiation-treated group and 54% in the untreated group ($p = 0.016$).[393] Moreover, OS was significantly improved for men treated with adjuvant radiotherapy (52% vs. 41% for men initially observed; $p = 0.023$). Of note, there was also a significant benefit of radiotherapy in those men with a detectable PSA after surgery. In this study, 9.1 men with pathologic T3 disease needed to receive adjuvant radiotherapy to prevent 1 death at a median follow-up of 12.6 years.

The role of hormonal therapy with radiation in the salvage or adjuvant settings has been studied in a phase III trial (NRG Oncology/RTOG 9601) that randomized post-radical prostatectomy patients with pT3pN0 or pT2pN0 with positive margins who had or developed elevated PSA levels from 0.2 to 4.0 ng/mL to radiation therapy plus placebo or radiation therapy plus bicalutamide (150 mg daily) for 24 months.[394] At a median follow-up of 13 years among the surviving patients, an improvement in OS (at 12 years, OS 76.3% for radiation plus bicalutamide and 71.3% for radiation plus placebo; HR, 0.77 [95% CI; 0.59, 0.99; $p = 0.04$]) and reduction in metastatic disease and prostate cancer–related deaths was seen with bicalutamide.

Patients treated initially with radiation therapy may be considered for salvage prostatectomy if they were surgical candidates at the time of diagnosis, have a life expectancy of more than 10 years, and have no metastatic disease. Biopsy confirmation of persistent disease in the gland and no evidence of spread are essential before surgery is considered. Despite refinements in case selection, incontinence rates remain high and virtually all patients are impotent after the procedure. Salvage treatments including cryotherapy and brachytherapy for postradiation recurrent prostate cancer may be considered for select patients.

Biochemical Recurrence

The disease state of a rising PSA or biochemical relapse refers to men who have no detectable

metastases on a scan and in whom the PSA level increases after radical prostatectomy, radiation therapy, or both. It does not refer to an increase in PSA level for patients in whom disease is managed by watchful waiting. Issues in management include whether the rising PSA value represents a local recurrence that could be eliminated with additional treatment to the prostate bed, whether it represents metastatic disease, or both.

In most cases, a rising PSA level represents micrometastatic disease that is not detectable on conventional imaging studies. The time to development of metastases is highly variable. In one series of patients experiencing a PSA recurrence following radical prostatectomy, the median time to the detection of metastatic disease was 8 years, and 63% of the patients with a rising PSA level remained free of metastases at 5 years.[395] Time to biochemical progression, Gleason score, and PSA doubling time were predictive of the probability and time to development of metastatic disease. In a follow-up report, strong risk factors for time to prostate cancer-specific mortality included PSA doubling time (< 3.0 vs. 3.0 to 8.9 vs. 9.0 to 14.9 vs. > 15.0 months), Gleason score (< 7 vs. 8 to 10), and time from surgery to PSA recurrence (< 3 vs. > 3 years).[396] PSA velocity at recurrence is significantly associated with an increased risk of all-cause mortality among men treated with radiation therapy with or without ADT.[397] A major issue for patients with a rising PSA level relates to the use of early versus deferred ADT. Although guidelines for evaluating and treating men in this state were updated in 2013, there is no gold standard.[346] An observational follow-up study of immediate ADT (within 3 months of PSA relapse) compared with deferred (initiation at time of metastasis, symptoms or a short PSA doubling time) in patients with prostate cancer and a PSA-only relapse demonstrated an adjusted mortality HR for immediate versus deferred androgen deprivation therapy of 0.91 (95% CI; 0.52, 1.60) translating into a similar 5-year survival.[398]

If the decision is made to begin ADT in a patient with a rising PSA value but no evidence of metastases, data suggest that intermittent androgen suppression may be a reasonable alternative to continuous androgen suppression. In a phase III noninferiority trial that enrolled 1386 men with nonmetastatic prostate cancer who had a rising PSA level of greater than 3.0 ng/mL 1 year after the completion of radiotherapy, men were randomly assigned to either ADT with a luteinizing hormone–releasing hormone (LHRH) continuously until their cancer became castration-resistant or intermittently (for 8 months in each cycle with restart when the PSA reached greater than 10 ng/mL) until progression, at which time they were switched to continuous ADT.[399] Median OS was 9.1 years for patients on continuous therapy compared with 8.8 years for the intermittent group (HR, 1.02; 95% CI; 0.86, 1.21; p for noninferiority [HR intermittent vs. continuous > 1.25] = 0.009). The majority of patients (59%) died of causes unrelated to prostate cancer, with more prostate cancer–related deaths in the intermittent arm (120 of 690) compared with the continuous arm (94 of 696; 7-year cumulative rates of disease-related deaths were 18% and 15%, respectively; p = 0.24). Time to the development of castration resistance was significantly improved in the intermittent arm (HR, 0.80; 95% CI; 0.67, 0.98; p = 0.024). Patients who received intermittent androgen suppression had reduced hot flashes, but otherwise there was no evidence of differences in toxicity, including myocardial events or osteoporotic fractures. Some reports have questioned the role for intermittent ADT citing trial design issues including wide noninferiority margins that included clinically important survival differences.[400]

ADT FOR SYSTEMIC RELAPSE

ADT that negates androgen effects is the standard approach for relapsed prostate cancer.

More than 90% of male hormones originate in the testes, with the remaining hormones synthesized in the adrenal gland. Surgical orchiectomy was the gold standard treatment, but is the least preferred by patients. ADT options can be divided into those that lower serum testosterone levels (such as gonadotropin-releasing hormone agonists or antagonists, and estrogens) and antiandrogens that do not lower testosterone but block androgen action at the level of the androgen receptor. Medical or surgical castration is associated with gynecomastia, impotence, loss of libido, weakness, fatigue, hot flashes, loss of muscle mass, changes in personality, anemia, depression, and loss of bone over time. Resistance and aerobic exercise can improve muscle mass, strength, and physical function.[401] There has been conflicting data regarding the risk of dementia in patients with prostate cancer receiving ADT.

Prolonged time on ADT that lowers testosterone can result in osteoporosis. Dual-energy x-ray absorptiometry scans may be used at baseline and to screen for the development of osteopenia and/or osteoporosis. Bisphosphonates, denosumab (a fully humanized anti-RANKL monoclonal antibody), and selective estrogen receptor modulators (SERMs) have been shown to increase bone mineral density in men receiving ADT.[402]

Prolonged ADT is frequently used in men without metastases, as in men receiving radiation therapy as definitive therapy for high-risk prostate cancer (see section on Therapy for Tumors Confined to the Prostate). The HALT examined the role of denosumab at a dose of 60 mg subcutaneously every 6 months in men receiving ADT for nonmetastatic prostate cancer. In the study, 1568 men were randomly assigned to either denosumab or to placebo.[403] Bone mineral density of the lumbar spine increased by 5.6% in the denosumab group, compared with a loss of 1.0% in the placebo group ($p < 0.001$) at 24 months, and there was also a decreased incidence of new vertebral fractures at 36 months (1.5%, vs. 3.9% with placebo; relative risk, 0.38; 95% CI; 0.19, 0.78; $p = 0.006$). In 2011, the FDA approved denosumab (60 mg every 6 months) to increase bone mass in men at high risk for fracture who are receiving ADT for nonmetastatic prostate cancer.

THERAPY FOR METASTATIC PROSTATE CANCER

ADT for Non–Castration-Resistant Metastatic Prostate Cancer

Non–castration-resistant metastatic prostate cancer is defined by metastases on an imaging study (either at the time of diagnosis or following local therapy) in patients who have noncastrate levels of testosterone. At this point, the risk of death from prostate cancer exceeds that of noncancer-related mortality. Response to ADT can be measured by a decline in PSA values, decrease in the size of nodal or visceral metastases, or improvement in cancer-related symptoms. Overall, 60 to 70% of patients with abnormal PSA levels will have normalization of the value to below 4 ng/mL after castration, 30 to 50% of measurable tumor masses will regress by 50% or more, and approximately 60% of patients will have palliation of symptoms. Serial bone scans will show improvement in only 30 to 40% of patients, and a scintigraphic flare on serial bone scans can occur following ADT between 3 and 6 months after initiation of therapy; this should not be confused with progression of skeletal metastases.[404] In an analysis of survival in more than 1000 patients treated with ADT, the PSA value measured at 7 months after initiating therapy was predictive of outcomes, with a median survival of 13 months for patients with a PSA nadir of greater than 4 ng/mL, 44 months for patients with a PSA nadir of greater than 0.2 ng/mL to less than 4 ng/mL, and 75 months for patients with a PSA nadir of less than 0.2 ng/mL.[405]

The initial rise in testosterone after treatment with a GnRH agonist can result in a clinical

flare of the disease. These agents should not be used as monotherapy for patients with severe pain, urinary symptoms, or spinal cord compromise. Under such circumstances, antiandrogens to block the flare response in combination with a GnRH agonist or the use of a GnRH antagonist that suppresses testosterone without a testosterone surge are recommended. The combination of an antiandrogen and a GnRH analog also has the additional potential to block the effects of adrenal androgens, which can contribute from 5 to 45% of the residual androgens present in tumors following surgical castration alone. Whether the antitumor effects of a combined or maximal androgen-blockade approach was superior to castration alone or to GnRH monotherapy was in question for many years. In 2000, the PCTCG published a meta-analysis of combined androgen blockade, and demonstrated that nonsteroidal antiandrogens conferred a small but significant improvement in 5-year survival over castration therapy alone (72.4% vs. 75.3%; HR, 0.92; $p < 0.005$).[406] In an update after a median of 5.2 years of follow-up of a phase III randomized trial that compared combined androgen blockade using luteinizing hormone–releasing hormone (LHRH) agonist plus 80 mg of bicalutamide with LHRH agonist alone in patients who had advanced prostate cancer, there was a significant improvement in OS for patients receiving combined androgen blockade (HR, 0.78; 95% CI; 0.60, 0.99; $p = 0.0498$), although there was no significant difference in cause-specific survival between the two groups.[407] Thus, several thousand patients have been enrolled in trials, with the results showing that antiandrogens may provide a very modest improvement in survival for patients treated with a combination of GnRH agonists or antagonists.

Nonsteroidal antiandrogens, such as flutamide, bicalutamide, and nilutamide, block the binding of androgens to the androgen receptor. They have been evaluated for several purposes: (1) to block the flare secondary to the initial rise in testosterone that results following administration of GnRH agonists; (2) to simultaneously inhibit testicular and adrenal androgens as part of a combined androgen-blockade approach.

Other approaches that have been investigated include high-dose bicalutamide (150 mg), which is associated with fewer hot flashes, less effect on libido, less muscle wasting, fewer personality changes, and less bone loss. Gynecomastia remains a substantial problem, but can be alleviated, in part, with prophylactic breast irradiation or the addition of tamoxifen. Whether this approach is equivalent to more traditional therapies that lower testosterone levels is questionable because the results of clinical trials have been conflicting. For patients with established metastatic disease, however, antiandrogen monotherapy was inferior to testosterone-lowering therapy.[408]

Early versus Delayed ADT. Recommendations for the initial management of patients with androgen-sensitive, metastatic, recurrent, or progressive prostate cancer were updated in 2006.[409] A continuing controversy is the question of early versus delayed ADT. Data in support of early ADT date back to the findings from early randomized studies in which diethylstilbestrol or orchiectomy was found to delay the development of metastases for patients with T3 disease. In a study conducted by the Medical Research Council, 938 patients with locally advanced or asymptomatic metastatic prostate cancer were randomly assigned to either immediate treatment (orchiectomy or medical castration) or to the same treatment deferred until an indication occurred. Treatment was commenced for local progression almost as frequently as for metastatic disease. Compared with patients treated with deferred therapy, patients treated with early therapy were less likely to have progression from M0 to M1 disease ($p < 0.001$), have pain ($p < 0.001$), and die of prostate cancer.[410]

Continuous versus Intermittent ADT in Metastatic Prostate Cancer. The use of continuous (long-term) ADT in patients with metastatic prostate cancer is associated with many adverse effects, including hot flashes, loss of libido, bone loss, muscle atrophy, as well as others. Androgen-dependent animal models have suggested that intermittent androgen deprivation increases the time to castration-resistant disease. A trial of intermittent versus continuous ADT in men with metastatic prostate cancer randomly assigned 3040 patients to intermittent or continuous ADT after an initial 7 months of treatment with an LHRH analog and an antiandrogen if PSA fell to 4 ng/mL or less.[411] The coprimary endpoints were to determine whether intermittent therapy was noninferior to continuous therapy for survival (upper boundary of HR, 1.20), and to assess whether QOL differed at 3 months. At a median follow-up of 9.8 years, the median survival for continuous and intermittent ADT was 5.8 and 5.1 years, respectively (HR for death with intermittent therapy, 1.10; 90% CI; 0.99, 1.23). Although intermittent therapy was associated with improved erectile function and mental health at 3 months, there was no difference thereafter. Since the confidence interval for survival exceeded the upper boundary for noninferiority, the findings were statistically inconclusive (i.e., could not rule out a 20% greater risk of death with intermittent ADT). A systematic review of randomized clinical trials of intermittent versus continuous ADT, including nine studies with 5508 patients, demonstrated no significant differences in OS or PFS with more prostate cancer–related deaths, with intermittent androgen deprivation balanced by more nonprostate cancer-related deaths with continuous therapy. Intermittent ADT was associated with improvement in general well-being, sexual function, and physical activity in some studies, as well as a median cost saving of 48%.[412]

Castration-Resistant Prostrate Cancer

The treatment of patients with disease that progresses during ADT requires documentation that the patient is medically castrate (serum testosterone level less than 50 ng/mL) and a determination of the extent of disease (Fig. 11-4). A rising PSA can occur in patients who have received ADT but have no sign of metastases (nonmetastatic CRPC). In these patients, radiographic imaging should be performed in an attempt to document metastases. In an analysis of the placebo group in a randomized, controlled trial of men with a rising PSA level—despite ADT and no radiographic evidence of metastases—bone metastases developed in 46% of men at 2 years, and the median metastasis-free survival was 25 months.[413] Higher baseline PSA (≥13.2 ng/mL) was significantly associated with a shorter time to first bone metastasis, OS, and bone metastasis–free survival. A higher PSA velocity was also associated with shorter overall and bone metastasis–free survival. The majority of men will experience disease progression on ADT, with the development of progression in bone, soft tissue, or visceral metastases (metastatic CRPC).

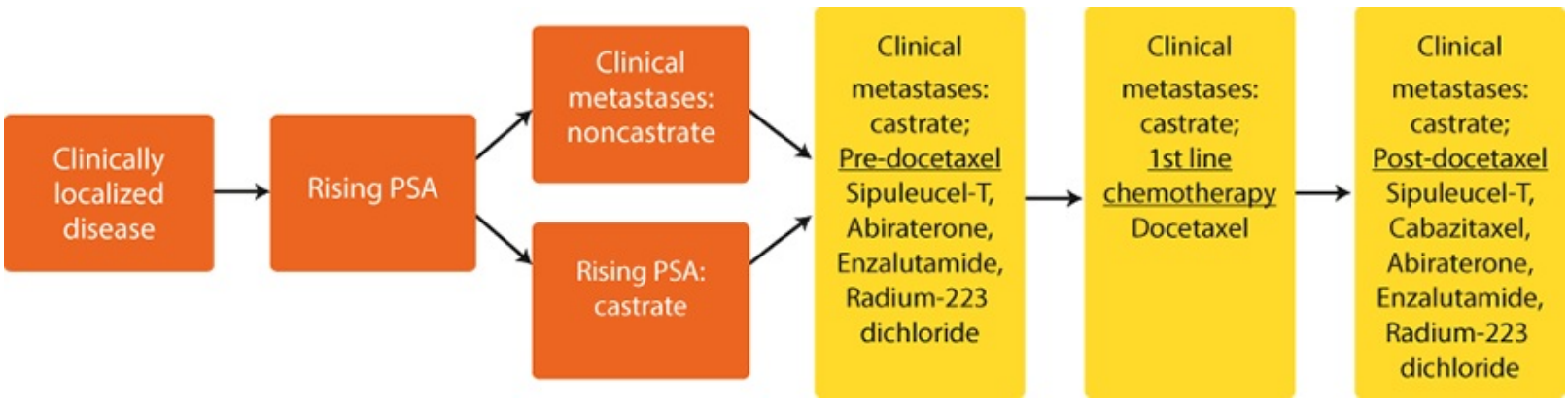

Fig. 11-4 Prostate cancer clinical states model; framework for castration-resistant prostate cancer (CRPC) management.

Adapted from Scher HI, Morris MJ, Basch E, et al. End points and outcomes in castration-resistant prostate cancer: from clinical trials to clinical practice. J Clin Oncol. 2011;29:3695–704. PMID: 21859988.

The term “hormone-refractory” is no longer accurate because progression of disease during ADT is not necessarily refractory to additional treatment targeting androgen signaling. Despite the development of CRPC, androgen receptor signaling continues to play a major role in many prostate cancers. Mechanisms leading to androgen receptor activation include androgen receptor overexpression, ligand-independent activation, de novo synthesis of intratumoral androgens, and alterations in the androgen receptor including splice variants and circulating subcastrate levels of androgens.[414,415] Patients who are taking an antiandrogen are first given a trial of antiandrogen withdrawal based on the observation that these agents, although initially providing benefit, can later contribute to prostate cancer progression. Thereafter, a second agent, such as another nonsteroidal antiandrogen, or ketoconazole with hydrocortisone, may be considered. Responses, when they occur, are frequently of short duration (2- to 4-month median), although there are patients who achieve a prolonged response. The development of new classes of agents including novel nonsteroidal antiandrogens, cytochrome P450 (CYP) 17 inhibitors, and androgen receptor–targeted compounds has already led to substantial improvements in outcome for patients with CRPC. Abiraterone acetate and enzalutamide have been approved, and other androgen receptor pathway-targeted agents (see the section on Novel Hormonal Agents) are under investigation in patients whose disease progressed on primary ADT and may represent effective second-line hormone therapy prior to chemotherapy.

For patients with overt symptomatic metastatic disease at the time of initiating ADT, disease typically relapses first with rising PSA levels, followed by progression on a radionuclide bone scan evaluation, then by symptoms. The presence of back pain should raise concern for possible spinal cord or cauda equina disease, and, if clinically indicated, an MRI should be performed. In approximately 10 to 15% of patients, disease will relapse with aggressive local or distant metastases, where the level of PSA appears to be disproportionately low for the tumor burden present. The results on repeat biopsy may indicate a neuroendocrine phenotype. With the use of novel therapies (e.g., abiraterone acetate and enzalutamide), it has been hypothesized that treatment-related neuroendocrine prostate cancer may arise.[416]

Treatment Evaluation Criteria. A major issue in the development of effective therapies for patients with castration-resistant disease has been designing endpoints for phase II clinical trials in prostate cancer. In 2008, the Prostate Cancer Clinical Trials Working Group (PCWG2) published recommendations to define eligibility and outcome measures in clinical trials that evaluate systemic treatment for patients with progressive prostate cancer and castrate levels of testosterone.[417] It was suggested that outcomes be reported independently for PSA, imaging, and clinical measures and that grouped categorizations be avoided, such as complete or partial response. In most trials, early changes in PSA and/or pain should not be acted on without other evidence of disease progression, and treatment should be continued for at least 12 weeks to ensure adequate drug exposure. Bone scans should be assessed as “new lesions” or “no new lesions,” changes in soft-tissue disease assessed by Response Evaluation Criteria in Solid Tumor (RECIST), and pain measured using validated scales. PCWG2 recommended an increased emphasis on time-to-event endpoints (i.e., failure to progress) as decision aids in assessing the activity of new agents and in proceeding from phase II to phase III studies. An

update from the PCWG3 recommends a complete baseline patient assessment (including tumor histology, prior systemic therapies, and response data) and a detailed reporting of disease subtypes based on an anatomic pattern of metastatic spread.[418] Trial outcome measures were added, including the time-to-event endpoint of symptomatic skeletal events as well as time to first metastasis and time to progression for trials in the nonmetastatic CRPC state. PCWG3 also introduces the concept of no longer clinically benefiting and the need to document progression in existing lesions as distinct from the development of new lesions. Serial biologic profiling of tumor samples, blood-based diagnostics, and/or imaging is also recommended to identify predictive biomarkers for use in prospective trials.

In addition to clinical assessments, measurement of circulating prostate cancer tumor cells has been studied in patients with metastatic CRPC as a prognostic marker[419] and to assess response to systemic therapy.[420] This has led to FDA approval of an assay to count circulating tumor cells in patients with metastatic CRPC. A decline in circulating tumor cell counts has been associated with a better survival outcome in patients with CRPC receiving novel hormonal agents, including abiraterone.

THERAPIES FOR METASTATIC PROSTATE CANCER

Novel Hormonal Agents

Numerous studies indicate that androgen signaling via biosynthesis of extragonadal or intratumoral androgens or an activated androgen receptor, despite low levels of circulating dihydrotestosterone, may contribute to CRPC progression. Phase I and II trials demonstrated that therapy with drugs that inhibit the androgen receptor axis can result in significant and prolonged declines in PSA levels in patients with CRPC both before (chemotherapy-naive) and after docetaxel therapy.[421]

Abiraterone and Enzalutamide for Metastatic CRPC. Two similarly designed, phase III, randomized 2:1, double-blind, placebo-controlled trials in patients with CRPC postdocetaxel therapy, with a primary endpoint of OS, have been completed.

Abiraterone acetate is an oral CYP17 inhibitor that inhibits androgen biosynthesis. In the first phase III trial, patients received abiraterone (1000 mg daily) or placebo plus prednisone (5 mg twice daily). OS was significantly longer in patients treated with abiraterone compared with placebo (14.8 months vs. 10.9 months; HR, 0.65; 95% CI; 0.54, 0.77; $p < 0.001$), as were all secondary endpoints: time to PSA progression (10.2 months vs. 6.6 months; $p < 0.001$), PFS (5.6 months vs. 3.6 months; $p < 0.001$), and PSA response rate (29% vs. 6%, $p < 0.001$).[422] Mineralocorticoid-related toxicities in patients receiving abiraterone included fluid retention, hypertension, and hypokalemia. Abiraterone acetate was FDA-approved in 2011 for postdocetaxel therapy. Abiraterone acetate was subsequently FDA-approved in 2012 for the treatment of metastatic prostate cancer without previous chemotherapy based on a phase III, randomized trial of abiraterone acetate (1000 mg) plus prednisone (5 mg twice daily) compared with placebo plus prednisone in chemotherapy-naive patients with CRPC.[423] Abiraterone acetate plus prednisone improved radiographic PFS compared with placebo plus prednisone (16.5 months vs. 8.3 months; HR, 0.53; 95% CI; 0.45, 0.62; $p < 0.001$) with a trend toward improvement in survival (median not reached vs. 27.2 months for prednisone alone; HR, 0.75; 95% CI; 0.61, 0.93; $p = 0.01$), as well as a significant delay in clinical decline and initiation of chemotherapy. In an updated analysis, the efficacy and favorable safety profile of abiraterone acetate plus prednisone was confirmed and there was an improvement in OS (median, 35.3 vs.

30.1 months; HR, 0.79; 95% CI; 0.66, 0.95; p = 0.0151); however, this did not reach the prespecified statistical efficacy boundary.[424] In the final OS analysis after a median follow-up of 49.2 months, OS was significantly better for patients receiving abiraterone, with a median of 34.7 versus 30.3 months for placebo (p = 0.0027).

Enzalutamide is a highly potent oral androgen receptor antagonist that blocks androgens from binding to the androgen receptor, prevents translocation of the androgen receptor to the nucleus, and inhibits androgen receptor binding to DNA.[425] A phase III trial in patients with CRPC postdocetaxel treatment compared enzalutamide with placebo.[426] An interim analysis performed in 2011 reported a median OS of 18.4 months in the enzalutamide arm compared with 13.6 months in patients receiving placebo, with an overall 37% risk reduction in death (HR, 0.63; 95% CI; 0.53, 0.75; p < 0.0001). Enzalutamide was superior to placebo with respect to all secondary endpoints (50% reduction in PSA, soft-tissue response rate, QOL response rate, time to PSA progression, and the time to the first skeletal-related event). A randomized, phase III trial that compared enzalutamide to placebo in asymptomatic or mildly symptomatic chemotherapy-naive men with CRPC demonstrated a significant benefit of enzalutamide over placebo with a 30% reduction in risk of death (HR for OS, 0.70; 95% CI; 0.59, 0.83; p < 0.0001), 81% reduction in risk of radiographic progression or death (HR for radiographic PFS, 0.19; 95% CI; 0.15, 0.23; p < 0.0001), and a delay in the median time to chemotherapy initiation of 17 months compared with placebo (28 months vs. 10.8 months; HR, 0.35; 95% CI; 0.30, 0.40; p < 0.0001).[427] A randomized, phase II trial (STRIVE) compared enzalutamide to bicalutamide in 396 men with CRPC (139 patients with nonmetastatic disease and 257 patients with metastatic disease) with ADT continued in both arms and a primary endpoint of PFS.[428] Enzalutamide reduced the risk of progression or death by 76% compared with bicalutamide (HR, 0.24; 95% CI; 0.18, 0.32; p < 0.001). Median PFS was 19.4 months with enzalutamide, versus 5.7 months with bicalutamide. A second randomized, phase II trial of enzalutamide compared with bicalutamide (TERRAIN) in men with asymptomatic or mildly symptomatic metastatic CRPC demonstrated a significant improvement in median PFS with enzalutamide (15.7 months; 95% CI; 11.5, 19.4) compared with patients in the bicalutamide group (5.8 months; HR 0.44; 95% CI; 0.34, 0.57; p < 0.0001).[429]

Although abiraterone and enzalutamide have changed the landscape for the management of CRPC, approximately 15 to 25% of patients have primary resistance and there is a high degree of cross-resistance, with response rates of 15 to 30% when patients are switched to the alternative agent. One study demonstrated that the detection in circulating tumor cells of the androgen receptor splice variant AR-V7, which lacks the ligand-binding domain, from men with CRPC is associated with resistance to enzalutamide and abiraterone.[430] Detection of AR-V7 in circulating tumor cells from men with metastatic CRPC does not appear to be associated with resistance to taxane chemotherapy.[431]

Abiraterone for Metastatic Non–Castration-Resistant Prostate Cancer. Two recently reported prospective, randomized clinical trials, LATITUDE and STAMPEDE, examined the impact on OS of adding abiraterone (with prednisone or prednisolone) to ADT. The LATITUDE trial randomized 1199 newly diagnosed, high-risk patients (defined by at least two of the following three high risk factors: Gleason score of 8 or more, at least three bone lesions, and the presence of measurable visceral metastasis) with noncastrate metastatic prostate cancer to ADT plus abiraterone with prednisone daily versus ADT plus placebo with the primary endpoints of OS and radiographic PFS.[432] Median survival was 34.7 months in the ADT-alone arm while in the abiraterone arm median survival was not yet reached (HR, 0.62; 95% CI; 0.51, 0.76; p <

0.001); and a difference in radiographic PFS in favor of the abiraterone arm (14.8 months, ADT alone vs. 33 months ADT with abiraterone; HR, 0.47; 95% CI; 0.39, 0.55; p < 0.001) was also seen. All secondary endpoints were significantly better with abiraterone, including time until pain progression, next therapy for prostate cancer, initiation of chemotherapy, PSA progression, and next symptomatic skeletal event. Abiraterone was well tolerated aside from grade 3 hypertension and hypokalemia events being higher in the abiraterone group. The STAMPEDE trial ranzomized 1917 newly diagnosed (95% of patients) and metastatic (52% of patients), node-positive (20% of patients) or high-risk locally advanced (28% of patients) (defined by at least two of the following: tumor stage T3/4, Gleason score ≥ 8, PSA ≥ 40 ng/mL) patients to either ADT alone or ADT with abiraterone plus prednisolone daily.[433] Local radiotherapy was mandated for patients with node-negative, nonmetastatic disease and encouraged for those with positive nodes. For patients with radiotherapy planned, treatment was to continue for 2 years and for all other patients including nonmetastatic with no radiotherapy planned and for patients with metastatic disease, treatment continued until radiologic, clinical, or PSA progression. The primary outcome was OS, and the intermediate primary outcome was failure-free survival (defined as radiologic, clinical, or PSA progression or death from prostate cancer). At a median follow-up of 40 months, there were 184 deaths in the combination group as compared with 262 in the ADT-alone group (HR, 0.63; 95% CI; 0.52, 0.76; p < 0.001); the HR was 0.75 in patients with nonmetastatic disease and 0.61 in those with metastatic disease. Treatment-failure events also favored the combination group (HR, 0.29; 95% CI; 0.25, 0.34; p < 0.001). Combination therapy was associated with fewer symptomatic skeletal events. Grade 3 to 5 adverse events occurred in 47% of the patients in the abiraterone plus ADT group and in 33% of the patients in the ADT-alone group. Both LATITUDE and STAMPEDE support the use of ADT plus abiraterone in men newly diagnosed with noncastrate metastatic prostate cancer.

Immunotherapy

A variety of studies using various immune-based therapies suggested a benefit in survival for men with metastatic CRPC. Sipuleucel-T is an autologous cellular vaccine composed of prostatic acid phosphatase and granulocyte-macrophage colony-stimulating factor. It is administered intravenously every 2 weeks for a total of three infusions designed to elicit an immune response to prostatic acid phosphatase. In a randomized 2:1, phase III, placebo-controlled trial of men with minimally symptomatic metastatic CRPC, patients who received sipuleucel-T had a median OS of 25.8 months compared with 21.7 months in patients who received placebo (HR, 0.78; 95% CI; 0.61, 0.98; p = 0.03).[434] No significant effect on PSA values or PFS was observed. The 36-month survival probability was 31.7% in the sipuleucel-T group versus 23.0% in the placebo group. Based on the 4.1-month improvement in OS, sipuleucel-T was approved by the FDA in 2010. Results from a phase II, randomized, double-blind, controlled study of PROSTVAC-VF, a vector-based vaccine targeting PSA, plus granulocyte–macrophage colony-stimulating factor demonstrated promising activity in patients with minimally symptomatic metastatic CRPC.[435] The final results from several other phase III immunotherapy studies are eagerly awaited. Another immunotherapy, ipilimumab, the fully humanized antibody that binds to CTLA-4, failed to improve survival after radiotherapy in postdocetaxel metastatic CRPC patients and did not result in an improvement in survival as compared to placebo in a randomized phase III trial in asymptomatic or minimally symptomatic patients with metastatic chemotherapy-naive CRPC.[436]

Chemotherapy

Chemotherapy for CRPC. Patients with metastatic CRPC who experience disease progression during ADT may be considered for systemic chemotherapy. Prior to 2004, chemotherapeutic regimens demonstrated antitumor activity determined by changes in measurable disease, a greater than 50% decline in the PSA level, and objective improvements in bone scan, but did not demonstrate an effect on OS. In 2004, two randomized trials (SWOG 9916 and TAX 327) were reported that compared docetaxel-based therapy to mitoxantrone and prednisone in patients with metastatic CRPC. A significant improvement in OS was demonstrated for patients who received docetaxel, with a median survival of more than 18 months.[437-439] Docetaxel was also superior to mitoxantrone with respect to pain response rate, PSA response rate, and quality-of-life indicies.[440] Based on these studies, the FDA approved the use of docetaxel (75 mg/m^2 every 21 days) together with prednisone as front-line therapy for men with metastatic CRPC. CALGB 90401 tested if the addition of bevacizumab to docetaxel and prednisone prolonged survival. There was no improvement in OS (22.6 months vs. 21.5 months; p = 0.181), although there was an improvement in PFS in patients receiving bevacizumab compared with patients receiving placebo (9.9 months vs. 7.5 months; p < 0.0001).[441] Four phase III, randomized trials that evaluated the addition of dasatinib, aflibercept, zibotentan, or lenalidomide to docetaxel did not demonstrate an improvement in survival.[442-445] The benefit of chemotherapy for patients with nonmetastatic CRPC has not been established.

Cabazitaxel is a microtubule stabilizing taxane that was FDA-approved as second-line chemotherapy after docetaxel, based on the results of a phase III trial of men with CRPC who previously received docetaxel and who were randomly assigned to either 25 mg/m^2 of cabazitaxel or to 12 mg/m^2 of mitoxantrone every 3 weeks in combination with 10 mg/day of prednisone.[446] Median survival was 15.1 months and 12.7 months for patients treated with cabazitaxel and mitoxantrone, respectively (HR, 0.70; 95% CI; 0.59, 0.83; p < 0.0001). Grade 3 to 4 neutropenia was the major serious toxicity in patients who received cabazitaxel, suggesting primary prophylaxis with G-CSF should be considered. Two recent studies have further defined the use of cabazitaxel in patients with metastatic CRPC. FIRSTANA, a three-arm, phase III trial, randomly assigned chemotherapy-naive patients with metastatic CRPC to cabazitaxel at 20 mg/m^2, cabazitaxel at 25 mg/m^2, or docetaxel at 75 mg/m^2 (all regimens included prednisone 10 mg daily) every 3 weeks.[447] The primary endpoint was OS, and the statistical design assumed a risk reduction in the hazard rate of 25% for the cabazitaxel groups over the docetaxel group, with a targeted HR of 0.75. Cabazitaxel did not demonstrate superiority in OS as compared to docetaxel in the chemotherapy-naive setting (HR for C20 vs. D75 was 1.01 (95% CI; 0.85, 1.20; p = 0.997), and HR for C25 versus D75 was 0.97 (95% CI; 0.82, 1.16; p = 0.757).[446] A second phase III noninferiority study (PROSELICA) of cabazitaxel at 20 mg/m^2 versus cabazitaxel at 25 mg/m^2 in patients with metastatic CRPC previously treated with docetaxel resulted in noninferiority for cabazitaxel at 20 mg/m^2 with less toxicity.[448] Mitoxantrone and other regimens that have demonstrated activity in CRPC may be beneficial as third-line therapy for patients with a good performance status.[449,450] In patients with neuroendocrine or small cell histologies, the use of platinum-containing chemotherapy regimens such as etoposide and cisplatin may be beneficial.[451,452]

Chemotherapy for Metastatic Non–Castration Resistant Prostate Cancer. An ECOG-led phase III randomized trial (CHAARTED) of chemohormonal therapy compared with hormone therapy for hormone-sensitive, newly metastatic prostate cancer is the first trial to demonstrate a

survival benefit for chemotherapy in the setting of newly diagnosed, castration-sensitive metastatic prostate cancer.[453] In the CHAARTED trial, 790 men were randomly assigned to receive ADT alone or ADT plus docetaxel every 3 weeks for six cycles within 4 months of starting ADT with a primary endpoint of OS. At a median follow-up of 29 months, the median OS was 42.3 months versus 52.7 months for the ADT and ADT plus docetaxel arms, respectively (HR, 0.63; 95% CI; 0.48, 0.82; p = 0.0006). The benefit was seen in patients with high-volume disease (visceral metastases and/or four or more bone metastases) with a median survival of 32.2 months for ADT alone and 49.2 months for ADT plus docetaxel (HR, 0.62; 95% CI; 0.46, 0.83; p = 0.0012). There was no significant benefit seen in patients with low-volume disease. A long-term analysis of a second phase III trial (GETUG-AFU 15) that evaluated ADT plus docetaxel versus ADT alone for hormone-sensitive metastatic prostate cancer has been published.[454,455] In a retrospective analysis by disease volume, the high-volume disease outcomes were similar to CHAARTED for ADT alone and there was a nonsignificant 4-month increase in OS with ADT plus docetaxel. Although this study did not demonstrate an overall benefit for chemohormonal therapy compared with ADT alone, approximately one-third fewer patients in GETUG-AFU 15 had high-volume disease as compared with the CHAARTED trial. Thus, GETUG-AFU 15 is underpowered for this analysis. The results of STAMPEDE, a randomized, controlled trial using a multiarm, multistage design have also been reported.[456] In this trial, 2962 patients with locally advanced or metastatic prostate cancer starting long-term ADT for the first time were randomly assigned to receive ADT alone, ADT plus docetaxel, ADT plus zoledronic acid, or ADT plus a combination of docetaxel and zoledronic acid. There was a clinically and statistically significant survival benefit from the addition of docetaxel but not zoledronic acid in men starting long-term ADT. Specifically, the median survival was increased by 10 months, from 67 months to 77 months with the addition of docetaxel to ADT (HR, 0.76; 95% CI; 0.63, 0.91; p = 0.003). Two systematic reviews with meta-analyses pooling data from the STAMPEDE, CHAARTED, and the GETUG-15 trials found that the addition of docetaxel to ADT led to an improvement in survival as compared to ADT alone.[457,458] Overall, these data support the use of docetaxel in men with noncastrate metastatic prostate cancer beginning long-term ADT.

Novel Targeted Therapies

Despite early studies with the dual MET-VEGFR tyrosine kinase inhibitor cabozantinib having suggested significant pain relief and clinical, soft-tissue, and bone scan responses in patients with CRPC, a randomized, phase III trial demonstrated no improvement in survival for metastatic CRPC patients receiving cabozantinib compared with prednisone alone.[459]

A phase II study of the PARP inhibitor, olaparib in 50 patients with metastatic CRPC (all had received docetaxel and 98% had received abiraterone or enzalutamide) demonstrated a response in 16 of 49 (33%) evaluable patients with 12 patients receiving the treatment for > 6 months.[460] Next-generation sequencing identified alterations in DNA repair genes in 16 of 49 patients (33%). Of these 16 patients, 14 (88%) had a response to olaparib, including all 7 patients with either biallelic somatic or germline *BRCA2* loss and 4 of 5 with *ATM* aberrations. Additional studies are ongoing to further define the role for PARP inhibitors in patients with metastatic CRCP and DNA repair gene alterations.

Bone-Targeted Therapy

The alpha-emitter radium-223 is a bone-seeking radionuclide that demonstrated an

improvement in time to progression in a randomized, phase II study, which led to a phase III trial of 921 men with metastatic CRPC with symptomatic bone metastases who had received, were not eligible for, or declined docetaxel. Patients were randomly assigned 2:1 to receive radium 223 dichloride or placebo every 4 weeks for six treatments.[461] At the updated analysis of 921 patients, OS was significantly improved with radium-223 dichloride, with a median survival of 14.9 months versus 11.3 months for men treated with placebo (HR, 0.70; 95% CI; 0.58, 0.83; $p < 0.001$).[462] Time to first symptomatic skeletal event, as well as all main secondary endpoints, were improved with radium-223 dichloride. The benefit was seen irrespective of prior docetaxel use. Toxicity was mild, with low myelosuppression rates. This study led to the FDA approval in 2013 of radium-223 dichloride for the treatment of patients with CRPC and symptomatic bone metastases with no known visceral metastatic disease.

Zoledronate has been shown to palliate symptoms and to reduce the frequency of skeletal-related events, such as new pain, need for radiation therapy, and microfractures.[463] Renal insufficiency has been reported with zoledronate and other bisphosphonate use, and serum creatinine should be monitored and the dose adjusted accordingly. An uncommon (2 to 4%) complication of bisphosphonate therapy is osteonecrosis of the jaw, the incidence of which increases with treatment duration and is associated with dental procedures.[464]

A phase III, noninferiority trial compared denosumab with zoledronate administered every 4 weeks for the prevention of skeletal-related events in men with CRPC and bone metastases.[465] The median time to first on-study skeletal-related event was 20.7 months (95% CI; 18.8, 24.9) with denosumab, compared with 17.1 months (95% CI; 15.0, 19.4) with zoledronic acid (HR, 0.82; 95% CI; 0.71, 0.95; $p = 0.0002$ for noninferiority; $p = 0.008$ for superiority). Hypocalcaemia was more common in patients treated with denosumab, and osteonecrosis of the jaw occurred infrequently in both arms. Either therapy is recommended for men with CRPC and bone metastases together with calcium and vitamin D supplementation.

The FDA approval of multiple agents for the treatment of CRPC has resulted in numerous therapeutic choices. This has led to reformulation of the prostate cancer clinical-states model in order to provide a framework for patient treatment to guide clinicians (see Fig. 11-4).[466,467]

PALLIATION

An important aspect of patient care is the palliation of pain. Durable relief in selected sites can be achieved with external-beam radiation therapy delivered in a focal or hemibody technique. Systemic therapies can also provide palliation. The combination of mitoxantrone and prednisone is FDA-approved for the palliation of pain.[468] Two bone-seeking radiopharmaceutical agents, strontium-89 and samarium-153, have been shown to reduce the pain of skeletal metastases despite the lack of a survival benefit.

SURVIVORSHIP AND ELDERLY CONSIDERATIONS

With early detection and treatment, significant numbers of men will be cured of prostate cancer by radiation or surgery. These patients may have a variety of adverse effects related to therapy, including urinary incontinence, erectile dysfunction, and posttreatment psychosocial issues. Prostate cancer is predominantly a disease of older men with coexisting medical issues, and ADT is associated with numerous adverse effects that may be particularly pronounced in older men, including decreased libido, impotence, decreased lean body mass and muscle strength, increased fat mass, decreased QOL, and osteoporosis.[469] It also has been recognized that metabolic complications such as insulin resistance, hyperglycemia, and

metabolic syndrome, which may be responsible for an increased risk of cardiovascular mortality, may also develop in patients receiving long-term ADT (12 months or longer).[470] Men receiving long-term ADT should be monitored for the development of diabetes, and those in whom an adverse lipid profile develops should be treated according to the established guidelines for hyperlipidemia. One study reported that the SERM toremifene significantly decreased fasting serum lipid levels in men with prostate cancer on ADT.[471] It has been suggested that men who receive as little as 6 months of ADT with radiation therapy may have an increased risk of cardiovascular-related mortality,[472] but this observation was not confirmed in other retrospective analyses[473-475] or in a meta-analysis.[476] Other studies suggest that men with previous cardiovascular disease may be at increased risk of cardiovascular morbidity while receiving ADT.[477] One report suggests that cardiovascular disease risk may be highest in the first 6 months of ADT in men who experienced two or more cardiovascular events before therapy.[478] There is conflicting data regarding the association of ADT and dementia, including Alzheimer disease in men with prostate cancer.

KEY POINTS

- Prostate cancer is classified into clinical states from clinically localized disease to clinical metastases to castration-resistant disease, for which the therapeutic objectives and prognosis are distinct.
- PSA has a role in the diagnosis and management of prostate cancer; however, limitations in PSA sensitivity, specificity, and positive and negative predictive values have led to different opinions regarding screening recommendations.
- The risks and benefits associated with different treatment modalities must be carefully considered when choosing the best therapeutic option for a particular patient and disease state.
- Chemotherapy, immunotherapy, newer hormonal agents including abiraterone and enzalutamide, and the alpha emitter radium-223 improve survival in men with metastatic castration-resistant prostate cancer.
- The addition of docetaxel or abiraterone to ADT in patients with noncastrate metastatic disease is associated with a significant survival benefit as compared to ADT alone.

MALIGNANT ADRENAL TUMORS

Malignant adrenal tumors are extremely rare cancers, with only limited information to guide specific treatment recommendations. Malignant adrenal cortical carcinoma is derived from the adrenal cortex, with approximately 60% of cases associated with hormone secretion leading to symptoms and signs of hypercortisolism, virilization, and mineralocorticoid excess. Localized disease is managed with surgery. The overall prognosis is poor, particularly in patients with larger tumors (> 5 cm) and/or evidence of local invasion. The adrenocorticolytic agent mitotane is commonly used for patients with metastatic disease; however, response rates are low with no clear survival benefit.[479] Although several studies suggest higher response rates with chemotherapy plus mitotane, it is not at all clear that this translates into an improvement in outcome. A retrospective analysis suggested a potential benefit for mitotane in the adjuvant

setting, and it is commonly used in patients at high risk of recurrence following surgery.[480] The FIRM-ACT study compared mitotane plus a combination of etoposide/doxorubicin/cisplatin (EDP) every 4 weeks or streptozocin every 3 weeks in patients with advanced adrenocortical carcinoma and demonstrated significant improvements in response and PFS with EDP plus mitotane, but no difference in OS.[481] Malignant pheochromocytomas arise from chromaffin tissue of the adrenal medulla and are extremely rare, accounting for approximately 10% of all pheochromocytomas. Functional pheochromocytomas secrete catecholamines and lead to an array of clinical symptoms, including the classic triad of headache, diaphoresis, and tachycardia. There is no curative therapy for malignant pheochromocytoma, and the mainstay of management includes surgical resection of the tumor. Based on limited data, no definitive recommendations regarding systemic therapy can be made; however, the association of pheochromocytomas with VHL has led to the use of VEGF receptor–targeted agents in this disease.

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GYNECOLOGIC CANCERS

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Recent Updates

Cervix Cancer

- The American Society of Clinical Oncology issued its first clinical practice guideline on management of invasive cervical cancer. (Chuang L, *J Clin Oncol* 2016)
- Human papillomavirus (HPV) vaccination of healthy women older than 25 years was highly effective against 6-month persistent HPV infection or cervical intraepithelial neoplasia (CIN), in a randomized, placebo-controlled trial. (Wheeler CM, *Lancet Infect Dis* 2016)

Endometrial Cancer

- High objective response rates were observed among patients with mismatch repair deficient, or hypermutated phenotype, endometrial cancer treated with immune checkpoint blockade (PD-1 inhibitor). The PD-1 inhibitor pembrolizumab is approved by the U.S. Food and Drug Administration (FDA) for microsatellite instability-high (MSI-H) or mismatch repair–deficient (dMMR) solid tumors that have progressed following prior treatment. (Mehnert JM, *J Clin Invest* 2016)

Ovarian Cancer

- The FDA recommended against any type of ovarian cancer screening for any patient, including patients at genetic increased risk for ovarian cancer. (http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm519413.htm)
- Weekly paclitaxel plus carboplatin intravenously or intraperitoneal carboplatin plus intravenous weekly paclitaxel or intravenous paclitaxel plus intraperitoneal cisplatin plus intraperitoneal paclitaxel all achieve similar survival results as first-line treatment for advanced ovarian cancer following cytoreductive surgery. (Walker JL, Society of Gynecologic Oncology, 2016)
- Bevacizumab was approved by the FDA for treatment of platinum-sensitive recurrent ovarian cancer in combination with carboplatin/paclitaxel or carboplatin/gemcitabine, followed by bevacizumab maintenance. (Coleman RL, *Lancet Oncol* 2017)
- Rucaparib, a PARP inhibitor, was approved as monotherapy for women with deleterious germline or somatic *BRCA* mutation–associated epithelial ovarian cancer who have received at least two prior lines of therapy. (Swisher EM, *Lancet Oncol* 2017)
- Treatment with niraparib as maintenance treatment after platinum-based therapy for platinum-sensitive recurrent ovarian cancer was associated with improved progression-free survival (PFS), regardless of germline *BRCA* mutation status or homologous recombination deficiency (HRD) status, although the benefit was much greater in the cohorts of patients with *BRCA* mutations or HRD. (Mirza MR, *N Engl J Med* 2016)
- Treatment with olaparib as maintenance after response to platinum-based therapy in platinum-sensitive recurrent ovarian cancer patients with a *BRCA1* or *BRCA2* mutation improved PFS in a phase III trial; a separate trial also showed a PFS benefit, regardless of *BRCA* mutation status. Olaparib is approved by the FDA in this maintenance setting. (Pujade-Lauraine E, *Lancet Oncol* 2017)
- Treatment with rucaparib maintenance after response to platinum-based therapy for platinum-sensitive recurrent disease improved PFS compared to placebo. (Coleman R, *Lancet* 2017)
- Long-term follow-up showed that first-line intraperitoneal cisplatin-based chemotherapy continued to show an overall survival advantage compared with intravenous chemotherapy for epithelial ovarian cancer. (Tewari D, *J Clin Oncol* 2015)

Uterine Sarcoma

- Olaratumab was approved by the FDA for treatment of metastatic sarcoma in combination with anthracycline therapy based on a randomized, phase II trial comparing the combination followed by maintenance olaratumab to doxorubicin alone. While the differences in PFS (6.6 months among patients assigned to olaratumab plus doxorubicin compared with 4.1 months among patients assigned to doxorubicin) and response rate (18.2% vs. 11.9%) did not reach statistical significance, there was a statistically significant improvement in overall survival with the combination (26.5 months with olaratumab/doxorubicin vs. 14.7 months with doxorubicin alone). (Tap WD, *Lancet* 2016)

OVERVIEW

Approximately 105,000 women in the United States were diagnosed with a gynecologic malignancy in 2016, of whom more than 31,000 were expected to die from this cancer (Figs. 12-1 and 12-2).[1] Management of gynecologic malignancies requires a multidisciplinary approach. Important roles for the medical oncologist and gynecologic oncologist include the decision making for, and clinical management of, chemotherapy concurrent with radiation for cervix cancer, adjuvant chemotherapy for epithelial and nonepithelial ovarian cancer, adjuvant treatment decisions for high-risk endometrial cancers, appropriate use of systemic therapies for recurrent and metastatic gynecologic cancers, and appropriate supportive care. Medical and gynecologic oncologists also play a role in identifying women who are potential carriers of a heritable predisposition to gynecologic (and other) cancers and in making appropriate referrals for genetic counseling and testing. Oncologists can help survivors of gynecologic malignancies to cope with issues related to premature, treatment-related menopause and may recommend appropriate screening for other cancers.

CERVIX CANCER

Cervix cancer is the third most common cancer worldwide and is the most common cause of death from gynecologic cancers worldwide. Although it is estimated that more than 500,000 new cases of invasive cervix cancer are diagnosed globally each year, the burden of the disease is greatest in developing countries, where more than 85% of the cases are found. In the United States, nearly 13,000 cases are diagnosed annually, and there are approximately 4000 cervix cancer deaths. In the United States, cervix cancer mortality rates are twice as high for black women as for white women (10.1 per 100,000 vs. 4.7 per 100,000).[2] The mean age at the time of diagnosis of cervix cancer is approximately 47 years. The relatively slow growth rate of most cervix cancers, and the causal association with human papillomavirus (HPV) infection, means that HPV vaccination, HPV testing, and Pap smear screening all offer opportunities for cancer prevention or early detection of preinvasive changes in the cells of the surface of the cervix, which can prevent the development of invasive cancer.

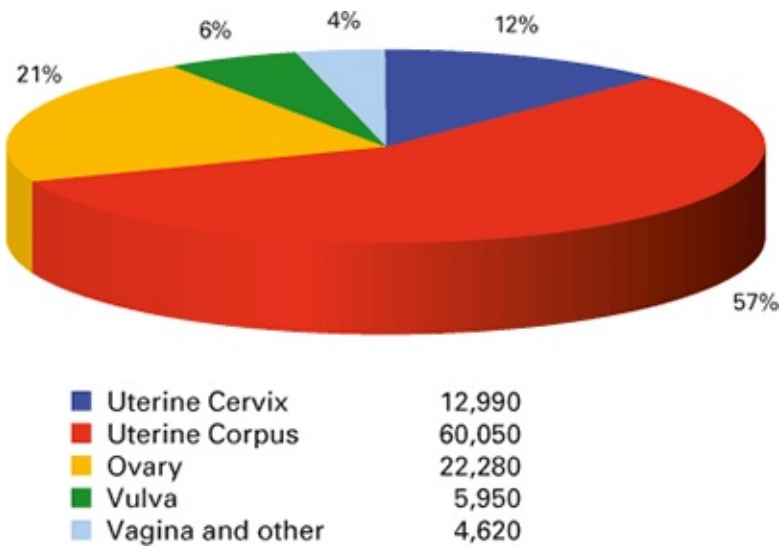

Fig. 12-1 Estimated new cases of gynecologic cancers in the United States in 2016.
Adapted from Siegel R, et al. CA Cancer J Clin. *2016;66:7–30. PMID: 26742998.*

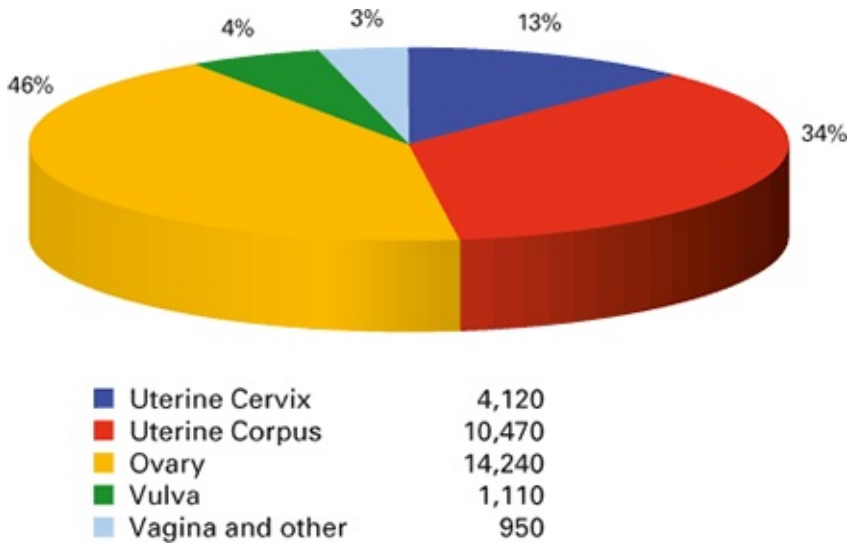

Fig. 12-2 Estimated gynecologic cancer deaths in the United States in 2016.
Adapted from Siegel R, et al. CA Cancer J Clin. *2016;66:7–30. PMID: 26742998.*

Cervix cancer histologies include squamous cell carcinomas, adenocarcinomas, or mixed histology tumors (Table 12-1). Neuroendocrine cancers of the cervix and small cell carcinomas of the cervix are rare histologies that carry a high risk for metastasis and death, even when apparently localized at the time of diagnosis. These rare histologic types require a specialized therapeutic approach.

RISK FACTORS

The major contributor to the development of invasive cervix cancer is the presence of persistent infection with one of the high-risk types of HPV. HPV is transmitted by sexual contact. Certain HPV types specifically infect mucosal surfaces. HPV infection rates range from 5 to 21% of women, with the highest rates being observed in Africa.[3] Although the virus clears without specific intervention in a majority of women infected with HPV, in some, the virus persists. With persistent infection, HPV genes *E6* and *E7* are incorporated into cervix cells, and viral proteins capable of binding to and inactivating tumor suppressor proteins (RB1 and TP53) are produced,

initiating carcinogenesis. Other risk factors for the development of cervix cancer include smoking (which increases the risk for persistent cervical dysplastic changes) and immunocompromise (such as HIV infection). Behavioral factors such as early age at coitarche, short interval between menarche and coitarche, having multiple sexual partners, and having partners who have had multiple partners—all of which increase the risk for exposure to HPV—are associated with an increased risk for cervix cancer. Use of an intrauterine device has been associated with a lower risk for cervix cancer, independent of HPV status.[4]

Of the more than 100 types of HPV, approximately 15 are considered high risk for causing cervix cancer; among these 15 high-risk types, HPV subtypes 16 and 18 are by far the most prevalent. HPV subtypes 16 and 18 are associated with approximately 70% of cervix cancer cases, with other high-risk subtypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) accounting for the rest.[5]

SCREENING AND PREINVASIVE DISEASE

Clinical practice guidelines that consider the global burden of cervix cancer, as well as the limitations of health care resources, have been developed for cervix cancer screening.[6] Pap smears are effective for detecting preinvasive cervical changes. Cytologists generally report Pap smear results using the Bethesda system, which accounts for specimen adequacy as well as for cytologic interpretation. The incorporation of HPV DNA testing into the screening process helps guide treatment choices and is recommended in all resource settings. Patients who test positive for high-risk HPV serotypes should be followed closely for the development of cancer. HPV testing is more sensitive for the detection of grade 2 or 3 cervical intraepithelial neoplasia (CIN) than is Pap smear liquid cytology testing. American Society of Clinical Oncology (ASCO) screening guidelines recommend “co-testing” with both cytologic evaluation and HPV testing every 5 years for women ages 25 to 65. Other guidelines recommend initiating screening at age 21 with Pap testing alone every 3 years. Women older than age 65 whose prior screening has been adequate and negative may discontinue screening.[7,8] Of note, the recommendation for discontinuation of screening for older women may merit reconsideration, as recent data show that when incidence rates for cervix cancer are corrected for hysterectomy prevalence in the United States, the rates of cervix cancer do not decline significantly in women ages 60 to 69.[9] Some guidelines include stand-alone HPV testing as a screening option for cervix cancer (replacing liquid cytology testing) for women age 25 or older; outside the United States, this is considered a reasonable option. In parts of the world where Pap and HPV testing are not readily available, visual inspection of the cervix with acetic acid has been shown to be a strategy that can decrease cervix cancer mortality.[10] Women who have had HPV vaccination should undergo screening per guidelines.

Table 12-1 **Histologic Subtypes of Cervix Cancer, Endometrial Cancer, Uterine Sarcomas, and Epithelial Ovarian Cancer**

Cervix Cancer	Endometrial Cancer	Uterine Sarcomas	Epithelial Ovarian Cancer
Squamous cell carcinoma	Endometrioid adenocarcinoma	Carcinosarcoma (mixed Müllerian tumors)	Serous or papillary serous carcinomas
Adenocarcinoma	Papillary serous carcinoma	Leiomyosarcoma	Endometrioid carcinomas
Mixed squamous cell carcinoma and adenocarcinoma	Adenosquamous cell carcinoma	Endometrial stromal sarcoma	Clear cell carcinomas
Neuroendocrine carcinoma	Clear cell carcinoma	High-grade undifferentiated sarcoma	Mucinous carcinomas
Small cell carcinoma		Adenosarcoma	Low-grade serous carcinomas

After an abnormal Pap smear or a positive test for high-risk HPV, a patient is referred for colposcopy for directed biopsies to determine whether there is evidence of CIN or invasive cancer. CIN is characterized by dysplastic changes in the epithelium. The more severe the morphologic changes, which are labeled CIN I, CIN II, and CIN III, the greater the risk for transformation into invasive cervix cancer. If a colposcopy shows low-grade changes (CIN I), the patient usually is observed because these changes will resolve without intervention in the majority of patients.[11] Some studies suggest that surveillance may also be reasonable for young patients with CIN II.[12] For patients with negative findings on colposcopy, HPV testing is helpful for determining which women are at risk for the development of CIN II or greater. In one study, among women with an abnormal Pap smear and negative colposcopy, the risk for developing CIN II or worse was 0.44% among patients with HPV-negative disease and 41.8% among patients with HPV-positive disease.[13] A diagnosis of CIN II or III generally requires an excisional procedure, usually a loop electrosurgical excision procedure or a cone biopsy, to rule out invasive carcinoma; however, in young women, as above, close surveillance may be considered.

CERVIX CANCER PREVENTION

Large, randomized, controlled phase III trials of several different HPV vaccines have shown that vaccination greatly reduces the incidence of development of premalignant lesions in the cervix, vagina, and vulva.[14] Ideally, the series of vaccinations should be completed prior to exposure to HPV. Unfortunately, data suggest that uptake and completion of HPV vaccination in the United States and globally is low, particularly among poor and uninsured women.[15] In women ages 24 to 45 who have not been infected with HPV, vaccination with the quadrivalent vaccine (which includes HPV serotypes 6, 11, 16, and 18) was effective at preventing premalignant disease.[16] Furthermore, in a global, phase III, placebo-controlled study of women older than age 25, up to 15% of whom had a history of HPV infection or disease, HPV vaccination prevented 6-month persistent HPV infection or the development of CIN I or worse in over 90% of vaccinated women.[17] The 9-valent HPV vaccine provides protection against five additional virus serotypes approved by the FDA and is the currently recommended vaccine.[18] National and international health organizations have strongly endorsed routine immunization of all girls and young women as an effective approach to reducing the worldwide burden associated with cervix cancer. HPV vaccination of boys and young men (up to age 21 for healthy men, up to age 26 for gay/bisexual or immunocompromised men) has been shown to decrease the risk for

development of external genital lesions related to HPV (i.e., genital warts, anal cancer) and is also recommended.[19] Two-dose, instead of three-dose, vaccination has been recommended for boys and girls under age 15, in the United States and internationally, and may improve vaccination rates at a lower cost. Consistent use of condoms has been associated with lower rates of HPV infection.

KEY POINTS

- Optimal use of established cervix cancer screening guidelines substantially reduces the risk for invasive cervix cancer. While there is some variability among screening guidelines, Pap testing plus HPV testing every 5 years is a recommended cervix cancer screening strategy for women age 30 and older. Women age 65 and older with prior adequate, negative screening can discontinue cervix cancer screening.
- Vaccination against HPV is an effective strategy to prevent the development of persistent infection and premalignant cervical abnormalities in girls and young women. HPV vaccination of boys and young men is associated with a decrease in the development of HPV-related genital warts and anal cancer. Routine HPV vaccination is recommended in order to decrease the global burden of HPV-related malignancies.
- Women who have received HPV vaccination are recommended to continue screening for cervix cancer.

INVASIVE CERVIX CANCER

Some women with invasive cervix cancer may present with abnormal vaginal bleeding (i.e., postmenopausal, intermenstrual, or postcoital), but most women with early cervix cancer have no symptoms. Bleeding accompanied by other symptoms, such as pelvic pain and vaginal discharge, usually indicates more advanced disease.

Staging of cervix cancer is performed by clinical examination. Table 12-2 details cervix cancer stages, provides an overview of treatment for patients in resource-rich settings, and provides estimates of 5-year overall survival. In practice in the United States, advanced imaging such as MR and PET are often incorporated for the purposes of treatment planning. ASCO has published a guideline for management of women with invasive cervical cancer that incorporates the global differences in resources for screening, surgery, and systemic treatment.[20] This guideline recognizes that not all global treatment settings will have access to full-course radiotherapy or to high-cost drugs like bevacizumab.

Patients with very-early-stage disease (stage IA1 without lymphovascular space invasion) can be treated with an extrafascial hysterectomy because the risk for lymph node involvement is low. The rate of long-term survival for patients with early-stage disease is greater than 95%. If a patient with such low-risk, early-stage disease wishes to maintain fertility, observation after conization may be considered if the cone margins are negative.

Patients with stage IA1 with lymphovascular space invasion, IA2, and IB1 disease are candidates for modified radical hysterectomy and lymph node dissection. Selected patients with stage IA or less than 2 cm stage IB cancer who desire fertility-sparing surgery may be candidates for trachelectomy or radical trachelectomy.

The survival benefit of postsurgical adjuvant radiation treatment for early-stage cervix cancer was demonstrated in a randomized trial (Gynecologic Oncology Group [GOG] 92).[21] Patients with stage IB cervix cancer who had undergone radical hysterectomy and lymph node dissection, and who met specified criteria for being at intermediate risk for relapse (lymph nodes negative but with a tumor having two of the following three pathologic features: large tumor diameter, deep stromal invasion, and capillary-lymphatic space invasion) were randomly assigned to receive adjuvant whole-pelvic radiation or no further treatment. Five-year overall survival was 88% for the group assigned to receive radiation compared with 79% for the group assigned to undergo observation. This study established postresection radiation as a standard intervention for early-stage, intermediate-risk cervix cancer. A subsequent study showed that administering concurrent cisplatin-based chemotherapy with radiation was superior to pelvic radiation alone for patients with certain high-risk pathologic features: positive lymph nodes, positive surgical margins, or positive parametria.[22] Thus, currently, patients with clinically early-stage, resectable cervix cancer undergo modified radical hysterectomy and lymph node dissection. Pathologic factors found during the surgery are used to determine which patients require adjuvant therapy. Patients with intermediate-risk features should be treated with adjuvant pelvic radiotherapy. Whether the addition of cisplatin to radiation will offer further benefit to this intermediate-risk group is being studied in a randomized phase III trial (GOG 263).

Table 12-2 **Cervix Cancer Staging, Surgical Treatment Overview, and Estimates of Overall Survival**

Stage (FIGO 2009)	Definition	Treatment Overview	5-Year Overall Survival (%)
0*	Carcinoma in situ	Observation (CIN I); LEEP or conization (CIN II, III)	100
I	Carcinoma limited to the uterus		80-95
IA	Invasive carcinoma diagnosed only by microscopy		
IA1	Lesions ≤ 3 mm depth of stromal invasion and < 7 mm horizontal spread	• If no lymphovascular invasion, extrafascial hysterectomy, or observation if cone margins negative and fertility desired, or trachelectomy if positive cone margins and fertility desired; or extrafascial hysterectomy or modified radical hysterectomy and consider LN mapping if positive cone margins • If lymphovascular invasion, modified radical hysterectomy with lymph node dissection, or if fertility desired, trachelectomy and lymph node dissection/sentinel LN assessment may be considered†; or pelvic external beam radiation + brachytherapy	
IA2	> 3 mm and < 5 mm depth of invasion and ≤ 7 mm horizontal spread	Modified radical hysterectomy with lymph node dissection, or if fertility desired, radical trachelectomy and lymph node dissection†; or pelvic external-beam radiation + brachytherapy	
IB	Lesions greater than IA2, or clinically visible lesions		85-90
IB1	Lesion ≤ 4 cm in greatest dimension	Radical hysterectomy with lymph node dissection/may consider sentinel LN assessment, or if fertility desired, radical trachelectomy and lymph node dissection/may consider sentinel LN assessment † Or pelvic external-beam radiation plus brachytherapy plus concurrent cisplatin-based chemotherapy	
IB2	Lesions > 4 cm in greatest dimension	Pelvic external-beam radiation plus brachytherapy plus concurrent cisplatin-based chemotherapy or radical hysterectomy + LN dissection	60-80
II	Tumor extends beyond the cervix but not to the pelvic side wall or to lower one-third of vagina		60-80
IIA1	No parametrial invasion and clinically visible lesion is < 4 cm in size	Radical hysterectomy + LN dissection (consider SLN mapping) or pelvic external-beam radiation plus brachytherapy plus concurrent cisplatin-based chemotherapy	
IIA2	Clinically visible lesion is > 4 cm in size	Pelvic external-beam radiation plus brachytherapy plus concurrent cisplatin-based chemotherapy or Radical hysterectomy + LN dissection (consider SLN mapping)	
IIB	Lesion extends to the parametria	Pelvic external-beam radiation plus brachytherapy plus concurrent platinum-based chemotherapy	
III	Tumor extends to the pelvic side wall or to lower one-third of the vagina, or causes hydronephrosis	Pelvic external-beam radiation plus brachytherapy plus concurrent platinum-based chemotherapy	35-45
IV	Tumor extends beyond the true pelvis; and/or invades the mucosa of the bladder or rectum; or distant metastases		5
IVA	Tumor extends beyond the true pelvis and/or invades the mucosa of the bladder or rectum	Pelvic radiation plus brachytherapy plus concurrent platinum-based chemotherapy	
IVB	Distant metastases	Palliative cisplatin-based chemotherapy with or without bevacizumab	

*FIGO no longer includes stage 0 in cervix cancer staging.
†Patients with high-risk pathologic features (positive lymph nodes, positive tumor margins, or positive parametria) require adjuvant cisplatin-based chemoradiation.
Abbreviations: CIN, cervical intraepithelial neoplasia; FIGO, International Federation of Gynecology and Obstetrics; LEEP, loop electrosurgical excision procedure; LN, lymph node.

Patients with high-risk features (positive lymph nodes, positive margins, or positive parametria) should receive adjuvant cisplatin-based chemoradiation.

Patients with larger tumors (stage IB2) are likely to have pathologic features found at the time of radical hysterectomy that require adjuvant radiation and, thus, may be better served with definitive platinum-based chemoradiation rather than radical hysterectomy and lymph node dissection. If surgery is elected as the initial treatment, the likelihood of finding high-risk features that necessitate postsurgery treatment with chemo–radiation is high, and, thus, morbidity may be higher.[23] It has not been determined whether hysterectomy following initial chemo–radiation improves outcomes. The long-term survival rates range from approximately 60% to 80%.

With extensive locally advanced disease (stage IIB to IVA) there is no role for primary

surgery. Standard treatment includes the simultaneous delivery of external-beam radiation with concurrent cisplatin-based chemotherapy and delivery of brachytherapy. Several phase III randomized trials have demonstrated that concurrent cisplatin-based chemoradiation yields superior progression-free and overall survival rates compared with radiation alone and is the standard of care.[24,25] Unfortunately, many patients do not receive optimal chemoradiation treatment, and such patients have poorer survival outcomes.[26] In a prospective study involving women with good access to antiretroviral therapy and standard chemoradiation, HIV infection was also associated with poorer survival.[27] A prospective, phase III trial is comparing cisplatin plus radiation therapy with or without carboplatin plus paclitaxel in patients with locally advanced (stage IB to IVA) cervix cancer to determine whether adding combination chemotherapy after cisplatin–radiation improves outcomes (NCT01414608).

METASTATIC AND RECURRENT CERVIX CANCER

The prognosis is poor for patients with metastatic cervix cancer and for those who have recurrence after primary treatment of localized disease. For carefully selected patients who have an isolated pelvic recurrence within a previously irradiated field, aggressive resection (i.e., pelvic exenteration) can be considered because it offers the potential to provide long-term disease-free survival for approximately 25% of patients.[28] Patients who have not previously undergone pelvic radiation therapy may undergo salvage radiation.

Cytotoxic agents with demonstrated activity include cisplatin, carboplatin, paclitaxel, topotecan, vinorelbine, gemcitabine, and ifosfamide. Although palliation of symptoms may be achieved with these drugs, the duration of response is generally less than 4 months. Since concurrent cisplatin and radiation is commonly used for high-risk early-stage and locally advanced disease, it is important to consider study results from patients with metastatic disease in terms of whether patients have had prior cisplatin-radiation therapy.

For patients with metastatic and recurrent cervix cancer, cisplatin plus topotecan achieved a significantly higher objective response rate, and superior progression-free and overall survival rates compared with single-agent cisplatin.[29] The combination of cisplatin plus paclitaxel is also associated with a higher response rate and better progression-free survival compared with single-agent cisplatin, but this regimen was not shown to improve overall survival. A four-arm randomized trial (GOG 204) compared four different cisplatin doublets (paclitaxel/cisplatin, vinorelbine/cisplatin, gemcitabine/cisplatin, and topotecan/cisplatin). None of the three experimental doublets was superior to paclitaxel/cisplatin, thus paclitaxel/cisplatin remained a standard first-line therapy for metastatic disease.[30] A subsequent randomized trial (GOG 240) investigated whether a nonplatinum doublet (topotecan/paclitaxel) may be as efficacious as a platinum doublet (paclitaxel/cisplatin), and whether the addition of bevacizumab to cytotoxic therapy improves outcomes. The results from the bevacizumab portion of this study showed that the addition of bevacizumab to chemotherapy increased overall survival by nearly 4 months, leading to FDA approval of bevacizumab for first-line treatment of metastatic cervix cancer.[31]

Because of the toxicities of cisplatin (delayed nausea and vomiting, neurotoxicity that may be compounded when cisplatin is combined with paclitaxel), there has been interest in determining whether carboplatin could replace cisplatin in the treatment of metastatic cervix cancer. The Japanese GOG conducted a randomized, phase III trial in women who had received no prior cisplatin or one prior cisplatin regimen (for most patients, prior cisplatin–radiation).[32] Patients were assigned to 24-hour paclitaxel on day 1 followed by cisplatin on day 2 as the standard

arm or to 3-hour paclitaxel followed by carboplatin on day 1 as the experimental treatment. Among the patients who had received prior cisplatin treatment, carboplatin/paclitaxel was not inferior to cisplatin/paclitaxel in terms of overall survival (17.5 vs. 18.3 months). However, among the patients who had not received prior cisplatin, cisplatin/paclitaxel was superior to carboplatin/paclitaxel (overall survival, 23.2 months vs. 13 months). Among all the patients enrolled, carboplatin/paclitaxel achieved similar objective response rates (58.8% vs. 62.5%) and progression-free survival (6.2 vs. 6.9 months) as cisplatin/paclitaxel.

The role of HPV-directed therapeutic vaccines and immune checkpoint inhibition in the treatment of cervix cancer is under active investigation. For example, prospective clinical trials are in progress to assess the efficacy of ipilimumab (NCT01711515) and nivolumab (NCT02257528).

HIGH-RISK HISTOLOGY CERVIX CANCERS

Small cell carcinoma of the cervix and neuroendocrine tumors of the cervix are high-risk histologies. The rarity of these histologic subtypes precludes the conduct of large, prospective trials. Treatment has been informed by experience with treating small cell histology lung cancers. Patients with neuroendocrine carcinomas are younger than patients with squamous cell carcinomas, are more likely to present with metastatic disease, and have poorer survival outcomes for all stages of disease. Patients frequently receive treatment with regimens including platinum and etoposide, similar to treatment for small cell carcinoma of the lung. Many patients are treated with concurrent radiation and chemotherapy.[33]

KEY POINTS

- Patients with high-risk pathologic features found after radical hysterectomy performed for early-stage cervix cancer (e.g., positive margins, positive parametria, positive lymph nodes) have improved overall survival with adjuvant cisplatin-based chemoradiation.
- Patients with stage IIB to IVA cervix cancer are treated with potentially curative cisplatin-based chemoradiation.
- A standard first-line treatment for patients with metastatic cervix cancer is cisplatin/paclitaxel plus bevacizumab. Bevacizumab is FDA-approved for this indication.
- For patients with recurrent, metastatic cervix cancer who have received prior cisplatin–radiation therapy, carboplatin/paclitaxel is also a reasonable treatment regimen. Carboplatin is generally associated with less toxicity than cisplatin.

ENDOMETRIAL CANCER

In 2016, approximately 60,000 women in the United States were diagnosed with endometrial cancer, and there were approximately 10,500 deaths attributed to the disease. It is the fourth most common cancer in U.S. women. Seventy-five percent of women diagnosed with endometrial cancer are postmenopausal, with a median age of 61. Approximately 80% of patients present with early-stage, uterine-confined disease. Although the risk for endometrial cancer is 40% lower for black women than for white women in the United States, the mortality

rate for black women is approximately 50% higher. Black women present with more advanced-stage disease and have a higher incidence of aggressive-histology tumors. The cause of this mortality discrepancy between black women and white women is likely complex, involving environmental, socioeconomic, and biologic factors.

Endometrial cancers have been classified as either type I or type II cancers. While this two-category classification may eventually be replaced with more refined categories that incorporate specific histologic and molecular abnormalities, currently, the type I and II classification remains of some utility. Type I cancers comprise approximately 85% of endometrial cancer and show endometrioid histology. Type II cancers have nonendometrioid histology, most commonly papillary serous or clear cell. The pathogenesis of type I endometrial cancers appears to be more closely related to the effect of unopposed estrogen on the glandular cells of the endometrial lining of the uterus. Estrogen stimulation leads to endometrial hyperplasia and complex hyperplasia with atypia, which may be regarded as in situ carcinoma of the endometrium. Women with simple endometrial hyperplasia have a low risk for the development of invasive adenocarcinoma; however, invasive cancer will develop in approximately 42% of women with complex endometrial hyperplasia with atypia.[34] The pathogenesis of type II endometrial cancer is less clear. The median age of women with type II endometrial cancers is greater than that of women with type I cancers. In general, women with type II cancers have not been considered to have conditions associated with excess estrogen exposure. However, a large epidemiologic study showed that women with type I and type II cancers did not differ in terms of parity, oral-contraceptive use, smoking, age at menarche, or diabetes. High mass index (and, thus, endogenous excess estrogen) was more likely to be associated with type I tumors than with type II tumors, but obesity also increases the risk of nonendometrioid histologies.[35] The risk for death is higher for type II cancers compared with type I cancers.[36] Endometrioid-histology endometrial cancers are more likely to be microsatellite instability–high than serous histology cancers. Genomic characterization is augmenting our understanding of endometrial cancer pathogenesis and will improve classification of these cancers. Data from The Cancer Genome Atlas categorized endometrial cancers into four mutational profile prognostic groups: ultramutated, microsatellite instability–high (MSI-H), copy number low, and copy number high.[37] It is anticipated that genomic mutation information will be used to stratify patients according to risk in clinical trial design and for treatment decisions. For example, as detailed later, immunotherapy may be appropriate for MSI-H endometrial cancers.

RISK FACTORS AND DISEASE PRESENTATION

The major risk factors for endometrial carcinoma are unopposed estrogen (e.g., estrogen-replacement therapy after menopause without concomitant use of progestins), obesity, diabetes mellitus, nulliparity, late menopause, complex atypical endometrial hyperplasia, and tamoxifen use. In the United States, nearly 60% of endometrial cancers are considered attributable to overweight/obesity, and as the rate of obesity increases, the incidence of endometrial cancer in 2030 is projected to increase by 55% compared with 2010.[38] Overweight postmenopausal women who intentionally lose weight have a lower risk for endometrial cancer compared with women whose weight remains stable or increases.[39] A case–control study showed that bariatric surgery for weight reduction was associated with a significantly reduced risk of endometrial cancer.[40] Independent of obesity, the metabolic syndrome has also been associated with an increased risk for endometrial cancer. Combined oral-contraceptive use may

decrease the risk for endometrial cancer. Smoking is associated with a lower risk, likely through an antiestrogenic effect. Women with germline mutations associated with hereditary nonpolyposis colon cancer (HNPCC) syndrome have a markedly increased risk for endometrial carcinoma.

The risk for endometrial cancer is three- to seven-fold higher for women receiving tamoxifen than for women who do not take the drug.[41] Tamoxifen-associated endometrial cancers had generally been considered to be well-differentiated, grade 1 or 2, and early-stage at presentation. However, data support an increased risk for higher-grade and poorer-risk histology endometrial cancers and carcinosarcomas among women treated with tamoxifen.[42] Oncologists caring for women taking tamoxifen should ask these patients about abnormal vaginal bleeding. Any abnormal bleeding requires evaluation; however, no clinical data justify routine screening for endometrial cancer among all women taking tamoxifen. In the randomized clinical Study of Tamoxifen and Raloxifene (STAR) trial, there was no significant difference in the incidence of endometrial cancer between the two study arms.[43]

Women with HNPCC syndrome carry a 20 to 60% lifetime risk for endometrial cancer, with *MSH6* mutations conferring a higher risk for endometrial cancer than for colon cancer.[44] HNPCC-related endometrial cancers occur at a younger age than do sporadic endometrial cancers. These women require special surveillance for endometrial cancer, which may include sonography and endometrial biopsy, even in the absence of abnormal uterine bleeding or other symptoms.[45] Because women with HNPCC are also at risk for ovarian cancer, consideration should be given to prophylactic hysterectomy and bilateral salpingo-oophorectomy after completion of childbearing.[46] Since endometrial cancer is the second most common malignancy in patients with Lynch syndrome, and is often the first cancer diagnosed in women with Lynch syndrome, there is interest in determining which women with a new diagnosis of endometrial cancer should be screened for Lynch syndrome. Some groups have recommended screening all patients with endometrial cancer for Lynch syndrome, while others have suggested that a combination of testing the tumor for microsatellite instability, MLH1 methylation, and mismatch repair protein expression is an efficient approach to identifying women with Lynch syndrome. Family history and patient age are not adequate for identifying all women with Lynch syndrome.[47]

The most common symptom associated with endometrial cancer is postmenopausal bleeding. Approximately 15% of patients with postmenopausal bleeding will have endometrial cancer; thus, all postmenopausal women with abnormal uterine bleeding require evaluation by endometrial sampling. Most endometrial cancers are localized to the uterus at the time of diagnosis, have a well-differentiated endometrioid histologic appearance, carry a lower propensity to spread, and are curable. However, some endometrial cancers are higher-grade with aggressive nonendometrioid histologies and are more likely to demonstrate high-risk features such as deep myometrial invasion, lymph node involvement, and metastatic spread at the time of diagnosis. These cancers have a higher risk for recurrence and poorer survival.[48]

KEY POINTS

- Sustained exposure to endogenous estrogen (obesity), exogenous estrogen (estrogen-replacement therapy without progestins), and tamoxifen use are major risk factors for endometrial cancer; oral-contraceptive use decreases the risk for endometrial carcinoma; smoking has not been associated with an increased risk.

- Women with HNPCC have a markedly increased risk for endometrial carcinoma and require annual screening. Since HNPCC also confers an increased risk for ovarian cancer, women with HNPCC should consider hysterectomy and risk-reducing oophorectomy after completion of childbearing.
- Women with endometrial carcinoma should be considered for Lynch syndrome screening. Tumor characteristics such as microsatellite instability, MLH1 methylation, and mismatch repair protein expression help identify patients who may carry Lynch syndrome germline DNA mutations.
- Women with postmenopausal bleeding require endometrial biopsy evaluation to rule out endometrial cancer.
- High-risk histologic subtypes of endometrial carcinoma such as papillary serous and clear cell carcinomas have a poorer prognosis than endometrioid carcinomas.

STAGING AND TREATMENT

Endometrial cancer is surgically staged. Postsurgical treatment recommendations are based on the surgical stage and the specifics of the endometrial cancer grade and histologic subtype. Histologic subtypes of endometrial cancer include endometrioid adenocarcinoma, papillary serous carcinomas, adenosquamous carcinomas, and clear cell carcinomas (Table 12-1). Uterine carcinosarcomas are considered by some to be high-risk histology endometrial carcinomas; however, most endometrial cancer treatment studies have not included carcinosarcomas. For this chapter, we have elected to present uterine carcinosarcomas separately. The standard surgical staging procedure for endometrial cancer includes hysterectomy, bilateral salpingo-oophorectomy, and washings and examination of the entire abdominal cavity. Whether routine pelvic and para-aortic lymph node dissection is necessary for all patients is controversial, but many recommend nodal staging for patients with risk factors such as deep invasion, lymphovascular space invasion, and grade 3 tumors (which include the higher-risk histologies: papillary serous and clear cell).[49,50] The use of sentinel lymph node dissection as a way to spare some patients full lymph node dissection is increasingly accepted.

Patients who are not candidates for surgery because of comorbidities and/or poor performance status can be treated with radiation, but outcomes will not be as favorable as with surgery. For selected young patients who desire fertility preservation, or for women at high risk for perioperative complications who have stage IA, grade 1 tumors, there are some data supporting progestin therapy and surveillance biopsies to assess for tumor regression.[51,52] Table 12-3 summarizes endometrial cancer staging, treatment, and survival rates.

Endometrial carcinomas are staged using the International Federation of Gynecology and Obstetrics (FIGO) system. This staging system was revised in 2009; older literature should be interpreted in light of the changes of certain stage definitions. Approximately 80% of patients with endometrial cancer have stage I disease at initial diagnosis. Stages II, III, and IV are found in 11%, 6%, and 2% of patients, respectively. Survival is substantially influenced by stage. Five-year survival is 83% for patients with stage I disease, 73% for those with stage II disease, 52% for those with stage III disease, and 27% for those with stage IV disease. In addition to stage, features associated with a poorer prognosis include older age, higher tumor grade, vascular invasion, and high-risk histologic subtypes (papillary serous and clear cell carcinomas). Lower-grade tumors are more likely to be estrogen and/or progesterone receptor–positive than

high-grade cancers. Endometrial cancers with mismatch repair defects have been described as having certain higher-risk features such as higher tumor grade and lymphovascular invasion, but survival outcomes did not differ between patients with or without mismatch repair defects.[53]

ADJUVANT TREATMENT OF COMPLETELY RESECTED DISEASE

Postsurgical adjuvant treatment strategies for endometrial cancer continue to evolve. The role of postresection adjuvant pelvic radiation has been investigated in randomized trials. In the GOG 99 study, all patients underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, and lymph node dissection. Patients with 1988 FIGO stage IB or IC, or stage II (occult) endometrial cancer, were randomly assigned to receive adjuvant pelvic radiation or no additional treatment. Patients were not permitted to receive vaginal brachytherapy. Although there was no significant difference in overall survival in this relatively good-risk population, the risk for pelvic and/or vaginal recurrence was significantly lower in the pelvic-radiation group compared with the no-additional-treatment group (12% vs. 3%). Data from GOG 99 were used to define low-risk and high-intermediate-risk subgroups of early-stage endometrial cancers. Low-risk patients are those with FIGO 1988 stage IA or IB (these patients would all be FIGO 2009 stage IA), grade 1 or 2 cancers. These patients have an approximately 6% risk for recurrence. Surgery alone is generally considered adequate treatment for most women with grade 1 or 2 endometrial cancers with less than 50% myometrial invasion (FIGO 2009 stage IA).[54] Patients in the GOG 99 high-intermediate risk group were defined using patient age and the following histologic features: grade 2 or 3, outer-third invasion of the myometrium, and lymphovascular invasion. Patients older than age 70 with one feature, older than age 50 with two features, or any age with all three features were considered high-intermediate risk. The risk for recurrence in this subgroup was 13% among patients assigned to pelvic radiation compared with 27% among patients assigned to no additional treatment. Thus, adjuvant pelvic radiation had been recommended for patients meeting these high-intermediate risk criteria, but results of more recent studies are influencing which patients should receive radiation and what type of radiation should be recommended.

Table 12-3 **Endometrial Cancer Staging, Treatment Overview, and Estimates of Overall Survival**

Stage (FIGO 2009)	Definition	Treatment Overview*	5-Year Overall Survival (%)
I	Tumor confined to the uterine corpus	Hysterectomy and complete surgical staging	83
IA	Tumor confined to the endometrium or tumor invades < 50% of the myometrium	**Endometrioid grade 1 or 2:** observe, may consider IVRT for grade 2; IVRT if LVI or age ≥ 60 **Endometrioid grade 3:** IVRT, may consider chemotherapy if LVI and positive cytology **Serous or clear cell:** IVRT; consider external-beam pelvic RT or chemotherapy if myometrial invasion or positive cytology	
IB	Tumor invades ≥ 50% of the myometrium	**Endometrioid grade 1 or 2:** observe or IVRT; may consider adjuvant chemotherapy if LVI and positive cytology **Endometrioid grade 3:** IVRT or pelvic RT; may consider adjuvant chemotherapy **Serous or clear cell:** chemotherapy and consider IVRT, and/or external-beam pelvic RT	
II	Tumor invades the cervical stroma but does not invade beyond the uterus	**Endometrioid grade 1, 2, or 3 or serous or clear cell:** IVRT or pelvic RT; may consider chemotherapy	73
III	Local and/or regional spread of tumor	Hysterectomy and complete surgical staging; adjuvant chemotherapy; or combined radiation and chemotherapy	52
IIIA	Tumor invades the uterine serosa and/or adnexa		
IIIB	Vaginal and/or parametrial involvement		
IIIC	Metastatic involvement of pelvic and/or para-aortic lymph nodes		30
IIIC1	Positive pelvic lymph nodes		
IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes		
IV	Tumor involves bowel or bladder mucosa or distant metastatic disease	If patient underwent surgery and has no residual disease in peritoneal cavity < 2 cm, consider adjuvant chemotherapy with or without external-beam pelvic radiation or IVRT	27
IVA	Tumor involves bowel mucosa and/or bladder mucosa		
IVB	Distant metastases, including intra-abdominal and/or inguinal lymph nodes	If disease is not potentially completely resectable, treatment is with palliative systemic therapy; consider hormone treatments for lower-grade cancers; combination chemotherapy for advanced, higher-grade, disseminated disease	

*Standards for postsurgical treatment of stage I, II, and III endometrial cancer are still evolving. Clinical trial participation should be encouraged. Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; IVRT, intravaginal radiation therapy (vaginal brachytherapy).

Other studies comparing adjuvant pelvic radiation to observation failed to a show significant benefit for pelvic radiation, although both surgical staging (whether lymph node dissection was done or not) and eligibility criteria (e.g., whether grade 3 tumors were excluded or not) made cross-trial comparison with GOG 99 outcomes difficult. The Randomized Trial of Radiation Therapy with or without Chemotherapy for Endometrial Cancer (PORTEC-2) compared adjuvant pelvic radiation with intravaginal brachytherapy for high-intermediate-risk endometrial cancer—excluding papillary serous and clear cell carcinomas—showed that outcomes are equivalent (pelvic recurrence rates, 5.1% with vaginal brachytherapy vs. 2.1% with pelvic radiation; no difference in metastatic disease, relapse-free survival, or overall survival), with less toxicity and superior quality of life, among patients assigned to adjuvant intravaginal brachytherapy, establishing vaginal brachytherapy as the adjuvant treatment of choice for these

patients.[55] Long-term follow-up (median follow-up, 20.5 years) of 568 patients with early-stage endometrial cancer treated with either whole pelvic radiation plus vaginal brachytherapy or with vaginal brachytherapy alone showed no survival benefit to whole pelvic radiation, and among women younger than age 60, pelvic radiation was associated with decreased survival and increased risk for second malignancies.[56] PORTEC-4 is an ongoing randomized trial comparing vaginal brachytherapy with observation for patients with stage I endometrial cancers (excluding serous and clear cell histologies). A large population-based study showed a survival benefit to adjuvant radiation (either pelvic or vaginal brachytherapy) in high-intermediate-risk and high-risk stage I endometrioid endometrial cancer, but no survival benefit in lower-risk patients.[57]

GOG 249 was a prospective, phase III study of patients with GOG-defined high-intermediate-risk stage I or II endometrial cancer. The study considered whole pelvic radiation plus optional vaginal brachytherapy for some patients to be the standard arm of the study. The experimental treatment was adjuvant paclitaxel/carboplatin chemotherapy plus intravaginal brachytherapy. With a median follow-up of 24 months, relapse-free survival was the same in both treatment arms (82% pelvic radiation, 84% vaginal brachytherapy plus chemotherapy) thus, adjuvant chemotherapy is not considered standard for this group of patients.[58] However, some endometrial cancer experts consider giving adjuvant chemotherapy for patients considered to be at “higher” than high-intermediate risk, such as a patient with grade 3 endometrioid cancer with deep myometrial invasion, lymphovascular invasion, and positive peritoneal cytology or a patient with a high-risk histology (serous or clear cell) with myometrial invasion and/or positive peritoneal cytology.

Adjuvant treatment decisions for patients with FIGO 2009 stage II, grade 1 or 2 endometrioid cancers can be difficult because of differences in study design between PORTEC-2 and GOG 249. Patients with FIGO 2009 stage II, grade 1 or 2 endometrioid histology and less than 50% myometrial invasion may be at sufficiently low risk that treatment with vaginal brachytherapy alone is reasonable based on PORTEC-2, while an argument could be made that patients with stage II, grade 1 or 2 endometrioid tumors and deeper myometrial invasion, and stage II, grade 3 endometrioid cancers may be treated with vaginal or pelvic radiation. The role of chemotherapy for these patients is not clear, but chemotherapy may be considered for patients with additional higher-risk features such as high-risk nonendometrioid histologies, deeply invasive tumors, lymphovascular invasion, and positive peritoneal cytology.

Endometrial cancers with serous or clear cell histology are generally higher-risk than endometrioid cancers; however, for patients with FIGO stage IA disease without myometrial invasion and without lymphovascular invasion, clinical outcomes appear similar to those with endometrioid histology.[59] Although histology-specific prospective data are lacking for patients with serous or clear cell tumors, a reasonable approach for early-stage cancers with these histologies is stage IA with no myometrial invasion—vaginal brachytherapy; stage IA with myometrial invasion or stage IB—chemotherapy and consider pelvic and/or vaginal brachytherapy stage II—chemotherapy and consider pelvic and/or vaginal brachytherapy.[60] Clinical trial participation is strongly encouraged for all patients with early-stage endometrial cancer because optimal treatment standards are not yet defined.

Patients with stage III (uterine serosa, vaginal or parametrial, or lymph node involvement) endometrial cancer are at risk for both local and distant failure. Optimal adjuvant treatment approaches have not yet been defined, but all stage III patients are generally offered some form of adjuvant treatment. The role of adjuvant chemotherapy in stage III endometrial cancer was established in a phase III trial (GOG 122). Patients with stage III and resected stage IV disease with no residual disease greater than 2 cm in the peritoneal cavity were randomly

assigned to receive adjuvant whole-abdomen radiation therapy or chemotherapy (cisplatin plus doxorubicin for eight cycles). Superior 5-year progression-free and overall survival rates were seen in the chemotherapy arm (55% vs. 42%).[61] The subsequent phase III trial (GOG 184) for stage III and completed resected stage IV patients gave all patients tumor-volume-directed radiation followed by chemotherapy with either doxorubicin–cisplatin or doxorubicin/cisplatin/paclitaxel. Three-year PFS was approximately 60% for both treatment arms.[62]

Two prospective studies evaluated whether and how to incorporate radiation into the adjuvant strategy for stage III and other high-risk endometrial cancer patients. GOG 258 compared paclitaxel/carboplatin chemotherapy alone to combined cisplatin plus tumor-volume-directed radiation followed by paclitaxel/carboplatin for stage III and IVA patients with less than 2-cm residual disease after resection or patients with stage I or II disease with serous or clear cell histology and positive peritoneal cytology. PORTEC 3 compared pelvic radiation (plus vaginal brachytherapy if there was cervix involvement) to cisplatin–radiation followed by paclitaxel/carboplatin for stage I, grade 3 or clear cell or serous histology plus myometrial invasion or stage II or III cancers. While toxicity and quality of life data from PORTEC-3 have been reported,[63] relapse-free survival data for GOG 258 and PORTEC-3 have been reported only in abstract as of June 2017. GOG 258 showed no difference in relapse-free survival between the cisplatin–radiation followed by paclitaxel/carboplatin treatment group compared to paclitaxel/carboplatin chemotherapy alone.[64] PORTEC-3 showed significantly improved 5-year failure-free survival in the cisplatin–radiation followed by carboplatin/paclitaxel treatment group compared with pelvic radiation alone.[65] While overall survival data are awaited from both trials, the relapse-free/failure-free survival data support a chemo–radiation followed by chemotherapy or an all chemotherapy adjuvant treatment strategy for these high-risk endometrial cancer patients, rather than radiation alone.

KEY POINTS

- Patients with early-stage, low-risk (stage IA, grade 1 or 2, nonserous, non–clear cell histology) endometrial cancer have a high chance of being cured with surgery alone and should be spared the toxicity of external-beam pelvic radiation.
- Patients with high-intermediate-risk endometrial cancer (definitions vary, but important parameters to consider are older age, grade 2 or 3 tumors, deep myometrial invasion, lymphovascular invasion, positive peritoneal cytology) may be offered adjuvant treatment with radiation, although optimal strategies (vaginal brachytherapy vs. whole pelvic radiation) have not been determined for each tumor/patient risk group.
- Chemotherapy has an important role in adjuvant therapy of completely resected stage III and IV endometrial cancer, but best chemotherapy regimens and how to incorporate radiation, which specific risk subsets of patients are most likely to benefit, and whether some patients can be treated with radiation alone, are not yet specifically defined. Data from two prospective trials in high-risk endometrial cancer support chemo–radiation followed by chemotherapy or an all-chemotherapy treatment over radiation alone.
- Serous and clear cell histology endometrial cancers (except if surgical stage IA with no myometrial invasion) should be treated with chemotherapy with consideration of

brachytherapy or radiation therapy.

METASTATIC OR RECURRENT DISEASE

Endometrial cancer, particularly type I, lower-grade endometrial cancer, is a hormonally sensitive malignant disease. Responses of up to 38% have been reported in studies of hormonal agents (medroxyprogesterone or alternating medroxyprogesterone and tamoxifen) for endometrial carcinoma. Clinical features that are predictors of response to a progestational agent include grade 1 or 2 histology, a long disease-free interval from diagnosis, and the presence of estrogen or progesterone receptors on the tumor cells. Grade 3 or undifferentiated and serous histology endometrial cancers rarely respond to hormone therapy, thus, chemotherapy is the primary treatment for most patients with metastatic, high-grade disease.

Chemotherapy agents that have demonstrated activity in metastatic endometrial cancer include the platinum agents (cisplatin and carboplatin), paclitaxel, and doxorubicin. The overall response rates to these single agents range from 25% to 35%. In metastatic or recurrent endometrial cancer, the combination of cisplatin plus doxorubicin was compared with doxorubicin alone (GOG 107). The cisplatin/doxorubicin combination produced a higher objective response rate (42% vs. 25%) and a slight improvement in progression free-survival (5.7 months vs. 3.8 months) but no difference in overall survival.[66] A subsequent phase III randomized trial (GOG 177) showed that the combination of cisplatin, doxorubicin, and paclitaxel yielded a small but significant improvement in overall survival compared with cisplatin plus doxorubicin (15.3 months vs. 12.3 months), with a greater risk for toxicity.[67] Results of a phase III trial comparing cisplatin, doxorubicin, and paclitaxel with paclitaxel and carboplatin (GOG 209) showed that these two regimens are equivalent in terms of progression-free and overall survival rates. These data support the use of paclitaxel/carboplatin as first-line therapy for women with metastatic endometrial carcinoma.[68] There is no standard second-line therapy or a standard approach for patients who have previously received paclitaxel/carboplatin as adjuvant therapy.

Targeted therapies for endometrial cancer are under active investigation. Endometrioid endometrial cancers frequently have mutations in the tumor suppressor gene phosphatase and tensin homolog (*PTEN*). *PTEN* mutations are much less common in nonendometrioid histology endometrial cancers. *PTEN* is a negative regulator of the phophatidylinositol-3 kinase/serine–threonine kinase (PI3K/AKT) pathway. Inhibitors of the mammalian target of rapamycin (mTOR), which is downstream of AKT, may have activity in endometrial cancer.[69] A phase II trial of the combination of the mTOR inhibitor everolimus plus letrozole achieved objective response in 32% of patients who had received up to two prior cytotoxic regimens. Responses were more likely among patients with endometrioid histology than among those with serous histology tumors.[70] This regimen is being compared to tamoxifen and medroxyprogesterone in a randomized trial (NCT02228681). The vascular endothelial growth factor inhibitor bevacizumab achieved objective response in 13.5% of previously treated patients, and 40% of patients remained progression-free at 6 months.[71] There is high interest in defining molecular subsets of endometrial cancer and identifying better targeted agents for this heterogeneous disease. A current phase III, placebo-controlled trial is investigating whether the addition of metformin to paclitaxel/carboplatin for advanced endometrial cancer improves survival (NCT02065687).

Immunotherapy is also under active investigation in endometrial cancer and is of particular interest for the subset of endometrial cancers that are mismatch repair–deficient (dMMR).

Early studies suggest that patients with MSI-H, dMMR tumors and/or a hypermutated phenotype may achieve high objective response rates with immune checkpoint inhibitors.[72] One PD-1 inhibitor, pembrolizumab, was FDA-approved in May 2017 for MSI-H or dMMR solid tumors that have progressed following prior treatment.

KEY POINTS

- Patients with low-grade, recurrent, and metastatic endometrial cancer may respond to progestin-based therapy.
- Patients with high-grade, recurrent, and metastatic disease may respond to cytotoxic chemotherapy. Active agents include platinum agents, paclitaxel, doxorubicin, and bevacizumab. The role of mTOR inhibition, particularly for endometrioid histology tumors, is under investigation. Paclitaxel/carboplatin is a reasonable first-line treatment option.
- The role of immune checkpoint inhibitors is under investigation. Biomarkers such as microsatellite instability and mismatch repair deficiency may identify patients likely to benefit from these agents.

UTERINE CARCINOSARCOMAS AND SARCOMAS

Uterine carcinosarcomas, leiomyosarcoma (LMS), endometrial stromal sarcomas, and adenosarcomas comprise approximately 4% of uterine cancers. These cancers differ from endometrial carcinoma in their prognosis and management. Among the uterine sarcomas, carcinosarcomas (also referred to as “uterine malignant mixed Müllerian tumors”) make up about 50%, LMS about 40%, and adenosarcomas and endometrial stromal sarcomas the remaining 10%. Careful histologic review is recommended for these rare and high-risk histologies, since the prognosis and management may vary greatly depending on the specific type of uterine sarcoma.

CARCINOSARCOMAS

Carcinosarcomas are high-risk tumors that show both carcinoma- and sarcoma-like histologic features that arise from a single malignant precursor. Molecular profiling has shown that mutations are the same or similar in the carcinomatous and sarcomatous portions of the tumor, supporting a common origin theory for the histologically different components. Mutations are common in TP53 and the PI3K pathway.[73] Carcinosarcomas are staged using the FIGO staging system for endometrial carcinomas. They have high rates of recurrence, even among patients with early-stage disease at diagnosis. Results of a phase III trial (GOG 150) established the role of adjuvant chemotherapy for completely resected FIGO stage I, II, III, or IV uterine carcinosarcoma. In this trial, women with minimal residual disease after surgical resection were randomly assigned to receive adjuvant whole-abdomen radiation or chemotherapy (cisplatin plus ifosfamide). Recurrence rates at 5 years were lower for patients in the chemotherapy arm (52% with chemotherapy vs. 58% with radiation) for all patients and for subgroups of patients by stage, establishing adjuvant chemotherapy as a standard recommendation for all stages of completely resected carcinosarcoma.[74]

For patients with advanced, measurable, recurrent carcinosarcoma, the combination of

paclitaxel plus ifosfamide yielded higher response rates (45% vs. 29%) and longer overall survival (13.5 months vs. 8.4 months) than did ifosfamide alone (GOG 161).[75] Since the combination of paclitaxel plus carboplatin achieved objective response in 54% of patients with measurable disease in a phase II trial (GOG 232B),[76] paclitaxel/carboplatin is being compared with paclitaxel/ifosfamide in a randomized, phase III trial for patients with carcinosarcoma of any stage (GOG 261). It is standard to consider two-agent adjuvant chemotherapy (e.g., paclitaxel/carboplatin, ifosfamide/paclitaxel or ifosfamide/cisplatin) for all patients with completely resected uterine carcinosarcoma. There is no standard second-line treatment for uterine carcinosarcomas.

LEIOMYOSARCOMAS

Leiomyosarcoma (LMS) is a high-risk cancer of the uterine smooth muscle with a propensity for early hematogenous dissemination. Patients with uterus-limited disease have a 50 to 70% risk for recurrence.[77] A randomized trial comparing adjuvant pelvic radiation with observation for stage I or II uterine sarcomas (enrolling mostly patients with carcinosarcomas and LMS) did not show a benefit for adjuvant pelvic radiation.[78] The current standard of care after resection of uterus-limited LMS is observation. Whether adjuvant chemotherapy could improve overall survival was investigated in an international phase III trial (GOG 277) with observation as the standard arm. Unfortunately, the study was closed early for slow accrual, leaving the question of whether to use adjuvant chemotherapy for uterine LMS unanswered.

Among the active agents for the treatment of advanced, metastatic LMS are fixed-dose-rate gemcitabine plus docetaxel,[79] doxorubicin (with or without olaratumab or ifosfamide), single-agent gemcitabine, ifosfamide, trabectedin, pazopanib, and dacarbazine. A prospective, phase III trial (GOG 250) showed that the addition of bevacizumab to gemcitabine/docetaxel did not improve response rates, nor PFS.[80]

Results from studies designed for soft-tissue sarcomas that include patients with uterine LMS are applicable to treatment decisions for advanced uterine LMS. The oral multikinase inhibitor pazopanib was approved for treatment of soft-tissue sarcomas that have progressed after prior cytotoxic therapy based on results of a phase III trial comparing pazopanib to placebo. PFS was 4.6 months among patients assigned to pazopanib compared with 1.6 months among those assigned to placebo. Objective response was observed in 6% of patients on pazopanib. There was no difference in overall survival.[81]

Trabectedin is a cytotoxic agent that is approved for treatment of LMS and liposarcomas based on results of a phase III trial comparing trabectedin to dacarbazine in patients who had received prior anthracycline therapy. The objective response rate was less than 10% in both arms, but PFS was improved among patients treated with trabectedin (4.2 months) compared with dacarbazine (1.5 months). There was no difference in overall survival.[82] Similar results were observed in the subset of patients with uterine LMS.[83] In a prospective, phase II study for patients with uterine LMS who had had no prior treatment (GOG 87M), trabectedin achieved a similarly low objective response (10%) and a median PFS of 5.8 months.[84] Although trabectedin plus doxorubicin achieved a high objective response rate as first-line therapy in a phase II trial for uterine LMS, there was significant toxicity (24% incidence of febrile neutropenia),[85] and a subsequent randomized trial of trabectedin plus doxorubicin compared with doxorubicin alone did not show superiority for the combination.[86]

A randomized, phase II trial of doxorubicin with or without the platelet-derived growth factor receptor alpha–directed antibody olaratumab, followed by olaratumab maintenance showed

improved overall survival with the addition of olaratumab (the differences in response rates—12% doxorubicin v. 18.8% doxorubicin plus olaratumab—and PFS—4.1 months with doxorubicin v. 6.6 months doxorubicin plus olaratumab--were not statistically different), leading to FDA approval of this agent for use in combination with doxorubicin in soft-tissue sarcomas.[87] There was a high risk of febrile neutropenia (14%) in both treatment groups. For patients with uterine LMS for whom doxorubicin treatment is being considered, it is reasonable to consider adding olaratumab to doxorubicin, followed by olaratumab maintenance for patients who are in response after six to eight cycles of doxorubicin.

ENDOMETRIAL STROMAL SARCOMAS AND ADENOSARCOMAS

True endometrial stromal sarcomas are low-grade tumors that nearly always express estrogen and progesterone receptors. While the risk for recurrence is about 30% for women with disease limited to the uterus at time of diagnosis, 10-year survival rates exceed 90% because of the hormone-sensitive, indolent disease pace of these low-grade cancers. Recurrence rates appear to be lower among women who have bilateral oophorectomy at the time of diagnosis. Treatment with hormone blockade approaches may be effective for patients with recurrent disease.

Adenosarcomas are mixed histology tumors in which the sarcomatous portion looks similar to low-grade endometrial stromal sarcoma, and the adeno portion appears benign. Prognosis and management is similar to that for low-grade endometrial stromal sarcoma, unless there is evidence of sarcomatous overgrowth. Adenosarcomas with sarcomatous overgrowth are high-risk cancers, the prognosis and treatment of which is driven by the high-grade portion of the tumor.

High-grade endometrial stromal sarcomas are sometimes called “high-grade undifferentiated sarcomas.” Unlike low-grade endometrial stromal sarcomas, these tumors do not generally express estrogen or progesterone receptors. Increasingly sophisticated histologic and molecular techniques are leading to subclassifications of these high-grade sarcomas, but thus far such classification does not dictate different treatment choices. A characteristic fusion gene has been identified in these cancers that may help with histologic diagnosis,[88] and may identify a subgroup of high-grade endometrial stromal sarcomas with a more intermediate behavior. Because of their rarity, there are no prospective studies addressing active agents for these tumors. Retrospective data and sarcoma treatment guidelines support treatment with doxorubicin-based or gemcitabine/docetaxel treatment. Enrollment on clinical trials for soft-tissue sarcomas is encouraged.

KEY POINTS

- Expert histologic review is recommended for patients with a diagnosis of a uterine sarcoma, since these rare cancers differ greatly in their clinical behavior and management.
- Patients with completely resected, stage I, II, III, or IV uterine carcinosarcoma are generally treated with adjuvant two-agent chemotherapy (paclitaxel/carboplatin, paclitaxel/ifosfamide, or ifosfamide/cisplatin).
- Observation is standard for patients with completely resected, uterus-limited LMS.

Adjuvant pelvic radiation does not improve pelvic recurrence rates or survival outcomes. There are no data showing improved survival with adjuvant chemotherapy, although no prospective, phase III trial comparing adjuvant chemotherapy to observation has been completed.

- Gemcitabine/docetaxel or doxorubicin-based treatment are reasonable first-line treatment options for patients with unresectable metastatic uterine LMS.
- Low-grade endometrial stromal sarcomas are hormone-sensitive tumors.

EPITHELIAL OVARIAN CANCER, FALLOPIAN TUBE CANCER, AND PRIMARY PERITONEAL CANCER

Ovarian cancer is the leading cause of gynecologic cancer death in the United States. It accounts for 3% of cancers among women in the United States, but it is the fifth most common cause of cancer-related death. It was estimated that approximately 22,000 women were diagnosed with ovarian cancer in the United States in 2016 and that approximately 14,200 women died from ovarian cancer in 2016. Epithelial ovarian cancer accounts for 90% of all cases of malignant tumors of the ovaries. Fallopian tube cancer and primary peritoneal cancer are much rarer, but share histologic, prognostic, and treatment response features with epithelial ovarian cancer. Some data suggest that the epithelial cells of the fallopian tube may be the site of origin for most ovarian carcinomas. Fallopian tube and primary peritoneal cancers are rarely studied prospectively as separate cancers; rather, patients with these cancers are generally eligible for clinical trials for epithelial ovarian cancer, and treatment strategies used for epithelial ovarian cancer are applied to patients with fallopian tube and primary peritoneal cancer. Epithelial ovarian cancers are adenocarcinomas, and they can be histologically subclassified as serous, endometrioid, mucinous, clear cell, and low-grade serous carcinomas. Global trends suggest a decrease in ovarian cancer mortality, which may be attributable, in part, to oral-contraceptive use.[89]

RISK FACTORS AND DISEASE PRESENTATION

Patients with early-stage ovarian cancer often have nonspecific symptoms, including irregular menses (if premenopausal), urinary frequency, persistent bloating, and constipation. With advanced disease, patients may have abdominal pain, bloating, dyspnea, emesis, early satiety, anorexia, and constipation. In early-stage disease, the major physical finding is a pelvic mass; patients with advanced disease may have large-volume ascites or palpable abdominal or pelvic masses on examination.

In the normal-risk population, ovarian cancer will develop in approximately 1 woman in 70. The mean age at diagnosis is 59 years. Increasing age is one of the strongest risk factors for the development of ovarian cancer. The age-specific risk for the disease steadily increases from ages 20 to 80 and then declines.

Family history is the next strongest risk factor after age. A woman with a single first-degree relative with ovarian cancer has a relative risk of 3.6 for the development of ovarian cancer, meaning her lifetime risk for ovarian cancer is approximately 5%. Even in the absence of a family history of breast or ovarian cancer, National Comprehensive Cancer Network (NCCN) guidelines recommend genetic testing for all women with epithelial ovarian, fallopian tube, or primary peritoneal cancer in order to identify women carrying germline deleterious mutations.

Carriers of deleterious mutations in *BRCA1* or *BRCA2* have a lifetime risk of ovarian cancer estimated at 16 to 60%, with the higher risk among women who are heterozygous for *BRCA1* mutation and have a strong family history of the disease.[90] Women with genetic mutations that are part of the HNPCC syndrome also are at increased risk for ovarian cancer. The lifetime risk likely varies depending on the specific mismatch repair enzyme mutation. For example, in one study, women with *MLH1* mutations had an estimated 20% lifetime risk, *MSH2* a 24% risk, and *MSH6* a 1% risk.[91] Other germline mutations associated with increased risk for ovarian cancer, include *BRIP1, RAD51C,* and *RAD51D.* Emerging data are elucidating whether there is a clinically relevant increased risk of ovarian cancer associated with other germline mutations.

Other risk factors for ovarian cancer include white race and diets high in animal fat. Nulliparity or first birth after age 35 years, infertility, late menopause, and early menarche increase the risk for ovarian cancer, perhaps because each of these factors is associated with prolonged, uninterrupted periods of ovulation, which might increase the probability of genetic errors occurring during repair of the ovary surface epithelium, which, in turn, may increase the risk for malignant transformation. Oral-contraceptive use is associated with a decreased risk for ovarian cancer. The relative risk is approximately 0.5 for women who used oral contraceptives for 5 years or more compared with those who never used them. Higher parity, tubal ligation, and hysterectomy have also been associated with decreased risk. Smoking does not appear to increase risk.

SCREENING FOR OVARIAN CANCER

There are no data to support the routine use of ovarian cancer screening of any type. The FDA issued a Safety Communication recommending against using screening tests for ovarian cancer screening in women at general risk and in women with a genetic increased risk for ovarian cancer.[92] A randomized trial of screening with CA125 and transvaginal sonogram compared with usual care enrolled 78,216 women ages 55 to 74. Screening did not decrease mortality, and there was evidence of harm from interventions required for women with false-positive screening results.[93] For women with strong family histories of breast/ovarian cancer and for women with *BRCA1, BRCA2,* or HNPCC genetic mutations, screening had been recommended in the past for the years until childbearing has been completed. However, since there are no data showing screening to be effective, screening is no longer recommended, since it might provide high-risk women with false reassurance and delay/dissuade the decision to undergo risk-reducing salpingo-oophorectomy (RRSO). In an uncontrolled study, more than 4000 women with a lifetime ovarian cancer risk estimated to be more than 10% were offered CA125 testing every 4 months and annual transvaginal sonogram. CA125 results were interpreted by the Risk of Ovarian Cancer Algorithm (ROCA). Although data from this uncontrolled study showed more early-stage cancers diagnosed within a year of screening compared to after screening stopped, the data cannot be interpreted as showing a survival advantage for screening.[94]

RISK-REDUCING SALPINGO-OOPHORECTOMY

Several studies indicate that performing a bilateral RRSO may substantially reduce the risk for ovarian cancer for women who are carriers of deleterious *BRCA1* or *BRCA2* mutations (approximately 80% lower risk for ovarian, fallopian tube, and peritoneal cancers with average follow-up of 5.6 years from the RRSO, and 77% reduction in all-cause mortality).[95] Longer follow-up of these patient cohorts will yield information about the consequences of estrogen deprivation. Hormone-replacement therapy is a concern for some premenopausal patients who

elect RRSO; however, the risks appear to be small.[96] Outcomes of RRSO may differ by the type of genetic mutation. Patients who are carriers of deleterious *BRCA1* mutations are at higher lifetime risk and derive greater ovarian cancer risk reduction than do *BRCA2* mutation carriers, whose lifetime risk is lower.[97] Other, non-*BRCA* germline mutations, such as Lynch syndrome–associated mutations, are also considered to confer sufficient ovarian cancer risk to merit recommendation for RRSO after completion of childbearing. RRSO should also be considered at approximately age 45 to 50 for women with deleterious mutations in *BRIP1, RAD51C,* or *RAD51D.*[98]

KEY POINTS

- Risk factors for ovarian cancer include increasing age; family history; carrying a deleterious mutation associated with *BRCA1, BRCA2,* an HNPCC-associated mutation, or germline mutations in *BRIP1, RAD51C,* or *RAD51D*; nulliparity; early menarche; late menopause; and infertility. Smoking is not associated with increased risk.
- Oral-contraceptive use decreases the risk for ovarian cancer.
- Screening for ovarian cancer is not recommended for the general population or for women at genetically increased risk, because of the high rate of false-positive test results and because there is no evidence that mortality is decreased by screening.
- NCCN guidelines recommend genetic counseling and consideration of genetic testing for all patients diagnosed with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.
- Risk-reducing bilateral salpingo-oophorectomy (RRSO) is recommended for carriers of deleterious mutations in *BRCA1* or *BRCA2* who have completed childbearing and for women with mutations in *BRIP1, RAD51C,* or *RAD51D.*

DIAGNOSIS, SURGICAL STAGING, AND NEOADJUVANT CHEMOTHERAPY

For premenopausal women, the majority of ovarian masses are functional cysts that usually decrease in size after several menstrual cycles. Performing a transvaginal ultrasound can assist in the differential diagnosis of cysts that do not regress. For postmenopausal women, a palpable pelvic mass is of greater concern as an indicator of malignant disease. A computed tomography (CT) scan of the chest, abdomen, and pelvis can help determine the extent of tumor involvement, but it cannot confirm that advanced disease is from an ovarian cancer primary. For a patient with ascites, a paracentesis may be performed to enable cytologic analysis of the fluid, if primary surgical debulking is not planned. The CA125 level is increased in more than 80% of patients with advanced ovarian cancer; however, only approximately 50% of patients with early-stage ovarian cancer have high CA125 levels. Normal CA125 levels should not deter the treating physician from further evaluating a suspicious pelvic mass.

The definitive diagnosis of ovarian, fallopian tube, or primary peritoneal cancer is made by surgical exploration. Prognosis is linked to the amount of residual tumor after surgical cytoreduction (debulking surgery). Optimal cytoreduction has been defined as no residual tumor measuring greater than 1 cm at the end of the surgical procedure, although a more contemporary definition is no gross residual disease. A standard approach in the United States

has been for all patients with suspected ovarian cancer to be considered for surgical cytoreduction followed by chemotherapy according to the surgical stage and amount of residual disease. However, a number of studies provide support for offering initial chemotherapy (neoadjuvant chemotherapy) followed by surgery to patients with clinically advanced ovarian cancer. One randomized trial showed equivalent outcomes for patients with stage III or IV ovarian cancer whether treated with neoadjuvant chemotherapy followed by surgery or with cytoreductive surgery followed by chemotherapy.[99] A subset analysis of this trial suggested that initial cytoreductive surgery achieved better outcomes among patients with stage III, lower-volume disease, whereas initial neoadjuvant chemotherapy achieved better outcomes among patients with stage IV bulky disease.[100] In a prospective, phase III trial, patients with high tumor burden stage IIIC or IV ovarian cancer were intraoperatively randomly assigned at time of laparoscopic evaluation to primary debulking surgery or neoadjuvant chemotherapy followed by interval debulking surgery. Rates of optimal debulking were the same with either surgical approach, major postoperative complications were significantly higher with primary debulking surgery.[101] An observational study of 1538 women with stage IIIC to IV ovarian cancer treated at National Cancer Institute–designated cancer centers showed that the use of neoadjuvant chemotherapy increased over time. In a matched-patient comparison, neoadjuvant chemotherapy was associated with poorer overall survival compared to primary debulking surgery among stage IIIC patients, but not among stage IV patients.[102]

ASCO and Society of Gynecologic Oncology practice guidelines recommend that all women with suspected epithelial ovarian cancer undergo evaluation by a gynecologic oncologist.[103] Women whose disease burden and medical status make it likely that an optimal cytoreduction will be possible with acceptable morbidity should be offered primary debulking surgery. Others should be offered neoadjuvant chemotherapy, after histologic confirmation of the diagnosis of invasive epithelial ovarian, fallopian tube, or peritoneal cancer.[103] Patients who are treated with neoadjuvant chemotherapy and who have evidence of response are offered subsequent cytoreductive surgery. Whether treated with initial debulking surgery or with neoadjuvant chemotherapy followed by cytoreductive surgery, patients who have a complete resection of all macroscopic disease have superior survival outcomes compared with patients in whom the disease cannot be completely resected.

Cytoreduction surgery for ovarian cancer includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node sampling, infracolic omentectomy, pelvic and peritoneal biopsies, and pelvic and peritoneal washings. In those cases with bulky disease, removal of all visible disease at the time of initial surgery will improve survival; this may include bowel resection where necessary. Appropriate surgical staging in ovarian cancer is particularly important for women with clinically early-stage disease. Failure to perform complete surgical staging may result in using chemotherapy when it may be unnecessary, or it may lead to an inappropriate decision to withhold adjuvant chemotherapy when disease in the abdominal cavity or regional lymph nodes has gone undetected. An initial appropriate staging procedure is more likely if the surgeon is a gynecologic oncologist.

It remains uncertain whether the superior survival outcomes seen with optimal surgical cytoreduction are attributable to the surgery itself or occur because the same tumor biologic factors that permit a successful surgery (such as the local growth pattern of the tumor) are also responsible for overall chemosensitivity, with low disease volume lowering the risk for inherent or acquired resistance to chemotherapy and slowing the rate of disease progression.

Table 12-4 **Epithelial Ovarian Cancer Staging, Treatment Overview, and Estimates of Overall Survival**

Stage	Definition	Treatment Overview	5-Year Overall Survival (%)
I	Tumor confined to the ovaries	Hysterectomy, bilateral salpingo-oophorectomy, lymph node sampling, washings, and complete surgical staging*	85-90
IA	Tumor limited to one ovary; capsule intact, no tumor on ovarian surface, no malignant cells in ascites or peritoneal washings	No adjuvant chemotherapy for grade 1 or 2 tumors; adjuvant platinum-based chemotherapy for grade 3 and clear cell tumors	
IB	Tumor limited to both ovaries; capsule intact, no tumor on ovarian surface, no malignant cells in ascites or peritoneal washings	No adjuvant chemotherapy for grade 1 or 2 tumors; adjuvant platinum-based chemotherapy for grade 3 and clear cell tumors	
IC	Tumor limited to one or both ovaries; capsule rupture or tumor on the ovarian surface or malignant cells in ascites or peritoneal washings	Adjuvant platinum-based chemotherapy	
II	Tumor involves one or both ovaries with pelvic extension		80
IIA	Extension and/or implants on uterus and/or fallopian tubes; no malignant cells in ascites or peritoneal washings	Adjuvant platinum-based chemotherapy	
IIB	Extension to other pelvic tissues; no malignant cells in ascites or peritoneal washings	Adjuvant platinum-based chemotherapy	
IIC	Pelvic extension with malignant cells in ascites or peritoneal washings	Adjuvant platinum-based chemotherapy	
III	Tumor involves one or both ovaries with peritoneal metastasis outside the pelvis and/or retroperitoneal or inguinal lymph node metastasis		15-50†
IIIA	Microscopic peritoneal metastasis beyond the pelvis		
IIIB	Macroscopic peritoneal metastasis beyond the pelvis, measuring ≤ 2 cm in greatest dimension		
IIIC—optimally debulked	Macroscopic peritoneal metastasis beyond the pelvis measuring > 2 cm and/or regional lymph node metastases; no residual disease > 1 cm at completion of cytoreductive surgery	Intraperitoneal platinum- and taxane-based chemotherapy, or intravenous taxane plus platinum chemotherapy (see text for detailed discussion)	30-50
IIIC—suboptimally debulked	Macroscopic peritoneal metastasis beyond the pelvis measuring > 2 cm and/or regional lymph node metastases; residual disease > 1 cm at completion of cytoreductive surgery	Intravenous platinum plus taxane combination chemotherapy (see text for detailed discussion)	10-20
IV	Distant metastases (excluding peritoneal metastases) to liver parenchyma or malignant pleural effusion	Intravenous platinum plus taxane combination chemotherapy (see text for detailed discussion)	5-10

*Fertility-sparing surgery (unilateral salpingo-oophorectomy, lymph node sampling, washings, and biopsies) may be appropriate for selected young patients with stage IA disease who have not completed childbearing.
†Survival is longer among patients who undergo optimal cytoreduction at time of initial surgery.

PROGNOSTIC FACTORS

The most important prognostic factor in ovarian cancer is tumor stage. Approximately 25% of women present with stage I disease, 15% with stage II, 42% with stage III, and 17% with stage IV. Table 12-4 gives an overview of ovarian cancer staging, treatment, and 5-year survival estimates. Other important prognostic factors include extent of residual disease at completion of cytoreductive surgery, tumor grade (particularly in stage I cancers), patient age, and performance status. Histologic subtype may also affect prognosis. For example, all clear cell carcinomas are considered to be grade 3, and mucinous carcinomas carry a less favorable prognosis for patients with advanced-stage disease. Some ovarian serous carcinomas are classified as “low-grade serous” carcinomas. These low-grade cancers differ from high-grade serous cancers in their molecular signatures (e.g., *p53* mutations are rare, but *KRAS* and

BRAF mutations and mitogen-activated protein kinase pathway alterations are more common), exhibit a more indolent disease course, and may be more resistant to platinum/taxane chemotherapy.[104] Mucinous ovarian cancers may also be more resistant to cytotoxic chemotherapy, but they are also more likely to present as early-stage cancers. Since primary mucinous cancers of the ovary are rare, consideration should be given to the possibility of metastatic disease from the gastrointestinal or pancreaticobiliary tract. While some studies have shown that ovarian cancer prognosis is more favorable among women with germline *BRCA1* or *BRCA2* mutations, other studies have not found this survival advantage over non-*BRCA* ovarian cancers.[105,106] Advances in our understanding of the molecular differences among ovarian cancers may lead to treatment changes involving therapies that are specifically directed to identifiable driver abnormalities.

CHEMOTHERAPY FOR EARLY-STAGE OVARIAN CANCER

Patients with early-stage ovarian cancer can be classified into favorable and less-favorable prognostic groups. Patients with stage IA or IB, grade 1 or 2 cancers have 5-year disease-free survival rates of greater than 90%. Two randomized trials for this favorable prognostic group failed to show a disease-free or overall survival benefit from chemotherapy.[107] Women with stage IA or IB, grade 1 or 2 ovarian cancer who have had complete surgical staging do not require adjuvant chemotherapy.

Patients with stage IA or IB, grade 3 cancer, all patients with stage IC disease, all patients with clear cell carcinomas, and patients with stage II disease have a less-favorable prognosis, with 5-year survival rates of 80 to 90%. A number of randomized trials have demonstrated that adjuvant chemotherapy can prolong the time to progression for women with high-risk, early-stage ovarian cancer. An analysis of data from more than 900 patients with high-risk, early-stage disease showed that adjuvant platinum-based chemotherapy led to an 11% improvement in 5-year PFS and an 8% improvement in 5-year overall survival compared with a strategy of observation until evidence of recurrent disease.[108] These data strongly support the recommendation for treating women with less-favorable prognosis, early-stage ovarian cancer (stage IA or IB, grade 3; all stage IC; all clear cell carcinomas; and stage II) with adjuvant platinum-based chemotherapy after complete surgical staging. The optimal duration of therapy for early-stage disease has not been defined. A retrospective study of patients with stage I or II clear cell carcinoma showed similar recurrence and survival rates among patients treated with three cycles of chemotherapy compared to patients who received six cycles.[109] Starting adjuvant chemotherapy less than 2 weeks, between 2 and 4 weeks, or more than 4 weeks after surgery did not alter survival among patients with stage I or II ovarian cancer.[110] A large phase III trial showed that adding 24 weeks of maintenance paclitaxel after three cycles of intravenous paclitaxel plus carboplatin did not improve progression-free or overall survival in patients with early-stage disease (85.4% with maintenance, 86.2% without, at 5 years).[111]

KEY POINTS

- Surgery for complete staging and tumor cytoreduction plays a key role in the management of epithelial ovarian cancer. Optimal surgery and appropriate surgical staging is more likely to be performed if the surgeon is a gynecologic oncologist.
- Neoadjuvant chemotherapy followed by surgical cytoreduction and primary debulking

surgery followed by adjuvant chemotherapy may yield equivalent outcomes for patients with clinically advanced epithelial ovarian cancer. Primary debulking surgery is preferred for patients with a high likelihood of achieving optimal cytoreduction (no residual tumor greater than 1 cm).

- Important prognostic factors include stage, optimal compared with suboptimal cytoreduction, tumor grade (particularly for stage I cancers), poorer-risk histology such as clear cell or mucinous cancers, patient age, and performance status.
- Patients with favorable-risk, early-stage ovarian cancer (stage IA or IB, grade 1 or 2 cancers) do not require adjuvant chemotherapy after complete surgical staging.
- Patients with less-favorable-risk, early-stage ovarian cancer (stage IA or IB, grade 3; all stage IC; all clear cell carcinomas; and stage II cancers) should receive adjuvant platinum-based chemotherapy after complete surgical staging.

FIRST-LINE CHEMOTHERAPY FOR ADVANCED OVARIAN CANCER

A series of randomized, phase III trials have been conducted in advanced ovarian cancer, the results of which have established combination platinum (cisplatin or carboplatin) and taxane (paclitaxel or docetaxel) chemotherapy as the standard of care for first-line treatment. Results generally have shown a significant improvement in overall survival with combination platinum/taxane regimens.

Carboplatin and cisplatin are equally efficacious for ovarian cancer, but their adverse-effect profiles differ. Carboplatin is more myelosuppressive, but cisplatin has a greater risk for nausea, vomiting, neurotoxicity, and nephrotoxicity. Carboplatin has been considered easier to combine with paclitaxel since it is less likely to augment the risk of neurotoxicity from the paclitaxel. However, there are a number of different treatment doses and schedules for either platinum-based drug with paclitaxel that are acceptable for ovarian cancer treatment.

Approximately 60 to 80% of patients with advanced ovarian cancer experience an objective response to platinum/taxane treatment with improvement of disease-related symptoms. For women with advanced ovarian cancer who had optimal cytoreduction at surgery, median PFS is approximately 26 months, and overall survival is approximately 60 months. For patients with suboptimal cytoreduction or stage IV disease, median PFS is 18 months and median overall survival is 38 months.

Newer agents and alternative treatment schedules that have shown activity in recurrent disease are being investigated in the first-line setting for advanced ovarian cancer. The angiogenesis inhibitor bevacizumab, which achieved objective responses in patients with recurrent ovarian cancer, was tested in a phase III trial for first-line treatment of stage III and IV ovarian cancer (GOG 218).[112] In this randomized, placebo-controlled study, patients who were assigned to treatment with paclitaxel plus carboplatin with bevacizumab followed by bevacizumab maintenance had a PFS of 14.1 months compared with 10.3 months for the patients assigned to chemotherapy without bevacizumab and without bevacizumab maintenance. Overall survival was not improved (median survival, approximately 39 months in all three arms). A PFS advantage of similar magnitude was observed in a similarly designed European study (ICON7 [International Collaboration on Ovarian Neoplasms]), which employed a lower dose and shorter duration of bevacizumab treatment.[113] The oral antiangiogenic agent pazopanib also prolonged PFS (pazopanib, 17.9 months, vs. placebo, 12.3 months) when given

after response to platinum/taxane chemotherapy, but did not prolong overall survival.[114] Neither bevacizumab nor pazopanib is approved for first-line treatment of ovarian cancer as of June 2017.

Weekly paclitaxel (termed “dose-dense paclitaxel”) plus every-3-weeks carboplatin was compared with standard every-3-weeks paclitaxel plus carboplatin in a phase III trial. The weekly paclitaxel/every-3-weeks carboplatin schedule was associated with an overall survival advantage of 72% compared with 65% at 3 years.[115] GOG 262 was a similar study comparing weekly paclitaxel with carboplatin to every-3-week treatment.[116] In GOG 262, the use of bevacizumab was optional for patients in both study arms, and patients were stratified prior to randomization for bevacizumab use. Among the patients who did not receive bevacizumab (16% of patients enrolled), the weekly paclitaxel regimen was associated with longer PFS (14.2 months vs. 10.3 months); however, among the patients who did receive bevacizumab, there was no PFS difference between the two treatment schedules/dose intensities (14.7 months vs. 14.0 months). Patients in the dose-dense paclitaxel arm had similar quality-of-life scores but more anemia and a higher rate of peripheral neuropathy. Another trial, ICON8, was a 3-arm study comparing every 3-week IV carboplatin/paclitaxel vs. every-3-week carboplatin plus weekly paclitaxel vs. weekly carboplatin plus weekly paclitaxel. Results, reported in abstract form, showed no difference in PFS among the 3 arms.[117]

Liposomal doxorubicin plus carboplatin was not superior to paclitaxel plus carboplatin as first-line treatment for patients with stage IC to IV disease in terms of survival outcomes; quality-of-life outcomes were also similar in the two treatment arms.[118]

The optimal first-line treatment for mucinous carcinomas of the ovary has not been established. Some favor gastrointestinal-type regimens that include 5-fluorouracil or capecitabine, leucovorin, and oxaliplatin, although trials for this rare cancer have been difficult to conduct.[119] Similarly, the optimal treatment regimens for low-grade serous carcinomas has not been established, with some favoring taxane/carboplatin treatment and others favoring hormonal approaches.[120] Clear cell carcinomas are considered a higher-risk histology that may be less sensitive to taxane/platinum therapy. However, in a phase III trial for stage I to IV clear cell carcinoma patients, irinotecan/cisplatin was not superior to paclitaxel/carboplatin.[121]

In terms of surveillance for relapse in patients who experience a complete clinical remission (normal serum CA125 level and no evidence of disease by CT scan) with first-line treatment for ovarian cancer, a randomized trial showed that there was no survival or quality-of-life advantage to routine monitoring of CA125 for detection of relapse because early treatment on the basis of rising CA125 levels did not improve survival.[122] However, in the United States posttreatment surveillance with CA125 levels is still commonly used, despite a lack of proven benefit and the high cost.[123]

FIRST-LINE INTRAPERITONEAL CHEMOTHERAPY AFTER OPTIMAL CYTOREDUCTION

Several randomized, phase III clinical trials demonstrated an advantage for intraperitoneal cisplatin-based therapy compared with intravenous treatment. In a large phase III trial (GOG 172), patients with optimally cytoreduced stage III ovarian cancer were randomly assigned to receive intravenous cisplatin plus paclitaxel or intraperitoneal cisplatin plus intravenous and intraperitoneal paclitaxel.[124] Patients assigned to the intraperitoneal treatment arm had significantly longer PFS (23.8 months vs. 18.3 months) and overall survival (65.6 months vs. 49.7 months) compared with patients assigned to intravenous-only therapy. Toxicity was greater in the intraperitoneal arm, with an initial decrease in quality of life; however, at 1 year,

there were no quality-of-life differences between the two treatment arms.[125] The use of intraperitoneal chemotherapy varies among academic medical centers, and it is more commonly used in the United States than in Europe. Combined data from two large GOG studies show that among 806 patients, the overall survival advantage for intraperitoneal therapy extends longer than 10 years and the risk for death decreased with each cycle of intraperitoneal therapy completed.[126] A Japanese randomized trial of weekly intravenous paclitaxel plus carboplatin compared with every-3-week intravenous paclitaxel/carboplatin showed a PFS of 28.2 months with weekly paclitaxel compared with 17.5 months with every-3-week treatment.[127] These PFS results appear very similar to those achieved in the GOG 172 intraperitoneal chemotherapy arm (23.8 months). This cross-trial observation prompted a three-arm study (GOG 252) comparing intravenous carboplatin plus weekly paclitaxel, intraperitoneal carboplatin plus weekly paclitaxel, and intravenous paclitaxel plus intraperitoneal cisplatin plus intraperitoneal paclitaxel. All patients in each arm also received bevacizumab starting with cycle 2. Median PFS was about 27 months in all three arms.[128] Areas of active investigation include whether and how to incorporate bevacizumab, poly (adenosine diphosphate [ADP]–ribose polymerase) (PARP) inhibitors (discussed in the sections on Maintenance Therapy after First-Line Treatment and Treatment of Recurrent Ovarian Cancer), and immunotherapy in first-line treatment.

KEY POINTS

- Standard first-line therapy for patients with stage III and stage IV ovarian cancer is platinum/taxane combination chemotherapy. The addition of bevacizumab to every-3-week paclitaxel/carboplatin followed by bevacizumab maintenance was associated with modest improvement in progression-free but not overall survival. The addition of pazopanib following chemotherapy was also associated with a modest improvement in progression-free but not overall survival. As of November 2017, neither antiangiogenic agent is FDA-approved for use in first-line treatment of ovarian cancer.
- Patients with optimally cytoreduced, stage III ovarian cancer had a significant overall survival advantage when treated with a combination of intraperitoneal cisplatin plus intraperitoneal and intravenous paclitaxel compared to an all-intravenous every-3-week regimen. In a subsequent study, weekly dose-dense intravenous paclitaxel with every-3-week carboplatin delivery or intraperitoneal carboplatin plus intravenous weekly paclitaxel or intraperitoneal cisplatin plus intraperitoneal and intravenous paclitaxel all yielded similar outcomes. Cross-trial interpretation of the data is difficult because of the use of bevacizumab in most patients on the later phase III trial.
- Carboplatin and cisplatin are equally efficacious for advanced ovarian cancer, but have important differences in their adverse-effect profiles.
- Although surveillance testing with CA125 for patients in first complete clinical remission is commonly performed in the United States, a prospective, randomized trial has shown that CA125 monitoring did not improve quality of life or survival outcomes.

SECONDARY SURGICAL PROCEDURES IN FIRST-LINE MANAGEMENT

In addition to its importance in staging and primary cytoreduction for ovarian cancer, surgery has additional roles in the management of ovarian cancer. Patients for whom primary surgical cytoreduction was not recommended but whose disease exhibited a response to neoadjuvant chemotherapy may be candidates for surgical resection of residual macroscopic disease. A European randomized trial demonstrated a survival advantage with interval surgical cytoreduction, performed after three cycles of cytotoxic drugs, for women with advanced ovarian cancer who had evidence of an initial response to chemotherapy and who have not had an initial attempt at complete surgical cytoreduction.[129] In contrast, GOG conducted a randomized trial to determine whether secondary surgery was beneficial for patients who had an initial attempt at complete cytoreduction but whose tumors were suboptimally debulked. In these patients, a second attempt at cytoreduction for those who were stable or improved with cisplatin plus paclitaxel was not superior to continued chemotherapy.[130]

In the past, some patients underwent a second surgery after the completion of chemotherapy to determine whether there had been a complete pathologic response to treatment (second-look laparotomy). A negative second look was defined as no visible disease and no microscopic evidence of disease on multiple biopsies from the abdominal cavity. Although second-look laparotomy provided prognostic information (patients with no microscopic evidence of disease on biopsy have longer overall survival than patients with microscopic or visible residual disease after chemotherapy), it did not improve survival outcomes and is no longer recommended as a standard part of ovarian cancer treatment.

MAINTENANCE THERAPY AFTER FIRST-LINE TREATMENT

Disease will recur in approximately 70% of women with advanced ovarian cancer who have a clinically defined complete response to standard chemotherapy with a platinum agent and a taxane. A number of studies have been conducted to determine whether consolidation or maintenance chemotherapy in the first-line setting can improve overall survival. In a large, prospective, randomized trial, women who had a complete clinical response to platinum/taxane first-line treatment were randomly assigned to receive three additional cycles of monthly paclitaxel or 12 additional monthly cycles.[131] Patients assigned to receive 12 cycles of consolidation paclitaxel had a median PFS of 28 months compared with a median of 21 months for patients assigned to receive three cycles. Data were premature for any demonstrable overall survival benefit, and early closure of this study means that survival data are unlikely to be meaningful. Patients who continue on prolonged paclitaxel treatment continue to have alopecia and are at risk for developing worsening peripheral neuropathy.

As detailed in the discussion of first-line treatment, GOG 218 and ICON7 showed that maintenance bevacizumab after first-line treatment with paclitaxel plus carboplatin plus bevacizumab provided an approximate 3.5-month improvement in PFS compared with the no-bevacizumab treatment arm. Similarly, as above, pazopanib given as maintenance therapy to responding patients following paclitaxel/platinum first-line treatment had improved progression-free but not overall survival. In contrast, consolidation with the epidermal growth factor receptor (EGFR)–targeted agent erlotinib did not improve survival outcomes after first-line platinum-based chemotherapy for patients with stage I, II, III, or IV ovarian cancer. No subgroup (EGFR status by immunohistochemistry, EGFR mutation, erlotinib rash) was found to benefit from erlotinib.[132] To date, consolidation with other chemotherapy agents has not been shown to be beneficial. The role of maintenance treatment with PARP inhibitors following first-line treatment of ovarian cancer is under active investigation.

KEY POINTS

- Consolidation treatment with paclitaxel provides a moderate prolongation of PFS at the cost of continued alopecia and increased risk for neuropathy.
- The addition of bevacizumab to paclitaxel/carboplatin followed by bevacizumab maintenance in first-line therapy of advanced ovarian cancer provides a modest prolongation in PFS but no overall survival advantage. Similarly, pazopanib given as maintenance after first-line paclitaxel/carboplatin improved progression-free but not overall survival. Neither bevacizumab nor pazopanib is FDA-approved, as of November 2017, for use in first-line treatment of ovarian cancer.
- Consolidation with other chemotherapy agents for patients in first clinical remission at completion of first-line platinum/taxane treatment has not been shown to be beneficial.
- The use of PARP inhibitors in first-line maintenance therapy is currently under investigation.

TREATMENT OF RECURRENT OVARIAN CANCER

Recurrent ovarian cancer is often classified according to whether the recurrent disease is platinum-refractory (defined as progressing during treatment with platinum-based therapy), platinum-resistant (defined as progressing within 6 months of completing first-line platinum-based therapy), potentially/intermediate platinum-sensitive (defined as progression more than 6 months but fewer than 12 months after completing first-line platinum-based therapy), or platinum-sensitive (defined as recurrence 12 months or more after the completion of first-line platinum-based therapy). In approximately 20% of women, advanced ovarian cancer does not respond to first-line treatment with platinum/taxane combination chemotherapy. These patients with platinum-refractory disease have a very poor prognosis and a very low likelihood of achieving an objective response to second-line therapy; they are excellent candidates for clinical trials of novel agents.

Platinum-Sensitive Recurrent Disease

Some patients with recurrent, platinum-sensitive ovarian cancer may be offered secondary cytoreduction surgery, particularly those who are likely to have a complete gross resection and who have had a relatively long disease-free interval. In a phase III trial, patients with platinum-sensitive recurrent ovarian cancer (6 or more months after last platinum treatment), good performance status, a prior complete resection and no or only low-volume ascites, were randomly assigned to cytoreductive surgery followed by platinum-based combination chemotherapy or to no surgery with immediate platinum-based combination chemotherapy. Patients assigned to surgical cytoreduction followed by chemotherapy had a significantly longer PFS compared to those treated with chemotherapy alone (19.6 months vs. 14 months).[133] GOG 213 is another prospective trial designed to study the same research question. Patients with platinum-sensitive recurrent ovarian cancer who are potential candidates for surgery are randomly assigned to secondary cytoreduction surgery followed by paclitaxel/carboplatin chemotherapy or to paclitaxel/carboplatin chemotherapy without surgery. GOG 213 differs from the DESKTOP III study in that patients were also assigned to receive or to not receive

bevacizumab in combination with paclitaxel/carboplatin. The overall survival data for the surgery research question in this study are not yet mature. The results of the chemotherapy research question are discussed as follows.

Patients who experience response to first-line treatment followed by progression or recurrence have a better prognosis than patients with platinum-refractory or platinum-resistant disease. They may enter a second complete clinical remission, although essentially all patients will ultimately recur again. Treatment options and prognosis are linked to the duration of disease control achieved with first-line treatment. Platinum-sensitive patients have a high likelihood of response to retreatment with platinum-based therapy. Randomized trials have shown that platinum-based combination therapy (carboplatin/gemcitabine or carboplatin/paclitaxel) is superior to a single-agent platinum for this patient population, and liposomal doxorubicin plus carboplatin was superior to paclitaxel plus carboplatin in terms of PFS (11.3 months vs. 9.4 months) and toxicity profile.[134]

The PARP inhibitor rucaparib was studied as monotherapy in a phase II trial for three separate cohorts of patients with platinum-sensitive recurrent ovarian cancer: *BRCA* mutant (germline or somatic), *BRCA* wild-type with loss of heterozygosity-high (LOH-H), and BRCA wild-type with LOH-low (LOH-L). Median progression-free survival was 12.8 months in the *BRCA* mutant cohort, 5.7 months in the LOH-H group, and 5.2 months in the LOH-L group. This study served to show that PARP inhibition may be effective in LOH-H ovarian cancers in addition to *BRCA* mutant tumors.[135] Despite this phase II study showing rucaparib activity in platinum-sensitive recurrent ovarian cancer, most patients in first platinum-sensitive relapse are treated with platinum combination chemotherapy.

Augmenting and maintaining response after platinum-based treatment in patients with platinum-sensitive disease is an area of active investigation, since nearly all patients who have had one recurrence will subsequently relapse again even if they enter a second complete clinical remission. In a phase III trial comparing gemcitabine plus carboplatin with or without bevacizumab, followed by bevacizumab maintenance for platinum-sensitive recurrent ovarian cancer, PFS was superior in the group assigned to receive bevacizumab (12.4 months with bevacizumab vs. 8.4 months with placebo).[136] Similarly, in GOG 213, (as above, the study assessing the role of surgery prior to chemotherapy for platinum-sensitive recurrence), patients were randomly assigned for the chemotherapy portion of the study to carboplatin/paclitaxel with or without bevacizumab followed by bevacizumab maintenance. In this study, the addition of bevacizumab to carboplatin/paclitaxel followed by bevacizumab maintenance improved progression-free (13.8 months with bevacizumab vs. 10.4 months without bevacizumab) and overall survival (42.2 months with bevacizumab vs. 37.3 months without). The addition of bevacizumab was associated with a statistically significant increased risk for intestinal perforation, venous thrombosis, and infection.[137] In 2016, bevacizumab was FDA-approved for treatment in combination with either gemcitabine/carboplatin or paclitaxel/carboplatin followed by bevacizumab maintenance in platinum-sensitive recurrent ovarian cancer.

PARP inhibition has also been studied as maintenance therapy after response to platinum-based therapy for platinum-sensitive recurrent ovarian cancer. In a blinded, placebo-controlled trial of patients unselected for *BRCA* mutation status, maintenance treatment with the PARP inhibitor olaparib following response to platinum-based therapy was superior to placebo for PFS (8.4 months with olaparib vs. 4.8 months with placebo), but there was no difference in overall survival.[138] These results have been confirmed in a subsequent phase III trial (SOLO-2) in which maintenance treatment with oral olaparib following response to platinum-based chemotherapy in patients with germline *BRCA1* or *BRCA2* mutations was associated with a

PFS of 19 months (olaparib maintenance) compared with 5.5 months (placebo).[139] Olaparib is FDA-approved as monotherapy for patients with germline *BRCA* mutations who have received three or more lines of therapy, and, as of August 2017, it is approved for maintenance treatment following platinum-based therapy for platinum-sensitive disease in the United States.

Another PARP inhibitor, niraparib, was also studied as maintenance treatment in patients whose recurrent ovarian cancer was responsive to platinum-based therapy for platinum-sensitive recurrent disease. In this study (ENGOT-OV16/NOVA), niraparib was associated with improved PFS, regardless of germline *BRCA* mutation status or homologous recombination deficiency status, although the benefit was much greater in the cohorts of patients with *BRCA* mutations (21 months vs. 5.5 months) or homologous recombination deficiency (12.9 months vs. 3.8 months), compared to patients with neither (6.9 months vs. 3.8 months).[140] Niraparib was approved by the FDA in 2017 as maintenance therapy following response to platinum-based therapy in platinum-sensitive recurrent ovarian cancer. Rucaparib, currently FDA-approved as monotherapy for recurrent disease after at least two lines of therapy in patients with germline or somatic *BRCA* mutations has also been studied in a placebo-controlled, phase III trial (ARIEL3) as maintenance therapy following platinum-based therapy for platinum-sensitive disease (NCT01968213). Results showed that PFS was prolonged with rucaparib compared to placebo in both the *BRCA* mutated cohort and the homologous repair–deficient cohort.[141]

Patients re-treated with carboplatin should be cautioned about the risk for acquired platinum allergy. Carboplatin is associated with an acquired hypersensitivity, generally seen in patients who have had multiple prior cycles of this drug. Reactions can range from minor itching and rash to respiratory distress, hypotension, and anaphylactic shock.

Low-grade serous carcinomas of the ovary differ from high-grade serous cancer in several ways, including frequent expression of hormone receptors. Maintenance treatment with an aromatase inhibitor following response to platinum-based chemotherapy has been associated with longer PFS compared to no maintenance therapy in this histologic subgroup of ovarian cancers.[142]

Platinum-Resistant Recurrent Disease

A number of chemotherapy agents can achieve objective responses for a minority of patients with platinum-resistant disease (generally, 10 to 20%). Among the agents with demonstrated activity in recurrent ovarian cancer are liposomal doxorubicin, topotecan, gemcitabine, docetaxel, weekly paclitaxel, oral etoposide, cyclophosphamide, pemetrexed, irinotecan, vinorelbine, bevacizumab, and PARP inhibitors. Patients with low-volume, or “elevated CA125-only,” recurrent disease may experience disease control with the use of hormone agents such as tamoxifen.[143] Bevacizumab in combination with either weekly paclitaxel or liposomal doxorubicin or topotecan has also been shown to improve response and PFS among patients with platinum-resistant ovarian cancer who have received no more than two prior regimens, and it is FDA-approved for this indication.[144]

For patients with an intermediate interval of time from completion of first-line platinum-based treatment (more than 6 months to less than 12 months), the response rate to platinum-based therapy is greater than 20%. While treatment with platinum or nonplatinum single agents has been considered appropriate for this group, a prospective, randomized study showed that there was no benefit to delaying platinum therapy in this group of patients by treating with nonplatinum therapy first.[145]

As previously discussed, PARP inhibitors are active in ovarian cancer, particularly in *BRCA* mutant cancers, but also in tumors with homologous repair deficiency. In a phase II trial of olaparib restricted to patients who carried germline *BRCA1* or *BRCA2* mutations, among the 195 patients with recurrent, platinum-resistant, heavily pretreated ovarian cancer (median number of prior therapies, 4.3), there were 60 objective responses (31%) and median PFS among the patients with ovarian cancer was 7 months.[146] Olaparib is approved in the United States for use as fourth-line single-agent therapy for recurrent ovarian cancer in patients with germline *BRCA1* or *BRCA2* mutations. Olaparib is also approved for patients with germline *BRCA1* or *BRCA2* mutations as maintenance therapy for platinum-sensitive recurrent ovarian cancer after a response to platinum-based chemotherapy (previously discussed).

The PARP inhibitor rucaparib is FDA-approved for treatment of patients with recurrent ovarian cancer who have had two or more lines of therapy and who have a deleterious *BRCA* mutation (germline or somatic). Objective responses were higher in platinum-sensitive (66%) compared to platinum-resistant (25%) tumors, and there were no responses in platinum-refractory tumors. PARP inhibitors may cause nausea, myelosuppression, and elevations in transaminases, and there have been rare cases of myelodysplasia and acute leukemia.

Most patients with recurrent ovarian cancer will receive a series of chemotherapy regimens throughout the course of their disease. The median time for disease control with any given agent is approximately 4 to 6 months. Treatment options differ in dosing schedules and adverse-effect profiles. Choices among the agents can be individualized according to prior treatments received, existing toxicities and comorbidities, patient convenience, *BRCA* mutation status, and patient preferences. All patients with refractory or recurrent ovarian cancer are appropriate candidates for clinical trial participation because no current strategy is known to result in long-term disease control or cure.

Patients who develop organ dysfunction from progressive ovarian cancer may be palliated by selected interventions such as paracentesis for relief of large-volume ascites, thoracentesis/pleurodesis for symptomatic pleural effusion, ureteral stent placement for hydronephrosis, bowel surgery/diversion for small or large bowel obstruction, or decompressing gastrostomy for persistent, symptomatic small-bowel obstruction.

KEY POINTS

- For patients with platinum-sensitive recurrent ovarian cancer, combination carboplatin-based treatment is appropriate. The longer the platinum-free interval, the higher the chance for objective response.
- The addition of bevacizumab to carboplatin/gemcitabine or to carboplatin/paclitaxel, followed by bevacizumab maintenance, improves PFS compared with chemotherapy alone in the treatment of first-recurrent, platinum-sensitive disease and is FDA-approved for this indication.
- PARP inhibitors (olaparib, rucaparib, and niraparib) have shown prolongation of PFS as maintenance therapy following response to platinum-based treatment of platinum-sensitive recurrence.
- Single-agent, nonplatinum agents (liposomal doxorubicin, gemcitabine, topotecan, weekly paclitaxel, oral cyclophosphamide, and others) achieve objective responses in 10 to 20%

of patients whose recurrence is less than 6 months from completion of first-line platinum-based therapy (platinum-resistant recurrent ovarian cancer).

- Bevacizumab combined with either liposomal doxorubicin or weekly paclitaxel or topotecan improves response rate and PFS compared with chemotherapy alone and is FDA-approved for this indication.
- Olaparib is a PARP inhibitor that is approved for the treatment of recurrent ovarian cancer as single-agent, fourth-line therapy in patients with deleterious germline *BRCA* mutations.
- Rucaparib is a PARP inhibitor that is approved as single-agent treatment for recurrent ovarian cancer following two or more lines of treatment, in patients with deleterious germline *BRCA* mutations or somatic *BRCA* mutations.
- In selecting from among treatment options for platinum-resistant recurrent ovarian cancer, the physician should consider patient performance status, adverse-effect profile of the agents, prior treatments, *BRCA* mutation status, dosing schedule, preexisting persistent toxicities, and patient preferences.

LOW MALIGNANT POTENTIAL TUMORS OF THE OVARY

Low malignant potential (LMP) tumors, also known as borderline ovarian tumors, are noninvasive ovarian cancer. Patients with LMP who wish to preserve fertility can undergo fertility-sparing surgery. All areas of visible tumor involvement should be removed at the time of surgery and carefully reviewed by the pathologist to confirm that there is no evidence of invasive disease. Patients who do not desire preservation of fertility may undergo standard surgical staging for ovarian cancer. Most women with LMP tumors have early-stage disease at diagnosis, and the 5-year overall survival rates for such patients are greater than 95%; PFS is greater than 80%. There is no evidence that adjuvant therapy (chemotherapy or radiotherapy) is beneficial for patients with LMP tumors of any stage if pathology review confirms that there is no evidence of invasive implants. Five-year overall survival rates for patients with stage III or IV LMP tumors are approximately 90%, and PFS rates are more than 65%.[147] Patients who are found to have histologic evidence of invasive cancer may be considered for adjuvant chemotherapy, as would be offered to patients with invasive epithelial ovarian cancer; however, data for this rare situation are limited.

KEY POINTS

- Patients with low malignant potential tumors may undergo fertility-sparing surgery if fertility preservation is desired.
- LMP tumors without evidence of invasive implants are not treated with adjuvant chemotherapy.

NONEPITHELIAL CANCERS OF THE OVARY

About 10% of cancers of the ovary are nonepithelial cancers. These tumors are classified as

either sex-cord stromal cell tumors of the ovary or germ cell tumors. Each of these groups is further subclassified by histology. These tumors differ markedly from epithelial ovarian cancer in prognosis and treatment. Sex-cord stromal tumors may be associated with familial syndromes. For example, Sertoli–Leydig cell tumors are associated with *DICER1* mutations, and sex-cord stromal tumors with annular tubules are associated with Peutz–Jeghers syndrome and *STK11* mutations.[148]

An additional rare subtype of ovarian cancer is small cell carcinoma, hypercalcemic type. The cell of origin of this tumor is still controversial. Nearly all women with this rare type of ovarian cancer are younger than age 40 (average, 23) and the median survival is less than 1 year. Recent studies report a genetic predisposition to small cell carcinoma of the ovary, hypercalcemic type. Recurrent germline and somatic mutations of *SMARCA4* have been identified and are considered to be the driver of this rare, aggressive subtype of ovarian cancer.[149]

SEX-CORD STROMAL CELL TUMORS OF THE OVARY

The sex-cord stromal tumors are subclassified as granulosa cell tumors and the androgen-producing tumors such as Sertoli–Leydig cell tumors. Serum levels of inhibin, estradiol, testosterone, and AFP may be elevated in patients presenting with an ovarian sex-cord stromal tumor.

Adult-type granulosa cell tumors are generally stage I at diagnosis and are diagnosed in women ages 40 to 70. Most granulosa cell tumors have a somatic mutation in *FOXL2,* which may be useful in diagnosis.[150] Serum inhibin levels, particularly inhibin B, may be elevated in granulosa cell tumors and should be measured as part of the disease evaluation. Since granulosa cell tumors frequently produce estrogen, women may have abnormal uterine bleeding, endometrial hyperplasia, and a concurrent endometrial cancer. The treatment for granulosa cell tumors is surgical resection. Patients with early-stage disease who desire fertility preservation may undergo fertility-sparing surgery. If the uterus is not removed, an endometrial biopsy should be done to rule out concurrent endometrial cancer. Patients who have completed childbearing should undergo hysterectomy and bilateral salpingo-oophorectomy. Adjuvant chemotherapy is not generally administered after complete resection of newly diagnosed disease. Granulosa cell tumors may recur, and it is typical for recurrences to be years or decades later. There are some data supporting the use of combination platinum-based chemotherapy for patients with recurrent, unresectable disease.[151,152] In a phase II study, bevacizumab achieved an objective response in 6 of 36 patients and yielded a median PFS of 9 months.[153]

Sertoli–Leydig tumors commonly present before age 40. More than 90% are stage I at diagnosis, and women can be offered fertility-sparing surgery. Androgen production can lead to virilization, hirsutism, and menstrual changes. Serum levels of testosterone and/or AFP may be elevated. Five-year survival rates are 70 to 90%, with prognosis related to stage and degree of tumor differentiation. Patients with advanced-stage disease have an unfavorable prognosis. Platinum-based chemotherapy may be considered for patients with poorly differentiated tumors and for patients with advanced or recurrent disease.

GERM CELL TUMORS OF THE OVARY

Germ cell tumors of the ovary usually affect adolescent girls and young women. Fertility-sparing surgery is appropriate for most patients. Fifty percent of germ cell tumors are

dysgerminomas; other histologies include yolk sac tumors, immature teratomas, embryonal cell tumors, nongestational choriocarcinomas, and mixed tumors. Dysgerminomas are more likely to be confined to one ovary at diagnosis (stage I) and carry a favorable prognosis. Patients with stage I dysgerminomas who have had complete staging surgery (with or without fertility preservation) do not require chemotherapy. Similarly, patients with stage I, grade 1 immature teratomas can be treated with surgery only. All other nondysgerminomas and higher-stage dysgerminomas should be treated with chemotherapy after surgical resection. Standard treatment is combination platinum/etoposide-based therapy, with most data supporting three to four cycles of bleomycin, etoposide, and cisplatin. With chemotherapy for these higher-risk germ cell tumors, patient outcomes are excellent. In a GOG study, 93 patients with completely resected nondysgerminoma received three cycles of bleomycin, etoposide, and cisplatin; 91 of 93 patients (96%) remained disease-free, with follow-up ranging from 4 to 90 months.[154] Serum levels of human chorionic gonadotropin (hCG) and alpha-fetoprotein (AFP) may be elevated in some germ cell tumors at diagnosis and can be used in follow-up monitoring. Most patients who have had fertility-sparing surgery either continue to menstruate during chemotherapy or resume normal menstrual cycles after completion of chemotherapy. The majority of women remain fertile, and pregnancy outcomes are favorable.

KEY POINTS

- Granulosa cell tumors are the most common sex-cord stromal tumors of the ovary. Estrogen production by the tumor may lead to endometrial hyperplasia with abnormal uterine bleeding; some patients have concurrent endometrial carcinomas. Serum inhibin B levels may be elevated in patients with granulosa cell tumors, and tumors show somatic *FOXL2* mutations.
- Granulosa cell tumors are commonly diagnosed at an early stage, and treated with surgical resection. Recurrences may occur many years after the initial diagnosis.
- Sertoli–Leydig cell tumors are usually early-stage at diagnosis and may be treated with fertility-sparing surgery. Serum testosterone levels may be elevated, and patients may present with virilization, hirsutism, and menstrual abnormalities.
- Dysgerminomas are good-risk germ cell tumors of the ovary. Patients with stage I dysgerminoma do not require chemotherapy. Nondysgerminomas (except stage I, grade 1 immature teratoma) have a high risk of recurrence unless adjuvant chemotherapy is administered. Patients with higher-stage dysgerminoma and patients with nondysgerminomas (except stage I, grade 1 immature teratoma) should receive combination platinum/etoposide-based chemotherapy. Fertility-sparing surgery is appropriate for most patients with ovarian dysgerminomas who desire fertility preservation.

GESTATIONAL TROPHOBLASTIC DISEASE

Gestational trophoblastic diseases are diseases of the human placenta that occur in women of childbearing age. There is a spectrum of malignant potential, from lesions with very low malignant potential (complete and partial hydatidiform moles) to invasive tumors with metastatic

potential (invasive moles and placental-site trophoblastic tumors) to tumors with exceedingly high risk for systemic metastases (gestational choriocarcinoma). Despite the risk for metastatic disease, nearly all women with gestational trophoblastic disease can be cured with the appropriate use of chemotherapy and with careful monitoring for treatment response, and with surveillance for evidence of relapse using sensitive beta-hCG assays.[155] A major role of the oncologist is to consider the possibility of gestational trophoblastic disease in women of childbearing age who present with a diagnosis of metastatic cancer.

Malignant gestational trophoblastic disease is classified as either nonmetastatic (disease is limited to the uterus) or metastatic. Patients with metastatic disease are further classified as low-risk (good prognosis) or high-risk (poorer prognosis). Risk assessment incorporates such variables as patient age, type of antecedent pregnancy, interval of time from the antecedent pregnancy, hCG level, largest tumor size, metastatic sites, number of metastases, and prior chemotherapy. Treatment recommendations are based on risk assessment. Most patients are candidates for a fertility-sparing approach. Patients with low-risk disease may be treated with single-agent methotrexate or dactinomycin.[155] For patients with high-risk disease, combination chemotherapy is administered, usually incorporating etoposide, methotrexate, and dactinomycin, alternating with cyclophosphamide and vincristine (EMA-CO). Response to chemotherapy is assessed by frequent assessment of the quantitative level of the serum hCG. Treatment is continued for several cycles after a negative hCG is achieved. Patients who began with low-risk disease but have a plateau or rising hCG on therapy may need to move to a higher-risk treatment regimen such as EMA-CO. Patients who do not achieve complete response on EMA-CO may be salvaged with platinum-based combination chemotherapy. Patients with high-risk disease and a high disease burden are at risk for potentially fatal bleeding or other serious events during the first cycle of treatment.

Placental-site trophoblastic tumors (PSTT) are high risk germ cell tumors. Most patients with PSTT will require hysterectomy. In patients with PSTT the hCG is low relative to the metastatic tumor burden. PSTT is staged using anatomic FIGO staging rather than the risk assessment parameters previously outlined.

KEY POINTS

- Gestational trophoblastic disease is highly curable, even when there is metastatic disease at presentation.
- The quantitative hCG level is followed to assess response to treatment, determine the development of treatment resistance, and evaluate for disease recurrence.

VULVAR CANCER

Ninety percent of vulvar carcinomas are squamous cell carcinomas. There are about 4000 cases annually in the United States, and these occur mostly in postmenopausal, older women. Risk factors include smoking, vulvar dystrophy, HPV infection, a prior history of cervix cancer, and immunodeficiency syndromes. Most vulvar cancers are localized at the time of diagnosis and managed with complete surgical resection of the primary tumor. For tumors with ≤ 1 mm of invasion, wide deep local resection may be adequate, followed by observation. For tumors with > 1 mm of invasion, radical or modified radical vulvectomy with assessment of lymph node

involvement is considered standard. Sentinel lymph node biopsies are increasingly incorporated in the surgical approach to vulvar cancer in order to decrease the morbidity associated with inguinofemoral lymphadenectomy. Patients with completely resected disease (with negative margins) and with negative lymph nodes may be observed. Patients with positive margins despite reexcision may be treated with adjuvant external-beam radiation. Five-year survival rates are estimated to be 70 to 93%. Patients with lymph node involvement are at greater risk for recurrence and death (5-year survival rate 25 to 41%) and are recommended to have adjuvant external-beam radiation or chemoradiation.[156] Similarly, patients with locally advanced disease that cannot be completely resected are treated with primary chemoradiation. Patients who have an excellent clinical response to chemoradiation may subsequently be considered for resection of residual disease if such resection is feasible and the patient is medically fit for surgery. Chemotherapy agents for use in chemoradiation for vulvar cancer include cisplatin and 5-fluorouracil.

Patients with locally recurrent disease should be considered for reexcision. Radiation may be considered if the recurrence is not resectable and the patient has not had prior radiation. Patients with multisite, unresectable metastatic disease may be offered palliative chemotherapy, although there are no prospective data evaluating the efficacy of systemic chemotherapy for metastatic vulvar cancer. Agents such as cisplatin, carboplatin, paclitaxel, vinorelbine, and erlotinib[157] are reasonable options for patients who are fit for chemotherapy.

The second most common cancer of the vulva is melanoma.

VAGINAL CANCER

Like vulvar cancer, most vaginal carcinomas are squamous cell carcinomas and are associated with HPV infection. Other risk factors include smoking, early age at first intercourse, multiple lifetime sexual partners, and a history of prior cervix cancer. Other histologies of vaginal cancer are rarer and include clear cell carcinoma (in utero diethylstilbestrol exposure increases the risk for vaginal–cervical clear cell cancers), melanoma, sarcoma, and adenocarcinoma. It is important to consider metastatic or recurrent disease from other sites (cervix, vulva, ovary, breast, endometrium, or uterus) in the evaluation of a new vaginal lesion, since metastatic disease is more common than primary vaginal carcinoma.

Most women with vaginal cancer present with abnormal bleeding. Diagnosis is established by biopsy. Colposcopy may be required to visualize the lesion. There are no prospective studies upon which to base treatment recommendations for vaginal carcinomas. Both surgery and radiation can be difficult because of the proximity of the bladder, urethra, and rectum. Only some stage I vaginal cancers can be managed surgically because of the proximity of these other structures. Small, upper vaginal lesions may be treated with surgery or radiation. For vaginal cancers that invade the paravaginal tissues but do not extend to the pelvic side wall, treatment with radiation can be considered; or treatment with platinum-based chemotherapy may achieve sufficient response to permit resection.[158]

For patients with more extensive, locally advanced disease, radiation or platinum-based chemoradiation is reasonable. Although there are no prospective comparison data showing chemoradiation to be superior to radiation alone, many physicians extrapolate the data from randomized trials in cervix cancer, and interpret data from retrospective studies in vaginal cancer, to support the recommendation of chemoradiation.

As with cervix cancer, patients with a central recurrence may be considered for pelvic exenteration surgery. Patients with unresectable, metastatic disease may be offered palliative

cytotoxic chemotherapy, but there are no prospective data to establish which agents are active.

GYNECOLOGIC CANCER IN THE ELDERLY

Currently, approximately half of women with ovarian cancer and endometrial cancer are older than age 65 at diagnosis. The proportion of patients with gynecologic cancers who are elderly will increase as the U.S. population ages. Older patients are underrepresented in clinical trials, and extrapolation of clinical trial–defined treatments to older patients may not always be appropriate.[159] Survival outcomes tend to be poorer among elderly patients.

A study of cervix cancer outcomes among elderly women showed that women older than age 70 were less likely to undergo surgery for early-stage disease or to have lymph node dissection performed with surgery. Survival rates for patients with potentially curable stage cervix cancers were significantly lower for women older than age 70 compared with younger women with same-stage disease.[160]

In a large cohort of women with high-grade endometrial cancer, women older than age 75 were less likely to receive surgery, chemotherapy, or radiation than their counterparts younger than age 55.[161]

Survival rates for ovarian cancer have also been shown to be worse in older women. It is difficult to determine whether the poorer outcomes in elderly patients with gynecologic cancers is attributable to inherent aggressiveness of the disease, poorer tolerance for treatment, comorbidities, or physician bias that leads to suboptimal treatment. It can be difficult to distinguish between underuse of potentially curative chemotherapy and appropriate reduction of treatment duration or dose intensity for toxicities and comorbidities when evaluating retrospective data of treatment outcomes in older women with gynecologic cancers. Geriatric assessment tools have been shown to predict the risk for severe treatment-related toxicities and survival outcomes.[162] The prospective use of such tools in clinical trials may help in developing age-appropriate treatment strategies to optimize outcomes. In a study of 212 women age 70 or older, patients with high Instrumental Activities of Daily Living scores were more likely to complete planned chemotherapy and less likely to experience significant treatment toxicities.[163]

SURVIVORSHIP

Survivorship issues for patients with gynecologic cancer range from loss of fertility, development of early menopause, risk for second malignancies, coping with persistent or late toxicities of treatment, and managing posttreatment depression, anxiety, and fear of recurrence. More detailed discussion of some of these issues may be found in Chapter 21 Symptom Management.

FERTILITY

For women who desire to maintain future fertility options and for whom the cancer survival prognosis is good, medical and gynecologic oncologists should consider whether egg-retrieval interventions may be appropriate prior to surgery, radiation, or chemotherapy interventions that would render the woman infertile. Some patients with early-stage cervix cancer, some with early-stage epithelial ovarian cancers, and most with sex-cord stromal tumors, germ cell tumors, and gestational trophoblastic tumors, may be candidates for fertility-sparing surgery. Young women with stage I, grade 1 endometrial cancer may be candidates for uterine conservation with progesterone treatment. Depending on patient age and whether postsurgery

treatments such as radiation and chemotherapy may be needed, egg retrieval prior to surgery may need to be considered even for patients who will have fertility-sparing surgeries.

MENOPAUSAL SYMPTOMATOLOGY

The decision about use of systemic posttreatment hormone-replacement therapy should be individualized, considering the patient's age, severity of menopausal symptoms, potential hormone-sensitivity of the cancer, and potential risks of hormone-replacement therapy (breast cancer, thromboembolism, stroke). In a placebo-controlled, randomized trial, oral estrogen-replacement therapy was not associated with increased recurrence risk in women who had undergone surgery for stage I or II endometrial cancer.[164] A meta-analysis suggested that hormone therapy in women with a history of ovarian cancer was not associated with an increased risk of ovarian cancer recurrence.[165] Although prospective data are lacking, in gynecologic cancers that are more likely to be hormonally driven, such as low-grade serous cancers, granulosa cell tumors, and low malignant potential tumors, hormone-replacement therapy/estrogen therapy would pose greater concerns.

For women whose main symptom is vaginal dryness/dyspareunia, local treatment options such as water-based lubricants or vaginal estrogens may be appropriate. Vaginal estrogen use has been associated with a lower likelihood of sexual dysfunction among women who have had RRSO.[166] Patients should be informed that there are some data showing systemic absorption of vaginal estrogens.[167] Another option is application of topical lidocaine to the vulvar vestibule prior to vaginal penetration.[168]

For patients with hot flashes who need a nonhormonal treatment, prospective clinical trials support the use of selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, gabapentin, and acupuncture.[169] Physicians should also consider other issues related to early menopause such as increased risk for osteoporosis.

RISK FOR SECOND MALIGNANCIES

As addressed in other sections of this chapter, ovarian cancer survivors with a *BRCA1* or *BRCA2*-associated heritable risk for ovarian cancer require appropriate screening or consideration of prophylactic surgery to manage their risk for breast cancer. Ovarian cancer and endometrial cancer survivors who have Lynch syndrome (HNPCC) require appropriate screening for other HNPCC-related malignancies. Rarely, chemotherapy or PARP-inhibitor treatment or chemotherapy/radiation treatments have been associated with second malignancies such as myelodysplastic syndromes or acute leukemia. Sarcomas have been reported following pelvic radiation for gynecologic cancer.

PERSISTENT AND LATE TOXICITIES

Taxane-induced peripheral neuropathy can be a chronic problem for gynecologic cancer survivors. Risk for severe neuropathy may be higher in older patients and in obese and diabetic patients. Some studies have identified a single nucleotide polymorphism that may predict severe taxane-induced neuropathy, although it is not yet known how this information should be used in clinical decision-making.[170] Patients who have received cisplatin or carboplatin may have ongoing renal electrolyte losses requiring long-term potassium or magnesium repletion. Ototoxicity is an uncommon, but irreversible, toxicity of platinum treatment. Patients who have received pelvic radiation are at higher risk for urinary frequency, diarrhea, incontinence, rectal

bleeding, radiation proctitis, radiation cystitis, vaginal agglutination, and dyspareunia, which may be late in onset and chronic in duration. Patients who have undergone lymph node dissection are at increased risk for lymphedema, and the risk is increased if pelvic radiation is required after nodal dissection.

COPING WITH FEAR OF RECURRENCE

Gynecologic cancer survivors may have ongoing challenges with psychosocial health. Studies have reported high levels of distress, depression, and anxiety, which may be ameliorated with good social support.[16] There is a need for research to define disease recurrence surveillance strategies that will optimize quality of life and minimize fear of recurrence among survivors of gynecologic cancer.

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MELANOMA

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Recent Updates

- The staging system has been updated to reflect the latest AJCC version, effective as of 2018. (*AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017)
- TVEC, a first-in-class oncolytic viral therapy, was approved by the FDA for intra-tumoral injection in patients with locally advanced melanoma. (Leiter U, *Lancet Oncol* 2016)
- DeCOG and MSLT-II studies assessed the benefit of completion lymph node dissection in patients with a positive sentinel lymph node, with no survival advantage for completion dissection observed in either trial. (Faries MB, *N Engl J Med* 2017)
- Adjuvant nivolumab was approved for the treatment of resected stage IIIB, IIIC, or IV melanoma. (Weber J, *N Engl J Med* 2017; FDA. FDA grants regular approval to nivolumab for adjuvant treatment of melanoma, 2017)

OVERVIEW

This chapter outlines the clinical and pathologic features of melanoma, the evaluation and management of patients with early- and advanced-stage disease, and provides details of therapeutic advances in systemic therapy. Rapid advances in immune therapy have significantly improved survival of patients with advanced metastatic melanoma.

EPIDEMIOLOGY

Current estimates are that invasive melanoma will develop in 1 of every 28 men and 1 of every 44 women in their lifetime. In the United States in 2017, an estimated 87,110 new cases of invasive melanoma were diagnosed, with 9730 estimated deaths as a result of melanoma.[1] The incidence of melanoma continues to rise and is the leading cause of death from cutaneous malignancies, accounting for 1 to 2% of all cancer deaths in the United States. Melanoma affects all age groups, with a median age at diagnosis of 63[2]; however, melanoma is the most common cancer in young adults, ages 25 to 29.[3]

RISK FACTORS AND GENETICS OF MELANOMA

Risk factors for the development of melanoma are both environmental and genetic. Exposure to sunlight (ultraviolet [UV] radiation) has been strongly implicated as a causative factor in the development of melanoma. UVB radiation appears to be more closely associated with the development of melanoma than UVA radiation. The rates of melanoma are higher for patients with a tendency to burn rather than tan when exposed to sunlight. The pattern of sun exposure

may also be important. Intermittent intense exposure and sunburns in areas only sporadically exposed to the sun (e.g., the back for men and the legs for women), rather than long-term exposure, may carry a higher risk of melanoma. Blistering sunburns, particularly in childhood, are associated with an increased risk of melanoma. However, melanoma can occur in any ethnic group and without significant sun exposure. There is growing evidence that use of tanning beds increases the risk for melanoma. In 2009, the World Health Organization International Agency for Research on Cancer classified UV light emitted from tanning beds as a human carcinogen based on multiple studies.[4]

High nevus counts and atypical nevi (dysplastic nevi) are also strongly associated with melanoma.[5] The percentage of melanomas that arise from melanocytic nevi ranges from 18 to 85%. Dysplastic nevi are both precursor lesions of melanoma and markers of increased risk for the development of melanoma. The presence of dysplastic nevi is associated with a 6% lifetime chance of melanoma. This risk is as high as 80% for patients who have dysplastic nevi and a family history of melanoma. Phenotypic traits associated with melanoma risk include skin pigmentation, hair color (red or blond), freckles, and light eye color (blue, green, or hazel). Other risk factors for melanoma include a personal history of melanoma or nonmelanoma skin cancers, immunosuppression, and xeroderma pigmentosum. While the overall incidence of melanoma continues to increase, the ratio of mortality to incidence has begun to decrease.

HEREDITARY BASIS OF MELANOMA: GENES INVOLVED IN MELANOMA SUSCEPTIBILITY

Although 10% of patients with cutaneous melanoma have a family history of melanoma, germline mutations and hereditary melanoma syndromes are very rare. Several genetic loci determine susceptibility to melanoma, the most important of these being *p16/CDKN2A*, a gene located on chromosome 9p21. The *CDKN2A* gene encodes two proteins, p16 and p14ARF, which are cell-cycle inhibitors. Of the members of melanoma-prone families, 25 to 40% have mutations in this gene. The risk for the development of cutaneous melanoma in an individual who is a *CDKN2A* mutation carrier is between 30 and 90% by age 80 and varies by geographic location.[6] Some familial melanoma occurs in the setting of the familial atypical multiple primary mole melanoma syndrome, also called the “dysplastic nevus syndrome.” A family history of melanoma in multiple first-degree relatives and younger age at diagnosis are important features of this syndrome. Up to 10% of patients with multiple primary melanomas have been identified to have a *CDKN2A* mutation. Pancreatic cancer is also seen in melanoma-prone families with *CDKN2A* germline mutations. Advances in sequencing techniques, including next-generation sequencing, have enabled geneticists to interrogate larger gene panels for melanoma susceptibility. Germline genetic testing for mutations in the *p16/CDKN2A* locus is available; however, the clinical utility of genetic testing for melanoma susceptibility is limited. Both the American Society of Clinical Oncology and the Melanoma Genetics Consortium have recommended that genetic testing for *CDKN2A* mutation be limited to the research setting and that it is not recommended for routine clinical use.

Other genetic factors that predispose to melanoma include xeroderma pigmentosum, a rare inherited disorder in which DNA repair mechanisms are compromised. In addition, *BRCA2* gene carriers have an increased risk for cutaneous melanoma. The melanocortin-1 receptor *(MCIR)* gene is one of the key genes that regulate skin color. Patients with *MCIR* variants are at increased risk for the development of melanoma.[7] At this time, diligent skin exams by trained physicians, as well as educating patients in skin self-exam, remain the standard of care for

screening patients, even in high-risk families. Germline mutations in BRCA1-associated protein (BAP1) have been described in several kindreds of familial uveal melanoma.[8]

BIOLOGY OF SPORADIC MELANOMA

Cutaneous melanomas have the highest average number of somatic mutations among any other cancer type.[9] These somatic mutations may result in neoantigens that can be recognized by the host immune response. The *BRAF* oncogene is the most common somatic mutation in melanoma, present in approximately 50% of tumors; additional mutations are summarized in Table 13-1.[10-13] A valine-to-glutamic-acid change at codon 600 (V600E mutation) is the most frequently observed *BRAF*-activating mutation, resulting in a constitutively active conformation of the kinase; it is present concordantly in the primary melanoma as well as metastatic lesions. Immediately upstream to *BRAF* is *NRAS,* which has an activating gene mutation in 15 to 20% of melanomas. Patients may also have mutations in NF-1 (neurofibromin-1), a protein that negatively regulates the renin–angiotensin system (RAS) pathway and is therefore also involved in RAS/mitogen-activated protein kinase (MAPK) pathway activation as its mechanism of melanoma pathogenesis. Molecular alterations in melanoma have been linked with subtypes of melanoma, anatomic location, and sun exposure. For example, activating mutations in *BRAF* are more common in melanomas arising in skin that has intense intermittent sun damage from sunburns and are less frequent in melanomas associated with long-term sun damage in areas such as the hands and face. *BRAF* mutation is also associated with younger age at onset of melanoma. Studies found that melanomas on mucosal membranes, acral skin (i.e., soles, palms, and nail beds), and skin with long-term sun damage (i.e., lentigo maligna melanoma) may have mutations in *KIT.*[14] Although these types of melanomas usually lack mutations in *BRAF* or *NRAS*, *BRAF* and *NRAS* mutations may occasionally be found in these subtypes, supporting the need for somatic tumor genotyping. Microphthalmia-associated transcription factor *(MITF),* the master regulator of melanocyte differentiation, has also been identified as an oncogene in melanoma. Activation of the phophatidylinositol-3 kinase (PI3K) pathway in melanoma is common. One of the main mechanisms of PI3K pathway activation is loss of phosphatase and tensin homolog (PTEN) through inactivating missense mutations or allele deletion. Uveal melanoma is associated with mutations in *GNAQ/GNA11.* Monosomy of chromosome 3 has been associated with the development of metastatic disease and poor overall survival (OS) of patients with uveal melanoma.[15] In addition, somatic mutations in the gene encoding BAP1 on chromosome 3 have been associated with worse outcomes.[16] The discovery of somatic genetic mutations and underlying aberrant signal transduction has provided a basis for the development of molecularly targeted therapy for patients with advanced melanoma. Figure 13-1 summarizes the signaling pathways that are frequently altered in melanoma and that serve as targets for approved or investigational therapies in melanoma.

Table 13-1 Molecular Alterations in Melanoma	
Oncogene	**Frequency**
BRAF	50%; Some association with superficial spreading melanoma
NRAS	15–20%
KIT	10%; Acral, mucosal, lentigo maligna melanoma
GNAQ/GNA11	50%; Uveal melanoma
NF1	15%

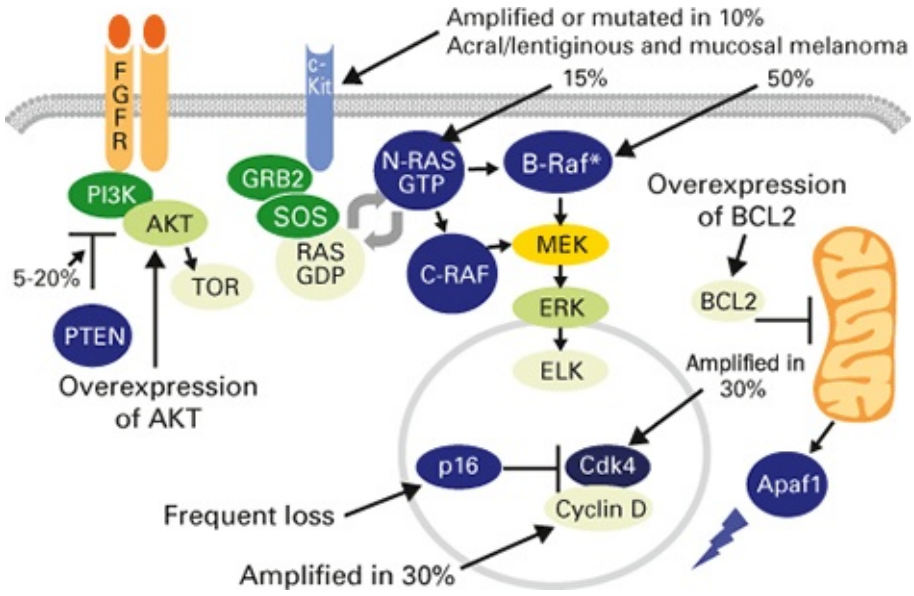

Fig. 13-1 Molecular alterations in melanoma.

KEY POINTS

- Risk factors for melanoma include sun exposure, dysplastic (atypical) nevi, increased number of benign nevi, family history of melanoma, and skin type with tendency to burn.
- Germline mutation in the *CDKN2A* gene is the most common cause of familial or inherited melanoma. However, sporadic melanomas represent the majority of melanomas, and germline genetic testing is not routinely indicated.
- Approximately 50% of melanomas have a somatic activating *BRAF* mutation.

PREVENTION AND SCREENING

The most important preventive measures are to reduce excessive sun exposure and avoid sunburns. Sunburns in childhood and adolescence increase the risk of melanoma later in life. Strategies to reduce exposure include avoiding the midday sun, regular use of sunscreen products with a sun protection factor of 30 or higher, and wearing sun protective clothing. Evidence from an Australian community-based randomized clinical trial showed that the regular

use of sunscreen prevents the development of melanoma[17]; however, sunscreen intervention studies often involve confounded formulation, inconsistent use, and underapplication. Chemoprevention with oral supplementation has never been confirmed in a prospective trial to reduce melanoma risk.

There is currently no national consensus regarding skin screening for melanoma in the United States, as no randomized controlled trial has shown that clinician screening reduces melanoma mortality.[18] The U.S. Preventive Services Task Force recommends that children and young adults ages 10 to 24 be counseled regarding sun protection[19]; the parents of younger children should be counseled similarly. A total body skin exam, which includes inspection of the entire skin surface, including the scalp, hair, nails, oral mucosa, eyes, genitals, and anus can be considered for at the time of the first wellness visit for adults ages 18 and older, with consideration of referral to dermatology for regular skin screening in patients with risk factors identified based on family history, skin type, moles, sun damage, and history of sunburn. Screening is not recommended for patients without risk factors.

There are no screening recommendations for mucosal melanoma or for ocular melanoma. Both of these are diagnosed on the basis of history and physical exam, followed by diagnostic evaluation.

CLINICAL PRESENTATION AND DIAGNOSIS

Early detection and treatment of melanoma are important for improving OS in patients with melanoma. The recognition of early-stage melanoma is based on the clinical appearance of the cutaneous lesion in addition to a history of change in an existing mole, including change in shape, color, or surface. More than 70% of melanomas are associated with an increase in size and a change in color of a pigmented cutaneous lesion. Most patients report a preexisting mole at the site of the melanoma. Itching, burning, or pain in a pigmented lesion should increase suspicion, although melanomas often are not associated with local discomfort. Bleeding and ulceration are signs of a more advanced melanoma. Most melanomas are varying shades of brown, but they also may be black, blue, or pink; therefore, any suspicious changing lesion should be considered for biopsy, regardless of color. The ABCDE method for recognizing melanoma involves assessing for asymmetry, border, color, diameter, and evolution. The “ugly duckling” method involves assessing for a pigmented lesion that looks different from other surrounding lesions and is therefore suspicious. Handheld instruments for skin-surface microscopy (dermoscopy) or epiluminescence microscopy are now available. These may aid dermatologists who are properly trained in their use in differentiating more reliably between benign and malignant skin lesions.

A biopsy should be performed on any skin lesion suspicious for melanoma. The proper biopsy technique is essential not only to establish a diagnosis but also to allow precise histologic staging that will determine the prognosis and treatment plan. For most clinically suspicious skin lesions, a complete excisional biopsy with a 1-to-2-mm margin of normal skin is preferred. Shallow shave biopsies or punch biopsies are not preferred for lesions that are suspicious for melanoma because of the possibility of heterogeneity in Breslow thickness throughout the tumor.

Cutaneous melanoma has been divided into four subtypes based on distinct clinical and histologic features. In descending order of frequency, these subtypes are superficial spreading melanoma, lentigo maligna melanoma, nodular melanoma, and acral lentiginous melanoma (Table 13-2 and Figs. 13-2 to 13-6). Histologic subtype does not directly correlate with

prognosis and is not included in the staging system; however, histologic subtype is correlated with specific genetic abnormalities. For example, superficial spreading melanomas are more likely to have a *BRAF* mutation, whereas lentigo maligna melanomas are more likely to have a mutation in *KIT.*[10] Primary melanomas also can arise from mucosal epithelial cells lining the respiratory, alimentary, and genitourinary tracts, although these mucosal melanomas are less common than cutaneous melanomas. Ocular melanomas arise from the pigmented layer of the eye that includes the iris, ciliary body, and choroid. These lesions are referred to as "uveal melanomas" and are the most common primary intraocular malignancies in adults.

KEY POINTS

- Reducing sun exposure is the main mechanism of melanoma prevention, with an emphasis on prevention of sunburns in early childhood and adolescence.
- Early detection and treatment of melanoma improves overall survival by increasing the likelihood of detection at an earlier stage.
- Suspicious or changing cutaneous lesions should be biopsied; an excisional biopsy is the preferred diagnostic test for cutaneous lesions that are suspicious for melanoma.

PROGNOSTIC FACTORS

A number of clinical and pathologic factors have been identified that influence the probability of survival of a patient with melanoma. The most important prognostic factors for patients with localized melanoma are the tumor thickness (Breslow thickness) and the presence or absence of ulceration. These factors are incorporated in the 8th (2016) edition of the American Joint Committee on Cancer (AJCC) staging system.[20] The single most prognostic factor is the depth of invasion (Breslow thickness) of the primary lesion, measured in millimeters from the uppermost layer of the epidermis to the deepest melanoma cell in the underlying dermis. Increasing thickness is associated with a higher risk of recurrence of melanoma and, therefore, death (Table 13-3). In addition, the thicker the primary melanoma, the more likely there is microscopic involvement of regional lymph nodes. Ulcerated melanomas (as assessed microscopically by pathologist evaluation) are associated with a poorer prognosis.

Table 13-2 **Four Histologic Subtypes of Cutaneous Melanoma**
Superficial Spreading Melanoma (Fig. 13-2)
■ Incidence: Accounts for 70% of all melanomas; tends to occur in young patients (median age, 50) ■ Anatomic site: Any; predominantly trunk and extremities; anatomic sites associated with intermittent sun exposure ■ Clinical appearance: Change in appearance of a large mole; asymmetry; irregular border; variegated color (brown, black, pink, white, gray, and blue); often arises in a precursor mole ■ Can be associated with *BRAF* mutation
Lentigo Maligna Melanoma (Fig. 13-3)
■ Incidence: Accounts for 4–10% of all melanoma; tends to occur more commonly in older patients ■ Anatomic site: Areas with chronic exposure to the sun; head and neck regions; distal extremities ■ Clinical appearance: Macular (flat) lesion; arising in a lentigo maligna, which often appears as a flat, light brown skin lesion ■ Can be associated with mutation in *KIT*
Nodular Melanoma (Fig. 13-4)
■ Incidence: Accounts for 15% of melanomas ■ Anatomic site: Any ■ Clinical appearance: Rapidly enlarging, elevated, or polypoid lesion; often arises in normal skin; often blue, black, or pink or can be amelanotic (ABCDE rule does not apply)
Acral Lentiginous Melanoma (Figs. 13-5 and 13-6)
■ Incidence: 5–10% ■ Anatomic site: Most commonly on the palms, soles, or subungual (under the nail bed) ■ Clinical appearance: Darkly pigmented, flat to nodular lesion, highly irregular borders ■ Can be associated with *KIT* mutation

Abbreviation: ABCDE, asymmetry, border (irregular), color (heterogeneous, variegated), diameter > 5 mm, evolution.

Adapted with permission from Balch CM, Buzaid AC, Soong S-J, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. J Clin Oncol. *2001;19:3635–3648. PMID: 11504745.*

Primary tumor mitotic rate is an independent prognostic marker of survival for melanoma. It is measured as the number of mitoses within 1 mm^2. Mitotic rate is not included in the updated staging system because substratifying T1 tumors using a 0.8-mm cut point showed a stronger association with outcome than did the presence or absence of mitoses; however, mitotic rate should be reported and reviewed, given its prognostic value.[21,22] Other poor prognostic factors include increasing level of invasion (Clark level), lack of tumor-infiltrating lymphocytes (TILs), and presence of microscopic satellites. Primary tumor location, patient age, and gender are clinical variables associated with prognosis. In general, patients with primary melanoma of the extremities have a significantly better clinical prognosis than those with primary lesions of the trunk and head. Older age and male sex are associated with worse outcomes. The involvement of regional lymph nodes is a poor prognostic sign, regardless of the primary tumor thickness. In

addition, the number of involved lymph nodes correlates with the risk for distant metastatic disease and, therefore, survival. Patients with clinically detected lymph nodes have a worse prognosis than patients with clinically occult lymph node involvement (observed on sentinel lymph node evaluation only).

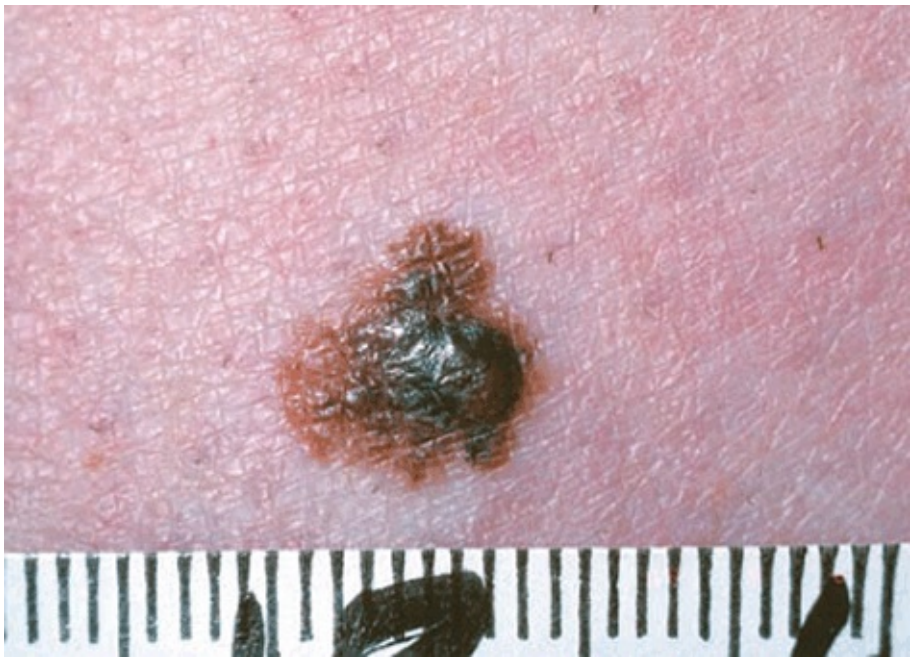

Fig. 13-2 Superficial spreading melanoma.

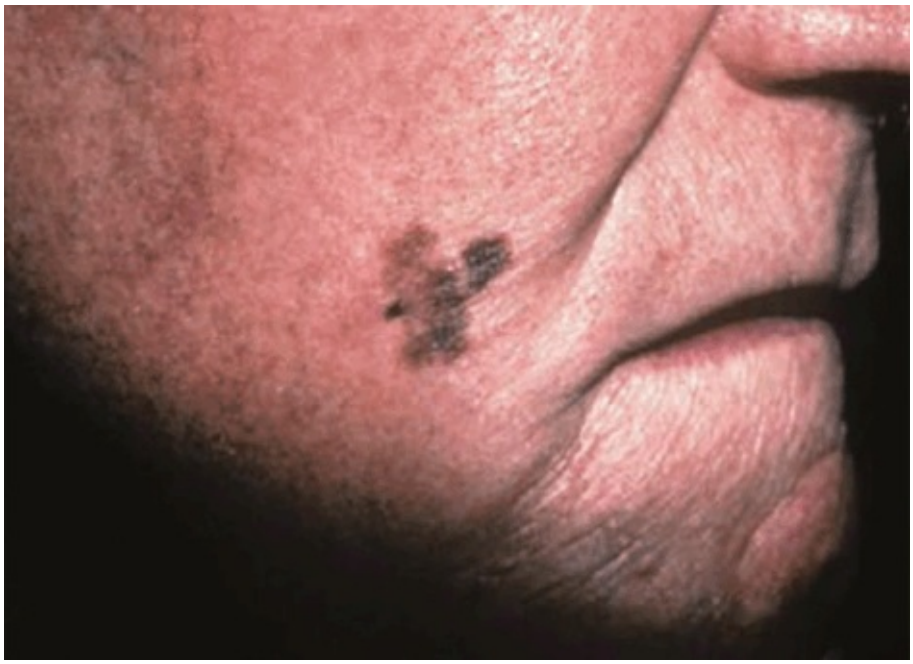

Fig. 13-3 Lentigo maligna melanoma.

STAGING SYSTEM

The tumor–node–metastasis (TNM) staging system for melanoma, which was developed by the AJCC and updated in 2016, classifies patients into groups with similar survival (Table 13-3).[20] The major changes in the latest updated staging system is that tumor thickness is classified to the nearest 0.1 mm rather than 0.01 mm and mitotic rate is not utilized for the staging of the primary tumor. In addition, there is a new subcategory in stage IV, M1d, indicating metastases

to the brain which is associated with a particularly poor prognosis. Stages I and II indicate melanoma limited to the primary skin lesion. Stage III melanoma indicates regional involvement (either lymph nodes or microsatellite, satellite, or in-transit metastases). Stage IV indicates distant metastatic disease beyond regional involvement. The T categories (primary tumor) are based on Breslow thickness and subdivided into “a” or “b” categories based on the absence or presence, respectively, of ulceration (and substratification of 0.8 to 1.0 mm for T1 melanomas only). The 5-year survival rates associated with each of the four stages are noted in the staging system in Table 13-3. It is estimated that at the time of initial diagnosis, about 80% of patients diagnosed with melanoma present with localized disease (stage I or II), 15% with regional disease (stage III), and 5% with distant metastatic disease.

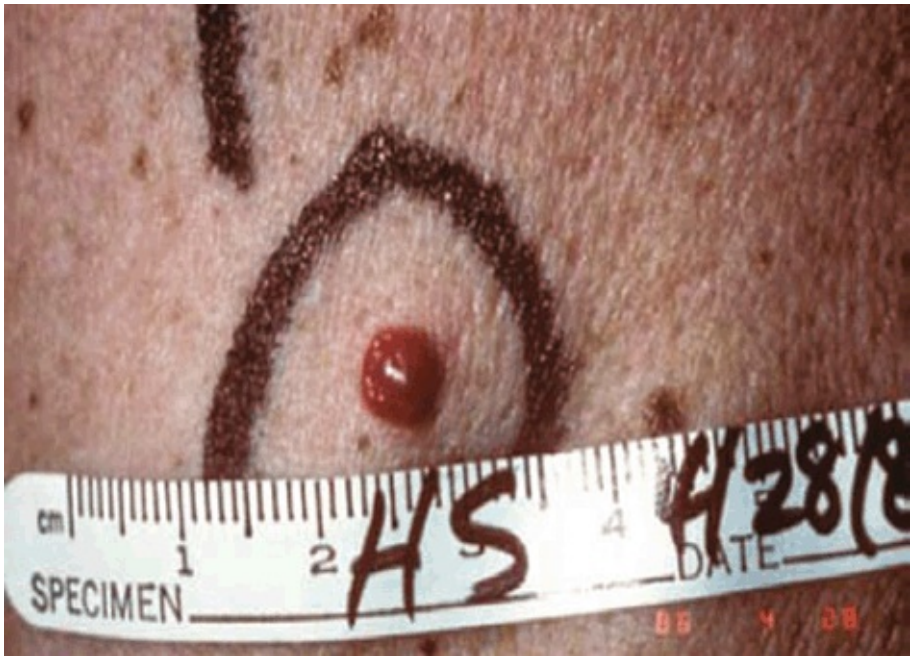

Fig. 13-4 Nodular melanoma.

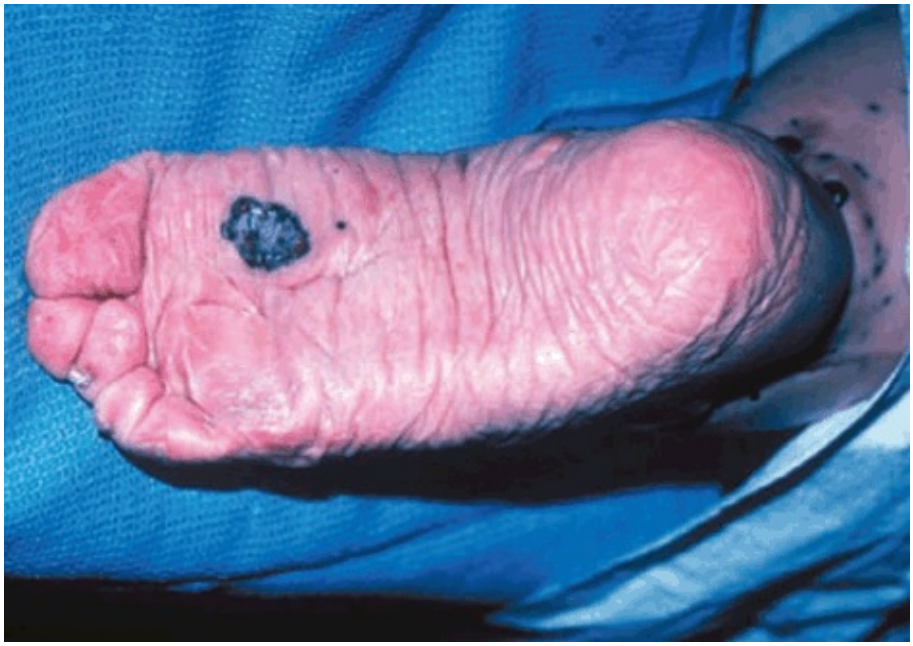

Fig. 13-5 Acral lentiginous melanoma with in-transit metastases.

Fig. 13-6 Acral lentiginous melanoma.

KEY POINTS

- Breslow thickness in millimeters and tumor ulceration status are the most significant prognostic factors of primary melanoma.
- Lymph node involvement and metastatic disease define stages III and IV melanoma, respectively, and are prognostic of decreased survival.

PATIENT EVALUATION

The initial evaluation of a patient with melanoma consists of a complete history and physical examination, including a total skin and lymph node examination, with a focus on the regional (draining) lymph nodes. The intent of this evaluation is to identify risk factors, signs or symptoms of metastases, dysplastic nevi, and additional primary melanomas. The purpose of the skin exam is to identify additional atypical lesions given the increased risk of additional skin cancers, to identify the primary melanoma in the case of a patient with an unknown primary site, and to identify in-transit metastatic lesions. The extent of the workup for patients with an initial diagnosis of melanoma is based on the risk of recurrence associated with the primary melanoma. In general, for low-risk melanomas (stage IA, IB, or IIA), no imaging evaluation for occult metastatic disease is indicated before proceeding with the definitive wide excision (and sentinel lymph node biopsy, when indicated; see section on Management of Regional Lymph Nodes). For patients with higher-risk primary melanomas (stage IIB, IIC, III), imaging should be considered, including cross-sectional imaging, followed by biopsy for pathologic confirmation of stage IV disease if any suspicious lesions are identified. Currently, no peripheral-blood tumor markers are sensitive and specific for melanoma. *BRAF* mutation status should be determined for all patients with stage IV melanoma, as well as peripheral-blood lactate dehydrogenase (LDH), which is prognostic of a worse survival in stage IV disease. The evaluation for patients with uveal and mucosal melanoma similarly involves a history and physical exam, with consideration of imaging in patients with unexplained symptoms or high-risk disease.

TREATMENT

Once melanoma has been diagnosed, the standard treatment is surgical excision of the primary lesion (Fig. 13-7). The extent of surgery depends on the thickness of the primary melanoma. Large surgical excisions are not necessary, and most wide excisions can be performed with primary closure. Findings from randomized clinical studies of optimal surgical margins have demonstrated that less radical surgery results in excellent local control with no adverse effect on survival.[23,24] Current recommendations for the optimal width of surgical margins are summarized in Table 13-4.

The wide excision should include underlying subcutaneous tissue down to the fascia. In cosmetically sensitive areas, such as the face, or anatomically difficult areas, such as the ears and hands, it may be difficult to achieve the desired margin. In those areas, at least a 1-cm margin should be obtained. Mohs micrographic surgery, in which the clinical lesion is excised with a narrow margin, followed by intraoperative margin assessment and additional narrow margin excisions as indicated until a negative margin is achieved, can be considered for melanoma in situ[25]; however, prospective, controlled data regarding the utility of Mohs surgery in invasive melanoma is lacking.

KEY POINTS

- Surgical wide excision is the treatment for early-stage melanoma. The extent of surgical margins depends on the thickness of the primary melanoma.
- Imaging evaluation for metastatic disease is not indicated for patients with stage I melanoma and most patients with stage II melanoma. Imaging should be considered for patients with melanoma stage IIB and above or for any patient with symptoms concerning for metastatic disease.
- Somatic *BRAF* mutation testing should be performed for all patients with stage IV melanoma.

MANAGEMENT OF REGIONAL LYMPH NODES

Clinically Occult (Normal) Regional Lymph Nodes

The surgical management of clinically occult lymph nodes is determined by the characteristics of the primary melanoma. There is a direct relationship between thickness of the primary melanoma and risk for regional lymph node involvement. Sentinel lymph node biopsy (SLNB) is a method for assessing regional nodal involvement/staging; it should be discussed with and offered to all patients with primary melanomas that are greater than 1 mm thick. For melanomas that are less than 1 mm thick, the likelihood of regional lymph node involvement is low (< 10%); therefore, SLNB can be considered in select patients with high-risk histologic features, such as ulceration of the primary melanoma or the thickest melanomas in the group being less than 1 mm. The false-negative rate for SLNB is approximately 4%. SLNB involves mapping of the specific nodes draining the skin surrounding the primary melanoma and biopsy of the identified sentinel node. Lymphoscintigraphy imaging is performed preoperatively to identify the regional nodal basin and facilitate intraoperative identification of the sentinel node or

nodes. SLNB is typically performed on an outpatient basis, with excisional biopsy of the sentinel nodes first, followed by wide local excision of the primary tumor.[26] If the sentinel lymph node is negative for melanoma, no further lymph node surgery is required. In patients with clinically occult (microscopic) melanoma detected in the sentinel lymph node, two prospective, randomized, controlled trials[27,28] that did not show any improvement in survival with completion lymph node dissection for the general intent to treat population compared to observation.

Table 13-3 **American Joint Committee on Cancer Staging System for Cutaneous Melanoma**

Definition of Primary Tumor (T)

T Category	Thickness	Ulceration Status
TX: primary tumor thickness cannot be assessed (e.g., diagnosis by curettage)	Not applicable	Not applicable
T0: no evidence of primary tumor (e.g., unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma in situ)	Not applicable	Not applicable
T1	≤ 1.0 mm	Unknown or unspecified
T1a	< 0.8 mm	Without ulceration
T1b	< 0.8 mm 0.8–1.0 mm	With ulceration With or without ulceration
T2	> 1.0–2.0 mm	Unknown or unspecified
T2a	> 1.0–2.0 mm	Without ulceration
T2b	> 1.0–2.0 mm	With ulceration
T3	> 2.0-4.0 mm	Unknown or unspecified
T3a	> 2.0–4.0 mm	Without ulceration
T3b	> 2.0–4.0 mm	With ulceration
T4	> 4.0 mm	Unknown or unspecified
T4a	> 4.0 mm	Without ulceration
T4b	> 4.0 mm	With ulceration

Definition of Regional Lymph Node (N)

N Category	Extent of Regional Lymph Node and/or Lymphatic Metastasis	
	Number of Tumor-Involved Regional Lymph Nodes	**Presence of In-Transit, Satellite, and/or Microsatellite Metastases**
NX	Regional nodes not assessed (e.g., SLN biopsy not performed, regional nodes previously removed for another reason) **Exception:** pathological N category is not required for T1 melanomas; use cN.	No
N0	No regional metastases detected	No
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (i.e., detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or three clinically occult (i.e., detected by SLN biopsy)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	

N3a	Four or more clinically occult (i.e., detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

Definition of Distant Metastasis (M)

M Category*	M Criteria	
	Anatomic Site	**LDH Level**
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Normal
M1d(1)		Elevated

AJCC Prognostic Stage Groups: Clinical (cTNM)

When T is...	*And N is...*	*And M is...*	*Then the clinical stage group is...*
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥ N1	M0	III
Any T	Any N	M1	IV

Abbreviations: CNS, central nervous system; LDH, lactate dehydrogenase; SLN, sentinel lymph node.

*Suffixes for M category: (0) LDH not elevated, (1) LDH elevated. No suffix is used if LDH is not recorded or is unspecified.

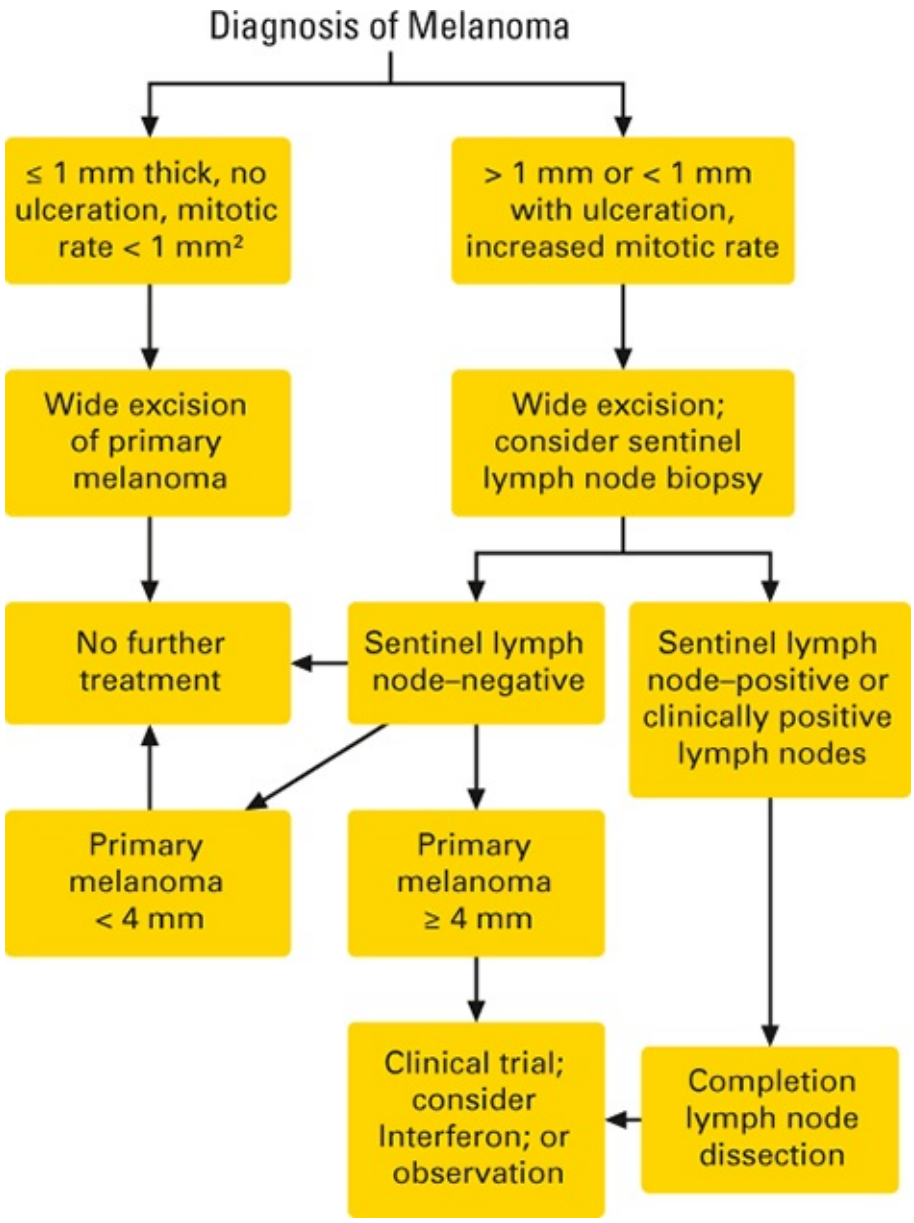

Fig. 13-7 Treatment algorithm for patients with newly diagnosed melanoma.

The Multicenter Selective Lymphadenectomy Trial (MSLT-I) is the largest trial to address the role of lymphatic mapping with SLNB in determining prognosis and effect on survival.[29] This trial evaluated the role of sentinel lymph node mapping compared with observation for patients with intermediate-thickness melanoma. Patients were randomly assigned to wide excision followed by serial ultrasound observation of regional lymph nodes with lymphadenectomy if nodal disease occurred, or to wide excision and SLNB with immediate lymphadenectomy if occult nodal disease was detected on biopsy. Overall, the 5-year melanoma-specific survival rates were similar for the two groups. However, even in the absence of a survival benefit, the SLNB procedure is a standard part of surgical staging because of the prognostic value of the biopsy result; patients with a positive SLNB are upstaged to stage III and have a worse survival than patient with a negative SLNB. In addition, patients who were discovered to have a clinical lymph node recurrence during observation had a worse survival than those patients who had a positive sentinel lymph node followed immediately by node dissection. A follow-up study, MSLT-II, compared the role of completion lymph node dissection compared with close surveillance for patients with sentinel lymph node-positive melanoma. No survival advantage was observed with

completion dissection. Therefore, a completion lymph node dissection is not considered a routine recommendation, but can be considered in specific patients after detailed discussion of the risk of lymphedema and the potential benefit of regional control.[28]

Table 13-4 Recommended Surgical Margins for Primary Melanoma

Tumor Thickness	Surgical Margin
≤ 1.0 mm	1.0 cm
1.0–2.0 mm	1.0–2.0 cm
2.01–4.0 mm	2.0 cm
> 4.0 mm	≥ 2.0 cm

KEY POINTS

- Sentinel lymph node biopsy is a useful staging procedure for melanoma and provides important prognostic information.
- Sentinel lymph node biopsy should be discussed and offered if the primary melanoma is greater than 1 mm thick. It should also be discussed and considered or offered for melanomas that are less than 1 mm thick but that have high-risk features such as ulceration.
- Completion lymph node dissection in patients with an involved sentinel node does not improve survival.

Clinically Detected (Enlarged) Regional Lymph Nodes

For patients who present with enlarged regional lymph node metastases detected by palpation or imaging and no evidence of distant metastatic disease, a biopsy (fine-needle aspiration or core biopsy of the enlarged node) should be performed for pathologic confirmation of stage III melanoma; once confirmed, a wide excision of the primary tumor as well as a regional lymph node dissection should be performed. The goal of nodal dissection is to optimize local–regional control of disease. Satellite metastases and in-transit metastases are surgically resected when limited to a resectable area. Negative margins are generally sufficient without large, wide excisions for in-transit lesions.

ADJUVANT THERAPY FOLLOWING SURGERY

The primary treatment for most patients with stages I and II melanoma is surgical resection. Postoperative adjuvant therapy can be considered for patients at high risk for recurrence (stage III disease). Adjuvant therapy options include clinical trials, ipilimumab, or close observation alone, which is also considered a reasonable option after surgery. High-dose interferon alpha-2b is also an adjuvant therapy option that has been approved since 1995 and can also be discussed as an option for adjuvant therapy.

Adjuvant Ipilimumab Therapy

Ipilimumab, a monoclonal antibody targeting CTLA-4, was initially approved as adjuvant therapy for melanoma in 2015 based on an improvement in recurrence free survival in the EORTC 18071 study. The study randomly assigned 951 patients with stage III melanoma to treatment with ipilimumab or placebo.[30] Ipilimumab (10 mg/kg) was administered every 3 weeks for four doses, followed by maintenance ipilimumab every 3 months for 3 years until relapse or toxicity. With a median follow-up of 2.7 years for the study cohort, the median recurrence-free survival (RFS) was significantly improved with ipilimumab (median, 26 months vs. 17 months); the melanoma 3-year RFS was 46.5% compared with 34.8% (hazard ratio [HR], 0.75; 95% CI; 0.64, 0.90; p = 0.0013). Subsequently, an overall survival benefit was also reported, with a 5-year OS of 65.4% for ipilimumab compared with 54.4% in the placebo group (HR for death, 0.72; 95% CI; 0.58, 0.88; p = 0.001).[31] However, adverse events of grade 3 or 4 occurred in 54.1% of the patients in the ipilimumab group and 5 patients (1.1%) died from immune-related adverse events. Of note, patients were randomly assigned from 2008 to 2011, prior to the availability of any drugs with survival benefit for metastatic disease. Given the serious risk of toxicity, including severe colitis, hepatitis, and hypophysitis, among other serious adverse events, along with the current context of several highly effective therapy options for metastatic disease, clinicians must carefully consider the risk of serious toxicity and death along with the potential benefit in their decision-making and informed consent process regarding the use of adjuvant ipilimumab. Patients treated with adjuvant ipilimumab should be monitored closely and the treatment should be discontinued if severe toxic effects occur.

Adjuvant Interferon Therapy

The U.S. Food and Drug Administration (FDA) recommended approval for interferon alpha-2b in 1995 based on study E1684 conducted by the Eastern Cooperative Oncology Group,[32] which demonstrated a 9-month prolongation in median RFS (1.7 years vs. 1.0 years; p = 0.002) and a 1-year prolongation in median OS (3.8 years vs. 2.8 years; p = 0.02). However, with longer follow-up, the benefit in terms of OS was no longer statistically significant. High-dose interferon alpha-2b has also been evaluated in three additional randomized clinical trials, consistently demonstrating an improvement in RFS, with manageable, predictable, and quickly reversible toxicity. It is approved for the adjuvant treatment of patients with stages IIB and IIC melanoma, in addition to stage III melanoma.

EORTC 18991 was a randomized clinical trial of adjuvant pegylated interferon alpha-2b compared with observation for patients with stage III melanoma.[33] In this study, 1256 patients were randomly assigned to observation or weekly pegylated interferon-alpha at a dose of 6 µg/kg/week for 8 weeks (induction) and then 3 µg/kg/week for an intended duration of 5 years (maintenance). There was no difference in OS or distant metastasis-free survival (DMFS) between the groups (DMFS and OS: HR, 0.88; 95% CI; 0.75, 1.03; p = 0.107). There was a significant reduction in hazard ratio for relapse for the patients treated with interferon, with risk reduction in RFS (HR, 0.82; 95% CI; 0.71, 0.96; p = 0.011) a median of 4 years of follow-up. Based on these data, the FDA approved pegylated interferon for treatment of patients with stage III melanoma.

Toxicities of high-dose interferon include flulike symptoms, fatigue, fever, chills, myalgia, anorexia, nausea, vomiting, headache, depression, and suicidal ideation. Significant laboratory abnormalities include elevated levels of hepatic transaminases, neutropenia, thyroid dysfunction, and anemia. Patients treated with high-dose interferon should be monitored closely

and the dose of interferon should be modified appropriately or discontinued if toxic effects occur. Low-dose interferon regimens have also been evaluated. A randomized, controlled trial evaluated low-dose interferon alpha-2a compared with observation, and there was no improvement in RFS or OS.[34]

In summary, high-dose interferon remains an approved adjuvant therapy option with a reasonable safety profile.

Other Adjuvant Approaches

A variety of approaches are being evaluated in clinical trials in the adjuvant setting. In general, melanoma vaccine approaches have not been effective to date in clinical trials. Given the overall high response rates and improvement in OS for patients with stage IV *BRAF*-mutated melanoma who are treated with a combination of BRAF and MEK inhibitors, adjuvant studies of these inhibitors are in progress for patients with stage III melanoma. Adjuvant therapy trials with programmed cell death protein 1 (PD-1) blockade are ongoing as well, given the efficacy of the PD-1–blocking agents pembrolizumab and nivolumab in advanced metastatic melanoma. The Eastern Cooperative Oncology Group (ECOG) adjuvant therapy study 1609 has also completed accrual and tested ipilimumab 3 mg/kg versus interferon versus10 mg/kg, with results awaited. The decision regarding adjuvant therapy requires a careful discussion of risk and potential benefit; close observation alone or clinical trials remain reasonable options as well.

Several clinical trials are evaluating the benefit of neoadjuvant systemic therapy prior to curative intent surgery, with early-stage trials reporting pathologic complete responses with PD-1 blockade, BRAF/MEK inhibition and with dual-checkpoint blockade. This approach is considered investigational, as the survival benefit has not been tested in a randomized, controlled trial; the optimal duration of neoadjuvant therapy has not been defined; pathologic complete response has not been defined as a surrogate for survival outcomes; and the duration and need for additional postoperative therapy are not defined.

KEY POINTS

- Participation in a clinical trial or close observation alone are reasonable postresection options for patients with stage III or high-risk stage II melanoma.
- Adjuvant therapy with ipilimumab may be considered following surgery for patients with high-risk melanoma (stage III).
- The decision regarding the use of adjuvant therapy requires a careful discussion of risk and potential benefit.

SURVEILLANCE AFTER PRIMARY THERAPY

Patients with a history of melanoma should be followed regularly for evidence of local–regional recurrence, distant metastatic disease, and additional primary melanomas. The most important components of surveillance are the history and physical examination. The physical examination should include a thorough skin examination because the risk of a second primary melanoma is increased for patients who have a history of melanoma. Lifelong annual (or more frequent,

based on individual patient risk factors) skin exam by a dermatologist is recommended. Regional lymph nodes should be thoroughly examined, especially for patients who have not had surgical resection of regional lymph nodes. The remainder of the examination should be comprehensive, with awareness of frequent metastases to the lung, liver, and brain. Patient education is an integral part of the treatment of patients with melanoma, and they should be educated about patterns of recurrence and the importance of communicating any new signs or symptoms to their physician. Patients should also be taught about the clinical characteristics of melanoma and the importance of safe sun-protection strategies. Educating family members about melanoma risk factors and changes in behavior related to sun exposure is important also.

The National Comprehensive Cancer Network has proposed surveillance guidelines for follow-up. In general, for patients with stage I or stage IIA melanoma, a history and physical examination are recommended at least every 6 months for 5 years and then annually or as clinically indicated, with an annual skin exam by a dermatologist recommended for the patient's lifetime. Imaging and blood tests are not recommended. For patients with stage IIB, IIC, or III melanoma, in addition to history and physical examination, imaging studies, including cross-sectional imaging, can be considered. However, there are no data to show that surveillance testing or imaging improves survival outcomes. Currently, there is significant variability in clinical practice, and guidelines permit flexibility in follow-up. Clinicians should have a low threshold for imaging in the presence of any new signs or symptoms of recurrence. Routine radiologic imaging to screen for asymptomatic recurrent or metastatic disease is not recommended after 5 years.

KEY POINTS

- Patients with a history of melanoma should be followed for recurrence with a history and physical exam, including lymph node exam, and should be followed for second primary melanomas with skin exams by a dermatologist.
- Cross-sectional imaging can be considered for patients with stage IIB or III melanoma.

TREATMENT OF METASTATIC MELANOMA

Metastatic melanoma can involve virtually any organ of the body, with the most common sites being lungs, skin, lymph nodes, liver, and brain. Prior to 2011, when available treatment options for stage IV melanoma included cytokine therapy and cytotoxic chemotherapy, in addition to metastatectomy in select patients, the OS for patients with metastatic melanoma ranged from 5 to 11 months, with a median survival of 9 months. However, as described in subsequent sections, effective treatments are now available for patients with metastatic melanoma, with improved outcomes for patients with this historically treatment-refractory disease.

The choice of treatment of patients with metastatic melanoma depends on multiple factors, including comorbidities, performance status, the sites and number of metastases, the pace of the disease, and the patient's preferences for treatment. New approaches in immunotherapy and molecularly targeted therapy have led to several FDA approvals of new agents. Treatment options for metastatic melanoma include participation in clinical trials, immunotherapy, molecularly targeted therapy, cytotoxic chemotherapy, intralesional therapy, and surgical resection of isolated metastases. There are no data on the appropriate sequencing of these

therapies. Therefore, the selection of treatment needs to be individualized, taking into account the overall condition of the patient, prior treatment, a molecular analysis for the presence of mutated *BRAF* gene, and the extent of metastatic disease. Patients with metastatic melanoma have a particularly high incidence of brain metastases. Surgery or radiation therapy (whole-brain or stereotactic radiosurgery) may be considered based on symptoms and number and location of lesions.

MOLECULARLY TARGETED THERAPY

The identification of activating mutations in *BRAF* in approximately 50% of melanomas in 2002 led to the development of molecularly targeted therapy in melanoma.[14] The MAPK pathway and oncogenic *BRAF* are attractive targets for the development of new therapies for patients with melanoma (Fig. 13-1), which has focused on the inhibition of BRAF and MEK. BRAF is a key protein kinase component of the RAS–RAF pathway.[13] This critical intracellular signaling pathway relays extracellular signals to the nucleus in order to regulate gene expression (Fig. 13-1). The most commonly identified mutation in the *BRAF* gene occurs in the region that encodes the kinase domain of the protein at position V600 and results in constitutive activation of the kinase. The majority of *BRAF* mutations are V600E. All patients with advanced cutaneous melanoma should have their tumors assessed for the presence or absence of an activating somatic *BRAF* mutation.

Potent and selective BRAF inhibitors have been developed that specifically inhibit mutated *BRAF* over other RAF kinases. Specific MEK inhibitors have also been developed. These include the FDA-approved vemurafenib and dabrafenib (BRAF inhibitors), and trametinib and cobimetinib (MEK inhibitors).

Vemurafenib is a potent inhibitor of the mutated *BRAF* V600E kinase. A pivotal phase III study (BRIM3) enrolled 675 patients with previously untreated metastatic melanoma with *BRAF* V600E mutation. Patients were randomly assigned to vemurafenib (960 mg orally twice a day) or dacarbazine (1000 mg/m^2 IV every 3 weeks).[35] The overall response rate was 48% in the vemurafenib arm, compared with 5% in the dacarbazine arm. At the 6-month evaluation, OS was 84% in the vemurafenib arm and 64% in the dacarbazine arm (HR, 0.37; $p < 0.001$). The estimated median PFS was 5.3 months in the vemurafenib arm and 1.6 months in the dacarbazine arm. Based on these results, the FDA approved vemurafenib for patients with *BRAF* V600E–mutated unresectable stage III or stage IV melanoma. When these results were updated with data from a median follow-up of 12.5 months, vemurafenib was still associated with an OS benefit compared with dacarbazine (median OS, 13.6 months vs. 9.7 months; HR, 0.70).[36]

The most frequent adverse events associated with vemurafenib are arthralgias, rash, nausea, photosensitivity, pruritus, and hand–foot syndrome. Cutaneous squamous cell carcinomas (SCCs) or keratoacanthoma can occur in approximately 25% of patients treated with vemurafenib. Mutations in *RAS,* particularly *HRAS*, are frequent in SCC that develops in patients treated with vemurafenib.[37] Patients should report any new or changing skin lesions to their physicians. Additionally, patients starting therapy should be advised about sun-protection measures. Surveillance for other sites of SCC is also a topic of consideration. The development of SCCs is an expected side effect and is not an indication for dose reduction or discontinuation of therapy. The lesions can be followed with resection as indicated. Electrocardiography should be performed before treatment and regularly thereafter because of the risk for QT prolongation.

Dabrafenib is a potent, ATP-competitive inhibitor of RAF kinases, including BRAF, which is highly active in melanoma, both as monotherapy and in combination with MEK inhibitors. A phase III trial randomly assigned 250 patients with *BRAF* mutated-positive melanoma to dabrafenib or dacarbazine. Median PFS was 5.1 months for dabrafenib and 2.7 months for dacarbazine.[38] Based on these results, the FDA approved dabrafenib for the treatment of unresectable or metastatic *BRAF*-mutated melanoma (V600E). Side effects include fever, skin rash, arthralgias, SCC, and very rarely, uveitis/iritis. Cardiomyopathy has been reported very rarely, and baseline echocardiography is recommended, as is ongoing monitoring. Ophthalmologic evaluation should be performed for any visual disturbances.

An alternative strategy to targeting the MAPK pathway is inhibition of MEK (MAPK/extracellular signal-regulated kinase), the immediate downstream signaling component in the MAPK pathway. A randomized phase III trial compared trametinib (MEK inhibitor) with dacarbazine chemotherapy for patients with *BRAF* V600E– or *BRAF* V600K–mutated advanced melanoma. Results showed improvement in PFS and OS in favor of trametinib.[39] The response rate for the trametinib arm was 22%. On the basis of these results, the FDA approved trametinib in 2013 for patients with unresectable or metastatic melanoma with *BRAF* V600E or *BRAF* V600K, though the drug is most commonly used in combination with the BRAF inhibitor dabrafenib, given the increased efficacy of dual-agent therapy (discussed in subsequent paragraphs). The toxicities of the MEK inhibitor include rash, diarrhea, and rarely, transient mild and reversible cardiac dysfunction and serous retinopathy. Baseline and ongoing monitoring with echocardiography is recommended.

The combination of BRAF and MEK inhibitors in patients with *BRAF*-mutated melanoma has demonstrated superior outcomes compared to single-agent BRAF inhibition in three randomized, phase III clinical trials. The COMBI-d trial compared the combination of dabrafenib and trametinib to dabrafenib and placebo in 423 previously untreated patients who had unresectable stage IIIC or stage IV melanoma and a *BRAF* V600E– or *BRAF* V600K–activating mutation. The overall response rate was 67% in the dabrafenib/trametinib group and 51% in the dabrafenib-only group ($p = 0.002$). The primary endpoint of PFS was longer with combination treatment. The rates of cutaneous SCCs were lower with the combination, whereas pyrexia was more frequent and more often severe. Additional follow-up confirmed a benefit for PFS and OS.[40] The COMBI-v study compared the combination of dabrafenib and trametinib to vemurafenib in 704 previously untreated patients. This open-label study did result in an OS advantage, with a 12-month survival rate of 72% in the combination group compared with 65% with vemurafenib alone (HR, 0.69; $p = 0.005$). The PFS was 11.4 months in the combination group, compared with 7.3 months in the vemurafenib arm.[41] Finally, the coBRIM study compared the combination of vemurafenib plus the MEK inhibitor cobimetinib with vemurafenib alone. The median PFS was 9.9 months with the combination, compared with 6.2 months with vemurafenib alone (HR, 0.51; $p < 0.0001$).[42] This combination of vemurafenib and cobimetinib gained FDA approval in 2015. Response rates were similarly higher for the combination in all three studies.

In summary, the FDA has approved two BRAF inhibitors (vemurafenib and dabrafenib) and two MEK inhibitors (trametinib and cobimetinib) for *BRAF*-mutated melanoma. These drugs are not approved for use in *BRAF* wild-type tumors, but are currently being tested in combination with other drugs in BRAF wild-type melanoma, including *NRAS* mutant melanoma. Vemurafenib and dabrafenib have similar efficacy, with objective response rates of approximately 50% and a median PFS of approximately 7 months. Both drugs have activity against V600E and V600K. Trametinib, the first FDA-approved MEK inhibitor, also has activity in patients with *BRAF*-

mutated melanoma. Combination therapy with BRAF and MEK inhibition results in increased response rates, with improvement in PFS and OS as compared with monotherapy, and is considered a standard treatment option, with two combination regimens approved (dabrafenib/trametinib and vemurafenib/cobimetinib). Of note, cobimetinib is approved only in combination with vemurafenib. The most common toxic effects of BRAF-targeted therapy are dermatologic complications (e.g., rash, photosensitivity, SCC, keratoacanthoma, hyperkeratoses), arthralgia, fatigue, nausea, and diarrhea. Secondary tumors, including second primary melanomas, rapid expansion of chronic myelomonocytic leukemia, and mucosal cancers, have been reported. Secondary SCC of the skin is seen much less frequently with BRAF/MEK combination therapy as compared to BRAF therapy alone; however, rates of pyrexia are higher in BRAF/MEK combination. Management of pyrexia includes antipyretics as well as dose holding or dose reduction for severe or refractory cases of pyrexia.

Although clinical activity of the selective BRAF inhibitors is impressive, complete responses are uncommon, and progressive disease develops in most patients as a result of acquired drug resistance. Understanding the molecular basis for primary- and secondary-resistance mechanisms to BRAF inhibitors is a major focus of investigation. Early evidence from direct sequencing of *BRAF* exons suggests that new point mutations in *BRAF* V600E are not present. Preliminary results from different labs have described several different potential mechanisms of resistance, including loss of PTEN function, activating *NRAS* mutations, mutated *BRAF* splice variants, and overexpression of mutated *BRAF*.[43] An analysis of patients receiving dabrafenib showed that patients with *BRAF*-mutated melanoma who have concurrent PTEN dysfunction exhibited lower response rates than patients whose tumors retained PTEN function.[44]

Alterations in the PI3K/serine threonine kinase (AKT) pathway also occur frequently in patients with melanoma. Therefore, approaches to simultaneously inhibit the MAPK and PI3K/AKT pathways are currently undergoing clinical development. Patients with *KIT*-mutated metastatic melanoma have also been treated with KIT inhibitors such as imatinib, with some clinical responses reported.[45]

KEY POINTS

- BRAF and MEK targeted therapies are effective and should be used only for patients with *BRAF* V600–mutated melanoma. Combination BRAF and MEK inhibition results in improved outcomes compared to single-agent BRAF inhibition.
- All patients with advanced cutaneous melanoma should have their tumors evaluated for the presence of an activating *BRAF* mutation. When available, extended mutational analysis should be performed, including *KIT, NRAS,* and other alterations for which other therapies and/or clinical trials may be available.

IMMUNOTHERAPY

Immunotherapy is an important treatment strategy for patients with metastatic melanoma and can also be considered as a first-line treatment option for patients with metastatic disease, regardless of *BRAF* mutation status. Breakthroughs in understanding T-cell activation and anergy have led to new therapeutic approaches. The use of targeted immunotherapy such as the PD-1 blocking antibodies pembrolizumab and nivolumab and the cytotoxic T-lymphocyte

antigen 4 (CTLA-4)–blocking antibody ipilimumab has clinical activity for patients with advanced melanoma.

CTLA-4 provides a regulatory mechanism on T-cell activation and serves a critical role in controlling the immune response. CTLA-4 blockade results in enhanced antitumor immunity, most likely through direct activation of T cells as well as inhibition of regulatory (suppressor) T cells. Ipilimumab is a monoclonal antibody directed against CTLA-4 that improved survival for patients with metastatic melanoma compared with dacarbazine, leading to FDA approval in the United States in 2011. Two large phase III trials have demonstrated improved survival with ipilimumab. In the first study, 676 patients with metastatic melanoma who were previously treated were randomly assigned to one of three arms in a 3:1:1 ratio: ipilimumab plus peptide vaccine (gp100), ipilimumab alone, or peptide vaccine alone. Ipilimumab (3 mg/kg) and/or peptide vaccine were given every 3 weeks for four doses.[46] Results showed that the median OS was 10.0 months and 10.1 months in the ipilimumab-containing arms and 6.4 months in the peptide-alone arm, respectively (HR 0.68; $p < 0.003$). The objective response rate was significantly improved in the groups of patients who received ipilimumab compared with those who received the peptide vaccine alone (5.7% and 10.9% vs. 1.5%). In a second phase III clinical trial, 502 patients with previously untreated metastatic melanoma were randomly assigned to ipilimumab (10 mg/kg) plus dacarbazine (850 mg/m^2 IV) or dacarbazine plus placebo with maintenance ipilimumab or placebo for patients with responding disease and no dose-limiting toxicity. Results of this study showed that median OS was longer in the group receiving ipilimumab compared with dacarbazine alone (11.2 months vs. 9.1 months), with higher survival rates in the group receiving ipilimumab at 1 year (47.3% vs. 36.3%) and at 3 years (20.8% vs. 12.2%; HR for death, 0.72; $p < 0.001$).[47] Overall incidence of grades 3 and 4 toxicity, especially hepatic toxicity, was significantly higher with ipilimumab. Objective responses were low (15.2% vs. 10.3%), but the response duration was long: 19.3 months with ipilimumab compared with 8.1 months for dacarbazine alone. Based on clinical activity results, the FDA approved ipilimumab as a single agent for the treatment of unresectable stage III or stage IV melanoma. Although different schedules and doses have been explored, the FDA-approved dose and schedule for unresectable stage III and stage IV melanoma is 3 mg/kg IV every 3 weeks for four treatments as a single agent and without maintenance treatment. Long-term survival at 8 to 10 years has been reported as well.[48]

Two important features of ipilimumab are unique as compared with molecularly targeted or cytotoxic cancer therapies. First, a small portion of patients receiving ipilimumab have radiographic evidence of disease progression during treatment before disease stabilizes or regresses. Guidelines for assessing responses to immunotherapies that take into account atypical response patterns have been proposed.[49] Responses with ipilimumab, for example, may occur much later than with targeted therapies, with disease regression at times occurring well after completion of ipilimumab therapy. Second, treatment with immunotherapy can result in immune-mediated adverse reactions because of T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common immune-related adverse reactions are colitis, hepatitis, dermatitis, and endocrinopathy. Endocrinopathies primarily include hypopituitarism (which can manifest as adrenal insufficiency or even adrenal crisis) and hypothyroidism. The majority of these immune-mediated reactions occur during treatment; however, a minority of them occur weeks to months after discontinuation of ipilimumab. Treatment of immune-mediated toxicity requires interruption of ipilimumab and use of corticosteroids, depending on the severity of symptoms. Patients receiving ipilimumab require close monitoring with blood tests, including for liver and thyroid

function, before and during treatment. Meticulous attention to gastrointestinal symptoms and other immune adverse events is required in order to safely prescribe this treatment.

A newer and more clinically effective approach to inhibit negative regulation of T-cell activation and thereby activate the immune response against melanoma is to block the PD-1/programmed death ligand 1 (PD-L1) pathway. PD-1, a T-cell coinhibitory receptor, and one of its ligands, PD-L1, play an important role in tumor cells' ability to evade the host's immune system. The FDA has approved two monoclonal antibodies targeting PD-1 for the treatment of advanced metastatic melanoma. Nivolumab, a fully human IgG4 monoclonal PD-1 antibody was initially evaluated in a phase I–II study, which included a large cohort of patients with melanoma. The objective response rate was 28%, with a favorable side-effect profile.[50] Nivolumab has been tested in a randomized phase III study in comparison with investigator-chosen chemotherapy (either dacarbazine or paclitaxel and carboplatin) for patients with disease progression after ipilimumab and, for patients with *BRAF* mutation–positive disease, a BRAF inhibitor. The response rate with nivolumab was 31.7%, compared with 10.6% with investigator-chosen chemotherapy.[51] Nivolumab has also been compared with dacarbazine for first-line treatment in a randomized phase III study of 418 patients. The 1-year OS rate was 72.9% with nivolumab, compared with 42.1% with dacarbazine (HR, 0.42; $p < 0.001$), and the objective response rate was 40%, compared with 13.9% ($p < 0.001$).[52] Finally, nivolumab has demonstrated improved PFS compared to ipilimumab in a randomized phase III trial of patients with untreated melanoma.[53]

Pembrolizumab is a humanized PD-1–blocking monoclonal antibody that the FDA approved in 2014 for the treatment of advanced metastatic melanoma. Pembrolizumab was initially tested in 135 patients with advanced melanoma with an objective response rate of 37%.[54] Treatment was well tolerated. Pembrolizumab has subsequently demonstrated a benefit for OS as compared with ipilimumab in a randomized phase III trial of 834 patients who had received no more than one prior systemic therapy for advanced disease. Patients were randomly assigned in a 1:1:1 manner to receive pembrolizumab 10 mg/kg every 3 weeks or every 2 weeks or ipilimumab 3 mg/kg every 3 weeks. The response and survival rates for the two pembrolizumab schedules were similar, and both were superior to ipilimumab. The estimated 1-year survival rates were 74.1%, 68.4%, and 58.2%, respectively (HR for death for pembrolizumab every 2 weeks, 0.63; $p = 0.0005$; pembrolizumab every 3 weeks, 0.69; $p = 0.0036$). The response rates were 33.7% with pembrolizumab every 2 weeks and 32.9% for every 3 weeks, compared with 11.9% with ipilimumab ($p = 0.001$ for both comparisons).[55] Pembrolizumab has also been demonstrated to be superior to chemotherapy in a randomized trial in patients with ipilimumab-refractory disease,[56] and it has been tested in a randomized dose comparison study of 2 mg/kg and 10 mg/kg every 3 weeks in patients with ipilimumab-refractory disease. The response rate was 26% for both doses in these patients with ipilimumab-refractory disease, and rates of severe adverse events were low in both arms.[57]

Treatment with PD-1 inhibitors is associated with immune-related adverse events, though these adverse events are less frequent and less severe than with ipilimumab. However, rare but serious pulmonary toxicity (immune-mediated pneumonitis) can occur with PD-1 inhibitors and requires careful monitoring. Clinical trials with anti–PD-L1 monoclonal antibodies are also ongoing, with clear activity for patients with advanced melanoma.[58-60] Tumor expression of PD-L1 may result in a higher response rate but is not an adequate biomarker of response, as patients may or may not have a response regardless of PD-L1 expression status. Combining anti–CTLA-4 and anti–PD-1 immunotherapy (dual-checkpoint blockade) has also been tested in several clinical trials. The combination of ipilimumab (anti–CTLA-4) plus nivolumab (anti–PD-1

antibody) was initially evaluated in a phase I study of 53 patients with advanced melanoma, with objective responses observed in 40% of patients.[61] The combination was also tested in a small randomized study of 109 patients with *BRAF* wild-type disease, with an objective response rate of 61% for the combination compared with 11% for ipilimumab alone ($p < 0.001$) and a complete response rate of 22% for the combination, with durable responses observed in 82% of the patents.[62] Grade 3 or 4 adverse events occurred in half of the patients treated with the combination of nivolumab and ipilimumab; these were largely immune-related adverse events and generally reversible. A larger randomized phase III clinical trial (CheckMate 067), enrolled 945 patients with unresectable stage III and stage IV melanoma. Patients were assigned single-agent nivolumab therapy (3 mg/kg every 3 weeks), combination nivolumab (1 mg/kg every 3 weeks) plus ipilimumab (3 mg/kg every 3 weeks), or ipilimumab alone (3 mg/kg every 3 weeks for four doses). After the initial four cycles in the nivolumab arms, nivolumab was continued as maintenance. Improved PFS was seen in patients receiving single-agent or combination therapy compared to ipilimumab. Significantly more toxicity was observed for the combination arm and need for treatment discontinuation was more frequent with the combination than with monotherapy.[63] Grade 3–4 treatment-related adverse events occurred for 55% of patients, including alanine aminotransferase elevation, diarrhea, and colitis, among other immune-related toxicities. The FDA approved the combination of nivolumab and ipilimumab in 2015 based on high rates of durable responses and improved PFS, with most toxic effects reversible and manageable.

Building on the success of targeted therapies and immunotherapies, ongoing studies are combining BRAF inhibitors with new immunotherapies. However, in the first phase I study that combined vemurafenib (BRAF inhibitor) with ipilimumab, unexpected hepatotoxicity led to early closure of the clinical trial, reinforcing the need for carefully conducted clinical trials of new combination treatments.[64] A familiarity with the recognition and management of immune-related toxicity is essential for clinical oncologists in the setting of multiple newly approved immune therapies. Delayed toxicity can be observed after patients have started subsequent lines of therapy, necessitating a very low threshold for evaluation and treatment of patients with immune-mediated adverse effects, including endocrinopathies such as adrenal insufficiency, which can be life-threatening if not detected and treated early. Patients with a history of immunotherapy with CTLA-4 or PD-1 blockade or other agents should be evaluated for adrenal insufficiency when presenting with vague symptoms such as fatigue, fever, nausea, or vomiting, with blood evaluation for adrenocorticotropic hormone and cortisol levels. Patients in whom adrenal insufficiency develops often require a long-term physiologic replacement-dose steroid therapy, such as hydrocortisone 20 mg daily.

Some studies have reported high durable response rates with single agent or dual-checkpoint blockade in patients with asymptomatic central nervous system (CNS) metastasis who do not require steroids, even in the absence of any local therapies such as surgery or stereotactic radiosurgery.[65] In this select group of asymptomatic patients, first-line immunotherapy can be considered a new standard treatment option, without localized resection or stereotactic radiation therapy to isolated or oligometastatic CNS lesions. The decision to proceed with systemic immunotherapy without local therapies in patients with CNS disease should be made after multidisciplinary review and discussion, and with short interval response assessment imaging at 6 weeks, or sooner as clinically indicated, with recommendation for local therapy options in patients who do not have a response.

The efficacy of immunotherapies in uveal melanoma is extremely low, and clinical trials remain the optimal treatment option for these patients. Patients with mucosal melanoma can

have durable responses with immunotherapy, although the response rates appear lower than those for cutaneous melanoma.

Aldesleukin (interleukin-2 [IL-2]) is a potent T-cell activator. IL-2 is a well-established melanoma therapy that can cause durable complete responses. The overall response rate is 16%, with a 6% complete response rate.[66] The current FDA-approved regimen consists of two 5-day courses of IL-2 separated by a rest period of 7 to 10 days. Two high-dose regimens have been used: 600,000 IU/kg or 720,000 IU/kg, administered every 8 hours. Repeat courses can be given at 8 to 12 weeks if the disease responds to treatment. Typically, two or three courses are given when there is a good response, with a maximum of five courses. The toxicity of IL-2 is clearly dose-related. The most common side effects include hypotension, diarrhea, renal dysfunction with oliguria, respiratory failure, fever, chills, and vomiting. Many of the adverse effects of this treatment result from a capillary-leak syndrome caused by the drug. Most of the side effects are self-limiting and resolve after discontinuation. Because of low response rates and the substantial toxicity of high-dose IL-2, its use should be restricted to carefully selected patients and should be administered by experienced clinicians at established cancer treatment centers. Careful assessment of cardiac and pulmonary function is mandatory prior to initiation of high-dose IL-2 therapy.

Ongoing clinical trials are investigating the role of adoptive immunotherapy using autologous activated tumor infiltrating T cells. Among patients treated at the NCI Surgery Branch, use of TILs with prior lymphodepletion resulted in significant responses.[67] Current studies are focused on optimizing this type of treatment and applying it at other cancer centers to assess feasibility.

Finally, intralesional immune therapy with T-VEC (talimogene laherparepvec), a first-in-class oncolytic viral therapy, was approved for use in melanoma in 2015. The drug is engineered to accomplish attenuation of the virus and selective replication within the tumor and to produce granulocyte macrophage colony-stimulating factor (GM-CSF), which acts to recruit antigen-presenting dendritic cells that induce antitumor immunity. T-VEC was compared with GM-CSF in a randomized phase III trial in patients with unresected stage IIIB to IV melanoma. A durable objective response lasting longer than 6 months (the primary endpoint of the study) was observed in 16.3% (95% CI; 12.1, 20.5) of patients, compared to 2.1% with GM-CSF (95% CI; 0, 4.5]; odds ratio, 8.9; $p < 0.001$).[68] While the majority of the responses occurred in the injected lesion, shrinkage in noninjected lesions was observed as well, suggesting a systemic induction of antitumor immunity.

KEY POINTS

- Immunotherapy with PD-1 blockade (nivolumab or pembrolizumab) is a standard first-line treatment option for patients for advanced metastatic melanoma, regardless of *BRAF* mutation status.
- Dual PD-1 and CTLA-4 checkpoint blockade with nivolumab/ipilimumab also results in durable long-term responses, though with increased toxicity compared to single agent PD-1 blockade. Nivolumab/ipilimumab may also be considered as first-line therapy for patients with metastatic disease, and this combination is FDA-approved for this indication.
- All patients receiving immunotherapy should be monitored closely for immune-related adverse events.

- For patients with metastatic melanoma, the optimal sequence of therapy has not been defined. The presence or absence of *BRAF* mutation will be an important factor in selecting appropriate treatment. For patients without a *BRAF* mutation, the initial focus will be immunotherapy—either single-agent anti–PD-1 therapy or in combination with ipilimumab. For patients with a *BRAF* mutation, initial treatment options include either BRAF/MEK-targeted therapy or immunotherapy. Factors such as performance status, comorbid conditions, and burden of disease and symptoms will influence the selection of initial therapy.
- Intralesional oncolytic viral therapy can be considered for select patients with locally advanced injection-accessible lesions.

CHEMOTHERAPY

Cytotoxic chemotherapy is considered a third- or fourth-line treatment option in melanoma, after clinical trials, immunotherapy and, if indicated, BRAF-targeted therapy. While response rates are low in the general intent-to-treat population in clinical trials, some patients can derive benefit, with objective responses reported in clinical trials that are durable in some patients, and with relatively little and very predictable toxicity.

Numerous chemotherapy agents have demonstrated modest activity in the treatment of metastatic melanoma. However, neither single-agent nor combination chemotherapy has been shown to consistently improve OS. Dacarbazine remains the only FDA-approved chemotherapy agent for the treatment of metastatic melanoma. The results from clinical trials have demonstrated overall response rates of approximately 10 to 20%. Median response durations are 3 to 4 months, and long-term complete responses are seen in only 1 to 2% of patients. Doses and schedules of dacarbazine vary widely, with no data to suggest that response rates are influenced by these variables. The most commonly used regimen is 1000 mg/m^2 IV repeated every 3 weeks. Dacarbazine is generally well tolerated. The most frequent side effects are nausea and vomiting, which can be ameliorated with antiemetics. Mild to moderate myelosuppression is a common dose-related side effect.

Temozolomide is a second-generation oral alkylating agent. The results from several phase II studies suggest that temozolomide is at least as effective as dacarbazine in metastatic disease. The FDA approved temozolomide, which crosses the blood–brain barrier, in 1999 for the treatment of primary brain cancer. Although not FDA-approved for melanoma, temozolomide is often used to treat patients with advanced melanoma because of its ease of administration. A 5-day regimen with a daily dose of 150 to 200 mg/m^2 on days 1 to 5 is given every 4 weeks. The major side effect is mild to moderate myelosuppression. Mild nausea and vomiting also are common but can be controlled with standard antiemetic therapy prior to each dose. Other chemotherapy drugs with single-agent activity include cisplatin, the taxanes, carmustine, fotemustine, lomustine, and vinblastine.

Several combination chemotherapy regimens have been evaluated for patients with metastatic melanoma, with limited benefit. Paclitaxel/carboplatin combination therapies have been evaluated, with modest activity for patients with metastatic melanoma. In one study, carboplatin and paclitaxel was associated with a 20% response rate and a median PFS of 4.2 months.[69]

RADIATION THERAPY

The main indication for radiation therapy for patients with metastatic disease is the palliative treatment of symptomatic lesions, including painful bone, skin, or subcutaneous metastases. Whole-brain radiation therapy or stereotactic radiosurgery may be helpful in palliating the symptoms of brain metastases for patients. However, now that intracranial responses are observed with BRAF inhibition and with PD-1 blockade, the timing and modality of CNS radiation requires multidisciplinary discussion of the treatment intent and risks of synergistic toxicity as well as the potential benefit. Radiation therapy also is indicated for spinal cord compression.

SURGICAL RESECTION

Surgical resection is a very effective palliative treatment for isolated metastases, offering quick palliation and, in some patients, long-lasting survival. Surgical excision of solitary metastases in visceral organs can lead to survival of more than 5 years in 5 to 20% of patients.

ISOLATED LIMB PERFUSION OR INFUSION

Isolated limb perfusion or infusion is used to treat patients with melanoma that is confined to a limb, such as unresectable local recurrence and in-transit metastases. The most commonly used chemotherapy agent is melphalan, which is used in conjunction with hyperthermia, delivered in the operating room as a one-time procedure. Response rates have ranged from 40 to 80%. Alternative approaches to management of in-transit metastases include surgery when feasible as well as systemic treatment approaches as described previously.

MELANOMA IN THE ELDERLY

Elderly patients with melanoma should be treated similarly to younger patients, with attention to specific elements unique to geriatric care. Elderly patients can benefit from a partnership and communication between providers from oncology, dermatology, and internal medicine to coordinate and streamline care in order to avoid repetition and the additional burden that excessive visits may place on elderly patients. Elderly patients were included in the clinical trials leading to the approvals of all targeted and immunotherapies with no signal of increased toxicity.

SURVIVORSHIP

Melanoma is one of the most commonly diagnosed cancers, with the majority of patients diagnosed with early-stage disease; therefore, survivorship constitutes a large element of patient care. Furthermore, given the large improvements in the efficacy of systemic immunotherapy, increasing numbers of patients are now survivors with no active disease after stopping systemic therapy for stage IV disease as well, with unique features of their care. Patients with a history of melanoma live with a long-term awareness of the possibility of recurrence or of the risk of second melanomas arising. Long-term and permanent toxicity should be taken into consideration when determining a treatment plan for stage IV melanoma, and especially for adjuvant therapy, as long-term consequences related to endocrinopathies, including infertility in young patients, are not yet well defined.

Quality of life can be affected by the anxiety surrounding serial follow-up imaging for patients with high-risk melanoma, cosmetic outcomes after surgery, and lymphedema following lymph

node dissection surgery. Patients or family members may have feelings of regret regarding prior sun exposure that may have increased the risk of melanoma, and prevention of high-risk exposure remains a lifelong concern for melanoma survivors. Many patients with melanoma are empowered by their ability to educate friends and family members about the risks of sun exposure and the importance of skin exams in patients at high risk. Patient- and survivor-led advocacy and philanthropy groups play an enormous role in promoting skin health and advances in melanoma therapies. Given that the number of melanoma survivors will continue to increase, research is needed to better define optimal surveillance strategies in order to balance the risks and benefits of screening, while minimizing patient anxiety.

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SARCOMA

Scott M. Schuetze, MD, PhD

Recent Updates

- Olaratumab is a recombinant human monoclonal antibody directed against platelet-derived growth factor receptor alpha. It was approved by the U.S. Food and Drug Administration (FDA) for treatment in combination with doxorubicin for adult patients with soft-tissue sarcoma with a histologic subtype for which treatment with an anthracycline is appropriate and in which the sarcoma is not amenable to curative treatment with surgery or radiation. The addition of olaratumab (15 mg per kilogram of body weight administered intravenously on days 1 and 8 of a 21-day cycle) to doxorubicin (75 mg per square meter of body-surface area administered intravenously on day 1) resulted in a median overall survival of 26.5 months and median progression-free survival (PFS) of 6.6 months, as compared with a median overall survival of 14.7 months and median PFS of 4.1 months in patients who received doxorubicin alone in a randomized, open-label, phase II study. (Tap W, *Lancet* 2016)

Liposarcoma

- Palbociclib, a selective cyclin-dependent kinase 4/6 inhibitor, may be considered as a treatment option for patients with locally advanced or metastatic well-differentiated/dedifferentiated liposarcoma per National Comprehensive Cancer Network (NCCN) guidelines. Palbociclib treatment for patients with progressing well-differentiated/dedifferentiated liposarcoma resulted in a median PFS of 18 weeks and a 57% to 66% PFS at 12 weeks in two single-arm, phase II studies. (Dickson M, *J Clin Oncol* 2013; Dickson M *JAMA Oncol* 2016)

Osteosarcoma

- The addition of zoledronate to standard chemotherapy in treatment for patients with high-grade osteosarcoma did not improve event-free or overall survival rates as compared with standard chemotherapy alone in a randomized, open-label, phase III trial. (Piperno-Neumann S, *Lancet Oncol* 2016)

OVERVIEW

Sarcoma is the term used for cancers of connective tissue. Most sarcomas arise from mesoderm-derived cells. Sarcomas of soft tissue and bone are uncommon, constituting less than 1% of cancers occurring in adults and about 15% of cancers in children. Sarcomas are heterogeneous, with more than 50 subtypes recognized in the World Health Organization (WHO) classification of tumors of soft tissue and bone.[1] In adults, soft-tissue sarcomas are about four times more common than sarcomas of bone (12,390 compared with 3260 cases, respectively, in 2017).[2] Approximately 40% of patients diagnosed with sarcoma will die from the disease, with the majority dying from metastatic disease.[2] Appropriate multidisciplinary treatment is essential for patients presenting with sarcoma. In most cases, complete surgical removal of the primary tumor is required for cure and is often an essential component in the management of oligometastases. Radiation is also important in many sarcoma subtypes to

provide optimal local control at the site of the primary tumor or palliation of tumor-related symptoms. With appropriate multidisciplinary management, the rates of long-term survival of localized osteosarcoma and Ewing sarcoma have improved from less than 20% to greater than 70%. Similar gains in cure rates have occurred in patients with pediatric rhabdomyosarcoma but have been less impressive in other soft-tissue sarcoma subtypes. Great improvement in long-term survival rates of patients with metastatic gastrointestinal stromal tumor (GIST) has occurred after the introduction of tyrosine kinase inhibitor therapy, with 20% to 30% of patients surviving 9 to 10 years after initiation of treatment.[3]

EPIDEMIOLOGY AND ETIOLOGY

The more common subtypes of sarcoma include GIST, leiomyosarcoma, liposarcoma, and undifferentiated pleomorphic sarcoma (UPS). The subtype designation UPS has replaced the term malignant fibrous histiocytoma in the WHO classification of tumors of soft tissue and bone. Approximately 10% to 15% of soft-tissue sarcomas cannot be characterized beyond noting that they are sarcomas (sarcoma, not otherwise specified). Other relatively common subtypes include synovial sarcoma, fibrosarcoma, malignant peripheral nerve sheath tumor, and angiosarcoma. Osteosarcomas and chondrosarcomas are the two most common sarcomas arising from bone in adults. Ewing sarcoma can arise in either bone or soft tissue. Figure 14-1 indicates the relative frequency of some of these sarcoma subtypes.

Most sarcomas occur in the absence of a genetic cancer predisposition syndrome or exposure to known environmental factors including toxins, radiation, or viruses. The incidence of sarcomas increases with age, although specific subtypes, such as Ewing sarcoma, rhabdomyosarcoma (embryonal and alveolar subtypes), and osteosarcoma, occur more frequently in children and young adults. Adults younger than age 35 are at increased risk for synovial sarcoma and desmoplastic small round cell tumors; adults older than age 60 are at increased risk for myxofibrosarcoma, undifferentiated pleomorphic sarcoma, and sarcoma, not otherwise specified.

There are many genetic syndromes associated with sarcoma. Examples are Li-Fraumeni syndrome (*TP53* mutation); retinoblastoma (*RB1* gene deletion); neurofibromatosis type 1 (*NF1* mutation); Gardner syndrome (*APC* mutation); McCune-Albright syndrome (*GNAS1* mutation); Bloom, Rothmund-Thomson, and Werner syndromes (associated with loss of helicase function); Costello syndrome (*HRAS* mutation); and Nijmegen breakage syndrome (*NBN* mutation), among others.[1] In an international genomic study of more than 1000 patients with sarcoma, recognized pathogenic germline variants were detected in about 10% of patients, and a significant minority had multiple genomic variants, suggesting an interacting contribution of rare mutations to sarcoma risk.[4] People with Li-Fraumeni syndrome are at significant risk for the development of osteosarcoma or soft-tissue sarcoma. In one large study of patients with sarcoma, germline *TP53* mutations were present in about 3% of cases.[5] Referral for genetic counseling and testing should be considered in individuals younger than 46 with soft-tissue sarcoma or osteosarcoma and a family history of soft-tissue sarcoma, osteosarcoma, breast cancer, central nervous system (CNS) tumor, or adrenocortical carcinoma in a first- or second-degree relative occurring before age 56.[6] Referral to a medical geneticist should also be considered in patients with multiple cancers of the types previously listed. The most common secondary cancers in patients with retinoblastoma syndrome are leiomyosarcoma and osteosarcoma. Individuals with neurofibromatosis type 1 have a 5% to 10% risk for the development of a soft-tissue sarcoma (malignant peripheral nerve sheath tumor or GIST) in

their lifetime. Desmoid tumors (aggressive fibromatosis) are associated with Gardner syndrome.

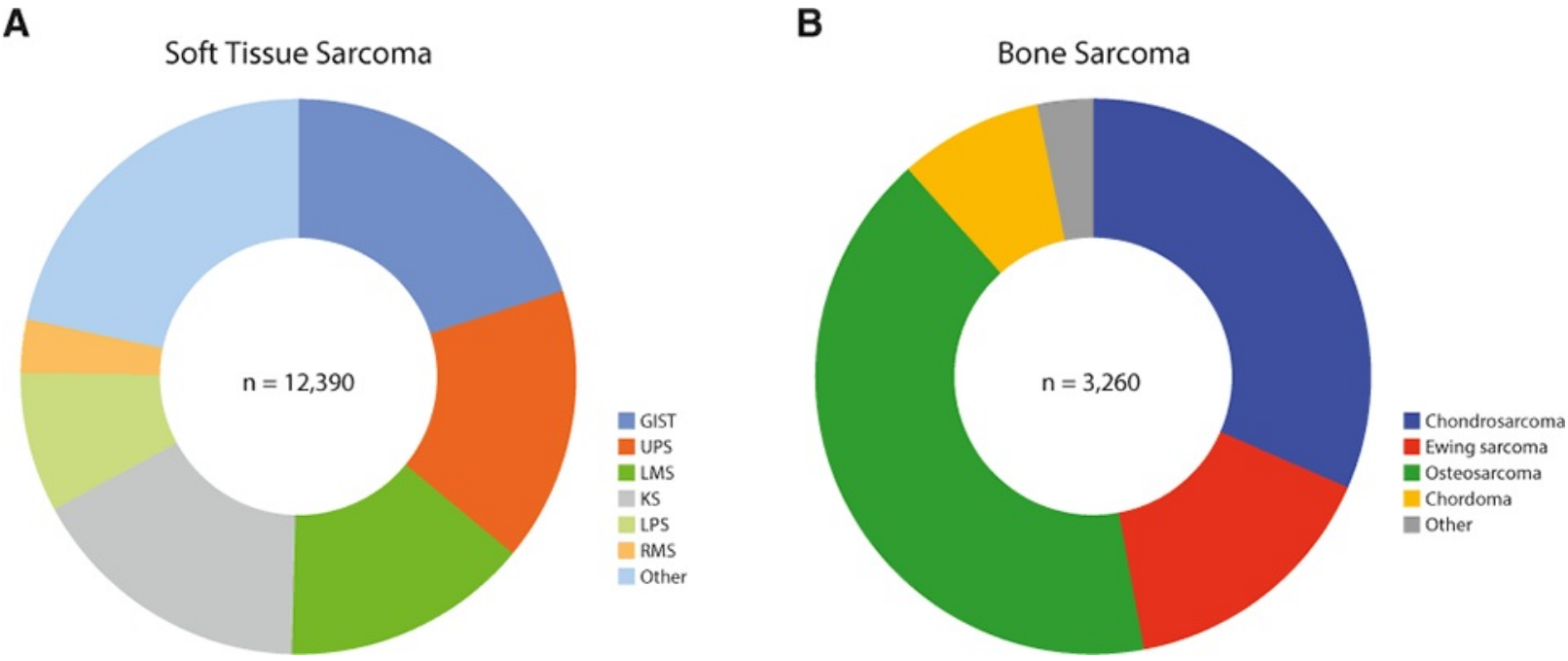

Fig. 14-1 Soft tissue and bone sarcomas: relative frequency.

The number of estimated cases and breakdown of subtypes for soft tissue and bone sarcomas is indicated. The area of each circle is proportional to the frequency of such tumors.

Abbreviations: GIST, gastrointestinal stromal tumor; MFH, malignant fibrous histiocytoma; UPS, undifferentiated pleomorphic sarcoma.

Some epidemiologic evidence associates occupational exposure to vinyl chloride or exposure to the imaging agent Thorotrast with the development of hepatic angiosarcoma, but few other environmental exposures are linked to sarcoma.[7] Studies have suggested that exposure to dioxins or phenoxyacetic acid herbicides, such as Agent Orange, increases the risk for sarcoma, but others have not; meta-analyses of such data remain inconclusive.[8-11]

There is a small but measurable long-term risk for soft-tissue or bone sarcoma after exposure to therapeutic radiation.[12] The mean latency time is 16 years (range, 4 to 30 or more). Angiosarcoma tends to have a shorter latency than other radiation-associated sarcomas. Analysis of sarcoma incidence in survivors of atomic bomb blasts suggested that moderate levels of ionizing radiation, lower than typically administered for therapy, also increased the risk for bone and soft-tissue sarcoma.[13,14] Although half of such sarcomas are high-grade, their prognoses do not appear to be worse than those of sporadic soft-tissue sarcomas of the same stage. Local control can be challenging because of the long-term effects of radiation on tissue planes and wound healing and the inability to deliver additional cytotoxic doses of radiation.

Other risk factors for the development of soft-tissue sarcoma include lymphedema (angiosarcoma) and human herpesvirus 8 infection (HHV-8; Kaposi sarcoma [KS]). KS is associated with concurrent HHV-8 and HIV infections but may also occur in the elderly in the absence of HIV. Trauma has not been causally linked to sarcomagenesis in humans but is undergoing active investigation in a transgenic mouse model of soft-tissue sarcoma.[15]

GENETIC CHARACTERISTICS

Sarcomas exhibit a wide range of genetic abnormalities, including complex chromosomal aberrations (e.g., leiomyosarcoma and undifferentiated pleomorphic sarcoma), chromosomal translocations involving transcription factors (e.g., Ewing sarcoma and synovial sarcomas), overexpression of ligands to receptor kinases (e.g., dermatofibrosarcoma protuberans and giant cell tumor of bone), gene mutations resulting in activated cellular kinases (e.g., GIST), gene amplification (e.g., well-differentiated liposarcoma), and regulatory protein inactivation (e.g., malignant peripheral nerve sheath tumor). among others (Table 14-1).[1] Approximately 30% to 40% of sarcomas have defined recurring specific genetic alterations, such as chromosomal translocation, gene amplification, or mutation, that contributes to pathogenesis. Given the broad differential diagnosis for many sarcomas, molecular analysis has proven useful in the definitive diagnosis of specific sarcoma subtypes. Modern analysis of chromosome translocations using fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR) can be performed on paraffin-embedded, fixed tissue. Tumor genome sequencing may add to diagnosis and prognostication for sarcomas in the future as genes characteristic of each subtype of sarcoma are recognized and validated.

KEY POINTS

- Sarcomas account for about 1% of cancer in adults; the incidence of sarcomas of soft tissue are 3 to 4 times more common than of bone.
- Individuals with certain genetic cancer susceptibility syndromes have an increased risk for sarcoma.
- Therapeutic radiation confers a small but definite risk for the development of sarcoma.
- HHV-8 infection is associated with Kaposi sarcoma.
- Approximately 30% to 40% of sarcomas have defined recurring specific genetic alterations such as chromosomal translocation, gene amplification, or mutation that contributes to pathogenesis.

CLINICAL PRESENTATION AND DIAGNOSIS

Soft-tissue sarcomas generally present as painless, growing masses, whereas bone sarcomas are often associated with pain in the region of bone involvement. Soft-tissue sarcomas are generally differentiated from benign tumors, such as lipomas, by either their texture (generally firmer) or their location (typically in deep to subcutaneous fat). Lipomas remain at least 100 times as common as their neoplastic counterpart. For many masses, a diagnosis of sarcoma can be determined with a core needle biopsy, although this procedure may not yield adequate tissue to classify tumor subtype or grade. When diagnostic material cannot be obtained by core needle biopsy, incisional biopsy is performed, with the understanding that the subsequent oncologic resection will likely need to encompass the prior biopsy site and scar. Fine-needle aspiration generally is inadequate to confirm the diagnosis of sarcoma, and its use usually is limited to confirming the recurrence of sarcomas. Similarly, attention must be paid to the biopsy technique when attempting to diagnose a sarcoma of bone because the technique used has implications for the extent of subsequent definitive surgery.

Dermal vascular neoplasms such as angiosarcoma and KS often appear as indistinct red,

purple, blue, or brown discoloration in the skin (Fig. 14-2). Often, a masslike lesion is not present. Angiosarcoma occurring in the dermis in the elderly and KS occurring in the setting of HIV/AIDS frequently involve the head/neck and are often multicentric. KS occurring in the absence of HIV infection (often referred to as "classic KS") frequently involves the legs and feet. Advanced KS (usually in the setting of AIDS) may involve lymph nodes (resulting in severe edema), the oropharynx, the gastrointestinal tract, or the respiratory tract. Approximately 30% of patients with HIV and cutaneous KS will have involvement of the gastrointestinal tract, which may result in dysphagia, blood loss/anemia, or obstipation. Diagnosis of cutaneous vascular sarcoma is usually made by skin biopsy and appropriate immunohistochemistry (e.g., CD31, CD34, and ERG for angiosarcoma and ERG and HHV-8 for KS).

Table 14-1 Representative Genetic Alterations in Sarcomas[1,15]

Class of Alteration	Sarcoma Subtype	Genetic Change	Frequency
Activating mutation	Gastrointestinal stromal tumor	*KIT* or *PDGFRA* mutation	> 90%
Ligand expression	Dermatofibrosarcoma protuberans	PDGF	~ 100%
	Giant cell tumor of the bone	RANK ligand	~ 100%
Inactivation/deletion	Myxofibrosarcoma	*NF1* mutation	~ 10% to 20%
	Malignant peripheral nerve sheath	*NF1* deletion	> 90%
Gene amplification	Well-differentiated and dedifferentiated liposarcoma	*CDK4, MDM2*	> 90%
Translocation	Synovial sarcoma	t(X;18) *SYT-SSXI* or *SYT-SSX2*	> 90%
	Ewing sarcoma	t(11;22) *EWSR1-FLI1*	> 85%
		t(21;22) *EWSR1-ERG*	5% to 10%
	Alveolar rhabdomyosarcoma	t(2;13) *PAX3-FOXO1*	~ 70%
		t(1;13) PAX7-FOXO1	~ 15%

KEY POINTS

- Soft-tissue sarcomas often present as painless, enlarging masses.
- Bone sarcomas are usually associated with pain.
- Core needle or incisional biopsy is required to obtain sufficient tumor material for definitive diagnosis and sarcoma subtype classification.

PATHOLOGIC FEATURES AND PROGNOSTIC FACTORS

Because of the diversity of sarcoma subtypes and their differential diagnoses, such as sarcomatoid carcinoma (which is treated as a carcinoma, not a sarcoma), uterine carcinosarcoma, melanoma, or lymphoma, the pathologist is a critical contributor to patient care. Important considerations for sarcoma staging include an evaluation of sarcoma grade and histologic subtype. It is important to recognize that pathologists may use different grading systems, with two grades (low and high), three grades (low, intermediate, and high), or four grades (grades 1 to 4, with higher numbers indicating more extensive involvement). Evaluation of the extent of sarcoma is generally accomplished by magnetic resonance imaging (MRI) or computed tomography (CT) of the site of the primary tumor and imaging of the chest. For

patients with high-grade sarcoma, a chest CT is usually performed to evaluate for the presence of lung metastasis and to serve as a baseline for future comparison. CT of the abdomen/pelvis is performed for sarcomas originating in the abdomen, pelvis, or retroperitoneum and for myxoid liposarcoma of an extremity, which has an unusual propensity to spread to these body regions. Myxoid liposarcoma may also spread to the spine or bone, for which additional imaging (e.g., spine MRI or technetium bone scan) is needed to fully stage the disease. For high-grade bone sarcomas, radionuclide bone scan or positron-emission tomography (PET) is recommended to evaluate the presence of metastases to bone. In the absence of symptoms, the yield from routine imaging of the brain in patients with tumors originating outside the head/neck region or left side of the heart is low. PET has relatively low accuracy in staging soft-tissue sarcomas because of false-negative and false-positive findings.

The American Joint Committee on Cancer (AJCC) staging system for soft-tissue sarcoma includes the tumor grade, size, and location, as well as the presence of nodal disease or overt metastatic disease (Table 14-2).[16] The preferred histopathologic grading system, as used in the 8th edition of the *AJCC Cancer Staging Manual,* is a three-tier (low, intermediate, and high) classification.[17] Nodal metastatic disease is an unfavorable prognostic feature, but it is associated with better overall survival than bloodborne metastatic disease. Nodal metastatic disease is observed in fewer than 10% of patients with soft-tissue sarcomas; however, certain subtypes of sarcoma, including angiosarcoma, clear cell sarcoma, epithelioid sarcoma, extraskeletal Ewing sarcoma, pediatric rhabdomyosarcoma, and synovial sarcoma, have a relatively higher propensity to spread through lymphatics. Sentinel node biopsy evaluations have been studied in the management of localized clear cell, epithelioid, and synovial sarcomas, but the yield of positive nodes is low.[18]

Histology, grade, and completeness of resection are the most important factors in determining the risk for relapse. Of primary importance in determining overall survival is tumor grade; overall survival is also dependent on the initial size and location of the tumor. For example, as the size of the primary tumor increases, the risk for relapse increases, even within a given stage (Table 14-3), and the 8th edition of *AJCC Cancer Staging Manual* now includes five categories of size for soft-tissue sarcoma.[19,20] It is important to recognize that sarcomas of different primary sites (and typically different histologic subtypes) are associated with different patterns of distant and local failure (Table 14-4). A nomogram using tumor histology, grade, size, depth, and patient age is available to help estimate the risk for death from soft-tissue sarcoma after definitive local therapy.[21] A separate validated nomogram to help estimate risk of recurrence and death after resection of retroperitoneal soft-tissue sarcoma is available.[22]

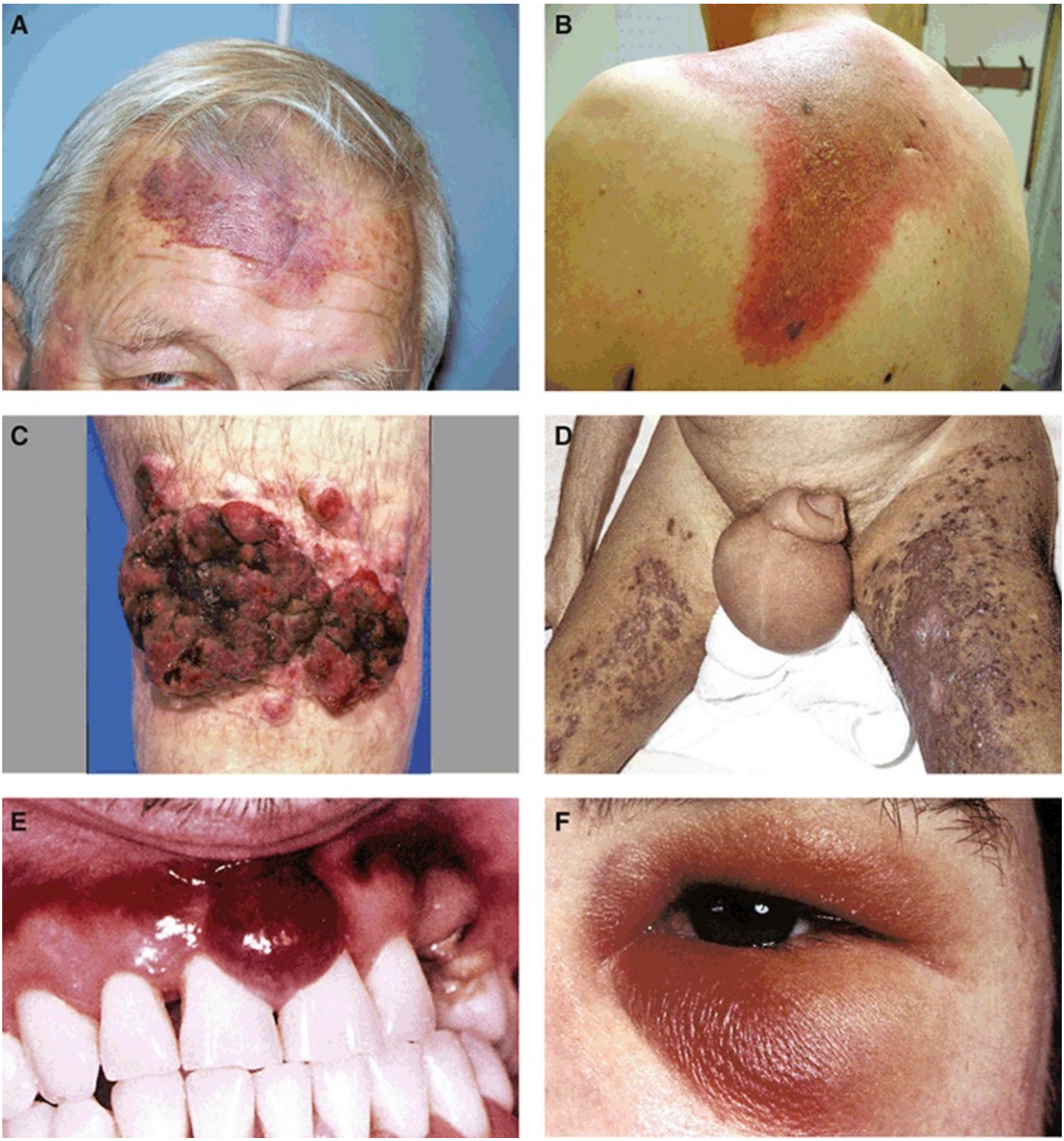

Fig. 14-2 Selected manifestations of angiosarcoma and Kaposi sarcoma.

(A) Angiosarcoma involving the scalp. (B) Angiosarcoma arising in prior radiation field. (C) Angiosarcoma associated with chronic lymphedema. (D) Kaposi sarcoma involving thighs causing lymphedema and scrotal edema. (E) Kaposi sarcoma of gingiva. (F) Kaposi sarcoma of head causing periorbital erythema and edema.

The AJCC staging system for bone cancers is shown in Table 14-5. Primary malignant lymphoma of bone and multiple myeloma are not included in the bone cancer staging system. Metastases of osteosarcomas to lymph nodes are extremely unusual and constitute stage IV disease. Patients with osteosarcoma with metastases only to the lungs have lower-stage disease because surgical resection of lung metastases can be curative.

Table 14-2 **American Joint Committee on Cancer Staging System for Soft-Tissue Sarcoma Arising in Trunk, Extremity, or Retroperitoneum**[16]

Stage	Three-Grade System	T*	N†	M‡
IA	Grade 1	T1	N0	M0
IB	Grade 1	T2, T3, T4	N0	M0
II	Grades 2 and 3	T1	N0	M0
IIIA	Grades 2 and 3	T2	N0	M0
IIIB	Grades 2 and 3	T3, T4	N0	M0
	Any grade	Any	N1	M0
IV	Any grade	Any	Any	M1

*T1, tumor of no more than 5 cm in greatest dimension; T2, tumor of more than 5 cm and less than or equal to 10 cm in greatest dimension; T3, tumor more than 10 cm and less than or equal to 15 cm in greatest dimension; T4, tumor more than 15 cm in greatest dimension.
†N0, no lymph node metastasis; N1, lymph node metastasis.
‡M0, no distant metastasis; M1, distant metastasis.
The original source for this material is the *AJCC Cancer Staging Manual*, 8th Edition (2017) published by Springer Science and Business Media LLC, www.springerlink.com.

KEY POINTS

- Tumor grade is a key factor in sarcoma staging, treatment, and patient prognosis. Patients with low-grade sarcoma have low risk for metastases and excellent prognosis. Patients with high-grade (grade 3) sarcoma are at high risk for metastases.
- The risk of sarcoma metastasis increases with increasing size of the sarcoma.
- Staging soft-tissue or bone sarcoma should include imaging of the lung because the lung is the most common location for metastases. Staging disease in patients diagnosed with intermediate- or high-grade bone sarcoma includes evaluation of bone for presence of metastases.

TREATMENT OF NON-GIST SOFT-TISSUE SARCOMAS

GENERAL PRINCIPLES

The primary curative treatment for most sarcomas of soft tissue is surgery. A planned oncologic resection to remove the tumor intact with a rim of normal tissue at the surgical margin (R0 resection) results in a lower risk for local relapse and better long-term patient survival than removal in which sarcoma touches the surgical margin (R1 resection).[23]

Table 14-3 5-Year Disease-Free Survival Rates According to Size of High-Grade Soft-Tissue Sarcoma	
Size of Tumor (cm)*	**5-Year Disease-Free Survival Rate (%)**
2.6 to 4.9	77
5.0 to 9.9	62
10.0 to 14.9	51
15.0 to 20.0	42
> 20.0	17

*Tumors 5 cm or smaller were generally treated with surgery; tumors larger than 5 cm were typically treated with surgery and radiation.

Adjuvant radiation to the site of the primary tumor is a standard of care for all intermediate- or high-grade soft-tissue sarcomas of the extremities or body wall that are larger than 5 cm. Adjuvant radiation is usually administered after resection of low-grade soft-tissue sarcomas that are larger than 5 cm and involve the extremities or body wall if the tumor is resected with a close (< 1 cm) or positive surgical margin and reoperation would be result in morbidity. Patients with soft-tissue sarcoma smaller than 5 cm occurring in an extremity or body wall do not uniformly require adjuvant radiation following an R0 resection.[24] One exception to the general guidelines for adjuvant radiation is well-differentiated liposarcoma/atypical lipomatous tumor that arises in a location amenable to additional nonmutilating surgery in a case of local recurrence. Adjuvant radiation is not used in this situation because this subtype of sarcoma has a very indolent clinical course and negligible risk for metastasizing. Radiation therapy using external-beam radiation[25] or brachytherapy[26] has been effective as an adjuvant to surgery for soft-tissue sarcomas of the extremities in randomized studies. A Canadian randomized study of preoperative as compared with postoperative radiation as an adjunct to complete resection of extremity soft-tissue sarcoma demonstrated similar rates of local disease control. Treatment arms were balanced with regard to tumor grade (83% of patients with intermediate- or high-grade sarcoma and 17% with low-grade sarcoma), size (65% with tumors 10 cm or larger), and location (80% in the leg and 20% in the arm). The risk for wound complications (delayed healing, infection, or need for reoperation) is increased (most significantly in the leg) with preoperative radiation, but the treatment field is smaller and the radiation dose is lower than with postoperative radiation.[27] The risk for late complications, including fibrosis and lymphedema, appears greater with the larger field treated and higher dose used in postoperative radiation.[28] One nonrandomized phase II study of preoperative image-guided radiation therapy for extremity soft-tissue sarcoma suggested that late-effect radiation toxicity (e.g., fibrosis, edema, and joint stiffness) may be significantly reduced by narrowing gross target volume exposed to high-dose radiation using three-dimensional conformal or intensity-modulated techniques.[29] Moderate or more severe radiation toxicity developed in approximately 10% of patients; however, 37% experienced postoperative wound complications. The in-field sarcoma 2-year relapse rate was 11%. The timing of radiation should be decided in conjunction with the orthopedic or surgical oncologist performing the definitive procedure because of the effect on the postoperative course and longer-term complications.

Table 14-4 **Site of Recurrence According to Primary Site of Soft-Tissue Sarcoma**

Primary Site	Local	Lung	Other	Multiple Sites
Extremity (%)	10	70	15	5
Trunk (%)	41	29	12	18
Retroperitoneum (%)	30	17	6	47

In contrast to the benefit of radiation for soft-tissue sarcomas of the extremities or body wall, there is no clear role for radiation for retroperitoneal or visceral sarcomas resected with clear or microscopically positive margins; the doses that can be administered postoperatively for abdominal sarcomas generally are not tumoricidal because of the dose limits for radiation for normal organs. Postoperative radiation may be used in highly selected cases in which the region of microscopic residual is known and regrowth of sarcoma in that location would cause significant morbidity. Preoperative radiation may be considered for high-grade or large abdominal or retroperitoneal sarcomas because the tumor serves as its own tissue expander, pushing normal abdominal components, such as the bowel, out of the radiation field. This anatomic feature increases the likelihood that a tumoricidal dose of radiation can be delivered to the abdomen. Intraoperative radiation has mostly been used for local control when sarcoma extends to the surgical margin adjacent to critical structures or after resection of local recurrence in a previously irradiated field; it is not widely available. New techniques such as image-guided radiation therapy or proton or carbon ion radiation are useful for treatment of sarcoma in anatomic areas where there is little tolerance for radiation scatter, such as the spine, sacrum, and base of the skull.

Table 14-5 **American Joint Committee on Cancer Staging System for Bone**[16]

Stage	Grade (four tiers)	T*	N†	M‡
IA	1 to 2 (low)	T1	N0	M0
IB	1 to 2 (low)	T2, T3	N0	M0
IIA	3 to 4 (high)	T1	N0	M0
IIB	3 to 4 (high)	T2	N0	M0
III	3 to 4 (high)	T3	N0	M0
IVA	Any	Any	N0	M1a
IVB	Any	Any	N1	Any
	Any	Any	Any	M1b

*T1, tumor of no more than 8 cm in greatest dimension; T2, tumor of more than 8 cm in greatest dimension; T3, discontinuous tumor in primary bone site.
†N0, no lymph node metastasis; N1, lymph node metastasis.
‡M0, no distant metastasis; M1a, lung metastasis; M1b, other distant metastasis.
The original source for this material is the *AJCC Cancer Staging Manual*, 8th Edition (2017) published by Springer Science and Business Media LLC, www.springerlink.com.

KEY POINTS

- Surgical resection remains the standard of care for most sarcomas.
- Adjuvant or neoadjuvant external-beam radiation is used for larger soft-tissue sarcomas (> 5 cm in greatest dimension) arising in extremities or body wall.
- Adjuvant radiation may be used for smaller soft-tissue sarcomas in areas in which local recurrence would be difficult to manage using surgery.
- Adjuvant radiation is usually avoided in the initial treatment of well-differentiated liposarcoma/atypical lipomatous tumors of the extremity or body wall because of the low risk for metastatic disease in this histologic type of sarcoma and the possibility for repeated resection if there is local recurrence.
- Adjuvant radiation is not generally recommended after resection of retroperitoneal or visceral sarcomas.

ADJUVANT CHEMOTHERAPY

The role of chemotherapy in the preoperative or postoperative setting for adult soft-tissue sarcoma remains controversial. Adjuvant chemotherapy is generally not used to manage soft-tissue sarcoma less than 5 cm in size, regardless of tumor grade, or confined to a superficial location because of the low risk for metastases. Notable exceptions to this rule are extraskeletal Ewing sarcoma and pediatric rhabdomyosarcoma, which are discussed later. Many of the trials of adjuvant chemotherapy have enrolled patients with AJCC stage IIB or III

disease because of the high risk for metastases. In 1997, the Sarcoma Meta-analysis Collaboration (SMAC) published the finding of significant benefit from adjuvant doxorubicin-based chemotherapy in time to local and distant recurrence and recurrence-free survival in patients with localized soft-tissue sarcoma.[30] There was a trend, that did not reach statistical significance, toward improved overall survival in patients receiving chemotherapy, with an absolute benefit of 4% (7% for patients with extremity sarcoma) at 10 years, representing improvement in survival rate from 50% to 54%. A newer meta-analysis that included more contemporary trials not included in the original SMAC analysis showed a statistically significant survival benefit for adjuvant chemotherapy, with an odds ratio of 0.56 and absolute average overall survival risk reduction of 10% for anthracycline/ifosfamide combination therapy.[31] Adjuvant treatment with doxorubicin without ifosfamide was associated with an absolute reduction in sarcoma recurrence risk of 9% but was not associated with a significant improvement in overall survival. An Italian randomized, multisite study of epirubicin/ifosfamide given for five cycles as compared with no adjuvant chemotherapy after resection of high-grade soft-tissue sarcomas greater than 5 cm (median diameter, 10 cm) of the extremities or the pelvic girdle observed an overall survival benefit for patients who received adjuvant chemotherapy.[32] With longer follow-up, the 5-year overall survival remained superior for the study arm that used adjuvant chemotherapy (66% vs. 46%; $p = 0.04$).[33] An overall survival benefit from adjuvant chemotherapy was not confirmed in a larger randomized study performed in Europe.[34] The study included sarcomas occurring at any site, but the majority were sarcomas of the extremity or proximal limb girdle. The study was designed to enroll only patients with grade 2 or 3 tumors; however, 6% of the patients had grade 1 sarcoma. Fewer than 75% of the patients randomly assigned to adjuvant chemotherapy completed five cycles of treatment, and the dose of ifosfamide used (5 g per square meter per cycle) was lower than the dose used in the aforementioned Italian trial. However, a retrospective analysis of the data set from this larger European Organization for Research and Treatment of Cancer (EORTC) trial and a previous EORTC randomized adjuvant chemotherapy trial reported a significant improvement in relapse-free survival for patients age 30 or older receiving chemotherapy but not in younger patients.[35] Any potential benefit from adjuvant chemotherapy along with the expected, and possibly severe, toxicity should be discussed with individual patients.

There are patients for whom adjuvant therapy is not indicated. Adjuvant chemotherapy for soft-tissue sarcomas that arise from visceral or abdominal sites has not shown a survival benefit, and surgery alone remains a good standard of care. In addition, there are a number of sarcoma subtypes (e.g., alveolar soft part sarcoma, epithelioid sarcoma, clear cell sarcoma, extraskeletal myxoid chondrosarcoma, and hemangiopericytoma) that are known to have poor sensitivity to doxorubicin/ifosfamide chemotherapy, in which the risks of adjuvant chemotherapy outweigh the potential benefit.

In contrast to adjuvant therapy for adult-type soft-tissue sarcoma, adjuvant or neoadjuvant chemotherapy and radiation have greatly improved overall survival for patients with pediatric rhabdomyosarcoma (e.g., embryonal and alveolar rhabdomyosarcoma) and extraskeletal Ewing sarcoma regardless of the age of the patient at the time of diagnosis. Although these sarcomas are typically seen in the pediatric population and are found less frequently in adults, treatment for adults follows the same schedules of therapy as those for pediatric patients when feasible. Neoadjuvant/adjuvant chemotherapy should be administered to all patients with embryonal or alveolar rhabdomyosarcoma or extraskeletal Ewing sarcoma who have a good clinical performance status, adequate organ function, and sufficient bone marrow reserve to tolerate such therapy. The treatment of extraskeletal Ewing sarcoma is similar to that of Ewing

sarcoma occurring in bone (see section on Ewing sarcoma). Based on phase III data, combination vincristine, dactinomycin, and cyclophosphamide form the backbone of adjuvant chemotherapy for most patients with primary pediatric-type rhabdomyosarcomas[36]; although for adult patients, doxorubicin is often substituted for dactinomycin until a cumulative dose of approximately 450 mg/m^2 is reached. In contrast to embryonal and alveolar rhabdomyosarcoma, for which chemotherapy is recommended, pleomorphic rhabdomyosarcoma is an "adult-type" high-grade soft-tissue sarcoma; thus, the role of adjuvant chemotherapy is less clearly defined. Spindle cell/sclerosing rhabdomyosarcoma is an uncommon variant that affects children and adults with a high rate of metastasis and relative resistance to chemotherapy in adults. Standard chemotherapy treatment of this disease has not been established.

KEY POINTS

- Adjuvant chemotherapy with anthracycline (doxorubicin or epirubicin) and ifosfamide reduces the risk of sarcoma recurrence and may improve overall survival in patients with chemotherapy-sensitive soft tissue subtypes who have a high risk for the development of metastases.
- Patients with localized extraskeletal Ewing sarcoma should receive neoadjuvant/adjuvant vincristine/doxorubicin/cyclophosphamide alternating with ifosfamide/etoposide if not medically contraindicated.
- Embryonal and alveolar rhabdomyosarcoma are aggressive cancers with a propensity for nodal and distant metastases. They are best managed using surgery, adjuvant radiation and/or multiagent chemotherapy at centers with experience in treating these "pediatric" soft-tissue sarcomas.

METASTATIC NON-GIST SOFT-TISSUE SARCOMA

As single drugs or in combination, anthracyclines such as doxorubicin and the alkylating agent ifosfamide yield the best response rates for metastatic non-GIST sarcoma (rates of 10% to 25% for each drug in various studies).[37] Doxorubicin and ifosfamide are not synergistic, although the combination may be used when patients are symptomatic and rapid reduction in tumor burden is desired for palliation. A randomized EORTC trial of doxorubicin 75 mg/m^2 per cycle combined with ifosfamide 10 g/m^2 per cycle demonstrated an improved objective response rate (26% with the combination and 14% with doxorubicin alone) but similar overall survival rates, as compared with the same dose of doxorubicin alone for up to six cycles in patients with localized unresectable or metastatic, high-grade soft-tissue sarcoma.[38] The median progression-free survival (PFS) was significantly higher (7.4 months for doxorubicin/ifosfamide vs. 4.6 months for doxorubicin), and the rate of primary progression was lower for the combination arm (13%) than the doxorubicin arm (32%). Study enrollment was limited to patients with good performance status and age younger than 60; however, 18% of patients receiving the combination discontinued treatment because of toxicity prior to completing six cycles, as compared with 3% of patients receiving doxorubicin alone. The rate of death from toxic effects was low (< 2%) and similar in the two treatment arms. A

recommendation by the authors on the basis of the study results is to use sequential single-agent therapy in the palliative setting when there are minimal symptoms from sarcoma and to consider combination therapy if sarcoma regression would relieve acute symptoms or improve the likelihood of tumor control from surgery or radiation. More recently, an open-label, randomized phase II trial of doxorubicin 75 mg/m^2 administered on day 1 in combination with olaratumab (a human recombinant monoclonal antibody directed against platelet-derived growth factor receptor alpha) administered on days 1 and 8 of each cycle, as compared with doxorubicin alone given for up to eight cycles and with continuation of single-agent olaratumab in patients with at least stable disease following cycle 8 demonstrated significant improvement in median PFS and OS in adults with locally advanced or metastatic soft-tissue sarcoma not previously treated with an anthracycline.[39] More than 50% of the patients in the trial had previously received chemotherapy for treatment of sarcoma. The median PFS and OS were 6.6 and 26.5 months, respectively, in the combination treatment arm and 4.1 and 14.7 months, respectively, in the arm treated with doxorubicin alone. Eighteen percent of the patients in the combination arm had an objective tumor response, as compared with 12% in the doxorubicin-alone arm. Neutropenia, mucositis, nausea, vomiting, and diarrhea were more common in the combination arm, but the rates of febrile neutropenia (13% vs. 14%) were similar between the combination and doxorubicin-alone arms. An infusion-related adverse reaction to the antibody occurred in 13% of the patients receiving olaratumab. The U.S. Food and Drug Administration (FDA) approved olaratumab in combination with doxorubicin as treatment for adults with soft-tissue sarcoma not curable by surgery or radiation and in which treatment with an anthracycline is appropriate. A randomized, double-blind, phase III trial of doxorubicin with or without olaratumab in a similar patient population to confirm results of the phase II trial completed enrollment in 2016; PFS and OS results are pending longer follow-up.

At least four studies have demonstrated activity of the combination of gemcitabine and docetaxel in leiomyosarcoma[40-42]; the combination is also active against undifferentiated pleomorphic sarcoma. Progression-free and overall survival rates were improved for patients who received gemcitabine/docetaxel as compared with gemcitabine alone, even at a higher gemcitabine dose.[42] However, as borne out by toxicity data, the docetaxel dose from this study (100 mg/m^2 per cycle) is too high for routine use, and many physicians recommend a docetaxel dose of 75 mg/m^2 per cycle.[42] A phase III trial confirmed activity of docetaxel administered at 75 mg/m^2 with gemcitabine for uterine leiomyosarcoma in which an objective tumor response rate of 32% and median progression-free survival (PFS) of 6 months was demonstrated.[43] No benefit in response rate, PFS, or overall survival was seen in this trial from the addition of bevacizumab to gemcitabine and docetaxel. There is no consensus as to the duration of therapy for metastatic disease. Some physicians treat until progression or toxicity, whereas others administer a defined number of cycles or to maximum clinical or tumor response and then closely follow patients off therapy for symptoms/signs of tumor progression. In the uterine leiomyosarcoma trial previously discussed, about 25% of patients with objective tumor response or stable disease stopped therapy as a personal preference after receiving a median of nine cycles of chemotherapy. The median time to progression after stopping treatment in this group was 6 months; this ranged to as long as 19.5 months, illustrating that some patients may have prolonged tumor control after chemotherapy.

Pazopanib is an oral multikinase inhibitor that was approved as treatment for patients with locally advanced or metastatic soft-tissue sarcoma after treatment with standard chemotherapy based on results of a phase III, randomized, placebo-controlled trial that demonstrated

significant improvement in median PFS in patients receiving pazopanib as compared with placebo (20 vs. 7 weeks).[44] Objective sarcoma responses were infrequent—6% in the group receiving pazopanib. Median overall survival was not significantly different between the groups taking pazopanib compared with those taking placebo (12.5 vs. 10.7 months). Patients with liposarcoma or GIST were not included in the trial. Notable severe toxicities experienced by more patients taking pazopanib compared with those taking placebo included fatigue, anorexia, nausea, mucositis, hypertension, diarrhea, rash/desquamation, hypopigmentation, and decline in cardiac ejection fraction. The recommended starting dose is 800 mg daily.

Trabectedin is a cytotoxic agent that was approved by the FDA for use in patients with unresectable or metastatic leiomyosarcoma or liposarcoma after prior treatment with an anthracycline-containing regimen. An early randomized, open-label, phase II study of trabectedin in patients with advanced/metastatic, pretreated leiomyosarcoma or liposarcoma demonstrated a longer median PFS and time to progression in patients treated with a 24-hour infusion once every 3 weeks as compared with a 3-hour infusion once weekly for 3 out of 4 weeks per cycle.[45] Treatment with trabectedin led to a 45% reduction ($p < 0.001$) in risk for sarcoma progression or death compared with dacarbazine in a randomized, open-label, international phase III study of trabectedin administered over 24 hours compared with dacarbazine treatment for patients with advanced/metastatic leiomyosarcoma or liposarcoma.[46] Patients had previously been treated with an anthracycline and at least one other chemotherapeutic regimen, excluding dacarbazine and trabectedin. Objective response rates were less than 10% and not significantly different between the trabectedin and dacarbazine arms (9.9% and 6.9%, respectively). The median PFS was 4.2 months with trabectedin compared with 1.5 months with dacarbazine. An interim analysis of overall survival showed a 13% difference ($p = 0.37$) in risk for death favoring trabectedin. Principal adverse events of trabectedin are neutropenia, anemia, thrombocytopenia, increased transaminases, increased creatine kinase, fatigue, and nausea. Treatment with trabectedin led to a 1.2% incidence of rhabdomyolysis and a 2.1% incidence of treatment-related death; this did not occur in the dacarbazine-treated arm. Trabectedin is a vascular irritant and may result in tissue necrosis after extravasation; therefore, it should be infused through a central venous catheter. Elderly patients (older than age 70) do not have increased adverse event rates from trabectedin compared with younger individuals.[47]

Eribulin is an antimitotic agent that inhibits microtubule function and has demonstrated improvement in overall survival compared with dacarbazine in patients with pretreated, locally advanced or metastatic leiomyosarcoma or liposarcoma in a phase III randomized, open-label trial.[48] A planned subgroup analysis stratified by sarcoma subtype identified a statistically significant improvement in PFS and OS in patients with liposarcoma treated with eribulin as compared with dacarbazine. There was a 1.2-month difference in median PFS and a 7-month difference in OS in favor of eribulin. No difference in PFS or OS was seen between treatment arms in patients with leiomyosarcoma. Based on these results, the FDA approved eribulin as treatment for patients with unresectable or metastatic liposarcoma who have previously received an anthracycline. Patients treated in the phase III study had previously received at least an anthracycline and one other chemotherapy. Eribulin 1.4 mg/m^2 was administered over 2 to 5 minutes on days 1 and 8 of a 21-day cycle. The most frequent adverse events were neutropenia, fatigue, nausea, alopecia, and constipation. Eribulin failed to demonstrate significant antitumor activity in synovial sarcoma as well as in a cohort with undifferentiated, unspecified, and fibrohistiocytic sarcomas in a four-cohort, single-arm, phase II trial.[49]

Because sarcomas are a biologically heterogeneous group of diseases, it is not surprising

that specific sarcoma subtypes have distinct sensitivity patterns to chemotherapy. Ifosfamide is particularly active for synovial sarcoma and myxoid liposarcoma and appears to be less active for leiomyosarcomas. Dacarbazine has modest activity against leiomyosarcoma, and paclitaxel is active against angiosarcomas. Studies have demonstrated activity of sorafenib against angiosarcomas and desmoid tumors, and sunitinib and cediranib against alveolar soft part sarcoma.[50-53] The combination of temozolomide and bevacizumab, and sunitinib have activity in solitary fibrous tumor.[54,55]

Improved understanding of the biology of certain connective-tissue tumors has led to the clinical introduction of serine/threonine and tyrosine kinase inhibitors in the management of disease. Angiomyolipomas are benign tumors that often occur in patients with tuberous sclerosis and lead to serious morbidity or death. Loss of tuberous sclerosis complex results in constitutive activation of the mammalian target of rapamycin complex 1 (mTORC1), which is thought to be responsible for tumor growth. Everolimus is an inhibitor of mTORC1, and treatment of patients with angiomyolipomas resulted in an objective tumor response rate of 42% using 10 mg everolimus daily compared with 0% using placebo in a double-blind, randomized trial.[56] The estimated tumor progression-free rates at 6 months were 98% for everolimus and 83% for placebo. Adverse effects attributed to everolimus in greater than 20% of patients were stomatitis, nasopharyngitis, acne-like skin reaction, headache, cough, and hypercholesterolemia. Everolimus is approved for the treatment of angiomyolipoma associated with tuberous sclerosis and not requiring immediate surgery. Inhibitors of mTORC1 (e.g., sirolimus and everolimus) also have activity in other perivascular epithelioid cell tumors (PEComas), including lymphangioleiomyomatosis.[57]

Other examples of rare connective-tissue tumors significantly affected by inhibitors of kinases include dermatofibrosarcoma protuberans (DFSP), with overexpression of platelet-derived growth factor, and tenosynovial giant cell tumor/pigmented villonodular synovitis (TGCT/PVNS), with overexpression of colony-stimulating factor 1. Both of these tumors may be effectively controlled using imatinib.[58,59] Treatment of DFSP with imatinib resulted in an objective response rate of 46% and a median time to progression of about 20 months, making it a good option for patients in whom wide resection would result in significant morbidity or in those who have unresectable or metastatic disease. Tumor control was similar using imatinib 400 mg once daily compared with 400 mg twice daily. Cyclin-dependent kinase 4 (CDK4) is frequently amplified along with MDM2 in well-differentiated and dedifferentiated liposarcoma. Treatment of patients with well-differentiated or dedifferentiated liposarcoma using the selective CDK4 inhibitor palbociclib resulted in one objective tumor response and a median PFS of 18 weeks in two separate single-arm, open-label, phase II trials.[60,61] Palbociclib 125 mg daily for 21 consecutive days every 28 days was better tolerated than 200 mg daily for 14 days every 21 days. The most common adverse events were neutropenia, anemia, and thrombocytopenia. Improved molecular and cytogenetic methods, including next-generation sequencing of sarcomas, are leading to additional associations of recurrent molecular changes within specific sarcoma subtypes. These changes will need to be validated as important drivers of oncogenesis, and new drugs targeting these changes will need to be evaluated in prospective, controlled trials before a “targeted” therapy is adopted as standard treatment.

KEY POINTS

- Doxorubicin and ifosfamide are the most effective single drugs for metastatic non-GIST

adult soft-tissue sarcomas. The benefit of these two drugs appears additive, not synergistic. Sequential single-agent treatment for metastatic disease is a reasonable approach for many patients with metastatic disease.

- Doxorubicin combined with olaratumab improved overall survival as compared with doxorubicin alone in patients with advanced or metastatic soft-tissue sarcoma.
- Gemcitabine/docetaxel is active in advanced/metastatic soft-tissue sarcoma.
- Trabectedin is active in patients with leiomyosarcoma or liposarcoma who have received prior treatment with an anthracycline. Eribulin is active in patients with liposarcoma who have received prior treatment with an anthracycline.
- Pazopanib is approved for treatment of advanced or metastatic non-GIST soft-tissue sarcoma (excluding liposarcoma) after treatment with chemotherapy, on the basis of improvement in PFS as compared with placebo.

KAPOSI SARCOMA

Treatment of KS varies by extent of the disease. Asymptomatic lesions may be observed without direct therapy. In patients with AIDS and KS, introduction of antiretroviral therapy (ART) resulting in a decline in viral load and an increase in CD4 cell count frequently leads to regression in Kaposi lesions with durable clinical response rates of greater than 60%.[62] Occasionally, and sometimes dramatically, patients with KS who subsequently receive ART experience a sudden flare or burst in KS lesion growth. This phenomenon, known as immune reconstitution inflammatory syndrome (IRIS) resulting from immune response against pathogens, may occur within weeks to a few months after initiation of ART despite control of virologic and immunologic parameters. In a cohort study of 150 patients with HIV-associated KS who began ART as the sole treatment for KS, 10 (6.6%) had progressive IRIS-associated KS.[63] In such instances, ART usually can be successfully continued, although chemotherapy also may be required for a time in order to control KS growth.[64]

The decision to provide local or systemic treatment for KS should be based on several factors, including assessment of disease abundance, site of the disease, rate of disease progression, patient-specific psychologic factors, and presence of organ dysfunction.[65] Patients should be educated about treatment options for the various stages of the disease. Local treatment may be possible for patients who have limited, nonbulky, and accessible lesions. Alitretinoin gel (0.1%) is the only topical patient-administered therapy approved by the FDA for the treatment of KS.[66] Other local treatments for KS include intralesional chemotherapy, radiation therapy, laser therapy, and cryotherapy, all of which can be effective at controlling local tumor growth. Radiation therapy has a role in the treatment of KS particularly when the disease is bulky and symptomatic and when rapid tumor shrinkage is required.[67] In a series of 36 patients with KS of the feet, a fractionation schedule of three fractions per week at 3.5 Gy per fraction (up to a total dose of 21.0 Gy) yielded an overall response rate of 91% (complete response, 80%).[68] Although discomfort from radiation therapy was frequent, it usually resolved without intervention within 2 weeks of completion of therapy.

Patients with KS-associated edema, extensive mucocutaneous disease, or symptomatic pulmonary or gastrointestinal involvement need a rapid response, which is achieved best with systemic chemotherapy. Many cytotoxic chemotherapy agents have moderate activity in KS, including bleomycin, vinca alkaloids, etoposide, taxanes, and anthracyclines.[65] Most of the

reports of drug activity in classic or HIV-associated KS are from small retrospective series, case reports, or relatively small phase II trials. Few larger randomized studies of chemotherapy for KS have been conducted. Because many anticancer agents are also metabolized by CYP450, the potential for drug reactions with ART is high. Liposomal formulations of doxorubicin and daunorubicin are the gold standard of clinical treatment for patients with extensive or advanced disease or for those who require rapid tumor shrinkage. In randomized, multicenter trials, each of the two available liposomal anthracyclines proved superior to conventional chemotherapy (bleomycin and vincristine, with or without nonliposomal doxorubicin) in terms of response rates and toxicity profiles.[69-71] Liposomal doxorubicin also has significant activity in classic KS and is usually given at a dose of 20 mg/m^2 every 3 weeks.[72] Patients with KS whose tumors initially respond well to this treatment may require further therapy. Among 98 patients who received pegylated liposomal doxorubicin, after a median follow-up of 50 months, 13% had experienced a relapse, most within the first year of stopping chemotherapy.[73] Paclitaxel is an established second-line therapy for KS treatment and has shown efficacy even for patients with AIDS-associated KS and anthracycline-resistant disease. For patients in whom one previous systemic chemotherapy regimen had failed, the response rates in two trials were 59% and 71%, respectively, and the median duration of response in these studies was 8.9 months and 10.4 months, respectively.[74,75] Drug-related adverse events occurring in the majority of patients were severe neutropenia and alopecia. Oral etoposide, vinorelbine, gemcitabine, bevacizumab, and imatinib have also been evaluated individually in patients with anthracycline-treated KS and demonstrated objective responses, but no randomized comparison of these agents has been reported.

KEY POINTS

- KS may be followed without the use of antineoplastic therapy when the disease burden is limited and asymptomatic.
- Immune reconstitution after introduction of ART in patients with AIDS-associated KS often leads to regression of KS but may result in tumor flare in 5% to 10% of cases.
- Liposomal anthracycline is a standard first-line chemotherapy for patients requiring treatment of KS because of tumor growth, tumor symptoms, or involvement of visceral organs.
- Paclitaxel is active in anthracycline-resistant KS.

GASTROINTESTINAL STROMAL TUMORS

BIOLOGY AND PRESENTATION

GISTs are sarcomas characterized by the presence of the CD117 (KIT) and/or DOG-1 (discovered on GIST) immunohistochemical markers, and most express stem cell marker CD34. Most GISTs have activating mutations in the *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) gene.[76] Approximately 10% to 15% of GISTs use alternative mechanisms for pathogenesis, including loss of function of the succinate dehydrogenase complex, inactivating mutation in *neurofibromin 1* and activating mutation in *BRAF*.[77] These latter three types of GISTs were previously referred to as “wild-type” before the molecular

changes were known.

GISTs are increasingly being recognized, making them the most common form of sarcoma (incidence, 5 to 10 cases per million persons in the United States). These tumors arise from the interstitial cells of Cajal, the pacemaker cells of the gastrointestinal tract. Approximately 65% of GISTs occur in the stomach, 25% in the small bowel, and the remainder in other sites along the gastrointestinal tract or in the abdomen. GISTs occurring in the setting of neurofibromatosis predominantly appear in the small intestine, including the duodenum, as multifocal tumors, and frequently exhibit a low mitotic rate.[78] The primary treatment for these tumors, when localized, is surgery, but many will recur in the peritoneum, liver, or both. Nodal, bone, and pulmonary metastasis from GIST have been described but are rare. GISTs are included in the 8th edition of the *AJCC Cancer Staging Manual.*[16] Tumors are staged based on size, mitotic rate, involvement of lymph nodes, presence of metastasis, and location of the primary GIST. The involvement of lymph nodes or presence of metastasis is classified as stage IV disease. GISTs are graded by mitotic rate. A low mitotic rate is five or fewer mitoses per 5 mm^2 (50 microscopic fields using 40× magnification); a high mitotic rate is more than five mitoses per 5 mm^2. The approximate risk for GIST recurrence after resection of localized disease in stomach or small bowel is shown in Table 14-6. The occurrence of tumor rupture prior to or during surgery is associated with a very high risk for GIST recurrence.

ADJUVANT THERAPY

The role of imatinib in the adjuvant setting has been the subject of a number of studies. A large randomized, prospective, placebo-controlled trial of imatinib after surgery for patients with GIST larger than 3 cm was stopped early because of a beneficial effect of imatinib on delaying disease recurrence; this led to the approval of imatinib in the adjuvant setting in the United States and Europe (the latter only for patients at substantial risk for relapse).[79] Only 3% of patients who received imatinib experienced disease progression at 1 year (the end of the mandated treatment), compared with 17% of patients who were assigned to the placebo arm. However, there was no demonstrable overall survival benefit, owing to the high response rate in patients receiving imatinib after recurrence was detected and the short follow-up of the study (a median of 15 months). A large randomized, open-label trial of imatinib taken for 1 year compared with 3 years after complete resection of high-risk GIST (> 50% risk of tumor recurrence) detected an approximate 20% improvement in relapse-free survival at 5 years for the cohort receiving 3 years of adjuvant imatinib (65% vs. 48%).[80] Importantly, overall survival was significantly better at 5 years in the group receiving adjuvant therapy for 3 years compared with 1 year (92% vs. 82%). Imatinib therapy can be associated with intolerable side effects, and one-quarter of the patients assigned to take imatinib for 3 years discontinued treatment early for reasons other than disease recurrence. Periorbital edema, muscle cramps, leukopenia, and elevation in serum creatinine were more common in patients assigned to 3 years of imatinib. Based on information currently available, it is reasonable to discuss adjuvant imatinib therapy for at least 3 years with patients who are at high risk for tumor relapse (a GIST that is both larger than 5 cm in maximum dimension and with more than five mitoses per 50 high-power field, GISTs that are either larger than 10 cm in greatest dimension or with more than 10 mitoses per 50 high-power field, or ruptured tumors). However, the optimal duration of adjuvant therapy in patients with high-risk GIST continues to be the subject of ongoing clinical trials.

Table 14-6 **Risk for GIST Recurrence after Resection**

Stage	Tumor Size (cm)	Mitotic Rate	Location	Observed Rate of Recurrence
I	≤ 5	Low	Small bowel	0–4%
IA	≤ 5	Low	Stomach	0–2%
IB	> 5–10	Low	Stomach	3–4%
II	> 5–10	Low	Small bowel	24%
	< 2	High	Stomach	Insufficient data
	> 2–5	High	Stomach	16%
	> 10	Low	Stomach	12%
IIIA	> 5–10	High	Stomach	55%
	> 10	Low	Small bowel	52%
	≤ 2	High	Small bowel	50%
IIIB	> 10	High	Stomach	86%
	> 2–5	High	Small bowel	73%
	> 5–10	High	Small bowel	85%
	> 10	High	Small bowel	90%

Source: Adapted from the *AJCC Cancer Staging Manual, 8th edition* (2017) published by Springer Science and Business Media, LLC.

ADVANCED DISEASE

Cytotoxic chemotherapy (including intraperitoneal chemotherapy) is ineffective for most cases of GIST. However, imatinib has remarkable activity against GIST. In early-phase studies of imatinib therapy for metastatic GIST, the Response Evaluation Criteria in Solid Tumors (RECIST) response rates were approximately 60%, at least 10 times the rates associated with previously available therapy.[81] In randomized phase II and phase III studies, a once-daily dose of 400 mg was as effective as 600 mg or 800 mg of imatinib daily.[82,83] As a result, 400 mg daily of oral imatinib is the standard treatment for metastatic GIST. The *KIT* phenotype of a GIST predicts for the responsiveness of the tumor to imatinib. Patients with mutations in exon 11 of *KIT* have a greater chance of response to imatinib than patients with exon 9 *KIT* mutations or wild-type *KIT*.[76] Tumors that harbor the platelet-derived growth factor receptor mutation *D842V* are particularly insensitive to imatinib, although other mutations in *PDGFR* are imatinib-sensitive.

The mutation in *KIT* (or in *PDGFRA*), and not mere expression of the protein, appears to correlate with sensitivity to imatinib and other tyrosine kinase inhibitors in GIST.

Patients with GIST harboring an activating mutation in exon 9 of *KIT* may benefit from a higher starting dose of imatinib (400 mg twice daily) based on the demonstration of a small, but statistically significant, improvement in median PFS compared with patients receiving 400 mg of imatinib daily.[84] A meta-analysis of two large randomized trials comparing imatinib 400 mg daily to 400 mg twice daily in the treatment of advanced or metastatic GIST confirmed a small PFS advantage and detected a higher objective response rate from the higher dose in patients with the exon 9 *KIT* mutations.[85] However, with a median follow-up of more than 40 months, documented GIST progression or death in patients with exon 9 mutations occurred in 40 of 42 and 42 of 49 patients randomly assigned to 400 mg and 800 mg daily, respectively. There was a trend toward improved survival in the patients receiving the higher dose, but it did not reach statistical significance. There was no difference in outcome between the standard- and high-dose groups among patients with the more common exon 11 *KIT* mutations. Dose-limiting side effects of imatinib include nausea and vomiting, diarrhea, rash, mucositis, and/or diuretic-resistant peripheral edema. At imatinib doses greater than 800 mg daily, dose-limiting toxicities are frequently encountered.

In contending with advanced disease progressing on first-line therapy (i.e., imatinib at an oral dose of 400 mg daily), a conventional approach is to increase the dose to a total daily dose of 800 mg (or 600 mg if the higher dose is not tolerated). About one-third of patients may have some degree of tumor control after escalation of imatinib dose.[82,83] For patients with imatinib-refractory disease or in patients intolerant of imatinib, sunitinib is the standard second-line therapy, as this agent was shown to be superior to placebo in a randomized phase III study in this setting.[86] The median duration of PFS in the arm receiving sunitinib was 24 weeks, compared with 6 weeks in patients treated with placebo; however, objective tumor responses were infrequent (fewer than 10% of patients). Overall survival was superior in the sunitinib compared with the placebo-treated arm. Patients less likely to benefit from sunitinib had primary mutations in exon 11 of *KIT* and secondary mutations had most likely developed, rendering GIST resistant to both imatinib and sunitinib. The most frequently reported side effects of sunitinib were fatigue, diarrhea, skin discoloration, and nausea, each occurring in more than 20% of patients. Hypertension and hypothyroidism are also known toxicities of sunitinib; they should be treated immediately when identified. Rare cases of fatal liver or cardiac events have been reported, and patients should be monitored closely while receiving therapy.

Regorafenib, at a dose of 160 mg daily for 3 out of every 4 weeks, is approved for treatment of GIST after the development of resistance to imatinib and sunitinib based on results of a randomized, blinded, placebo-controlled trial.[87] Median PFS was 5 months for patients receiving regorafenib compared with 1 month for patients receiving placebo. The most common severe adverse regorafenib-related events were hypertension and hand–foot skin reaction, which occurred in 24% and 20% of patients, respectively.

Surgery can play a role in the treatment of metastatic disease. In some patients, the tumor progresses in a limited number of disease sites (e.g., one or two deposits of progression in the background of responding disease). Patients with this pattern of limited progression on imatinib (isolated secondary resistance to imatinib) may have a long period before future progression if the resistant clone is resected and imatinib therapy is continued. All such patients should receive postoperative maintenance imatinib, owing to rapid progression without systemic treatment. Treatment of patients with multiple sites of disease progression (generalized

resistance to imatinib) warrants a change in systemic therapy because patients with resection of disease almost universally experience further progression within a few months after surgery in the setting of multifocal disease progression.[88] A resumption of imatinib following progression after second- or third-line therapy may be considered in patients with GIST previously controlled (responsive or stable for > 6 months) by imatinib if a clinical trial is not available. In one small randomized, placebo-controlled trial, median PFS was delayed 1 month in patients receiving imatinib rather than placebo; however, allowing for crossover from placebo to imatinib after progression, there was no difference between the arms in overall survival.[89]

KEY POINTS

- Most GISTs have activating mutations in the *KIT* or *PDGFRA* gene.
- Surgery is the best curative treatment for primary GIST.
- For patients with localized GIST at high risk (> 50%) of recurrence, imatinib 400 mg daily for 3 years after surgery delays time to recurrence and improves overall survival.
- Imatinib at a dose of 400 mg daily is a good standard of care in first-line therapy for metastatic GIST. For progressive disease, treatment with an increased dose of imatinib may be tried. If there is further progression of disease, treatment is changed to sunitinib.
- Patients with exon 9 *KIT*-mutant GISTs may benefit from a higher initial starting dose of imatinib (i.e., 400 mg twice daily) when tolerated; GIST tumors with *PDGFRα D842V* mutations are resistant to imatinib.
- Sunitinib is approved for second-line therapy for patients with imatinib-refractory GIST or who cannot tolerate imatinib.
- Regorafenib is approved for third-line therapy of GIST after failure of imatinib and sunitinib.
- Surgical resection may be appropriate, in conjunction with tyrosine-kinase inhibitor therapy, for patients with progressive metastatic disease limited to one or a few sites.

BONE SARCOMAS

OSTEOSARCOMA

Osteosarcomas are the most common tumors of bone, with two peaks of incidence: one between ages 10 and 20 and a smaller peak between ages 60 and 80. Disease in the latter age group is often associated with Paget disease of bone. Osteosarcomas generally arise in the metaphysis of the bone (between the bone end [epiphysis] and the shaft [diaphysis]). They are characterized by lytic and blastic features in admixed bone. If the tumors extend to soft tissue, they can cause both a periosteal reaction (Codman triangle) and ossification in a pattern perpendicular to the surface of the bone.

Adjuvant and/or neoadjuvant chemotherapy is the standard of care for most patients with osteosarcomas. The exception is superficial low-grade osteosarcomas, for which adjuvant chemotherapy is not indicated. For conventional osteosarcomas, six cycles of cisplatin/doxorubicin were found to be as effective as a more complex seven-drug regimen in

one randomized multicenter study.[90] Data regarding the use of methotrexate remain somewhat controversial in adult patients; however, doxorubicin/cisplatin/high-dose methotrexate is a standard therapy in patients younger than age 40 who have normal cardiac and renal function. In older adults, high-dose methotrexate is associated with delayed clearance, risk of nephrotoxicity, and acute lung injury. Muramyl tripeptide, a nonspecific immune stimulator, was shown to improve overall survival when used in the adjuvant setting in one large cooperative group study; however, the compound is unavailable for use in the United States, though it was approved for adjuvant use in patients younger than age 30 in Europe.[91,92]

The response of osteosarcomas to neoadjuvant chemotherapy can be assessed by pathologic examination at the time of operation, which provides prognostic information. However, there is no evidence that changing therapy improves overall survival in patients with osteosarcoma who had a poor response to preoperative chemotherapy. EURAMOS-1, a large international randomized, phase III trial, evaluated the addition of interferon in patients with less than 10% residual tumor (good histologic response) and the addition of ifosfamide and etoposide in patients with 10% or more residual tumor (poor histologic response) after two cycles of MAP (methotrexate/Adriamycin [doxorubicin]/Platinol [cisplatin]). Pegylated interferon alpha-2b administered subcutaneously for 18 months after completion of MAP resulted in a 17% improvement in event-free survival (EFS), which was not statistically significant.[93] The 3-year EFS rate for patients receiving interferon was 77%, compared with 74% in patients who did not undergo interferon treatment. One-quarter of the patients randomly assigned to interferon did not start the therapy, and grade 3/4 adverse events were reported in 50% of the patients. There was no reduction in osteosarcoma relapse or survival benefit from the addition of ifosfamide and etoposide to MAP in patients with a poor histologic response to preoperative MAP.[94] The 3-year EFS rate was 55% in the control group and 53% in the group receiving ifosfamide and etoposide. In patients with localized osteosarcoma at enrollment, 60% were free from disease relapse 3 years after study entry compared to about 20% of patients with metastatic osteosarcoma. Renal failure and acute myelogenous leukemia were more frequent in the patients receiving ifosfamide and etoposide; however, the rates of secondary cancers, collectively, were not statistically different between the treatment arms. Because patients with poorly responding osteosarcoma treated with chemotherapy have higher survival rates than patients who do not receive additional chemotherapy, all patients should be offered a full course of chemotherapy for treatment of primary osteosarcoma regardless of histologic response. The addition of zoledronate to combination chemotherapy did not improve the EFS or overall survival rates in patients with localized or metastatic osteosarcoma in a randomized, open-label, phase III trial.[95] EFS at 3 years was 63% in the control group and 57% in the group receiving zoledronate.

Osteosarcomas typically metastasize to the lung. Resection of pulmonary metastases (stage IVA disease) is one of the few examples in solid tumors of possible cure in a significant minority of patients with metastatic disease.[96] Patients with fewer than three pulmonary metastases who are more than 2 years from diagnosis to the development of lung metastases have the best survival rates after metastasectomy.

Ifosfamide plus etoposide with or without methotrexate has activity in relapsed osteosarcoma.[97,98]

KEY POINTS

- Chemotherapy is used in the neoadjuvant/adjuvant setting to treat osteosarcoma. Doxorubicin and cisplatin are commonly used as standard therapy, and high-dose methotrexate should be included in treatment of children and young adults (younger than age 40) with normal renal function. The addition of ifosfamide and etoposide to first-line chemotherapy does not improve survival.
- Resection of lung metastases (metastasectomy) should be considered for patients with osteosarcoma. The patients who are most likely to benefit are those who have a relatively prolonged disease-free interval and three or fewer lung metastases.

CHONDROSARCOMA

Chondrosarcomas are the second most common tumor of the bone and usually affect patients older than 60. There is no role for chemotherapy in the management of most chondrosarcomas, which are typically low- to intermediate-grade tumors that resemble cartilage both macroscopically and microscopically and are highly chemotherapy-resistant. On radiographs, chondrosarcomas generally appear as a radiolucent area with obvious bony destruction and a moderate number of discrete calcified areas and often involve the medullary cavity. They often have scalloped edges consistent with a multinodular growth pattern. Metastases from conventional chondrosarcoma often involve lung, follow an indolent growth rate, and may be managed by surgery if limited in number. Dedifferentiated chondrosarcoma occasionally responds to chemotherapy used for osteosarcoma. Patients with mesenchymal chondrosarcoma, another high-grade variant that resembles Ewing sarcoma on routine staining, may benefit from chemotherapy. Extraskeletal mesenchymal chondrosarcoma is not a cartilaginous tumor but rather a soft-tissue malignancy that often occurs in deep soft tissues; it has a relatively indolent growth rate, has a high risk of dissemination, and is relatively chemotherapy-resistant.[1]

EWING SARCOMA

Ewing sarcoma typically occurs in the bones of children and less commonly in adults. Extracranial (peripheral) primitive neuroectodermal tumor arises in soft tissues and is more common than skeletal Ewing sarcoma in adults. Askin tumor is a Ewing-like neoplasm that typically arises in the soft tissues of the chest or pleura of young adults. These tumors are part of a spectrum of diseases referred to as the “Ewing sarcoma family of tumors (ESFT),” which are characterized by varying degrees of differentiation and are always considered high-grade. On microscopy, Ewing sarcoma appears as monotonous sheets of small round blue cells that express high levels of a cell surface glycoprotein (CD99) and the nuclear factor FLI-1, which can be detected using immunohistochemistry. However, expression of CD99 and FLI-1 are not specific for Ewing sarcoma, and molecular studies may be performed to detect the characteristic chromosome translocations present in the disease. Most Ewing sarcomas have reciprocal translocation involving EWSR1 and FLI-1 or ERG, which may be detected by FISH or PCR. Skeletal Ewing sarcoma usually affects the shaft of the bone in an infiltrative pattern called “onion-skinning,” which is easily visible on CT scans. Multimodality therapy with surgery, chemotherapy, and radiation is the standard of care for ESFT and results in rates of cure of greater than 50% in patients presenting with localized disease. Approximately 20% to 30% of patients presenting with metastases may be long-term survivors after multimodal therapy.[99,100]

Local treatment of the primary site of disease is usually performed after an initial 12 weeks of chemotherapy. Complete resection of the tumor is preferred, which reduces the risk for local recurrence and secondary radiation-associated malignancy. Radiation is administered as an adjuvant for the treatment of microscopic residual tumor or if surgery cannot be performed with acceptable morbidity. Radiation-induced sarcomas develop in approximately 1% to 2% of long-term survivors of Ewing sarcoma who were treated with radiation for local tumor control.[99,101]

The addition of ifosfamide and etoposide to the combination of vincristine/doxorubicin/cyclophosphamide (VDC) is the standard chemotherapy for this malignancy, and this regimen yielded improvement in relapse-free and overall survival compared with vincristine/doxorubicin/dactinomycin/cyclophosphamide in patients with nonmetastatic Ewing sarcoma.[99] A randomized trial of cyclophosphamide/vincristine/doxorubicin given in cycles alternating with ifosfamide/etoposide administered every 2 as compared with every 3 weeks for a total of 14 cycles in patients younger than age 50 with localized Ewing sarcoma demonstrated improvement in recurrence-free survival, with an absolute difference of 8% at 5 years for the arm receiving dose-dense treatment, which resulted in fewer distant relapses.[101] The toxicity profile and frequency did not differ between arms. Secondary malignancies, including acute leukemia, osteosarcoma, and lymphoma, occurred in about 3% of patients. Late recurrence of Ewing sarcoma more than 5 years after initial diagnosis occurs in approximately 10% to 15% of children and adolescents, with about 25% of the late recurrences developing more than 10 years after diagnosis.[102] Patients treated for cure of Ewing sarcoma should be evaluated every 2 to 4 months for 3 years, then every 6 months for 2 years, then annually for symptoms/signs of sarcoma recurrence and long-term complications of therapy.

For metastatic Ewing sarcomas, the simpler combination of VDC was shown to be as effective as the five-drug combination used for primary disease, probably because patients progressing on the three-drug regimen could cross over to ifosfamide and etoposide at the time of progression.[99] In patients receiving VDC, dactinomycin is usually substituted for doxorubicin after a cumulative dose of 375 to 450 mg/m^2 has been administered. Assuming patients have received the standard multidrug regimen for Ewing sarcoma, options for therapy are limited, and these patients are good candidates for clinical trials. Relapsed or refractory ESFT may respond to treatment with cyclophosphamide plus topotecan or irinotecan plus temozolomide.[103,104]

GIANT CELL TUMOR OF BONE

Giant cell tumor of bone (GCT) is considered a benign disease, though it often causes severe morbidity from destruction of bone. In a small number of cases, GCT has the potential to metastasize (primarily to the lungs). The tumor is composed of malignant stromal cells that secrete receptor activator of nuclear factor kappa B (RANK) ligand and recruit multinucleated osteoclast-like cells that result in bone lysis. Patients usually present with lytic bone destruction, pain, and restricted mobility of the joint adjacent to the lesion. Current primary management involves complete curettage of the lesion, often followed by intralesional adjuvant therapy with heat, freezing, or chemicals (e.g., phenol). About 10% to 20% of tumors will recur locally, often necessitating joint resection and replacement; metastasis occurs in about 1% of cases. Denosumab, an inhibitory monoclonal antibody to RANK ligand, administered monthly resulted in lack of tumor progression in the large majority of patients in a phase II trial.[105] Significant adverse events that occurred during denosumab treatment included osteonecrosis of the jaw in 1% of patients, hypocalcemia in 5%, and hypophosphatemia in 3%. Based on the high rate of

tumor control and relatively low rate of adverse effects from denosumab treatment of GCT, the FDA approved denosumab 120 mg administered subcutaneously monthly (after initial treatment with 120 mg on days 1, 8, and 15 in the first month to rapidly achieve higher serum levels of denosumab) for treatment of patients with unresectable GCT or in situations in which complete resection would result in severe morbidity (e.g., GCT involving the pelvis or sacrum or requiring joint replacement) in adults and skeletally mature adolescents.

KEY POINTS

- Chondrosarcomas are the second most common bone sarcoma in adults. They are generally low to intermediate grade and are chemotherapy-resistant.
- Neoadjuvant/adjuvant chemotherapy using five drugs (VDC-IE) is standard treatment of localized Ewing sarcoma of bone or soft tissue. Radiation may be used in the case of positive tumor margin during surgery or for unresectable, localized disease.
- Metastatic Ewing sarcoma may be treated with vincristine, doxorubicin, dactinomycin, and cyclophosphamide.
- Metastatic bone sarcomas may be cured by appropriate multidisciplinary management.
- GCT causes osteoclast activation resulting in lysis of bone and carries a small risk of metastasis. Denosumab blocks differentiation and activation of osteoclasts in GCT and halts further bone destruction in the majority of cases.

SURVIVORSHIP

Survivors of childhood cancer are at risk for the development of secondary cancers, including sarcomas. The Childhood Cancer Survivor Study identified a 9-fold higher risk for a secondary sarcoma among survivors of childhood cancer compared with the general population.[106] Moreover, the significant improvement in long-term survival rates of children and adults with sarcoma, especially Ewing sarcoma, osteosarcoma, and rhabdomyosarcoma, from multimodality treatment comes at a heavy cost for a minority of patients. Serious late effects of treatment include secondary malignancy, infertility, cardiomyopathy, nephropathy, neuropathy, hearing impairment, and limb dysfunction. The cumulative incidence of secondary malignancy in children treated for sarcoma is about 1% to 3% at 10 to 20 years, with the highest risk in patients who received chemotherapy and radiation. There is a 3-fold to 6-fold higher risk for secondary cancer in children treated for sarcoma than in an age-matched general population.[107,108] Adults treated for sarcoma with chemotherapy and/or radiation are also at risk for long-term complications, including secondary malignancies and radiation-induced fibrosis and lymphedema. Symptomatic cardiomyopathy develops in approximately 1% to 2% of patients treated for sarcoma with doxorubicin and ifosfamide, and renal tubular and/or glomerular dysfunction develops in 5% to 10%, with the risk related to the cumulative dose received. Infertility is most often related to exposure to alkylating agents and affects postpubescent men more often than women. The Children's Oncology Group has guidelines for the long-term follow-up of survivors of childhood, adolescent, and young adult cancer available at www.survivorshipguidelines.org.

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CENTRAL NERVOUS SYSTEM TUMORS

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Recent Updates

Glioma

- The 2016 World Health Organization Classification of Tumors of the Central Nervous System provides a major update from its 2007 predecessor, most importantly incorporating the use of molecular profiling to help classify tumors. The 2016 edition adds newly recognized entities while removing some older variants, which now have less diagnostic relevance. (Louis DN, *Acta Neuropathol* 2016)
- The long-term results of RTOG 9802, which investigated the use of radiation plus procarbazine–lomustine–vincristine in high-risk low-grade glioma, confirmed that chemotherapy has the largest effect in patients with *IDH*-mutant tumors. Although 1p/19q codeletion status was not available, greater response to chemotherapy was seen with oligodendrogliomas/oligoastrocytomas when compared to histologic astrocytomas. (Buckner JC, *N Engl J Med* 2016)
- Results of EORTC 22033-26033 (temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma) serve as an adjunct to data from RTOG 9802. Although not powered for subgroup analysis, the study indicated that radiotherapy may contribute to better progression-free survival (PFS) only in tumors that were *IDH* mutants without 1p/19q codeletion. This would support the general consensus that codeleted tumors are more responsive to chemotherapy than non-codeleted gliomas. (Baumert BG, *Lancet Oncol* 2016)
- Although the treatment of glioblastoma in elderly patients has been controversial, new data support the use of concurrent temozolomide with hypofractionated radiation therapy as well as adjuvant chemotherapy in this vulnerable population, when tolerated. (Perry JR, *N Engl J Med* 2017)
- A phase III study supports that a shorter 1-week course of radiotherapy is noninferior to a longer 3-week course in elderly and/or frail patients with a newly diagnosed glioblastoma. (Roa W, *J Clin Oncol* 2015)
- Gliomas with mutations in isocitrate dehydrogenase produce significantly elevated levels of 2-hydroxyglutarate. Proton magnetic resonance spectroscopy can detect levels of this oncometabolite, providing a noninvasive biomarker of tumor status and response to treatment. (Choi C, *J Clin Oncol* 2016)
- Clear data regarding the use of immunotherapy in glioma are still pending, but one patient with multifocal glioblastoma had a significant (although temporary) response to chimeric antigen receptor–engineered T cells targeting the tumor-associated antigen interleukin-13 receptor alpha 2 (IL13Ra2). (Brown CE, *N Engl J Med* 2016)
- The use of checkpoint inhibitors is being extensively investigated in gliomas, but preliminary data do not suggest significant efficacy in most patients. This may be due to their lack of extensive intratumoral inflammatory cells and relatively low mutational rate. (Sampson DH, *J Clin Oncol* 2017)

Brain Metastases

- Immunotherapy with checkpoint inhibitors is being used in several tumor types, but treatment response in brain metastases has been unclear. Investigators have found response to pembrolizumab in brain metastases from melanoma and non-small cell lung cancer without significant neurotoxicity. (Goldberg SB, *Lancet Oncol* 2016)

Primary CNS Lymphoma

- A phase I/II trial in patients with primary CNS lymphoma investigated the use of induction chemotherapy with methotrexate, rituximab, and temozolomide followed by consolidation hyperfractionated whole-brain radiotherapy and temozolomide. The regimen had an objective response rate of 85.7%; 2-year overall survival and PFS were 80.8% and 63.6%, respectively.

Significant late neurotoxicity was not seen. (Glass J, *J Clin Oncol* 2016)

OVERVIEW

Primary central nervous system (CNS) tumors consist of a diverse range of pathologic entities, each with a distinct natural history. The updated 2016 World Health Organization (WHO) classification broadly categorizes CNS tumors into several groups, often with the incorporation of molecular features in addition to histology.[1] Tumors of neuroepithelial tissue comprise most of the malignant primary CNS tumors such as astrocytic tumors (including glioblastoma), oligodendroglial tumors, and embryonal tumors (e.g., medulloblastoma). In contrast, tumors of the meninges (e.g., meningioma) represent the most common benign primary CNS tumor. Other less common primary CNS tumor categories include tumors of the cranial and paraspinal nerves (e.g., vestibular schwannoma), tumors of the sellar region (e.g., craniopharyngioma), hematopoietic neoplasms (e.g., primary CNS lymphoma), and germ cell tumors. Metastatic tumors, which represent the overwhelming majority of intracranial masses in adults, are also included in the classification. CNS tumors vary significantly in their response to treatment and often require an individualized approach. Although surgery and radiation therapy remain fundamentals of treatment, molecular profiling of tumors has opened up exciting avenues for systemic targeted therapy.

GRADING AND CLASSIFICATION

Histologic grading plays a key role in determining prognosis and therapeutic interventions. The use of different grading systems for brain tumors had caused considerable confusion in the past. However, since 1993, the WHO classification system has been the internationally accepted four-tiered grading system. This includes a general grading scheme to describe a scale of malignancy across the various subtypes of primary CNS tumors (Table 15-1)[1]:

- Grade I tumors include well-circumscribed tumors with low proliferative potential that may be excised with curative intent.
- Grade II tumors are more infiltrative and cellular. Although relatively slow-growing, they often recur and tend to progress to higher grades of malignancy.
- Grade III tumors demonstrate histologic evidence of malignancy, such as cytologic atypia and increased mitotic activity.
- Grade IV tumors are more cytologically malignant, mitotically active, and prone to necrosis. Endothelial/vascular proliferation may also be seen. These tumors are usually rapidly fatal.

This system extrapolates from the grading of astrocytomas as they have been more extensively evaluated and systematically defined. Astrocytoma grading is based on four key histologic features: increased cellularity (in grade II astrocytomas), mitotic activity (in grade III astrocytomas), and endothelial proliferation and necrosis (in grade IV astrocytomas). Grade I astrocytomas have none of these characteristics. Of note, molecular markers in primary CNS tumors are also increasingly being used to better define groups of patients with significantly different prognoses irrespective of the tumor grade (e.g., isocitrate dehydrogenase [*IDH*] mutation in high-grade glioma).[2]

It is important to understand that the entire classification and grading schema for diffuse gliomas has gone through a dramatic change. A finite number of genetic markers (*IDH1* and *IDH2* mutational status, chromosome 1p/19q codeletion, *p53* mutations, *ATRX* mutations, and mutations in the *TERT* promoter) have redefined classification and now are just as important as histologic diagnosis. The 2016 edition of the WHO Classification of CNS tumors provides a major update to the classification of these tumors, and supplements histology with these genetic markers in establishing pathologic diagnosis.[1] Examples include the classification of gliomas based on the presence of *IDH* mutation and/or 1p/19q codeletion, as well as the creation of a new entity, diffuse midline glioma-H3K27M mutant, which is more commonly seen in children.

EPIDEMIOLOGY

Primary malignant CNS tumors represent approximately 2% of all cancers but account for a disproportionate share of morbidity and mortality. They are the most common solid tumor in children and are the second leading cause of death from cancer in children, with leukemia being the first. CNS tumors are the third leading cause of cancer-related death for adolescents and young adults (ages 15 to 34). Malignant brain tumors occur more frequently in men, whereas meningiomas are more common in women. The median age-adjusted incidence for primary brain tumors is 21 cases per 100,000 individuals per year, varying from 5.3 in children and adolescents to 27.4 in adults. Of all primary brain tumors, approximately one-third are meningiomas, one-third are gliomas, and the remainder are a variety of other benign and malignant tumors (Fig. 15-1). Of all primary gliomas, 54% are glioblastomas (Fig. 15-2).[3] In children, embryonal tumors such as medulloblastoma are the most commonly seen CNS tumor.

Table 15-1 World Health Organization Classification and Grading of Selected Primary CNS Tumors

	I	II	III	IV
Diffuse astrocytic tumors				
Diffuse astrocytoma, *IDH* mutant		X		
Anaplastic astrocytoma, *IDH* mutant			X	
Glioblastoma, *IDH* mutant				X
Glioblastoma, *IDH* wild type				X
Diffuse midline glioma, H3K27M mutant				X
Oligodendroglial tumors				
Oligodendroglioma, *IDH* mutant and 1p/19q codeletion		X		
Anaplastic oligodendroglioma, *IDH* mutant and 1p/19q codeletion			X	
Other astrocytic tumors				
Pilocytic astrocytoma	X			
Subependymal giant cell astrocytoma	X			
Pleomorphic xanthoastrocytoma		X		
Anaplastic pleomorphic xanthroastrocytoma			X	
Ependymal tumors				
Subependymoma	X			
Myxopapillary ependymoma	X			
Ependymoma		X		
Ependymoma, RELA fusion-positive (II or III)		X	X	
Anaplastic ependymoma			X	
Embryonal tumors				
Medulloblastoma (all subtypes)				X
Atypical teratoid/ rhabdoid tumor				X
Tumors of the cranial and paraspinal nerves				
Schwannoma	X			
Neurofibroma	X			
Malignant peripheral nerve sheath tumor (II, III, or IV)		X	X	X
Meningiomas				
Meningioma	X			
Atypical meningioma		X		
Anaplastic (malignant) meningioma			X	
Tumors of the sellar region				
Craniopharyngioma	X			

With permission of Springer from Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Classification of tumors of the central nervous system: a summary. *Acta Neuropathol.* 2016;131:803-820.
Abbreviations: IDH, isocitrate dehydrogenase.

It has been difficult to identify environmental factors associated with primary brain tumors. Although there is limited evidence that long-term use of cell phones may increase the risk of brain tumors, reports are conflicting and convincing evidence is lacking.[4] A large national study of 358,403 cell-phone subscribers in Denmark followed from 1990 to 2007 (3.8 million person-years) revealed no evidence of increased risk in primary brain tumors, particularly in gliomas.[5] Ionizing radiation is the only environmental risk factor reliably considered to increase the risk of brain tumors. Radiation treatment for children with tinea capitis, acute lymphocytic leukemia, craniopharyngioma, or non-Hodgkin lymphoma has been associated with an increased risk of subsequent brain tumors, especially gliomas. The risk of primary CNS lymphoma, but not other types of primary brain tumors, is increased for patients with immunodeficiency conditions such as HIV infection.[6]

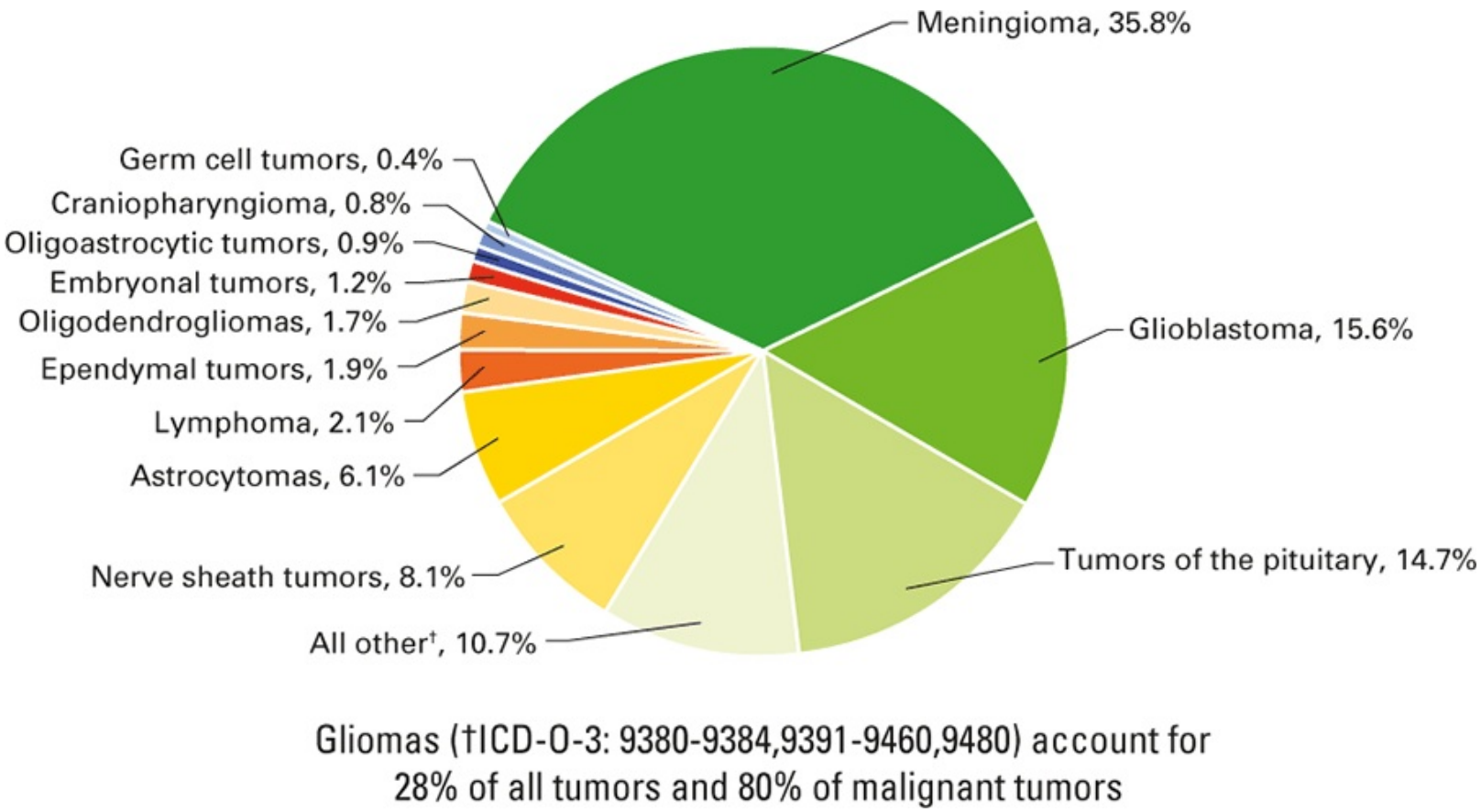

Fig. 15-1 Distribution of primary brain and CNS tumors by histology (326,711 patients).

Abbreviation: CNS, central nervous system.

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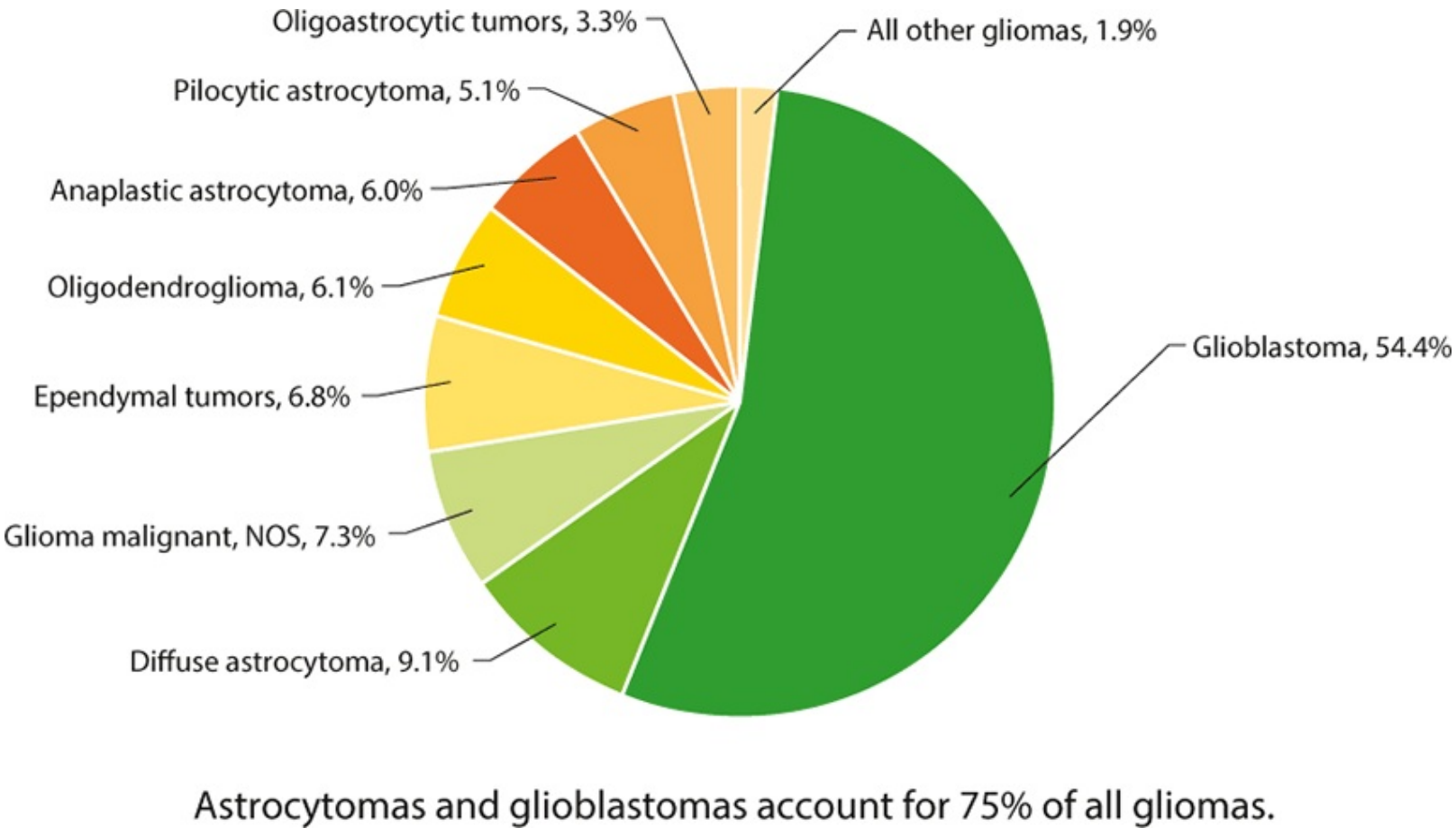

Fig. 15-2 Distribution of primary brain and CNS gliomas by histology subtypes (92,504 patients).

Abbreviations: CNS, central nervous system; NOS, not otherwise specified.

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MOLECULAR EPIDEMIOLOGY

Genetic predisposition to primary CNS tumors is relatively uncommon, although they may be associated with several familial cancer syndromes (Table 15-2).[7,8] For example, astrocytomas are associated with Li–Fraumeni syndrome, neurofibromatosis type 1 (NF1), tuberous sclerosis, and Lynch syndrome. Medulloblastoma is associated with Li–Fraumeni syndrome, basal cell nevus syndrome, and familial adenomatous polyposis.

Table 15-2 Genetic Syndromes Associated with Primary CNS Tumors

Genetic Syndrome	Gene Alteration(s)	Associated Primary CNS Tumors
Basal cell nevus (Gorlin) syndrome	*PTCH1*	Medulloblastoma
Cowden syndrome	*PTEN*	Gangliocytoma
Li-Fraumeni syndrome	*TP53*	High-grade glioma Medulloblastoma
Neurofibromatosis 1	*NF1*	Malignant peripheral nerve sheath tumor Low-grade astrocytoma (usually pilocytic astrocytoma)
Neurofibromatosis 2	*NF2*	Vestibular schwannoma (frequently bilateral) Meningioma
Tuberous sclerosis	*TSC1, TSC2*	Subependymal giant cell astrocytoma
Familial adenomatous polyposis	*APC*	Medulloblastoma
Lynch syndrome (hereditary nonpolyposis colorectal cancer)	*MSH2, MLH1, MSH6, PMS2*	Glioblastoma
Von Hippel-Lindau syndrome	*VHL*	Hemangioblastoma

Germline polymorphisms in the *CDKN2B* and *RTEL1* genes have been associated with a greater risk of developing primary glioblastoma, whereas germline polymorphisms in *CCDC26* are associated with lower-grade tumors, 1p/19q codeletion, and *IDH* mutations.[9-11] For example, one particular single-nucleotide polymorphism near the *CCDC26* gene, rs55705857, is present in nearly 40% of patients with oligodendroglial tumors and gliomas with *IDH* mutations, compared with approximately 8% of the normal population.[12]

KEY POINTS

- Although histologic grading and pathology remain important, the 2016 WHO Classification of Tumors of the CNS now incorporates the use of molecular profiling to help classify tumors. These genetic markers can significantly change prognosis and management.
- Exposure to ionizing radiation is a well-established risk factor for primary CNS tumors.
- Most patients with primary CNS tumors have no identifiable risk factor. The exceptions

are those patients who have a primary CNS tumor associated with one of the familial cancer syndromes, including neurofibromatosis, Li–Fraumeni syndrome, Lynch syndrome, and familial adenomatous polyposis.

- Immunodeficiency is a risk factor for primary CNS lymphoma.

CLINICAL FEATURES AND DIAGNOSTIC EVALUATION

SYMPTOMATOLOGY

The presenting symptoms of a brain tumor are related to mass effect, parenchymal infiltration, hydrocephalus, and tissue destruction. Headaches are a common presenting symptom and occur in approximately 35% of patients. The sudden onset of headaches in a patient who has not previously had them is most characteristic, especially if the headaches are more severe in the morning and are associated with nausea, vomiting, or focal neurologic deficits. Seizures occur in approximately one-third of patients with gliomas, especially in those with low-grade tumors. However, seizures may be associated with any CNS tumor. Focal neurologic deficits are related to the location of the tumor. Altered mental status may develop in 15 to 20% of patients with gliomas. Personality changes and/or psychiatric problems can be the presenting symptom, often preceding the tumor diagnosis by months or years, particularly with low-grade gliomas and primary CNS lymphoma (PCNSL). Posterior fossa masses and, less commonly, supratentorial masses may obstruct the third or fourth ventricle resulting in hydrocephalus, causing headache, nausea, vomiting, somnolence, lethargy, or coma.

DIAGNOSTIC IMAGING

Computed tomography (CT) of the brain is limited in its ability to assess brain tumors, and it typically shows a mass that may be enhanced with the use of contrast medium. Low-grade gliomas may be isodense with normal brain parenchyma and may not enhance with contrast. Hyperdense lesions on CT are highly suggestive of tumors with high nuclear-to-cytoplasmic ratios such as lymphoma (primary or metastatic), metastatic sarcoma, and metastatic renal cell carcinoma. Lesions in the posterior fossa may not be identifiable in CT scans. Although magnetic resonance imaging (MRI) is generally much more helpful in evaluating brain tumors, CT imaging can be helpful in certain situations, such as in assessing hemorrhage or tumor involvement of the skull/bone.

MRI is more sensitive than CT for confirming the presence of a brain tumor. In T_1-weighted MRI scans, a brain tumor appears as a mass lesion that may enhance with contrast; there may also be signal abnormality on T_2-weighted scans, especially prominent on fluid attenuation and inversion recovery (FLAIR) images. Contrast enhancement is indicative of a breakdown in the blood–brain barrier, and it usually increases with higher grades of malignant disease. Ring enhancement is characteristic of glioblastoma and is a consequence of central tumor necrosis. However, some low-grade (benign) tumors, like pilocytic astrocytoma, may also demonstrate contrast enhancement. Conversely, some high-grade tumors may not enhance with contrast. Contrast enhancement does not reflect the true extent of disease, as the blood–brain barrier may remain intact at the rim of the infiltrating tumor.[13,14]

MRI perfusion imaging may demonstrate increased blood flow in high-grade tumors, whereas MRI diffusion imaging may show reduced water movement, presumably secondary to increased cellularity and increased interstitial pressure. Although not definitive, MRI

perfusion/diffusion imaging can assist clinical decision-making regarding tumor progression, pseudoprogression, and radiation necrosis. Both magnetic resonance spectroscopy (MRS) and positron-emission tomography (PET) provide physiologic information about the tumor and may provide supplemental information in special clinical scenarios. For example, ^{18}F-fluorodeoxyglucose–PET can be useful in helping to differentiate high-grade glioma from radiation necrosis, as tumor is more likely to be hypermetabolic. The sensitivity and specificity of MRS in differentiating tumor histology or radiation necrosis are currently too low to recommend its routine use. However, other types of MRS and PET imaging may be more useful in specific situations. For example, the development of proton MRS for evaluation of 2-hydroxyglutarate (2HG) has provided a noninvasive biomarker to assess tumor status and treatment response in IDH-mutant gliomas.[15]

DIAGNOSTIC PATHOLOGY

For nearly all patients, the definitive diagnosis of a CNS tumor requires a surgical biopsy or resection with histologic examination of the tissue. However, patients with brainstem gliomas may not be candidates for biopsy because of the operative risk, and imaging can be diagnostic. Also, patients with CNS germ cell tumors may have elevated levels of serum or cerebrospinal fluid (CSF) human chorionic gonadotropin or alpha-fetoprotein, which may confirm the diagnosis for germ cell tumors.

Accurate pathologic diagnosis requires review by an experienced tumor neuropathologist, as the rate of discordant diagnoses between general pathologists and neuropathologists is very high. The diagnosis may change substantially for more than one-third of patients when pathologic review is performed by an experienced neuropathologist.

Certain CNS tumors have characteristic histologic features (e.g., “fried egg” appearance of oligodendroglioma). Nevertheless, the key role of immunohistochemistry and molecular markers in diagnosis and prognosis is undisputed. Markers of good prognosis in gliomas include 1p/19q codeletion,[16] *MGMT* promoter hypermethylation,[17] and *IDH* mutation.[18] Furthermore, 1p/19q codeletion and *IDH* mutation independently predict response to chemotherapy in anaplastic oligodendroglioma,[19] whereas *MGMT* promoter hypermethylation is associated with a greater likelihood of benefit from temozolomide in glioblastoma.[20] Current clinical trials are using these biomarkers for either stratification or patient inclusion.

STAGING

Most primary brain tumors remain localized, so extensive staging procedures are not necessary. Medulloblastoma, primitive neuroectodermal tumor, CNS germ cell tumors, ependymoma, and primary CNS lymphoma are exceptions, as they frequently spread by way of the subarachnoid space to the leptomeninges. Consequently, MRI of the spine and/or cytologic examination of CSF are necessary to diagnose these tumors.

KEY POINTS

- The best imaging tool for CNS tumors is MRI. Contrast enhancement on MRI is the primary imaging hallmark of high-grade tumors. Physiologic imaging methods such as PET and MRS may be useful in specific clinical scenarios.

- Examination of brain tumor tissue by experienced neuropathologists is essential to establish an accurate diagnosis. Genomic profiles of the tumor increasingly aid in diagnosis and pathologic classification.
- 1p/19q codeletion and *IDH* mutation independently predict response to chemotherapy in anaplastic oligodendrogliomas. Testing for these mutations has become standard in these tumors.
- Patients with medulloblastoma, primitive neuroectodermal tumor, CNS germ cell tumors, ependymoma, and primary CNS lymphoma are at higher risk for CNS dissemination and may require MRI of the entire spine and CSF examination for tumor staging.

GENERAL TREATMENT STRATEGIES

SURGERY

The goals of surgery are to obtain sufficient representative tissue to ensure accurate histologic diagnosis, to reduce mass effect while preserving neurologic function, to shrink the tumor by cytoreduction, and to treat hydrocephalus (if present). Surgery remains the initial therapy for nearly all patients with brain tumors and can be curative for most benign tumors, including meningiomas and some low-grade gliomas (e.g., pilocytic astrocytoma). Unfortunately, most gliomas are characterized by diffuse infiltration of brain parenchyma, making curative resection impossible. In these cases, relief of mass effect with debulking results in symptomatic improvement and provides time for safe administration of subsequent treatment. Postoperative MRI is usually performed immediately (before the development of postsurgical contrast enhancement) to assess the adequacy of resection.

Current stereotactic techniques allow for biopsy specimens to be obtained from nearly any part of the brain, including the brainstem. Biopsy alone is generally reserved for patients with tumors in critical functional portions of the brain, where resection would result in unacceptable neurologic deficits. In addition, patients with primary CNS lymphoma or CNS germ cell tumors may need only biopsy because primary treatment usually involves chemotherapy and/or radiation therapy. Biopsy or resection is increasingly being offered for recurrent tumors that progress after standard therapy to relieve mass effect as well as to characterize the pathology and genetic profile of the recurrent malignancy. This is especially important for high-grade tumors, which may have tremendous intratumoral heterogeneity. In addition, initial treatment may sometimes select for the evolution of a previously minor subpopulation of clones; these clones may become the target of the next line of treatment.

Meningiomas may be incidentally discovered on imaging. In the presence of benign radiographic features, meningiomas may be followed with imaging without biopsy or resection.

RADIATION THERAPY

External-beam radiation therapy is an essential component of treatment for many patients with brain tumors. It can be curative for some patients, and it prolongs survival for others. Radiation often is also the primary treatment for patients with metastatic brain tumors, epidural spinal cord compression, and leptomeningeal metastases. Whereas whole-brain radiation therapy (WBRT) may be administered for certain tumors, such as medulloblastoma or primary CNS lymphoma, involved-field radiation using multiple field techniques has become the standard treatment for most patients with glioma. Involved-field radiation is as effective as WBRT, and it

reduces the dose and volume of radiation to normal brain tissue, potentially reducing late neurotoxic effects.

Radiation therapy, especially when used concurrently with temozolomide, commonly causes increases in the radiographic size of preexisting contrast-enhancing lesions, as well as new areas of contrast enhancement, soon after treatment. This can improve spontaneously without any further treatment.[21] This phenomenon has been labeled “pseudoprogression” and is crucial to recognize, as it mimics tumor progression.[22]

Later effects of therapeutic radiation include radionecrosis and leukoencephalopathy. Radionecrosis presents as a focal mass lesion with contrast enhancement and mass effect. The clinical scenario is difficult to distinguish from recurrent tumor and may require surgical resection to relieve mass effect and establish a histologic diagnosis. Radiation-induced leukoencephalopathy often occurs months to years after treatment, and usually appears as diffusely increased T_2/FLAIR signal abnormality on MRI, with associated atrophy. Patients with characteristic MRI changes may be asymptomatic or severely compromised with dementia, gait instability, and urinary incontinence. The frequency of radiation injury is related to total radiation dose, fraction size, volume of brain radiated, treatment technique, and patient age. In general, morbidity is reduced by using smaller fraction size, lower total dose, and smaller treatment volumes.

Stereotactic radiotherapy techniques have demonstrated efficacy for well-circumscribed lesions, such as meningiomas, that require treatment, and for patients with a limited number of brain metastases. However, for infiltrative primary brain tumors, the clinical efficacy of stereotactic radiotherapy has not been proven. In two phase III trials, investigators found no survival advantage for patients with glioblastoma who were receiving radiation with a stereotactic boost or brachytherapy, compared with patients receiving standard conventional involved-field radiotherapy.[23,24] The clinical benefits of other focal radiation techniques, such as the use of nonspecific or targeted radioactive isotopes, are being investigated; these techniques and are not currently recommended for routine clinical use. Evidence is emerging that retreatment with external-beam radiation, especially fractionated stereotactic radiation, may be beneficial in patients with high-grade gliomas whose tumors have recurred despite initial radiation and optimal chemotherapy.[25,26] The magnitude of efficacy in relation to potential harm, in comparison with other treatment approaches, remains to be determined.

CHEMOTHERAPY

Although chemotherapy provides only modest benefit for most patients with primary brain tumors, it has a role in palliation and in adjuvant treatment. Alkylating agents continue to be the mainstay of treatment in gliomas. Temozolomide, the most commonly used agent, penetrates the intact blood–brain barrier and provides survival benefit for patients with glioblastoma[20,27]; however, the effect is typically not durable. Lomustine (CCNU), a nitrosourea, in combination with procarbazine and vincristine (PCV) has antitumor activity in patients with low-grade gliomas[28] and anaplastic oligodendroglioma, especially those tumors with both mutant *IDH* and 1p/19q codeletion.[29] Platinum drugs have antitumor efficacy for medulloblastoma[30] and germ cell tumors. High-dose methotrexate regimens result in clear clinical benefit for patients with primary CNS lymphoma.[31] Bevacizumab, a vascular endothelial growth factor (VEGF) pathway inhibitor, has been approved by the U.S. Food and Drug Administration (FDA) for use in patients with recurrent or progressive glioblastoma following radiation therapy and temozolomide.[32] Unfortunately, it does not prolong survival in most patients with newly

diagnosed glioblastoma, although patients with proneural subtype glioblastoma may have a survival benefit.[33-35] Multiple other agents that target aberrant signaling pathways are under investigation. Although the use of immunotherapy in cancer is expanding rapidly, its efficacy in glioma is still unclear. One promising example is chimeric antigen receptor (CAR) T cells—one patient with multifocal glioblastoma had significant regression of tumor after both intracranial and intrathecal infusions of interleukin-13 receptor alpha 2–targeted CAR T cells.[36] The use of checkpoint inhibitors is being extensively investigated in glioma, but preliminary data suggest efficacy in only a small minority of patients, such as those with hypermutant tumors in the setting of mismatch repair deficiency.[37,38]

Efforts have been made to increase the efficacy of chemotherapy by improving delivery. These techniques have included intra-arterial chemotherapy with or without blood–brain barrier disruption, intratumoral administration of agents by convection-enhanced delivery, and placement of intratumoral biodegradable polymers. The efficacy of local administration of various agents directly into brain tumors has generally been modest. However, on the basis of survival benefit shown in clinical trials, the FDA has approved the use of carmustine-impregnated degradable polymers for the treatment of newly diagnosed high-grade gliomas and recurrent glioblastoma.[39,40]

IMPORTANT SUPPORTIVE CARE AGENTS

Corticosteroids, antiepileptic drugs, and anticoagulant drugs are important ancillary agents for the treatment of patients with brain tumors. Corticosteroids are indispensable for controlling cerebral edema. Unfortunately, the long-term use of these agents can result in substantial toxic effects, including myopathy, hyperglycemia, peripheral edema, and Cushing syndrome. Dexamethasone is often the drug of choice because of its minimal mineralocorticoid activity and long half-life.[41] Corticosteroids are generally recommended for temporary relief of symptoms, and should be started at the minimum dose necessary and tapered as quickly as deemed possible, especially in asymptomatic patients.[42] Bevacizumab may also be considered to control severe edema secondary to radiation necrosis.[43]

Antiepileptic drugs are administered for the treatment of seizures. Clinical trials have demonstrated that some antiepileptic agents, including phenytoin, phenobarbital, and carbamazepine induce common hepatic enzyme systems, such as cytochrome P450 enzymes. Induction of these enzymes results in decreased exposure to chemotherapy agents and other drugs metabolized by the same enzyme systems, including warfarin and small-molecule inhibitors. In contrast, valproate inhibits cytochrome P450 and may reduce chemotherapy metabolism with a consequent increase in toxicity. Newer antiepileptic drugs, such as levetiracetam, zonisamide, lacosamide, lamotrigine, topiramate, and pregabalin, do not typically interact with current treatment regimens. These agents are preferred when feasible because they may avoid the enzyme interactions previously noted.

Clinical trials have not yet demonstrated a discernible benefit for the use of routine prophylactic antiepileptic therapy for patients with no history of seizure.[44,45] Similarly, there is no clear evidence supporting the efficacy or lack of efficacy of antiepileptic therapy in the postcraniotomy setting.[46] Prospective, randomized trials have demonstrated a lack of efficacy of perioperative seizure prophylaxis[47]; however, the heterogeneity of included patients and the use of older antiepileptic agents in these trials have led to limited acceptance of these results. If antiepileptics are initiated perioperatively, current practice recommendations are to taper and discontinue use after the first postoperative week.[48] Patients who have had a seizure should be

maintained on antiepileptic therapy after surgery.

Clinically apparent venous thromboembolism (VTE) or pulmonary emboli that require anticoagulation may occur in 20 to 30% of patients with primary brain tumors. Presumably, injury to brain parenchyma results in the release of tissue thromboplastins and increases the risk of clotting. Spontaneous bleeding during anticoagulation occurs in only 2% of patients with malignant glioma and does not appear to be higher than the rate seen in non-anticoagulated patients.[49,50] Low-molecular weight heparin is generally considered to be more effective than warfarin in patients with active malignancy.[51] Patients with CNS tumors should receive anticoagulation for established VTE as recommended for other patients with cancer. Anticoagulation should be avoided in the setting of active intracranial bleeding (or, especially, hemorrhagic brain tumors), thrombocytopenia, or coagulopathy.[52] Clinical trials evaluating newer oral anticoagulants, including factor Xa inhibitors (e.g., apixaban, edoxaban, and rivaroxaban) and direct thrombin inhibitors (e.g., dabigatran) have not assessed the safety of these drugs in patients with brain tumors. Further clinical evaluation is necessary before these drugs can be recommended for routine use in this population.

KEY POINTS

- The primary roles of surgery for primary brain tumors are to obtain tissue for diagnosis, reduce mass effect, and reduce the tumor-cell burden.
- Patients with primary CNS lymphoma or germ cell tumors may require only biopsy, since the primary therapy is chemotherapy, radiation therapy, or both.
- Stereotactic radiosurgery is effective in well-circumscribed tumors such as meningiomas and in patients with a limited number of brain metastases.
- Newer antiepileptic drugs, such as levetiracetam, are preferred for seizure prophylaxis because they may avoid potential enzyme interactions.
- Patients with CNS tumors should receive anticoagulation for established VTE as recommended for other patients with cancer, except in the setting of active intracranial bleeding (or, especially, hemorrhagic brain tumors), thrombocytopenia, or coagulopathy.

MOLECULAR PATHOGENESIS IN DIFFUSE GLIOMAS

Research in the past decade has rapidly increased the current understanding of the pathobiology of diffuse gliomas. Several molecular abnormalities have been discovered that seem to play key roles in glioma development. Precise molecular characterization of diffuse gliomas is still subject to discussion and extensive research, but diffuse gliomas are currently considered to fall within three broad categories[3,53]:

1. Gliomas arising from mutations in *IDH* with 1p/19q codeletion. These gliomas consist predominantly of oligodendroglial tumors. The 5-year survival of patients with these tumors typically ranges from 50 to 80%, although with aggressive treatment consisting of radiation and PCV chemotherapy, median survivals of 12 to 18 years have been observed.[54,55]
2. Gliomas arising from mutations in *IDH* and *ATRX* without 1p/19q codeletion. These gliomas predominantly consist of grade II and grade III astrocytomas, along with secondary

glioblastomas (i.e., glioblastoma that has arisen from a lower-grade glioma). The 5-year survival of patients with these tumors typically ranges from 25 to 50%.

3. Gliomas arising from mutations other than in the *IDH* or *ATRX* genes and without 1p/19q codeletion. These gliomas consist predominantly of primary glioblastoma (i.e., de novo glioblastoma). The 5-year survival of patients with these tumors is less than 5%.[56]

The classification does not account for many other more recent discoveries (e.g., the high prevalence of *TERT* promoter mutations in both oligodendrogliomas and primary glioblastomas, despite a lower prevalence in lower-grade astrocytomas).[57] However, it provides a framework to better understand some of these crucial genetic alterations along with their associated prognostic and predictive implications.

IDH MUTATION

Mutations in the *IDH* gene are probably early genetic abnormalities in glioma development. *IDH1* mutations result in the excess accumulation of 2-hydroxyglutarate (2HG), an oncometabolite, which contributes to the formation and progression of gliomas.[58] As described earlier, MR spectroscopy can non-invasively detect 2HG in *IDH*-mutant gliomas. Although first described in tumor samples of glioblastoma,[59] *IDH* mutations have since been found in most diffuse gliomas other than primary glioblastoma.

Somatic tumor *IDH* mutation is a clear indicator of favorable prognosis in high-grade gliomas[18] (Fig. 15-3) and has recently been demonstrated to independently predict survival benefit from the addition of combination chemotherapy (i.e., PCV) to subsequent radiation therapy in patients with anaplastic oligodendroglioma and anaplastic oligoastrocytoma.[19] Multivariate analysis has demonstrated that the survival advantage from the addition of PCV to radiation therapy in *IDH*-mutated tumors is observed in both 1p/19q codeleted and non-codeleted subsets; however, the chemotherapy benefit seems much more significant in the patients with codeletion.

1P/19Q CODELETION

Most oligodendrogliomas and anaplastic oligodendrogliomas (along with some histologic oligoastrocytomas and anaplastic oligoastrocytomas) have been observed to have a combined loss of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). This codeletion of 1p/19q was demonstrated to be secondary to an unbalanced pericentromeric translocation event[16] and seems to be instrumental in the development of oligodendrogliomas. Several candidate genes have been identified, including *CIC* and *FUBP1*, which may represent the genetic alteration underlying the 1p/19q codeletion.[53,60]

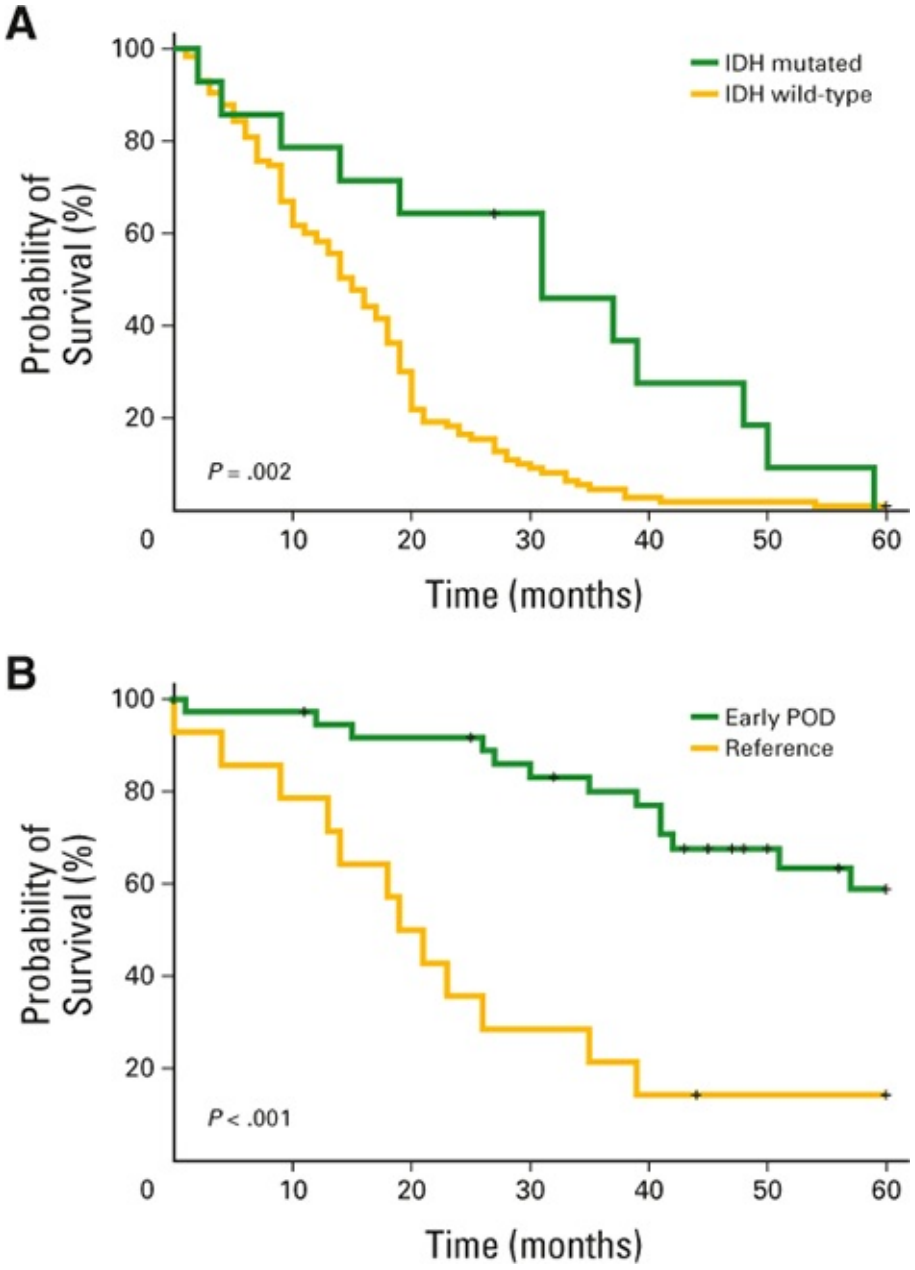


Fig. 15-3 Survival of adult patients with malignant gliomas with or without *IDH* gene mutations.

(A) For patients with glioblastomas, the median survival was 31 months for the 14 patients with mutated *IDH1* or *IDH2*, compared with 15 months for the 115 patients with wild-type *IDH1* or *IDH2*. (B) For patients with anaplastic astrocytomas, the median survival was 65 months for the 38 patients with mutated *IDH1* or *IDH2*, compared with 20 months for the 14 patients with wild-type *IDH1* or *IDH2*. Patients with both primary and secondary tumors were included in the analysis. For patients with secondary glioblastomas, survival was calculated from the date of the secondary diagnosis.

Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009;360:765-773. PMID: 19228619.

Many studies have demonstrated that 1p/19q codeletion is associated with a good prognosis in patients with oligodendrogliomas (Fig. 15-4).[16] More recently, 1p/19q codeletion has been determined to not only indicate a better prognosis in patients with anaplastic oligodendrogliomas and anaplastic oligoastrocytomas, but also predicted improved survival with addition of combination chemotherapy (i.e., PCV) to radiation compared to radiation therapy alone.[29,54]

ATRX MUTATION

Somatic mutations in the *ATRX* gene are commonly seen in grade II and grade III astrocytomas

and are mutually exclusive with 1p/19q codeletions.[53,61] Although there are no current therapeutic options to target the *ATRX* gene, astrocytomas with mutant *ATRX* may have a more favorable prognosis compared to astrocytomas without *ATRX* loss.[62]

GENETIC ALTERATIONS IN GLIOBLASTOMA

The Cancer Genome Atlas (TCGA) has shed light on the heterogeneity of the genetic landscape of glioblastoma.[59,63] Common somatic genetic alterations include (1) epidermal growth factor receptor (*EGFR*) mutation and amplification, (2) loss of the *PTEN* tumor suppressor gene, (3) *RB1* gene deletion and mutation, (4) *CDKN2A* and *CDKN2B* gene deletions, and (5) *NF1* gene mutations and deletions. Other abnormalities such as *TP53* mutations are also commonly observed in other diffuse gliomas.

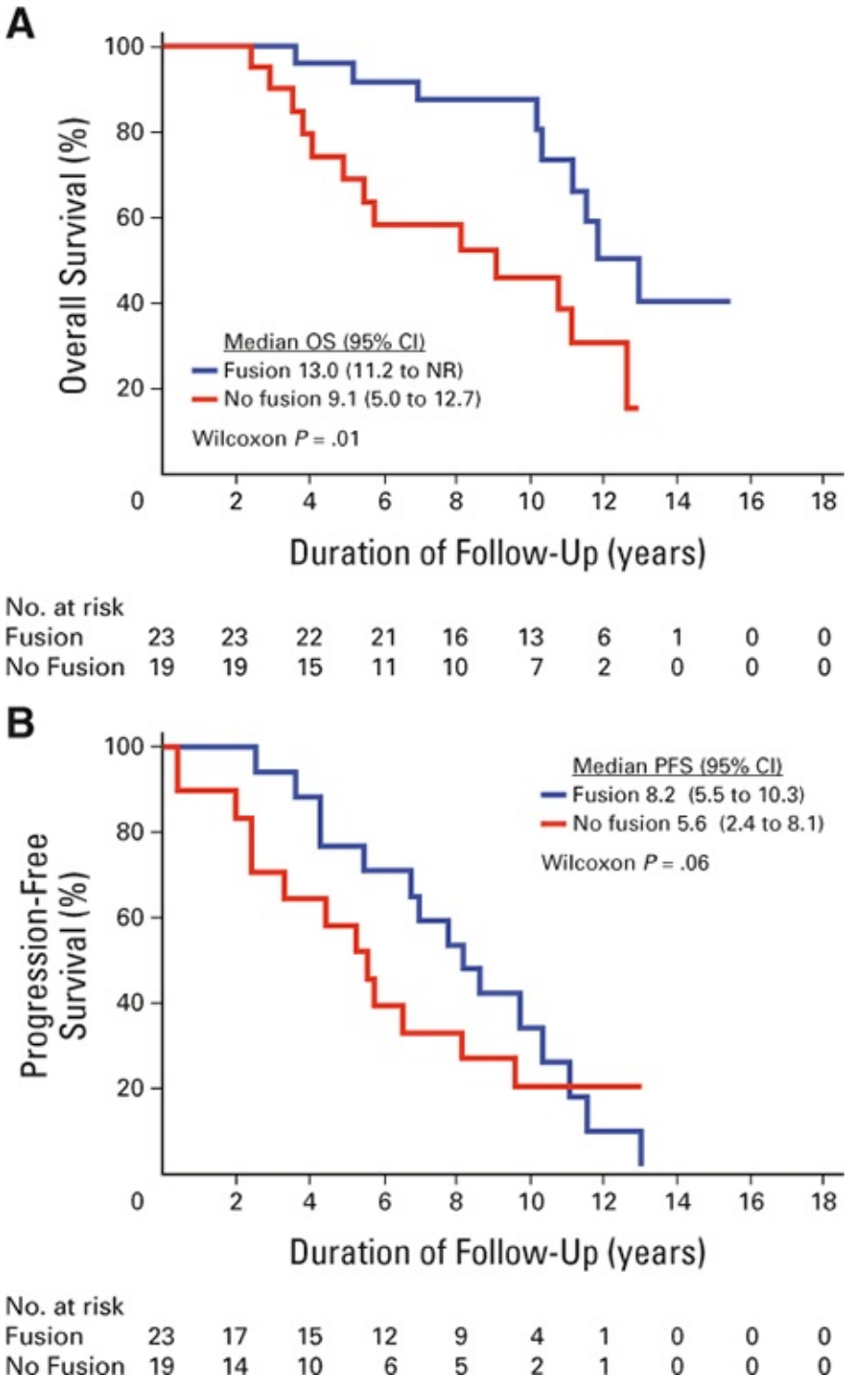


Fig. 15-4 Survival distribution of patients with low-grade oligodendroglioma/oligoastrocytoma by 1p/19q translocation (fusion) status.

Abbreviations: NR, not reported; OS, overall survival; PFS, progression-free survival.

Reprinted (or adapted) from Jenkins RB, Blair H, Ballman KV, et al. A t(1;19)(q10;p10) mediates the combined deletions of 1p and 19q and predicts a better prognosis of patients with oligodendroglioma. Cancer Res. 2006;66(20):9852-9861 with permission from AACR. PMID: 17047046.

Gene expression profiling of glioblastoma samples has identified specific subtypes of patients with differing clinical outcomes. These subtypes have been classified as proneural, classical, neural, and mesenchymal.[64-66] There is a subset of proneural glioblastoma with a distinctive pattern of DNA methylation (glioma-CpG island methylator phenotype [G-CIMP]) that has a particularly favorable prognosis.[67] The G-CIMP pattern is strongly associated with the presence of an *IDH* mutation.[63,68] Another report has further refined the subtypes of glioblastoma by defining six epigenetic subgroups based on methylation profiling.[69]

O^6-METHYLGUANINE–DNA METHYLTRANSFERASE (*MGMT*) PROMOTER METHYLATION

MGMT is a DNA repair enzyme that plays a crucial role in DNA repair. Alkylating agents such as temozolomide lead to methylation of nucleotide bases in genomic DNA. Although some of these lesions are fixed by base excision repair, O^6-methylguanine is a serious cytotoxic lesion that requires MGMT for its repair.

Hypermethylation of the *MGMT* promoter–associated CpG island has been described in approximately one-third of glioblastomas. *MGMT* promoter methylation prevents transcription of the *MGMT* gene and subsequent expression of the DNA repair enzyme. Consequently, patients with *MGMT* promoter–methylated tumors are expected to receive more benefit from temozolomide than patients whose tumors lack it. The favorable prognosis of patients with *MGMT* promoter–methylated glioblastoma is well described, along with its association with a greater likelihood of benefit from temozolomide.[17,20,67]

KEY POINTS

- 1p/19q codeletion and *IDH* mutation independently predict response to chemotherapy and prognosis in anaplastic oligodendroglioma. Tumors that are *IDH*-mutated without 1p/19q codeletion may have a mutation in *ATRX*, which is commonly seen in grade II and grade III astrocytomas.
- Patients with *MGMT* promoter–methylated glioblastoma have a better prognosis than patients whose tumors lack *MGMT* methylation. Furthermore, *MGMT* promoter methylation predicts a greater efficacy of temozolomide.

DIAGNOSIS AND MANAGEMENT OF ASTROCYTOMAS

GRADE IV ASTROCYTOMA (GLIOBLASTOMA)

Grade IV astrocytomas are primarily represented by glioblastoma, the most common type of primary malignant brain tumor. Glioblastoma was classically described as glioblastoma multiforme, although this latter term has fallen out of favor. Hallmark features of grade IV

astrocytoma consist of increased cellularity, marked nuclear pleomorphism, and frequent mitoses, as well as endothelial proliferation and areas of palisading necrosis. The median age at diagnosis is approximately 65. The onset of symptoms is often abrupt and is most commonly related to mass effect. Seizures are relatively common. Intracranial bleeding is the presenting symptom for fewer than 3% of patients.

T_1-weighted MRI scans with the use of gadolinium contrast typically show a heterogeneously enhancing mass lesion with low signal intensity in the center. In biopsy specimens, the central portion of the lesion often contains tumor necrosis, while the ring-enhancing portion is associated with increased vascular permeability. The surrounding low-signal component corresponds to intact brain parenchyma diffusely infiltrated by tumor cells. Studies involving the use of serial stereotactic biopsies have demonstrated isolated tumor cells well beyond any signal abnormality visible on imaging.[13]

Molecular aberrations such as *IDH* mutations and *MGMT* promoter hypermethylation provide prognostic information for patients with glioblastoma. Patients with *IDH*-mutated glioblastoma are usually younger (median age, 32) and have a median survival of 31 months. Those with *IDH* wild-type tumors are older (median age, 59) and have a median survival of only 15 months.[18] *MGMT* promoter methylation is also associated with a prolonged survival in glioblastoma compared with those without methylation (18.2 months vs. 12.2 months, $p < 0.001$).[17]

Approximately 3% of glioblastomas have chromosomal abnormalities resulting in aberrant fusion genes and proteins containing and constitutively activating the fibroblastic growth factor receptor (FGFR). The effectiveness of small-molecule FGFR inhibitors in this subset of patients is being evaluated in clinical trials.

Surgery

The mainstay of treatment for glioblastoma remains surgical removal of as much tissue as possible without creating an unacceptable neurologic deficit. In general, the outcome is better for patients with maximal surgical resection.[70] Patients with glioblastoma who do not have residual contrast-enhancing tumor after surgery have prolonged survival compared with patients with incomplete resections (17.9 months vs. 12.9 months, $p < 0.0001$).[71] Unfortunately, even in the absence of residual contrast enhancement, the extremely infiltrative nature of this tumor makes true complete surgical resection impossible. Some analyses have indicated improved survival when residual tumor volume is less than 5 cm^3 with at least a 70% extent of resection.[72]

Radiation

Radiation therapy has been the standard treatment for glioblastoma since the early phase III clinical trials conducted by the Brain Tumor Study Group, in which postoperative involved-field radiation therapy improved survival over supportive care alone (median survival, 35 weeks vs. 14.5 weeks).[73] Currently, involved-field radiation (only to areas of tumor involvement, not whole brain) consisting of 60 Gy delivered in 30 fractions is considered standard. Overall survival (OS) is worse with radiation doses of less than 50 Gy[74] and no better with doses higher than 60 Gy.[75] However, a shorter course of radiation over 3 weeks (40 Gy in 15 fractions) has been evaluated in a phase III clinical trial of elderly patients with glioblastoma because of their poorer prognosis.[76] This trial demonstrated that the shorter course of radiation produced outcomes similar to those for standard radiation (60 Gy in 30 fractions) in elderly patients. More recently, another phase III study demonstrated that a 1-week course (25 Gy in 5 daily fractions) of radiotherapy was noninferior to a 3-week course (40 Gy in 15 daily fractions) in patients with

newly diagnosed glioblastoma who were elderly and/or had a poor functional status.[77]

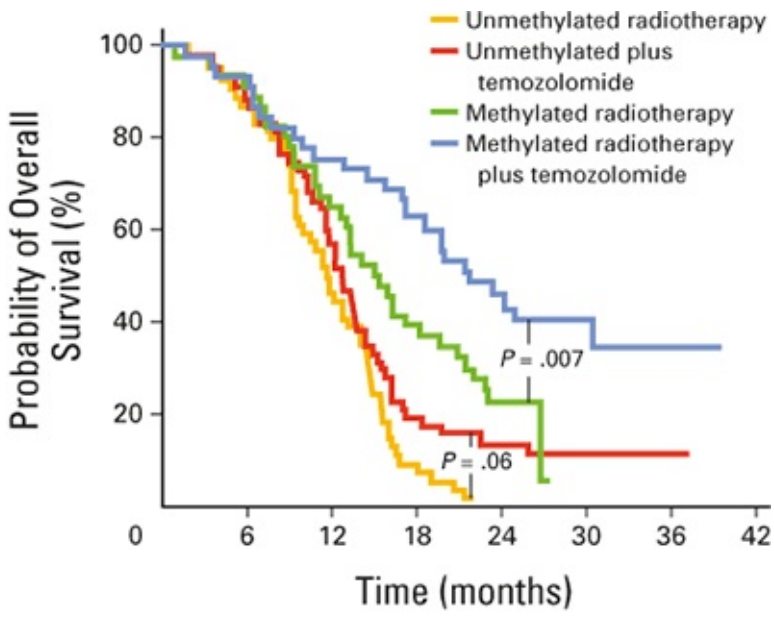
Multiple attempts to improve the therapeutic efficacy of radiation by using altered fraction schemes and radiation sensitizers have failed to produce substantially better results. Phase III randomized trials in patients with glioblastoma showed no benefit to adding either stereotactic radiosurgery or brachytherapy to radiation plus carmustine.[23,24]

Chemotherapy

Temozolomide. The benefit of adding temozolomide to radiation for patients with glioblastoma has been convincingly demonstrated. In a phase III clinical trial, patients with newly diagnosed glioblastoma were randomly assigned after surgery to receive radiotherapy alone (daily fractions of 2 Gy given 5 days a week for 6 weeks, for a total of 60 Gy) or radiotherapy plus concurrent daily oral temozolomide (75 mg/m^2 of body-surface area per day, 7 days a week from the first to the last day of radiotherapy) followed by six cycles of adjuvant temozolomide (150 to 200 mg/m^2 daily for 5 days of each 28-day cycle). Median survival and 2-year survival rates for patients receiving temozolomide were increased by 2.5 months (from 12.1 months to 14.6 months) and 16.1% (from 10.4% to 26.5%), respectively.[27] These results have established this temozolomide–radiation regimen as the current standard of care following surgical resection for patients with glioblastoma.

Within the same phase III trial, a companion correlative laboratory study demonstrated that *MGMT* promoter methylation was associated with superior survival, regardless of treatment received, and greater efficacy of temozolomide (Fig. 15-5).[17,20] In both the initial and 5-year analyses of this trial, survival differences between patients receiving radiation plus temozolomide and those receiving radiation alone were greatest in patients with *MGMT* promoter–methylated glioblastoma (median survival, 23.4 months vs. 15.3 months, p = 0.004). However, there was still a significant, although more modest, improvement in survival in patients whose tumors did not have *MGMT* promoter methylation (median survival, 12.6 months vs. 11.8 months, p = 0.035).[20]

Alternative adjuvant temozolomide regimens have been assessed, but they have not demonstrated superiority over the standard combined regimen. For example, a phase III randomized clinical trial compared standard adjuvant temozolomide (150 to 200 mg/m^2 of body surface area for 5 days during each 28-day cycle) to a dose-dense regimen of temozolomide (75 to 100 mg/m^2 on days 1 to 21 every 4 weeks).[78,79] There was no difference in median survival, regardless of *MGMT* methylation status. However, the dose-dense regimen was associated with more toxicity.



No. at risk							
Unmethylated radiotherapy	54	47	25	5	0	0	0
Unmethylated radiotherapy plus temozolomide	60	53	34	11	7	4	1
Methylated radiotherapy	46	42	30	18	8	0	0
Methylated radiotherapy plus temozolomide	46	42	34	28	16	7	1

Fig. 15-5 Survival in patients with glioblastoma.

By *MGMT* promoter methylation status and treatment (radiation alone or radiation plus temozolomide).

Abbreviation: MGMT, O^6-methylguanine–DNA methyltransferase.

From Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med. 2005;352:997–1003. Copyright 2005. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. PMID: 15758010.

Temozolomide in Elderly Patients. It remains controversial whether elderly patients with glioblastoma experience similar benefits from the standard regimen of radiation therapy (RT) and temozolomide. The original clinical trial excluded patients older than age 70[27]; however, patients between ages 60 and 70 did have an improvement in 2-year survival with combined therapy when compared with radiation alone (21.8% vs. 5.7%).[20] Other clinical trials have demonstrated the feasibility of combined therapy in the elderly, but have raised concerns for increased neurotoxicity in up to 40% of patients.[80,81] A phase II clinical trial demonstrated the feasibility of a shorter course of radiation concurrent with temozolomide in elderly patients.[82] Neurotoxicity was reported in only 10% of patients. An international phase III trial evaluating RT alone versus RT plus temozolomide in elderly patients with glioblastoma was recently conducted. Results from this study have shown that the addition of temozolomide to RT significantly improved OS (median, 9.3 months vs. 7.6 months, $p < 0.0001$) and progression-free survival (PFS) (median, 5.3 months vs. 3.9 months, $p < 0.0001$) compared to RT alone.[83] As would be expected, patients with MGMT methylated tumors had the most benefit from the addition of temozolomide to RT (median OS almost doubled).

Elderly patients with poor performance status and multiple comorbidities may not be candidates for concurrent radiation and chemotherapy. Two phase III clinical trials have

explored single-modality therapy (radiation alone vs. temozolomide alone) for newly diagnosed glioblastoma.[84,85] One trial demonstrated that temozolomide alone as initial therapy is at least noninferior to standard doses of radiation alone in elderly patients (8.6 months vs. 9.6 months, noninferiority $p = 0.033$). Furthermore, patients with *MGMT* methylated tumors had prolonged event-free survival with temozolomide compared with radiation (8.4 months vs. 4.6 months, $p < 0.05$), whereas the opposite was true for patients with *MGMT* unmethylated tumors (3.3 months vs. 4.6 months, $p < 0.05$).[85] The second trial also noted similar OS between elderly patients who received temozolomide and those who received hypofractionated radiation. The second trial demonstrated an improvement in survival with temozolomide compared with standard doses of radiation (60 Gy) (median survival, 8.3 months vs. 6.0 months; $p = 0.01$), but no difference in survival when compared with a hypofractionated course of radiation (34 Gy; median survival, 8.3 months vs. 7.4 months; $p = 0.12$).[84] Although progress has been made, a single standard approach for elderly patients with glioblastoma has not yet been established.

Bevacizumab. Bevacizumab is a monoclonal antibody that sequesters VEGF; it is thought to reduce abnormal angiogenesis in tumors such as glioblastoma. VEGF pathway inhibitors can rapidly reduce vascular permeability, leading to a dramatic reduction in contrast enhancement, as well as potential reductions in T_2-weighted signal on MRI, mass effect, and clinical symptoms. A reduction in contrast enhancement with a corresponding increase in T_2-weighted signal abnormality may represent progressively infiltrating nonenhancing tumor. Hence, the use of bevacizumab can confound the interpretation of tumor progression with contrast-enhanced MRI.

The addition of bevacizumab to standard chemoradiation with temozolomide has been assessed in two large phase III clinical trials. Neither of these trials demonstrated an improvement in OS with bevacizumab compared with placebo (median survival, 15.7 months vs. 16.1 months; $p = 0.21$; 16.8 months vs. 16.7 months; $p = 0.10$).[33,34] PFS was prolonged (median, 10.7 months vs. 7.3 months; $p = 0.007$ in one study; 10.6 vs. 6.2 months; $p < 0.001$ in the other); however, this outcome is difficult to interpret because of the impact of bevacizumab on vascular permeability, which can confound the determination of progression. Retrospective analysis of the AVAglio data suggests that patients with *IDH1* wild-type proneural subtype glioblastoma may have prolonged OS with upfront bevacizumab treatment.[35] In addition to survival analyses, the studies differed in the effect of bevacizumab on quality of life. One of the studies showed improvements in several measures of quality of life,[33] whereas the other revealed worsened neurocognitive function and decreased quality of life after the use of bevacizumab.[34] Both studies indicated a higher rate of adverse events, including thromboembolic events and hypertension, with the use of upfront bevacizumab compared to placebo.

Tumor-Treating Fields (TTFields). This is a device that delivers alternating electromagnetic fields to electrodes placed on the shaved scalp. It is approved for use in the treatment of patients with both newly diagnosed (after concurrent chemoradiation) and recurrent glioblastoma. The intervention has also been investigated in the postresection setting for patients with newly diagnosed glioblastoma. A randomized, phase III trial of temozolomide with or without TTFields alongside adjuvant temozolomide enrolled 695 patients who had completed concurrent chemoradiation. The final data demonstrated a significant increase in median OS of the patients treated concurrently with temozolomide and TTFields compared with patients treated with temozolomide alone (21 months vs. 16 months, $p < 0.00062$).[86] However, this trial was not blinded and a sham intervention was not considered feasible. Quality of life and gross cognitive function were noted to be comparable in the two arms. On the basis of these data,

the FDA has approved TTFields for use in newly diagnosed glioblastoma after concurrent chemoradiation.

Pseudoprogression

When concern for tumor progression arises after first-line therapy, it is essential to consider pseudoprogression prior to initiating alternative therapy. It is now well established that pseudoprogression can mimic true tumor growth, especially in patients whose tumors exhibit *MGMT* promoter methylation.[87] On MRI, both progression and pseudoprogression are characterized by increased contrast enhancement, T_2-weighted signal abnormality, and mass effect, with or without clinical deterioration (Fig. 15-6).[88] No imaging method can reliably distinguish the difference. For patients whose MRI scans appear worse within 1 to 3 months after completion of radiation, especially in tumors with *MGMT* promoter methylation, it is reasonable to continue adjuvant temozolomide with or without increasing the corticosteroid dose and to perform a repeat MRI scan in 1 to 2 months. In addition, both pseudoprogression and radiation necrosis may improve with bevacizumab, 7.5 mg/kg intravenously every 3 weeks.[42] Only patients with continued deterioration in imaging should proceed to different therapy.[21]

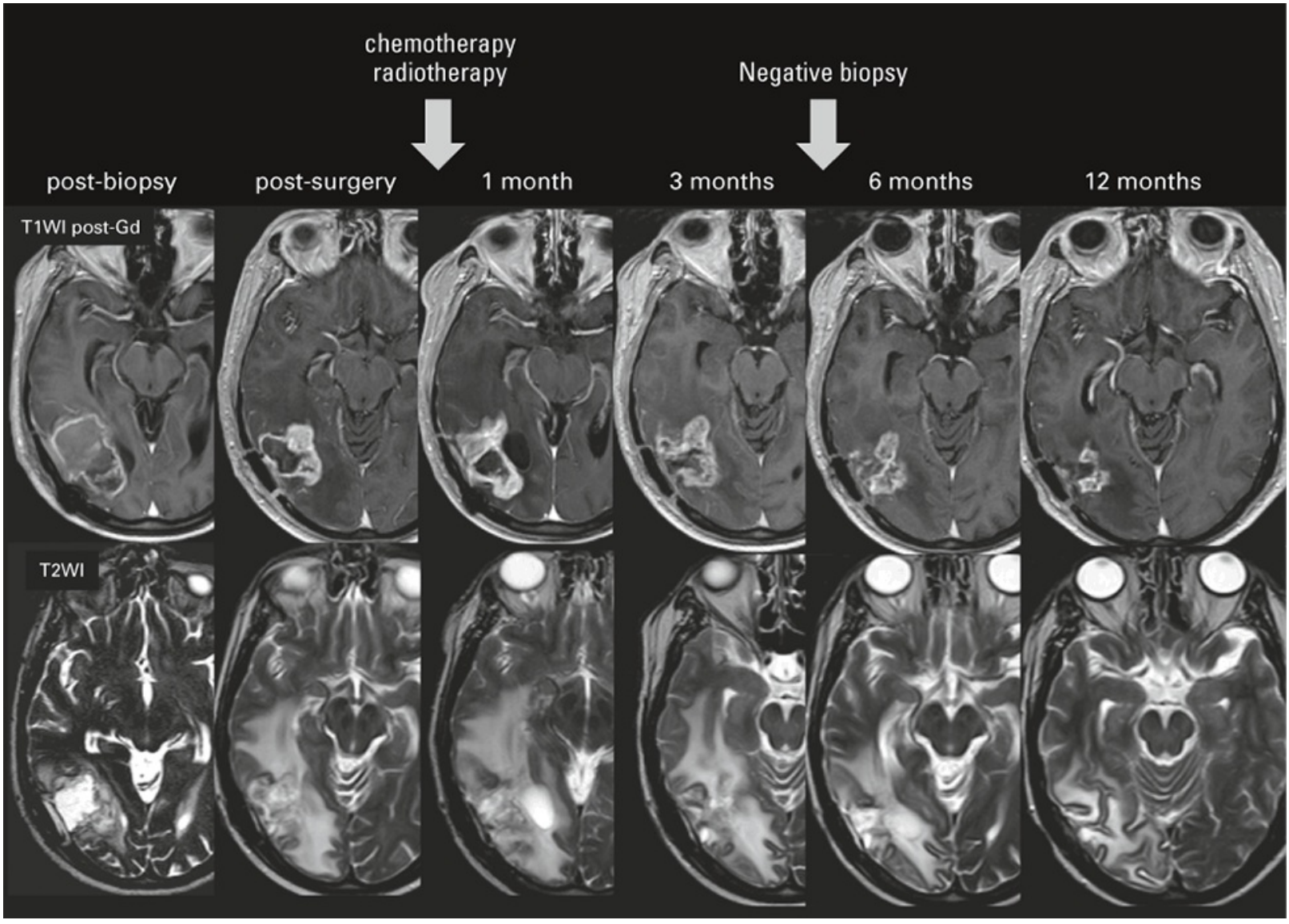


Fig. 15-6 Pseudoprogression in a 59-year-old man with glioblastoma.

MRI obtained 1 month after concurrent radiation and temozolomide demonstrated an expansion of the right temporal lesion. Reductions in both the enhancing portion and the surrounding abnormal hyperintense area in the T_2-weighted imaging were seen in the follow-up MRI examination.

Abbreviations: MRI, magnetic resonance imaging; T1WI post-Gd, T_1-weighted image post-gadolinium; T2WI, T_2-weighted image.

Reprinted from Hygino da Cruz LC, Jr., Rodriguez I, Domingues RC, Gasparetto EL, Sorensen AG. Pseudoprogression and pseudoresponse: imaging challenges in the assessment of posttreatment glioma. AJNR Am J Neuroradiol. Dec 2011;32(11):1978-1985. Copyright 2011 by American Journal of Neuroradiology. PMID: 21393407.

Recurrence. Treatment options for glioblastoma that has recurred after RT and temozolomide must be tailored to the individual. The value of additional RT or chemotherapy at the time of tumor progression remains under investigation. Participation in a well-designed clinical trial should be considered. Unfortunately, all standard therapies have limited benefits, and a focus on symptom control with end-of-life care may be appropriate.

For patients with resectable disease who have good neurologic function and performance status, a second resection may be done (with or without placement of carmustine-impregnated wafers).[38] In 2009, the FDA approved bevacizumab as treatment for recurrent glioblastoma following failure of RT and temozolomide. Phase II clinical trials of other VEGF pathway inhibitors have demonstrated encouraging response rates and have shown some evidence of both increased PFS at 6 months and median survival compared with historical experience (Table 15-2).[89] Nitrosoureas may also be used to treat recurrent glioblastoma.[90] Phase II data suggested that adding lomustine to bevacizumab may help in recurrent glioblastoma.[91] A subsequent phase III clinical trial demonstrated that the addition of bevacizumab to lomustine did not improve survival when compared with lomustine alone, conveying that although bevacizumab may improve PFS it may not increase OS.[92] The use of irinotecan with bevacizumab has been investigated, but it is unclear whether it provides any additional benefit; however, it probably increases toxicity.[93,94] The role of bevacizumab in combination with re-irradiation in recurrent glioblastoma is also being evaluated.[95]

TTFields has also been approved by the FDA for the treatment of recurrent glioblastoma. Results from a phase III, randomized trial of TTFields compared with physician's choice of chemotherapy for patients with recurrent glioblastoma demonstrated no difference in OS. Although it did not provide a survival advantage, TTFields was considered comparable to chemotherapy and was associated with fewer serious adverse events and better quality of life.[96] However, the benefit of TTFields is debated since there is no evidence from phase III clinical trials that chemotherapy itself extends survival in this patient population. Once again, these trials were not blinded and there was no sham intervention.

KEY POINTS

- The current standard of treatment for glioblastoma in patients under age 70 is maximum safe resection followed by radiation with concurrent and adjuvant temozolomide.
- The addition of upfront bevacizumab to standard chemoradiation in patients with newly diagnosed glioblastoma does not improve OS, and is not considered standard of care. Further investigation is necessary to determine whether upfront bevacizumab confers a survival benefit in certain subsets of patients (such as those with proneural subtype glioblastoma).

- Elderly patients with good functional status likely derive some benefit from concurrent hypofractionated radiation with concurrent and adjuvant temozolomide.
- Pseudoprogression may mimic tumor progression in patients with glioblastoma treated with radiation with or without temozolomide and should be considered before switching therapy, especially in patients with MGMT methylated tumors.
- Both bevacizumab and tumor-treating fields are approved by the U.S. Food and Drug Administration for the treatment of glioblastoma that has recurred after standard therapy with radiation and temozolomide.

GRADE III ASTROCYTOMA (ANAPLASTIC ASTROCYTOMA)

Anaplastic astrocytomas represent the category of grade III astrocytomas. These are differentiated from lower-grade astrocytomas by the presence of increased mitotic activity. There is a high propensity of anaplastic astrocytoma to transform into glioblastoma. The median age at diagnosis is approximately 55. Patients with anaplastic astrocytomas may present with seizures, focal neurologic deficit, headaches, or mental status changes. MRI usually demonstrates a contrast-enhancing mass, although some lesions may not enhance. The prognosis of patients with anaplastic astrocytoma varies greatly with *IDH*-mutation status. Patients with *IDH*-mutated tumors have a median survival of 65 to 112 months, whereas patients with *IDH* wild-type tumors have a median survival of only 20 months.[18,97] Anaplastic astrocytomas lacking the *IDH* mutation often behave like glioblastomas.

Surgery

The standard initial treatment remains surgical debulking to the maximum level that will not compromise neurologic function. Removal of sufficient tissue for comprehensive pathologic evaluation is necessary to distinguish anaplastic astrocytoma from glioblastoma. In particular, a histologic diagnosis of anaplastic astrocytoma in a patient with a heterogeneously enhancing mass lesion on MRI suggests that the tissue is not representative of the true diagnosis (likely glioblastoma). Also very important is establishing *IDH* status, which as noted can carry significant prognostic implications.

Radiation

Similar to patients with glioblastoma, postdebulking radiation therapy has been demonstrated to prolong survival in patients with anaplastic astrocytoma and is a standard component of treatment.[72,98] Most practitioners currently treat with 55.8 to 60 Gy in 1.8- to 2.0-Gy fractions.

Chemotherapy

The role of adjuvant chemotherapy in anaplastic astrocytoma remains controversial, as results from earlier trials must now be revisited in light of new data regarding tumor genetics. Most importantly, *IDH*-mutant anaplastic astrocytomas carry a much better prognosis as well as likely better response to treatment (including radiation and chemotherapy). Retrospective analyses indicate that temozolomide may improve OS when administered concurrently with radiation.[97] A phase III international trial (EORTC 26053 or “CATNON”) is ongoing, in which patients with anaplastic glioma without 1p/19q codeletion are randomly assigned to either

radiation alone or radiation with temozolomide during radiation and/or after radiation. Interim results indicate improved OS with post-RT temozolomide (HR reduction for OS of 0.645, p= 0.0014), further supporting adjuvant chemotherapy.[99] Until more data become available, *IDH* wild-type anaplastic astrocytomas are generally treated like glioblastoma, with postoperative chemoradiation followed by adjuvant temozolomide. Although studies do support improved survival with PCV in *IDH*-mutant non-codeleted tumors, the survival advantage appears much more pronounced in codeleted tumors (i.e., oligodendrogliomas). Because of its decreased toxicity and probable efficacy, temozolomide (both concurrent with and after radiation as adjuvant chemotherapy) is often similarly used in *IDH*-mutant non-codeleted anaplastic astrocytomas.

Recurrence

Chemotherapy is of benefit for anaplastic astrocytoma that recurs following radiation. Nitrosourea-based regimens have demonstrated response rates of approximately 30% in anaplastic astrocytoma.[100] Similarly, temozolomide was granted accelerated FDA approval on the basis of its activity in recurrent anaplastic astrocytoma (complete response, 6%; partial response, 28%; stable disease, 32%).[101] A randomized clinical trial compared the efficacy of PCV versus temozolomide in chemotherapy-naive patients with high-grade glioma and determined that there was no difference in outcome in patients with anaplastic astrocytoma (hazard ratio, 0.79; p = 0.48).[102] Bevacizumab has also demonstrated an objective response in recurrent anaplastic astrocytoma (partial response, 64%; stable disease, 8%).[103]

KEY POINTS

- Anaplastic astrocytomas have a high propensity to transform into glioblastoma.
- Although standard therapy has not yet fully been established, anaplastic astrocytomas (both *IDH* wild-type and *IDH* mutant) are often treated like glioblastoma, with maximal safe resection followed by radiation with concurrent and adjuvant temozolomide.

GRADE II ASTROCYTOMAS (DIFFUSE ASTROCYTOMA)

Grade II astrocytomas are mostly diffuse astrocytomas, but this group also includes other rare tumors (pilomyxoid astrocytoma and pleomorphic xanthoastrocytoma). These tumors are diffusely infiltrative and cellular. In the past, these were thought to be uniformly indolent, but more recent data show that *IDH* mutation and 1p/19q codeletion status delineate prognosis and treatment response.[56,106]

The median age at diagnosis is approximately 45. Patients with diffuse astrocytoma typically present with seizures. Diffuse astrocytomas usually appear as lesions with low attenuation or isodensity on CT scans. These tumors may not take up contrast material on MRI, and if contrast enhancement is present it may be wispy and faint. Focal intense enhancement may indicate areas of anaplastic transformation. When feasible, biopsy or preferably resection should be performed to obtain a sample of the contrast-enhancing portion, because the prognosis is typically related to the most anaplastic part of the tumor.

Older studies described prognostic factors in diffuse astrocytoma including older age (40 or

older), tumor diameter greater than or equal to 6 cm, Karnofsky performance status less than 70, tumors that cross the midline, presence of enhancement on imaging, and neurologic deficits prior to surgery.[104,105] However, more recent literature shows that *IDH* mutation and 1p/19q codeletion are much more accurate in predicting prognosis and survival. Grade II gliomas with both *IDH* mutation and 1p/19q codeletion are the most indolent, with much better survival.[106] Tumors with *IDH* mutation but no codeletion have an intermediate prognosis, while tumors lacking both *IDH* mutation and 1p/19q codeletion have the worst survival and are prognostically closer to glioblastoma (regardless of WHO histologic grade).

The treatment of diffuse astrocytoma remains controversial, especially as older studies were not able to address *IDH* mutation and/or 1p/19q codeletion. Because of the relative rarity of low-grade gliomas, clinical trials have historically combined diffuse astrocytomas with other low-grade tumors such as oligodendrogliomas, oligoastrocytomas, and pilocytic astrocytomas. Consequently, the results of many studies are difficult to interpret conclusively. New studies of patients with diffuse glioma now stratify patients based on their *IDH1*, *IDH2*, and 1p/19q chromosomal status instead of their histologic subtype (e.g., astrocytoma vs. oligodendroglioma).

A number of studies have demonstrated the presence of *BRAF* fusion events and the V600E activating *BRAF* mutations in a substantial percentage of pediatric gliomas, including pilomyxoid astrocytomas, pleomorphic xanthroastrocytomas, and ganglioglioma, opening up potential new therapeutic avenues.[107] There are case reports of successful treatment of progressive *BRAF* V600E–mutated anaplastic pleomorphic xanthoastrocytomas with vemurafenib, a *BRAF* inhibitor.[108]

Surgery

Symptomatic diffuse astrocytoma should be resected to debulk the tumor. Complete resection of all the tumor area with abnormal T_2-weighted signal results in superior outcomes when the risk of neurologic injury from resection is low. Retrospective single-institution data demonstrated that smaller preoperative and postoperative tumor volume (measured by FLAIR sequences on MRI) and greater extent of resection were associated with superior survival after adjustment for other known clinical variables.[109] Similar findings were observed in a prospective, multicenter clinical trial.[110] Unfortunately, complete resection is not feasible for all patients because of tumor location. Complete resection is generally limited to small unilateral tumors or tumors that do not involve critical brain structures. A practical approach is to resect as much of the abnormal tissue as possible without causing substantial neurologic deficit.

The surgical management of small asymptomatic diffuse astrocytomas is more controversial. No randomized controlled clinical trials have explored this question.[111] Either upfront surgical resection or a wait-and-watch approach may be considered.[112,113] If conservative management is planned, a biopsy is recommended in order to obtain a pathologic diagnosis.

Radiation

A phase III clinical trial has evaluated the role of immediate radiation versus delayed radiation therapy in patients with low-grade glioma.[114] Patients were randomly assigned to receive either 54 Gy of radiation immediately after surgery or no immediate radiation. In the latter arm, radiation was administered at the time of progression. This study demonstrated that radiation therapy beginning immediately after diagnosis extends the time to recurrence compared with delayed radiation at time of tumor progression (median PFS, 5.3 years vs. 3.4 years; $p <$

0.0001). However, there was no change in median OS (7.4 years vs. 7.2 years; p = 0.87). More recently, EORTC 22033-26033 (temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma) similarly showed that radiotherapy was associated with better PFS compared to temozolomide in patients whose tumors were *IDH* mutants without 1p/19q codeletion (which will be the case with most diffuse astrocytomas)[115]; OS has yet to be reached.

In the absence of a clear OS benefit, rationale exists for delaying radiation in an attempt to prevent radiation-induced neurologic damage. Prospective data had initially demonstrated that tumor growth, the use of antiepileptic drugs, and radiation fraction sizes greater than 2 Gy were associated with neurocognitive decline.[116] By contrast, RTOG 9802, a phase III trial of radiation alone versus radiation followed by chemotherapy with PCV, demonstrated minimal long-term neurotoxicity. In fact, a majority of patients showed improvement in neurocognitive testing over time, suggesting that untreated infiltrating glioma has a negative impact on neurocognitive function whether or not it is clinically apparent to the patient and their physicians.[28,117] Thus, for patients with minimal symptoms or well-controlled seizures, it is acceptable to either treat at the time of initial diagnosis or defer radiation until there is evidence of symptomatic tumor growth.

Two randomized clinical trials have explored the dose–response relationship of radiation in low-grade gliomas. The first trial compared postoperative or postbiopsy radiation doses of 45 Gy and 59.4 Gy. No differences in 5-year PFS (47% vs. 50%; p = 0.94) or 5-year OS (58% vs. 59%; p = 0.73) were observed.[118] The second trial explored higher doses of radiation therapy (50.4 Gy vs. 64.8 Gy). Survival at 5 years was similar with higher doses of radiation (72% vs. 64%; p = 0.48), but a higher 2-year incidence of grade 3 to 5 radiation necrosis was noted (2.5% vs. 5%).[119] In light of the above evidence, doses of 45 Gy to 54 Gy delivered in 1.8 Gy to 2.0 Gy fractions are acceptable.

Chemotherapy

The role of adjuvant chemotherapy for patients with low-grade astrocytoma remains under investigation. Results from a phase III trial in which radiation alone was compared with radiation followed by chemotherapy with PCV suggested that chemotherapy is associated with superior median OS (13.3 vs. 7.8 years; p = 0.003).[28,117] Chemotherapy had the largest effect in patients with *IDH*-mutant tumors. Although 1p/19q codeletion status was not available, greater response to chemotherapy was seen with oligodendrogliomas/oligoastrocytomas when compared to histologic astrocytomas.

The toxicity associated with PCV has limited its general acceptability. Many practitioners recommend the use of temozolomide either as initial therapy or at the time of recurrence for diffuse astrocytomas. However, data supporting initial therapy with temozolomide in these tumors are limited. As noted above, EORTC 22033-26033 (temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma) showed that radiotherapy was associated with better PFS in tumors that were *IDH* mutants without 1p/19q codeletion.[115] Longer follow-up will be required to determine the reliability of these preliminary observations.

KEY POINTS

- Diffuse astrocytomas can be indolent tumors; however, eventual anaplastic

transformation is relatively common.

- Prognosis and survival of patients with diffuse astrocytoma is highly dependent on *IDH* mutation and 1p/19q codeletion status.
- In asymptomatic patients with small tumors, delaying treatment such as surgical resection and radiation therapy (after biopsy confirmation of the diagnosis) may be considered. The optimal timing for treatment remains to be determined.
- Maximal safe resection is recommended if the diffuse astrocytoma is large and/or symptomatic.
- No clear survival advantage is seen with immediate postresection radiation therapy compared with delayed radiation at time of progression. Similarly, higher doses of radiation do not improve survival.
- Radiation may be more important than chemotherapy for *IDH*-mutant diffuse astrocytomas without 1p19q codeletion.

GRADE I ASTROCYTOMAS

Grade I astrocytomas are relatively uncommon and include pilocytic astrocytoma and subependymal giant cell astrocytoma. These well-circumscribed tumors are typically seen in children and young adults and are associated with excellent outcomes.[120]

Pilocytic astrocytomas most frequently present in the cerebellum (40%) followed by supratentorial regions (35%). Tandem duplication at chromosome 7q34 occurs in 66% of pilocytic astrocytomas, resulting in a *BRAF-KIAA1549* gene that is unique to these tumors.[121] Radiographically, pilocytic astrocytomas are frequently cystic with an associated contrast enhancing mural nodule.[122] Contrast enhancement in these low-grade tumors is secondary to capillary proliferation with glomeruloid and hyalinized vessels. Pilocytic astrocytomas are potentially curable with complete surgical resection.

Subependymal giant cell astrocytomas (SEGA) are periventricular tumors that occur in about 1 in 10 patients with tuberous sclerosis and are the most frequent cause of decreased life expectancy in this disease.[123] It is recommended that patients with tuberous sclerosis undergo a brain MRI every 1 to 3 years until the age of 25 to screen for new occurrences.[124] Acutely symptomatic SEGA (i.e., those associated with increasing ventricular enlargement) should be surgically resected. Asymptomatic SEGA may either be surgically resected or treated with a mammalian target of rapamycin (mTOR) complex inhibitor such as everolimus, which is FDA-approved for this indication.[125] *TSC1* and *TSC2* are both tumor suppressor genes; when they are deficient, mTOR complex 1 is constitutively upregulated, causing abnormal cell growth and proliferation. Everolimus inhibits mTOR complex 1, correcting the molecular defects contributing to tuberous sclerosis with potential shrinkage of associated tumors.

Even if surgical resection is incomplete, grade I astrocytomas typically remain indolent. Radiation may be considered in such circumstances but is typically deferred until significant tumor progression. Cytotoxic chemotherapy is of uncertain value.

KEY POINT

- Grade I astrocytomas are more common in children and young adults. Surgical resection is usually curative.

DIAGNOSIS AND MANAGEMENT OF OLIGODENDROGLIAL AND OLIGOASTROCYTIC TUMORS

Tumors containing oligodendroglial elements are relatively uncommon, accounting for only 9.5% of gliomas (see Fig. 15-2). Nevertheless, they are important to note because of their unique natural history and sensitivity to chemotherapy. Characteristic molecular features of oligodendroglial tumors include *IDH* mutation and 1p/19q codeletion. Oligoastrocytic tumors seem to represent a hybrid entity, as they contain both oligodendroglial and astrocytic components. At the molecular level, *IDH*-mutant oligoastrocytic tumors may either have *ATRX* mutations (more astrocytoma) or 1p/19q codeletion (more oligodendroglioma); 1p/19q codeletion is generally associated with superior survival outcomes compared with patients with 1p/19q intact tumors.[16] It is not clear at this point whether the designation of oligoastrocytoma versus oligodendroglioma makes any difference for prognosis or management as long as the tumor has a 1p/19q codeletion.

ANAPLASTIC OLIGODENDROGLIOMAS AND ANAPLASTIC OLIGOASTROCYTOMAS

Anaplastic oligodendroglioma and anaplastic oligoastrocytoma are grade III gliomas and are discussed together because of their similar management strategies. These tumors typically demonstrate high cellularity, nuclear pleomorphism, and frequent mitoses. However, abundant endothelial proliferation and tumor necrosis may also be seen and do not automatically raise the grade of the tumor to IV. The median age at diagnosis is approximately 50. Mass effect or seizures are typically seen at presentation. MRI reveals a variably contrast-enhancing mass in most patients.

Treatment of anaplastic oligodendroglioma and anaplastic oligoastrocytoma includes optimal surgical debulking followed by radiation with or without chemotherapy. Support for the use of chemotherapy and radiation after resection of anaplastic oligodendroglioma and anaplastic oligoastrocytoma comes from two phase III trials, one conducted in North America and the other in Europe. In the North American trial, patients with anaplastic oligodendroglioma and anaplastic oligoastrocytoma were randomly assigned to receive PCV for four cycles prior to radiation or radiation alone.[53] Patients with *IDH*-mutant codeleted tumors benefited from the addition of PCV to radiation (median survival, 14.7 years vs. 6.8 years). PCV improved survival in patients with *IDH*-mutant non-codeleted tumors, but the survival advantage was less substantial (5.5 years vs. 3.3 years) (Fig. 15-7).[19] For patients without *IDH* mutation, chemotherapy did not significantly prolong survival.

In the European trial, patients received PCV after radiation. Results were very similar to the North American results. Some long-term results demonstrate longer median survival in patients with 1p/19q codeleted tumors who received both radiation and PCV compared to those who received radiation alone. In contrast, patients with non-codeleted tumors did not have statistically significant improvement in OS with the addition of PCV.[29] Taken together, these two randomized trials support the standard use of radiation and chemotherapy with PCV for patients with anaplastic oligodendroglioma and anaplastic oligoastrocytoma with *IDH* mutation and 1p/19q codeletion. Ongoing international trials segregate patients into 1p/19q codeleted and non-codeleted tumors.[127,128] The use of PCV in *IDH*-mutant non-codeleted tumors

(astrocytomas) is less clear, and patients with these tumors often receive temozolomide therapy instead because of its lower toxicity.

Prospective trials have demonstrated that temozolomide is effective in patients with recurrent anaplastic oligodendroglioma and anaplastic oligoastrocytoma after RT and prior chemotherapy with PCV. One study demonstrated an objective response rate of 44%.[129] The relatively low frequency of cumulative myelosuppression with temozolomide makes it a sound treatment option in the setting of recurrent disease.

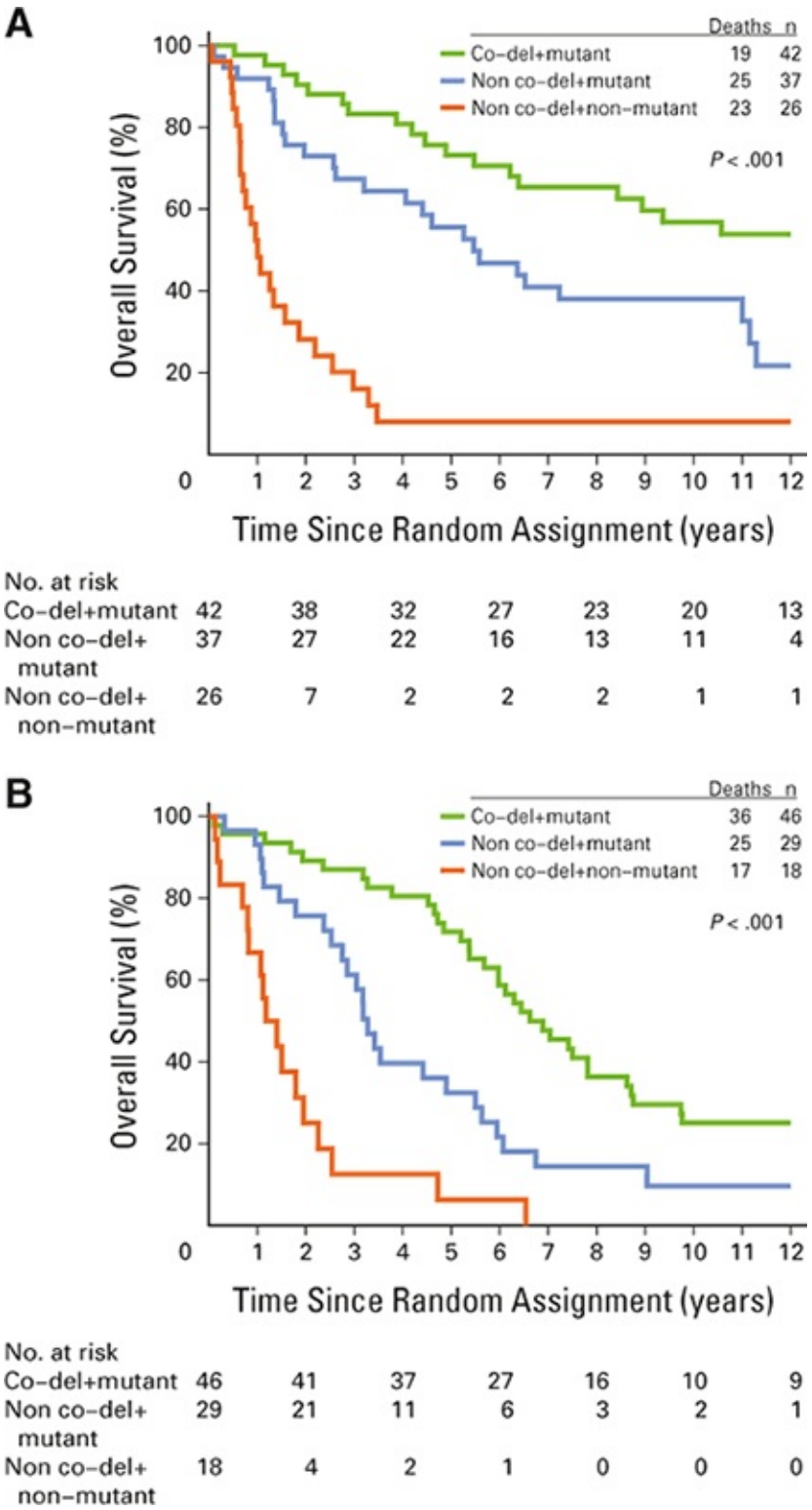


Fig. 15-7 Kaplan–Meier estimates of OS for patients with anaplastic oligodendroglioma or anaplastic astrocytoma whose tumors were *IDH* mutants with 1p/19q codeletion, mutants with no codeletion, and nonmutants with no codeletion after procarbazine–lomustine–vincristine (PCV) plus radiotherapy (RT) and RT alone.

(A) Median survivals after PCV plus RT were 14.7 years (95% CI; 6.4, not reached), 5.5 years (95% CI; 2.6, 11.0), and 1.0 years

(95% CI; 0.6, 1.9) ($p < 0.001$), respectively. (B) Median survivals after RT alone were 6.8 years (95% CI; 5.4, 8.6), 3.3 years (95% CI; 2.5, 4.9), and 1.3 years (95% CI; 0.8, 1.9) ($p < 0.001$), respectively.

Reprinted with permission from Cairncross JG, Wang M, Jenkins RB, et al. Benefit from procarbazine, lomustine, and vincristine in oligodendroglial tumors is associated with mutation of IDH. J Clin Oncol. 2014;32:783-790. PMID: 24516018.

OLIGODENDROGLIOMAS AND OLIGOASTROCYTOMAS

Oligodendrogliomas and oligoastrocytomas are both grade II gliomas with oligodendroglial elements. The median age at the time of diagnosis of oligodendroglioma is approximately 40. Patients typically present with seizures, although focal neurologic deficits, changes in mental status or personality, or symptoms of increased intracranial pressure are also seen. MRI is the preferred imaging modality because these tumors may not be visible on CT scans. The tumor is most prominent as increased signal intensity on T_2-weighted scans. There may be decreased signal (hypointensity) on T_1-weighted scans and occasional scant contrast enhancement. The disease course of oligodendrogliomas and oligoastrocytomas is more indolent than that of grade II astrocytomas.

As previously described (see section on Grade II Astrocytomas), controversy exists regarding the optimal management of oligodendrogliomas and oligoastrocytomas, as these tumors have classically been studied together with other low-grade gliomas. Further, treatment decisions are now based more on tumor genetic profile (in terms of *IDH* mutation and 1p/19q codeletion status) than on histologic grade.

Seizure control with antiepileptic drugs without additional antitumor therapy has been a common management strategy for small, minimally symptomatic tumors with a characteristic appearance on imaging.[111-113] However, this precludes a pathologic diagnosis. Highly symptomatic tumors should undergo maximal safe resection.[109,110] Deferring radiation until disease progresses or symptoms worsen is reasonable, as the optimal timing remains unclear.[114] If radiation is administered, results from a phase III clinical trial suggest that chemotherapy with PCV after radiation leads to a marked improvement in OS (13.3 years vs. 7.8 years; $p < 0.003$).[28,117]

KEY POINTS

- Oligodendroglial tumors are characterized by both *IDH* mutation and 1p/19q codeletion and have a more indolent course than astrocytomas.
- In patients with anaplastic oligodendroglioma or oligoastrocytoma with *IDH* mutation and 1p/19q codeletion, chemotherapy with procarbazine, lomustine, and vincristine (PCV) after radiation significantly improves OS.

EPENDYMAL TUMORS

Ependymal tumors are CNS tumors that usually arise from the ependymal lining of the ventricular system of the brain or the central canal in the spinal cord. In children, this tumor is more commonly found in the posterior fossa; in adults, the tumor is somewhat more common in the spinal cord. Supratentorial lesions outside the ventricular system are infrequent.[130] Ependymomas are currently separated into five categories by the WHO classification. Subependymomas and myxopapillary ependymomas are rare grade I tumors that are usually

curable with complete resection alone. Ependymomas (grade II), ependymomas-RELA fusion–positive (grade II or III, seen mostly in children) and anaplastic ependymomas (grade III) should be completely resected if possible.[131] Separate from histology, molecular profiling has confirmed distinct molecular subgroups of ependymomas that depend on the location in the brain. Supratentorial ependymomas are divided into RELA fusion–positive and RELA fusion–negative tumors.[132] For infratentorial ependymomas, Group A tumors are characterized by relatively increased DNA methylation and usually occur in infants and young children; they are associated with a poorer prognosis. Group B tumors do not have the increased DNA methylation and have much better outcomes; they primarily occur in older children and adults.[133] Both the lower-grade and anaplastic lesions may disseminate along the leptomeningeal surface. Incompletely resected, anaplastic, or disseminated disease is usually treated with radiation therapy. Studies have shown that ependymomas may respond to platinum-based chemotherapy regimens, but the clinical benefit of chemotherapy remains speculative, and response rates are low overall.[134,135] Many clinical trials are underway to further define the role of chemotherapy in this disease.[136,137]

MEDULLOBLASTOMA

Medulloblastoma is the most common malignant brain tumor in children, but young adults are also at risk. Medulloblastoma occurs in the posterior fossa; it may be located in either the cerebellar hemispheres or the vermis and may involve the fourth ventricle. Obstructive hydrocephalus is relatively common because of this proximity of the tumor to the fourth ventricle. Symptoms at presentation may include loss of balance, incoordination, diplopia, dysarthria, and signs of hydrocephalus such as headache, nausea, vomiting, and gait instability.

Molecular pathology studies have demonstrated that there are discrete subtypes of medulloblastoma with variable prognoses. The genetically defined subtypes have been incorporated into the new WHO 2016 classification: WNT, sonic hedgehog (SHH), Group 3, and Group 4 (Fig. 15-8).[138] The WNT group has the best prognosis, with long-term survival in more than 90% of patients. Patients in the SHH group and Group 4 have an intermediate prognosis, and Group 3 patients, with overexpression of *MYC*, have the worst prognosis. Although the molecular characterization has not yet resulted in specific therapies, the aberrant pathways identified may lead to targeted treatments specific for each molecularly defined entity. Preclinical studies have shown that the mutant beta-catenin in WNT-activated medulloblastoma induces an abnormal fenestrated blood–brain barrier, which may allow for high levels of intratumoral chemotherapy.[139] This could explain the improved treatment response and survival observed in this subtype of medulloblastoma—SHH-activated medulloblastomas appear to have an intact blood–brain barrier, which probably contributes to their decreased chemoresponsiveness.

MRI usually shows a contrast-enhancing mass lesion involving the cerebellum, although some medulloblastomas do not enhance. These tumors have a high propensity to seed the leptomeninges focally, as well as to spread through the subarachnoid space to involve the ventricles, cerebral convexity, and spinal leptomeningeal surfaces. MRI of the entire craniospinal axis is necessary for staging; preoperative CSF examination may not be possible because of the risk of herniation from a posterior fossa tumor.

Maximal surgical resection is important, because residual tumor after surgery confers a worse prognosis.[140] A worse prognosis is also seen with positive CSF cytology or the presence of leptomeningeal metastases on MRI.[141] Surgery alone is not curative; however, surgical

resection followed by radiation to the craniospinal axis with a boost to the site of the primary tumor (usually the posterior fossa) can be curative. In addition, adjuvant chemotherapy (following radiation therapy) with a platinum drug (cisplatin or carboplatin), etoposide, and an alkylating agent (either cyclophosphamide or lomustine) plus vincristine has increased the cure rate compared with the use of radiation therapy alone. Postradiation chemotherapy is a mainstay of treatment in children with medulloblastoma, particularly because this limits the total dose of radiation required in treating the still-developing CNS. On the basis of this experience, adults with medulloblastoma are usually offered chemotherapy; however, it is important to note that there are no prospective data demonstrating any long-term benefit for its use in adults who have received full-dose craniospinal radiation. With appropriate initial therapy, 5-year event-free survival is achieved in more than 80% of patients with average-risk medulloblastoma. Patients with disseminated disease at diagnosis fare much worse, with a 5-year event-free survival of 36%.[30] There are no robust data on the optimal management of patients with recurrent medulloblastoma. However vismodegib, a small-molecule inhibitor of the SHH pathway, has demonstrated activity in patients with recurrent SHH-type medulloblastoma,[142] and high-dose chemotherapy with autologous stem cell transplantation may result in longer survival in some patients.[143,144]

KEY POINTS

- Genetically distinct subgroups of ependymoma carry significant prognostic implications.
- Supratentorial ependymomas are now classified by the presence (or lack) of the RELA fusion, while infratentorial ependymomas are separated into Group A (hypermethylated phenotype) and Group B (no hypermethylated phenotype) tumors.
- Medulloblastoma typically occurs in the cerebellum of children.
- Treatment for medulloblastoma includes maximal safe resection followed by irradiation of the craniospinal axis (with a boost to the posterior fossa) and a platinum-based chemotherapy regimen.

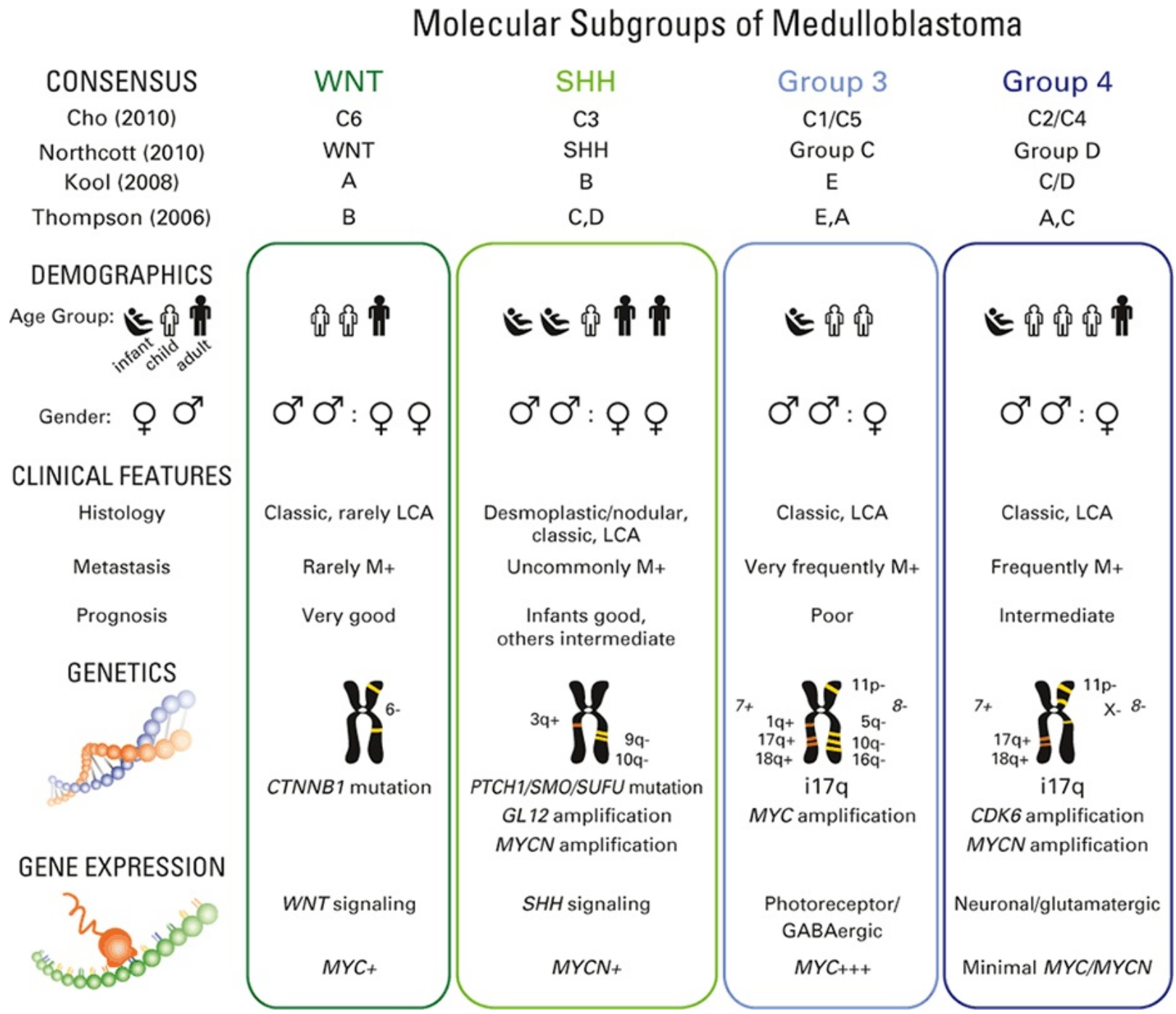


Fig. 15-8 Comparison of the various subgroups of medulloblastoma, including their affiliations with previously published papers on medulloblastoma molecular subgrouping.

Abbreviations: LCA, large cell/anaplastic; M+, metastatic; SHH, sonic hedgehog.

Reprinted with permission from Taylor MD, Northcott PA, Korshunov A, et al. Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol. 2012;123:465-472. Copyright The Author(s) 2011. PMID: 22134537.

VESTIBULAR SCHWANNOMA (ACOUSTIC NEUROMA)

Vestibular schwannomas, also known as “acoustic neuromas,” are usually benign, indolent tumors that arise from the vestibular branch of the eighth cranial nerve. Vestibular schwannomas account for approximately 6% of intracranial tumors and 85% of cerebellopontine angle tumors.[145] The median age at diagnosis is 55.[146] Tumors are typically unilateral, but bilateral vestibular schwannomas may occur in neurofibromatosis type 2 (NF2). Unilateral sensorineural hearing loss and tinnitus are the most common symptoms at presentation and are suggestive of a diagnosis of vestibular schwannoma. Patients may also have other cranial nerve deficits, such as facial weakness or numbness, trigeminal neuralgia,

and unsteadiness on ambulation. MRI is the imaging method of choice and will typically reveal an enhancing mass in the vicinity of the internal auditory canal. Complete tumor resection is usually curative, although this may not be feasible because of its proximity to several cranial nerves. Stereotactic radiosurgery is a viable option for smaller tumors. Observation may also be considered for small asymptomatic tumors, but close follow-up is needed because of the risk of progressive hearing loss. It has been shown that bevacizumab can reduce the size of some NF2-associated vestibular schwannomas, with associated hearing improvement and acceptable toxicity.[147]

MENINGIOMA

Meningiomas are usually benign and originate in the dura covering the brain and spinal cord. The incidence of the tumor is approximately 2 per 100,000 individuals. There is a female preponderance, and the median age at diagnosis is approximately 65. The frequency of meningioma is increased for patients with NF2. An association between meningioma and breast cancer has also been observed.[148] Although meningiomas can express receptors for androgen, estrogen, progesterone, and somatostatin, hormone therapies directed at these receptors have not demonstrated consistent therapeutic efficacy.[149,150]

Genomic analyses have revealed that meningiomas fall into two broad categories.[151] Meningiomas with *NF2* mutations and/or chromosome 22 losses were more likely to be atypical, genomically unstable, and localized in the cerebral and cerebellar hemispheres. Meningiomas without *NF2* mutations had an increased mutation burden in *TRAF7*, *KLF4*, *AKT1*, and *SMO*. Tumors lacking *NF2* mutations with oncogenic mutations in *SMO* or *AKT* tend to be skull-based.[152]

Patients with meningiomas may present with typical features of mass lesions in the brain, including seizures or focal neurologic deficits. Asymptomatic meningiomas may also be incidentally detected on CT or MRI scans that are obtained for other reasons. The tumors have a characteristic appearance on MRI, usually consisting of uniform contrast enhancement along the dura and distinct separation from brain parenchyma. Contrast enhancement extending from the mass lesion, known as the “dural tail,” is characteristic, but it is not present in all cases. Marked parenchymal edema is frequently seen.

Many incidentally discovered meningiomas do not require treatment. For patients with an asymptomatic benign meningioma, observation may be appropriate. Epidemiologic evidence suggests that as many as two-thirds of these patients will not have symptoms over time.[153] When there is substantial mass effect with or without symptoms, the treatment of choice is usually complete resection. Surgery is often feasible if the meningioma is located over the cortical convexity, olfactory groove, anterior sagittal sinus, or posterior fossa. However, the possibility of resection may be limited for tumors in other sites, including sphenoid, parasagittal, orbital, tentorial, or clival locations. Under those circumstances, external-beam radiation therapy or focal stereotactic radiotherapy may be extremely useful for tumor control. No pharmaceutical interventions have reproducibly demonstrated antitumor efficacy for meningiomas; however, the abovementioned novel genetic insights[151,152] have opened new avenues for exploring targeted therapeutics.

Meningiomas may occasionally have atypical histologic features or be frankly malignant. Patients with atypical or malignant meningiomas are commonly treated with surgical resection followed by radiation therapy, either external-beam radiation therapy or stereotactic radiosurgery. Those who experience relapse despite optimal surgery and radiation therapy

often have progressive debilitation before death. Although several pharmaceutical approaches have been assessed, they have had minimal, if any, efficacy.[154]

KEY POINTS

- Vestibular schwannomas are benign tumors that often cause unilateral hearing loss and tinnitus; surgical resection, if possible, is often curative.
- Meningiomas are typically benign, dural-based tumors, with a preponderance in women and the elderly.
- Genomic analyses suggest that meningiomas with *NF2* mutations and/or chromosome 22 losses are more likely to be atypical and follow a more aggressive course than meningiomas without these genetic aberrations.
- In many patients with meningioma, observation is appropriate. For patients who are symptomatic, surgical removal is the most common treatment.
- Atypical and malignant meningiomas are rare but have a more aggressive course with recurrences that may require re-resection and radiotherapy.

PRIMARY CNS LYMPHOMA

Primary CNS lymphoma is a variant of non-Hodgkin lymphoma that involves the CNS without evidence of systemic disease. More than 95% of primary CNS lymphomas are diffuse large B-cell lymphomas. Primary CNS lymphomas constitute approximately 2 to 3% of all brain tumors. The tumor is more common in men, and the median age at diagnosis is approximately 55.[155] The majority of patients diagnosed with primary CNS lymphoma are immunocompetent; however, patients with a compromised immune system (e.g., those who have undergone solid organ transplantation, have congenital immunodeficiency, or have HIV infection) are at increased risk for this disease. Epstein–Barr virus (EBV) is frequently associated with primary CNS lymphoma in immunocompromised individuals, and EBV DNA may be found within the tumor.

Patients present with a variety of symptoms characteristic of either focal or multifocal mass lesions. The MRI scan usually shows homogeneous contrast-enhancing tumors within the periventricular deep white matter. Multifocality is common. Heterogeneous contrast enhancement is sometimes seen, especially in patients with a compromised immune system. It is extremely important to consider CNS lymphoma in the differential diagnosis of brain tumors. Administration of corticosteroids may result in complete disappearance of the contrast-enhancing lesion, making diagnosis difficult. Consequently, when CNS lymphoma is considered in the differential diagnosis, corticosteroids should be avoided, unless mass effect is causing serious and immediate complications. Obtaining specimens of suspected lesions by biopsy is critically important because many malignant and nonmalignant CNS conditions can mimic a CNS lymphoma. Unlike systemic large B-cell lymphomas, for which both chemotherapy and radiation therapy are effective and treatment for localized disease is curative, CNS lymphoma usually responds to initial therapy but then typically relapses. As with systemic lymphoma, the role of surgery is restricted primarily to obtaining appropriate tissue for diagnosis. Appropriate staging evaluation includes slit-lamp examination of the eyes (to assess for ocular lymphoma), MRI of

the spine, lumbar puncture (if there are no contraindications such as increased intracranial pressure or bleeding diathesis), bone marrow biopsy, and CT scan of the chest, abdomen, and pelvis to rule out systemic lymphoma. Some experts recommend PET scan as well. HIV testing is also appropriate.

Standard treatment regimens for diffuse large B-cell lymphoma (e.g., rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone [R-CHOP]) are not active in primary CNS lymphoma, most likely because of poor blood–brain barrier penetrance.

High-dose methotrexate–based regimens are the backbone of treatment for CNS lymphoma, but it is not yet clear what additional treatments (such as chemotherapy, RT, and/or stem-cell transplantation) provide the best outcome. High-dose methotrexate followed by consolidation WBRT is associated with better outcomes than WBRT alone.[156] Furthermore, high-dose methotrexate (3.5 g/m^2, day 1) plus cytarabine has demonstrated high rates of complete remission compared with high-dose methotrexate alone in a randomized phase II trial, in which all patients received consolidation WBRT (complete response rate, 46% vs. 18%; p = 0.009).[157]

Although WBRT was previously considered to play a central role in the initial treatment for this disease, this is now more controversial because of the risk of later neurotoxicity with dementia secondary to leukoencephalopathy.[158] Another clinical trial is currently assessing the impact of adding consolidation low-dose WBRT to a high-dose methotrexate based chemotherapy regimen.[159] To avoid neurotoxicity, clinicians frequently defer WBRT until recurrence if complete remission has been achieved with chemotherapy. Many studies have demonstrated that radiation may be eliminated from first-line therapy.[31,160] Chemotherapy-only regimens such as high-dose methotrexate with temozolomide and rituximab have shown long-term survival (complete response rate, 66%; 4-year survival, 65%).[161] However, hyperfractionation of RT with lower doses are also being evaluated in hopes of balancing efficacy with decreased neurotoxicity. The NRG Oncology/RTOG 0227 phase I/II trial treated patients with induction chemotherapy (methotrexate, rituximab, and temozolomide) followed by consolidation hyperfractionated whole-brain radiotherapy (1.2 Gy twice daily for 15 fractions; total 36 Gy) and temozolomide.[162] The regimen had an objective response rate of 85.7% and 2-year OS and PFS were 80.8% and 63.6%, respectively. Significant late neurotoxicity was not seen.

Stem-cell transplantation may allow effective consolidation without the need for up-front radiation. Omuro et al. demonstrated excellent initial disease control in patients with newly diagnosed primary CNS lymphoma treated with rituximab/methotrexate/vincristine/procarbazine (R-MVP) followed by high-dose chemotherapy and autologous stem-cell transplantation (HCT-ASCT). Two-year PFS and OS were 81% in patients who had undergone transplantation (only patients who had complete or partial response to initial chemotherapy underwent transplantation). Minimal early neurotoxicity was seen.[163] In another German study, patients with primary CNS lymphoma were similarly treated with induction chemotherapy followed by HCT-ASCT; 5-year OS was also high, at 79%.[164] Additional clinical trials are currently ongoing to evaluate the role of high-dose chemotherapy consolidation with stem cell transplantation.[165,166]

The doses of methotrexate described above (3.5 to 8.0 g/m^2) are potentially lethal if not followed by active measures to reduce associated toxicity. Multiple doses of leucovorin must be administered starting approximately 24 hours after treatment to minimize toxicity to normal cells (leucovorin rescue), and urinary alkalinization with intravenous sodium bicarbonate is utilized to enhance methotrexate excretion. Methotrexate levels need to be monitored to confirm effective

elimination. Prolonged exposure may be secondary to accumulation of methotrexate in third-space fluid collections (e.g., pleural effusions). Such fluid collections should be drained prior to treatment with methotrexate.

Strategies for the treatment of recurrent disease include re-induction with high-dose methotrexate, potentially high-dose chemotherapy with autologous stem cell transplantation, WBRT, and use of rituximab, combination chemotherapy, or high-dose cytarabine.

The initial therapy for patients with compromised immune systems is treatment of the cause of immunosuppression. The prognosis for such patients is usually worse than that for immunocompetent patients. Despite a compromised immune system, chemotherapy may still be an option for some patients; others may be able to receive only palliative radiation.

KEY POINTS

- Primary CNS lymphomas are usually diffuse large B-cell lymphomas.
- EBV is frequently associated with primary CNS lymphoma in immunocompromised individuals.
- High-dose methotrexate–based chemotherapy regimens are effective in primary CNS lymphoma. Treatment with high-dose methotrexate requires careful attention to supportive care issues, such as the need for leucovorin rescue, alkalinization of the urine, and monitoring of methotrexate levels.
- Autologous stem cell transplantation is a promising option for consolidation in patients with good functional status who respond to a methotrexate-based chemotherapy regimen.

METASTATIC DISEASE TO THE NERVOUS SYSTEM

BRAIN METASTASES

Metastases to the brain are the most common intracranial tumors in adults and are 10 times more common than primary brain tumors. Brain metastases are diagnosed in 8 to 10% of patients with cancer during their lifetime[167,168]; however, autopsy series suggest that the true incidence of brain metastases in adults is approximately 20%.[169] Brain metastases are most commonly associated with cancers of the lung, breast, melanoma, or an unknown primary cancer. These lesions result from hematogenous spread and are most common at the junction of the gray and white matter, where the caliber of blood vessels narrows, thereby trapping tumor emboli. A total of 80% of brain metastases occur in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brainstem.[160] Approximately 80% of patients have a history of a systemic cancer, and 70% have multiple brain metastases seen on MRI. Systemic malignancies with a high propensity for metastasis to the CNS include melanoma, small cell lung cancer, and choriocarcinoma (and other germ cell tumors). Although brain metastases are most often seen from non–small cell lung cancer (NSCLC) and breast cancer (because of the greater frequency of these malignancies in the population), these generally have relatively less neurotropism.

The presenting signs and symptoms of these lesions are similar to those of other mass lesions in the brain. The best diagnostic test is MRI with contrast. Not all brain lesions in patients with cancer are metastases. In one prospective study of patients with systemic cancer

who were thought to have single brain metastasis, 11% of biopsy specimens of brain tissue showed primary brain tumors or infections.[170]

The management of brain metastases requires an individualized approach, as these patients have highly heterogeneous primary disease processes. Considerations for therapy depend on multiple variables, such as the number and location of the brain metastases, histology of the primary cancer, tumor molecular characteristics, degree of extracranial disease, and performance status.

Two randomized, prospective studies have shown that surgery plus WBRT is superior to WBRT alone in patients with one surgically accessible brain metastasis. In one trial, patients who received surgery plus radiation survived 6 months longer than patients who received radiation alone (median, 40 weeks vs. 15 weeks; $p < 0.01$).[171] The second trial demonstrated similar results (median survival, 10 months vs. 6 months; $p = 0.04$).[172] Multivariable analyses indicated that patients who were younger and did not have systemic disease benefited primarily from surgery, while those with active systemic disease did not live longer if the metastasis was surgically resected. Many other patients with one or two brain metastases are not surgical candidates because of complicating factors such as an inaccessible tumor location.

Stereotactic radiosurgery (SRS) is increasingly being used in addition to or in place of surgery for patients with one to three metastases. Local control rates with SRS are high, ranging from 80 to 90%.[174] In a phase III clinical trial, patients with one to three brain metastases were treated with WBRT either with or without a SRS boost. Patients who received SRS in addition to WBRT therapy were more likely to maintain a stable or higher performance score at 6 months (43% vs. 27%; $p = 0.03$). Patients with a single brain metastasis also seemed to have a survival advantage (6.5 months vs. 4.9 months; $p = 0.04$).[175] After surgery, radiation to the resection cavity with SRS has been shown to decrease local recurrence compared with surgery alone. One phase III trial randomly assigned 132 patients who had undergone a complete resection of one to three brain metastases (maximum diameter of resection cavity, ≤ 4 cm) to either SRS of the resection cavity or observation.[176] Freedom from local recurrence at 1 year was 43% in the observation group and 72% in the SRS group (hazard ratio, 0.46, $p = 0.015$), indicating that SRS significantly lowers local recurrence. SRS may be preferred as an independent treatment in patients who have surgically inaccessible lesions who cannot undergo craniotomy because of the operative risk or who have more than one lesion in different parts of the brain. Limitations include the inability to obtain tissue diagnosis or reduce mass effect; also, lesions must generally be less than 3 to 4 cm in order to be safely treated. Furthermore, SRS may increase cerebral edema, resulting in mass effect that requires either corticosteroids or resection of radionecrotic tissue.

In patients who have undergone a surgical resection or SRS, the role of WBRT is controversial. In a phase III clinical trial, patients with one to three brain metastases were treated with either surgery or SRS and then randomly assigned to either WBRT (30 Gy in 10 fractions) or observation. WBRT reduced the incidence of both intracranial progression (48% vs. 78%; $p < 0.001$) and neurologic death (28% vs. 44%; $p < 0.002$); however, OS was similar in the two groups (10.9 months vs. 10.7 months; $p = 0.89$).[177] Similar results have been found in multiple other studies.[171,178-180] Many studies have raised concerns regarding cognitive impairment with the addition of WBRT.[181] Another phase III trial compared the survival and cognitive outcomes of patients receiving WBRT or SRS after metastasis resection. Patients with one resected brain metastasis were randomly assigned to either postoperative SRS or WBRT. Median OS was similar between the two groups (12.2 months for SRS and 11.6 months for WBRT), and cognitive deterioration occurred sooner and more frequently with

WBRT.[182] With these results, ways to limit the cognitive toxicity of WBRT are actively being investigated. Data from a placebo controlled phase III clinical trial suggest that memantine concurrent with WBRT may delay cognitive decline.[183] Another clinical trial is evaluating hippocampal sparing during WBRT as a strategy to reduce neurocognitive decline.[184]

Definitive therapy with either surgical resection or SRS may not be an option in several situations. Patients with tumors that almost always disseminate widely, such as small cell lung cancer and lymphoma, are not candidates for either surgical resection or SRS. These patients and others with multiple brain metastases should receive WBRT as standard therapy. In other situations, such as brain metastases secondary to gestational trophoblastic neoplasia, surgical resection is avoided because of the high risk of intracranial hemorrhage.

Chemotherapy is rarely used as primary therapy for brain metastases. However, it may be curative in specific tumors, such as lymphoma, germ cell tumors, and gestational trophoblastic neoplasia; chemotherapy may be incorporated into the treatment plan for both brain and systemic metastatic disease in these patients, often in combination with radiation therapy. CNS metastases of most tumors (e.g., NSCLC, carcinoma of unknown primary site, breast cancer, renal cell carcinoma, and melanoma) are not sensitive to chemotherapy, and brain metastases may present after the failure of multiple prior therapies. Furthermore, many chemotherapy drugs have poor blood–barrier penetration.

Nevertheless, in some patients tumor regression was seen in response to systemically administered chemotherapy or targeted agents. It has been reported that CNS metastases from EGFR-mutant NSCLC have responded to pulsatile high-dose erlotinib.[185] In anaplastic lymphoma kinase (ALK)–rearranged NSCLC, extended survival in the setting of brain metastases has been seen with the ALK inhibitor crizotinib.[186] Ceritinib, an ALK inhibitor with better blood–brain barrier penetration, can be effective in crizotinib-refractory brain disease from ALK-rearranged NSCLC as well.[187] In terms of breast cancer, the combination of lapatinib and capecitabine has demonstrated efficacy in brain metastases secondary to HER2-positive disease.[188] Dabrafenib is helpful in *BRAF*-mutant melanoma that has metastasized to the brain.[189] Lastly, untreated metastases from melanoma and NSCLC have responded to checkpoint inhibitors such as pembrolizumab.[190]

KEY POINTS

- Brain metastases are 10 times more common than primary brain tumors. The most common primary tumors are lung and breast cancers, melanoma, and cancer of unknown primary origin.
- Surgical resection and SRS are of benefit to patients with a single brain metastasis who have a good Karnofsky performance score and controlled or absent systemic tumor.
- The addition of SRS after resection of brain metastasis decreases local recurrence and has better cognitive outcomes compared to WBRT.
- ALK inhibitors and EGFR tyrosine kinase inhibitor can be effective in ALK-rearranged and EGFR-mutant NSCLC, respectively.
- Patients with *BRAF*-mutant melanoma metastatic to the brain benefit from treatment with dabrafenib.

LEPTOMENINGEAL METASTASES

Leptomeningeal metastases occur in approximately 5% of patients with cancer and are more frequently recognized as patients with cancer live longer and as diagnostic studies improve.[191] The leptomeninges are most commonly involved with breast cancer, lung cancer, and melanoma. The tumor reaches the leptomeninges by hematogenous spread or by direct extension from preexisting tumor deposits within the dura or brain parenchyma. Tumor cells are disseminated throughout the neuraxis by the flow of the cerebrospinal fluid. Patients present with signs and symptoms referable to one or more of the following:

- Local injury to nerves traveling through the spinal fluid (cranial nerve palsies, weakness, paresthesias, or pain).
- Direct invasion into the brain or spinal tissues or interruption of blood supply to those tissues (focal findings or seizures).
- Obstruction of normal CSF flow pathways, increased intracranial pressure, and hydrocephalus (headache, nausea, vomiting, and dizziness).
- Interference with cognitive function (encephalopathy).

The diagnosis is made by examination of the CSF or MRI of the brain and spinal cord. Initial analysis of CSF demonstrates malignant cells in 50% of affected patients; however, in nearly 10% of patients with leptomeningeal involvement, the cytologic examination remains persistently negative.[192] Increasing the number of lumbar punctures (up to six) and the volume of CSF removed (10 mL per lumbar puncture) increases the yield of positive cytology. CSF analysis usually demonstrates mild protein elevation, pleocytosis, and possible low glucose concentrations. Radiographic studies may demonstrate diffuse and/or nodular contrast enhancement of the leptomeninges or hydrocephalus without a mass lesion.

In patients with leptomeningeal disease from solid tumors, median survival is 4 to 6 weeks without therapy, with death resulting from progressive neurologic dysfunction. Leptomeningeal metastases are often a manifestation of end-stage disease. Palliative care may be the most appropriate for patients with poor performance status, significant neurologic dysfunction, and/or uncontrolled systemic disease. Corticosteroids and analgesics may offer limited temporary improvement. Radiation therapy may be considered for the treatment of symptomatic sites. Ventriculoperitoneal shunting can be considered for palliative relief of refractory symptomatic hydrocephalus.

For patients who have minimal systemic disease, no significant neurologic deficits, and an acceptable performance status, a more aggressive approach may be considered. Unfortunately, no specific treatment has definitively demonstrated an improvement in OS. Imaging to assess for normal CSF flow should be considered, as blockage of flow by tumor deposits in the subarachnoid space reduces drug delivery and increases the risk of toxicity of intrathecal therapy. In the presence of CSF flow abnormalities, radiation therapy may be attempted to attain normal CSF flow. Radiation therapy may also be used to treat areas of bulky disease and other symptomatic sites. Additionally, high-dose systemic methotrexate[193] or cytarabine[194] may be considered.

If CSF flow is normal, intrathecal therapy with methotrexate, liposomal cytarabine, or thiotepa may increase the median survival to 3 to 6 months. Drugs can be administered intrathecally through an Ommaya reservoir or by repeated lumbar punctures. Liposomal

cytarabine is a sustained-release formulation of the drug that requires less frequent administration, but it is more likely to cause an acute aseptic meningitis. The major complication of intrathecal methotrexate is a necrotizing leukoencephalopathy that may develop after months of therapy for the few patients who do have prolonged survival. This devastating toxicity is most common in patients who receive cranial radiation therapy prior to or concurrently with intrathecal methotrexate.

Leptomeningeal metastases from hematologic malignancies may have a much better response to systemic (e.g., high-dose methotrexate in secondary CNS lymphoma) and intrathecal chemotherapy. These patients can achieve extended survival.

KEY POINTS

- Leptomeningeal metastases are manifested by symptoms and signs of injury to brain parenchyma, cranial nerves, and/or spinal nerves.
- Treatment of leptomeningeal metastases from solid tumors is often limited to symptom control because it is minimally effective and because leptomeningeal metastases frequently occur in the context of widespread systemic metastases.

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LEUKEMIAS

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Recent Updates

Acute Myeloid Leukemia

- Tyrosine kinase inhibitors such as midostaurin and sorafenib can improve event-free and possibly overall survival when added to 3+7 therapy. (Stone RM, *N Engl J Med* 2017; Röllig C, *Lancet Oncol* 2015)
- CPX-351, a liposomal formulation of cytarabine and daunorubicin, improves event-free and overall survival in older adults with untreated secondary AML compared to 3+7 induction chemotherapy. (Lancet JE, *J Clin Oncol* 2016)

Acute Lymphoblastic Leukemia

- The CD22 antibody-drug conjugate, inotuzumab ozogamicin, improves complete remission rates and prolongs progression-free and overall survival compared to standard-of-care chemotherapy in adults with relapsed or refractory B-cell acute lymphoblastic leukemia, but sinusoidal obstruction syndrome (veno-occlusive disease) occurs in approximately 10% of patients. (Kantarjian HM, *N Engl J Med* 2016)
- The CD19/CD3 bispecific T-cell engaging (BiTE) antibody, blinatumomab, improves remission rates and prolongs event-free and overall survival compared to standard-of-care chemotherapy in adults with relapsed or refractory Philadelphia chromosome-negative B-cell acute lymphoblastic leukemia. (Kantarjian HM, *N Engl J Med* 2017)
- For younger adults with CD20-positive Philadelphia chromosome-negative B-cell acute lymphoblastic leukemia, the addition of rituximab improves event-free survival when added to multiagent chemotherapy. (Maury S, *N Engl J Med* 2016)

Chronic Lymphocytic Leukemia

- The Bcl-2 inhibitor, venetoclax (ABT-199), has high activity in relapsed or refractory chronic lymphocytic leukemia. (Roberts AW, *N Engl J Med* 2016)

Immunotherapy

- CAR T-cell therapy was approved for use in certain children and young adults with relapsed or refractory B-acute lymphoblastic leukemia. (Prasad V, *Nat Rev Clin Oncol* 2018; Bach PB, *JAMA* 2017)

OVERVIEW

The term “leukemia” describes a number of related cancers of the blood-forming organs characterized by increased growth and/or impaired maturation. Leukemias are classically defined by their rapidity of growth (acute vs. chronic) and by the origin of the healthy cell the leukemia most resembles (myeloid vs. lymphoid). Thus, the four major forms of leukemia are acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL). Other leukemias include some of the mature B-cell, T-cell, or natural killer (NK)–cell neoplasms such as B-cell prolymphocytic leukemia,

hairy cell leukemia, and the chronic T-cell leukemias. About 62,130 new cases of leukemia were expected in the United States in 2017, with 24,500 leukemia-related deaths (Table 16-1 and Fig. 16-1).[1,2]

In this chapter, we will also discuss the myelodysplastic syndromes (MDSs) and the myeloproliferative neoplasms (MPNs), which, together with AML, encompass disorders that the World Health Organization (WHO) classifies as myeloid neoplasms.[3] MDS is a heterogeneous group of clonal stem cell disorders characterized by peripheral-blood cytopenias and an inherent tendency for leukemic transformation, with between 30,000 and 40,000 new cases estimated to occur in the United States per year.[4,5] MPNs are clonal stem cell diseases with proliferation of one or more hematopoietic cell lineages. Besides CML, the classic MPNs include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).[3,6] Chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia, mastocytosis, and unclassifiable MPNs are other diseases currently recognized by the WHO as MPNs. Several other entities, such as chronic myelomonocytic leukemia, atypical CML, and juvenile myelomonocytic leukemia show myelodysplastic and myeloproliferative features and are classified as MDS/MPN neoplasms, as are MDS/MPN with ring sideroblasts and thrombocytosis and unclassifiable MDS/MPN.[3]

ETIOLOGY

The cause of leukemia is usually unknown. However, in addition to a familial/genetic predisposition in some individuals, exposure to certain infectious pathogens, radiation, chemicals, and chemotherapeutic agents has been associated with an increased incidence of leukemia.

GENETIC PREDISPOSITION

Genetic predisposition for the development of leukemia is well established. Single germline mutations in several genes (e.g., in *GATA2, RUNX1, CEBPA,* and *SRP72*) have recently been identified as causes of familial nonsyndromic MDS/AML predisposition syndromes.[7] Syndromes that are characterized by defective DNA repair, such as Fanconi anemia, ataxia telangiectasia, and Bloom syndrome, also have an increased incidence of acute leukemia.[8] Similarly, bone marrow failure syndromes associated with ribosomal abnormalities, including Diamond–Blackfan anemia, Shwachman–Diamond syndrome, and dyskeratosis congenita also have an increased incidence of acute leukemia. The same is true for germline mutations in *TP53* and abnormalities in chromosome number, such as those associated with Klinefelter and Down syndromes. A high rate of concordant leukemia has long been noted in identical twins, particularly infants. Often thought to reflect a shared, inherited, or genetic susceptibility, molecular analyses have provided evidence that leukemias from twin pairs have a common clonal origin, with initiation of leukemia in one twin fetus and the spread of clonal progeny to the co-twin via vascular anastomoses and the need for further postnatal exposures and/or genetic events to produce clinical disease.[9]

Table 16-1 **2017 U.S. Leukemia Estimates**[1]		
	New Cases	**Deaths**
Acute lymphocytic leukemia	5,970	1,440
Chronic lymphocytic leukemia	20,110	4,660
Acute myeloid leukemia	21,380	10,590
Chronic myeloid leukemia	8,950	1,080
Other leukemia	5,720	6,730

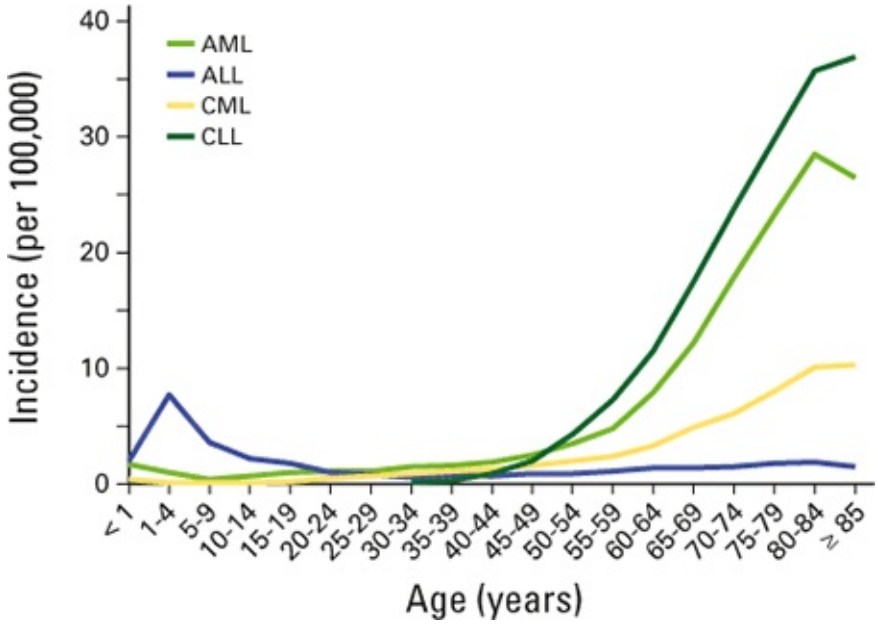

Fig. 16-1 Incidence of acute and chronic leukemias in the United States.

Surveillance, Epidemiology, and End Results (SEER) Cancer Registry estimates of age-specific incidence rates of AML, ALL, CML, and CLL in the United States, SEER 18 areas, 2009–2013. Rates are given per 100,000 and are age-adjusted to the 2000 U.S. standard population.[2]

ONCOGENIC VIRUSES

Human T-cell lymphotropic virus type 1 (HTLV-1) is a causative agent of adult T-cell leukemia/lymphoma. This enveloped, single-stranded RNA virus is found in geographic clusters in southwestern Japan, the Caribbean, intertropical Africa, the Middle East, South America, and Papua New Guinea. It spreads horizontally by sexual contact or through blood products or vertically from mother to fetus. Although endemic in these geographic areas, adult T-cell leukemia will develop in only 3 to 5% of patients infected with the virus and has a very long latency period, estimated at 30 years or more.[10] Epstein–Barr virus is associated with the endemic African form of Burkitt lymphoma/leukemia.[11] The immunodeficiency-related type of Burkitt lymphoma is seen most often in patients with human immunodeficiency virus (HIV) infection and is more common when the CD4 T-cell count is > 200/μL, that is, early in the progression of HIV infection. The association of HIV with the endemic form of Burkitt lymphoma is less clear.[11]

RADIATION

Ionizing radiation is leukemogenic.[12] The incidences of AML, CML, and ALL were increased in individuals who received radiation therapy for ankylosing spondylitis and in survivors of the atomic bomb blasts at Hiroshima and Nagasaki. The highest rates of leukemia were associated with higher doses of radiation, particularly if the radiation was absorbed over a shorter period of time. Younger individuals seem more susceptible to the leukemogenic effects of radiation. The incidence of leukemia peaks between 5 and 10 years after radiation exposure, regardless of patient age. The incidence of chromosomal aberrations has been reported to be higher than expected for individuals living in areas with high natural background radiation (often because of radon), but a higher incidence of acute leukemia has not been consistently observed.

Concern has been raised about the possible leukemogenic effects of extremely low-frequency, nonionizing electromagnetic fields emitted by high-energy wires and step-down transformers. Several studies have been conducted with mixed results, and if there is any leukemogenic effect of such radiation, the magnitude of the effect is likely small.[13]

CHEMICALS

Extensive occupational exposure to benzene and benzene-containing compounds may lead to marrow damage that eventually can manifest as aplastic anemia, MDS, or AML.[14] Benzene is widely used in industry, particularly as starting material for chemicals used to make plastics, resins, synthetic fibers, dyes, detergents, drugs, and pesticides, and as a component of crude oil, gasoline, and cigarette smoke. Other associations between occupational exposure to chemicals and subsequent leukemia are not as persuasive. Most studies have found a small but consistent increase in AML among cigarette smokers.

DRUG- AND THERAPY-RELATED LEUKEMIAS

Therapy with antineoplastic agents is a major identifiable cause of acute leukemia, with alkylating agents being most commonly associated with therapy-related leukemia.[15] Among the various alkylating agents, melphalan and the nitrosoureas seem to be particularly associated with increased risk; however, all alkylating agents are likely leukemogenic, with an increased incidence of leukemia observed after prolonged exposure and dose-intense regimens.

The leukemias associated with alkylating agents often present initially as MDS before progressing to AML; they have no other distinct morphologic features, and on cytogenetic examination frequently exhibit whole or partial loss of chromosomes 5 or 7 or, less often, trisomy 8. These leukemias typically develop 4 to 6 years after chemotherapy. Patients treated with topoisomerase II inhibitors also are at risk for therapy-related leukemia. In contrast to leukemias associated with alkylating agents, disease caused by topoisomerase II inhibitors tends to have a shorter latency period (1 to 2 years), lacks a myelodysplastic phase, carries a monocytic morphology, and frequently involves 11q23.3 abnormalities; less commonly, translocations of 21q22 are involved.[16] Patients with lymphoma who undergo autologous hematopoietic cell transplantation (HCT) are at increased risk for leukemia, with a cumulative incidence as high as 10%. Overall, approximately 50% of patients with therapy-related neoplasms have adverse cytogenetics, and approximately one-third have mutations in the *TP53* gene, which at least partly explains why these neoplasms tend to have lower therapeutic response rates than does de novo disease.[17,18]

KEY POINTS

- Leukemias, MDSs, and MPNs encompass a highly diverse group of clonal diseases of the hematopoietic system.
- Familial/genetic predisposition and exposure to certain infectious pathogens, radiation, chemicals, and chemotherapeutic agents have been associated with an increased incidence of these hematopoietic neoplasms.

ACUTE MYELOID LEUKEMIA

AML is primarily a disease of older adults, with a median age of 67 years at diagnosis and age-adjusted incidence rates that increase progressively with advancing age.[1,2]

PATHOGENESIS

AML is a clonal disorder thought to occur as a result of acquired somatic genetic lesions that accumulate in a stepwise fashion in hematopoietic progenitor cells.[19,20] The concept that relatively rare leukemic stem cells with self-renewing properties underlie and maintain the disease is supported by xenotransplantation studies. Nevertheless, the cellular origin of AML remains uncertain, with ongoing controversy as to whether these leukemias arise from transformed hematopoietic stem cells or (at least in a subset of cases) emerge from genetic events that occur in more mature progenitor cells.[21]

Recurrent chromosomal abnormalities and gene mutations have long been recognized as a hallmark of AML. Large-scale analyses of AML genomes have provided detailed insight into the complexity and dynamic nature of AML and demonstrated disease evolution over time with coexistence of competing clones at any point during the course of the malignancy.[22-26] These studies have identified more than 200 different recurrent mutations in leukemia genes; several of these are typically present in any given patient and are assumed to be part of the pathogenesis of the disease (so-called “driver mutations”), while several others that are present are random (passenger) mutations.[24] Among the driver mutations, some are mutually exclusive, suggesting that they complement each other functionally. Patterns of comutation compartmentalization define more than 10 molecular AML subgroups that have distinct diagnostic features and clinical outcomes.[26]

These genomic analyses have identified the large majority of the recurrent gene mutations that occur in AML with a frequency of at least 5%. An increasing number of these mutations are entering clinical practice because they affect risk assessment and may guide therapy and/or offer rational drug targets. Currently, the most prominent among these are mutations in fms-related tyrosine kinase 3 (*FLT3*), nucleophosmin (*NPM1*), and clonal chromosomal abnormalities (CCA)AT/enhancer binding protein-alpha (*CEBPA*). For other mutations, such as those in *IDH1, IDH2, DNMT3A, KMT2A* (previously named *MLL*), *RUNX1, KIT, TP53, TET2,* spliceosome complex components, *PHF6,* and *ASXL1,* increasing data similarly indicate that they may provide useful prognostic and possibly therapeutic information.

Some of these mutations, particularly those associated with DNA methylation and chromatin modification, are thought to occur very early in the development of AML, while others, such as tyrosine kinase receptor mutations appear to be acquired later in the development of AML. Those that occur early sometimes persist in patients who have achieved what otherwise appears to be a complete remission and can lead to subsequent relapse. Clonal hematopoiesis with such mutations can be found in up to 10% of otherwise normal individuals over age 70 and

has been termed “clonal hematopoiesis of indeterminate potential.”[27,28] The risk of this evolving to AML appears to be low, although some data suggest that individuals who subsequently receive chemotherapy for an unrelated malignancy are at higher risk for the development of therapy-related AML.[29,30]

CLINICAL PRESENTATION

Pathophysiologically, the leukemia stem cells give rise to progeny that fails to differentiate and continues to proliferate in an uncontrolled fashion. The resulting clonal population of immature myeloid cells then outcompetes and/or suppresses normal hematopoietic cells in the bone marrow. In some patients, particularly those with myelomonocytic or monocytic leukemias, AML cells accumulate in extramedullary sites (termed “myeloid sarcomas” or “chloromas”) such as lymph nodes, spleen, liver, skin (leukemia cutis), gums, or, in 1 to 3% of cases, the central nervous system (CNS).[31] Thus, the signs and symptoms of AML are a result of decreased normal hematopoiesis and infiltration of healthy organs by leukemic blasts: most patients present with anemia and thrombocytopenia and, consequently, fatigue, dyspnea, easy bruising, or overt bleeding. The white blood cell count may be elevated, normal, or low, but most patients will have granulocytopenia, and one-third will present with signs of substantial or life-threatening infection.

DIAGNOSIS

Examination of the peripheral blood and a bone marrow aspirate are part of the routine diagnostic workup of a patient with suspected AML.[32] A bone marrow trephine biopsy is not routinely required, but should be obtained if the aspirate is dilute, hypocellular, or inaspirable. A lumbar puncture is required in patients with clinical symptoms suspicious for CNS involvement. Cytogenetic and molecular studies are essential for risk stratification. The 2016 revision of the WHO classification categorizes a myeloid neoplasm as AML if 20% or more blasts are present in the peripheral blood or bone marrow when the disease occurs de novo or evolves from a previously diagnosed MDS or MDS/MPN or a blast transformation from a previously diagnosed MPN, or if a myeloid sarcoma is present. As exceptions from this general rule, neoplasms with t(8;21)(q22;q22.1), inv(16)(p13.1q22) or t(16;16)(p13.1;q22), or acute promyelocytic leukemia (APL) are considered to be AML regardless of the blast count (Table 16-2).[3]

Morphology and Immunohistochemistry

AML cells are typically 12 to 20 μm in diameter with discrete nuclear chromatin, multiple nucleoli, and azurophilic granules in the cytoplasm (Fig. 16-2). Specific patterns of reactivity with immunohistochemical stains, in particular myeloperoxidase and nonspecific esterase, can be used to assign AML blasts to one (or more) cell lineage(s). Although the French-American-British Cooperative Group classified AML based on morphology and immunohistochemistry,[33] cytochemical stains have largely been replaced by immunophenotypic analyses of AML cells.

Immunophenotype

Most cases of AML express antigens characteristic of neutrophilic or monocytic differentiation, including CD13, CD15, CD33, CD64, CD117, myeloperoxidase, and CD34.[34] Leukemias with monocytic features express CD14 together with other monocyte-associated antigens. Erythroid leukemias frequently express CD36, CD71, and CD235a (glycophorin A), whereas

megakaryocytic leukemias express CD41 and CD61. Although the antigens detected on leukemic blasts generally represent antigens found on normal hematopoietic cells, they usually are present in abnormal combinations and/or amounts, allowing multidimensional flow cytometry to identify AML blasts in peripheral blood or marrow samples. In 10 to 20% of cases, the AML blasts also express antigens usually restricted to B- or T-cell lineages, especially CD2, CD7, CD19, and CD56. Expression of single lymphoid antigens does not seem to independently influence the natural history or therapeutic response of these leukemias.

Cytogenetic and Molecular Abnormalities

In approximately 60% of AML cases, one or more acquired cytogenetic abnormalities can be identified by routine karyotyping on G-banded metaphases or interphase fluorescence in situ hybridization (FISH).[35] These may result from the gain or loss of an entire chromosome, but more often include translocations, partial loss of a chromosome, smaller insertions or deletions, or inversions (see Chapter 2: Molecular Biology). Certain abnormalities—recognized by the WHO as AML with recurrent cytogenetic abnormalities (Table 16-2)—are seen repeatedly and are associated with distinct morphologic or clinical subtypes of leukemia. Most prominent among these are APL and the leukemias with translocations involving core-binding factors (CBFs). APL accounts for approximately 10 to 15% of AML cases and is characterized by a fusion protein between the promyelocytic leukemia (*PML*) gene and the retinoic acid receptor alpha (*RARA*) gene (*PML-RARA*) that virtually always results from a translocation between chromosome 15 and chromosome 17, t(15;17)(q24.1;q21.2) but can be cryptic or arise from other complex cytogenetic rearrangements. The resultant abnormal fusion protein acts as a dominant-negative inhibitor of healthy *PML* and *RARA* function. This fusion protein recruits nuclear co-repressors and histone deacetylases, inhibiting the transcription of genes needed for myeloid differentiation.[36] The t(8;21)(q22;q22.1) translocation results in fusion of the CBF-alpha subunit on chromosome 21 (*RUNX1T1*) with the *RUNX1* gene on chromosome 8, whereas inv(16)(p13.1q22) or t(16;16)(p13.1;q22) result in fusion of CBF-beta on the q arm of chromosome 16 with *MYH11* on the p arm; the *CBFB-MYH11* leukemias often present with myelomonocytic cell characteristics and eosinophilia. The t(8;21) and inv(16) CBF leukemias each account for 5 to 7% of AML cases in adults, but are more common among children and adolescents.[37] Other recurrent cytogenetic abnormalities are translocations between the *KMT2A* gene located at 11q23.3 and any one of several partners (constituting approximately 5% of adult AML cases), trisomy 8 (seen in approximately 10%), and partial or full deletions of chromosomes 5 and 7 (each accounting for 4 to 7%). The latter abnormalities are more common in older patients with AML and in cases associated with prior exposure to alkylating agents.

Table 16-2 **2016 World Health Organization Classification of Acute Leukemia**[3]

	Classification
Acute myeloid leukemia and related neoplasms	AML with recurrent genetic abnormalities AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* APL with *PML-RARA* AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* AML with t(6;9)(p23;q34.1); *DEK-NUP214* AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM* AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1* Provisional entity: AML with *BCR-ABL1* AML with mutated *NPM1* AML with biallelic mutations of *CEBPA* Provisional entity: AML with mutated *RUNX1* AML with myelodysplasia-related changes Therapy-related myeloid neoplasms AML, NOS AML with minimal differentiation AML without maturation AML with maturation Acute myelomonocytic leukemia Acute monoblastic/monocytic leukemia Pure erythroid leukemia Acute megakaryoblastic leukemia Acute basophilic leukemia Acute panmyelosis with myelofibrosis Myeloid sarcoma Myeloid proliferations related to Down syndrome Transient abnormal myelopoiesis Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm	
Acute leukemias of ambiguous lineage	Acute undifferentiated leukemia Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR-ABL1* MPAL with t(v;11q23.3); *KMT2A* rearranged MPAL, B/myeloid, NOS MPAL, T/myeloid, NOS
B-lymphoblastic leukemia/lymphoma	B-lymphoblastic leukemia/lymphoma, NOS B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); *BCR-ABL1* B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1) *ETV6-RUNX1* B-lymphoblastic leukemia/lymphoma with hyperdiploidy B-lymphoblastic leukemia/lymphoma with hypodiploidy B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3); *IL3-IGH* B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1* Provisional entity: B-lymphoblastic leukemia/lymphoma, *BCR-ABL1*-like Provisional entity: B-lymphoblastic leukemia/lymphoma with *iAML21*
T-lymphoblastic leukemia/lymphoma	Provisional entity: Early T-cell precursor lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma	

Abbreviations: AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; MPAL, mixed phenotype acute leukemia; NOS, not otherwise specified.

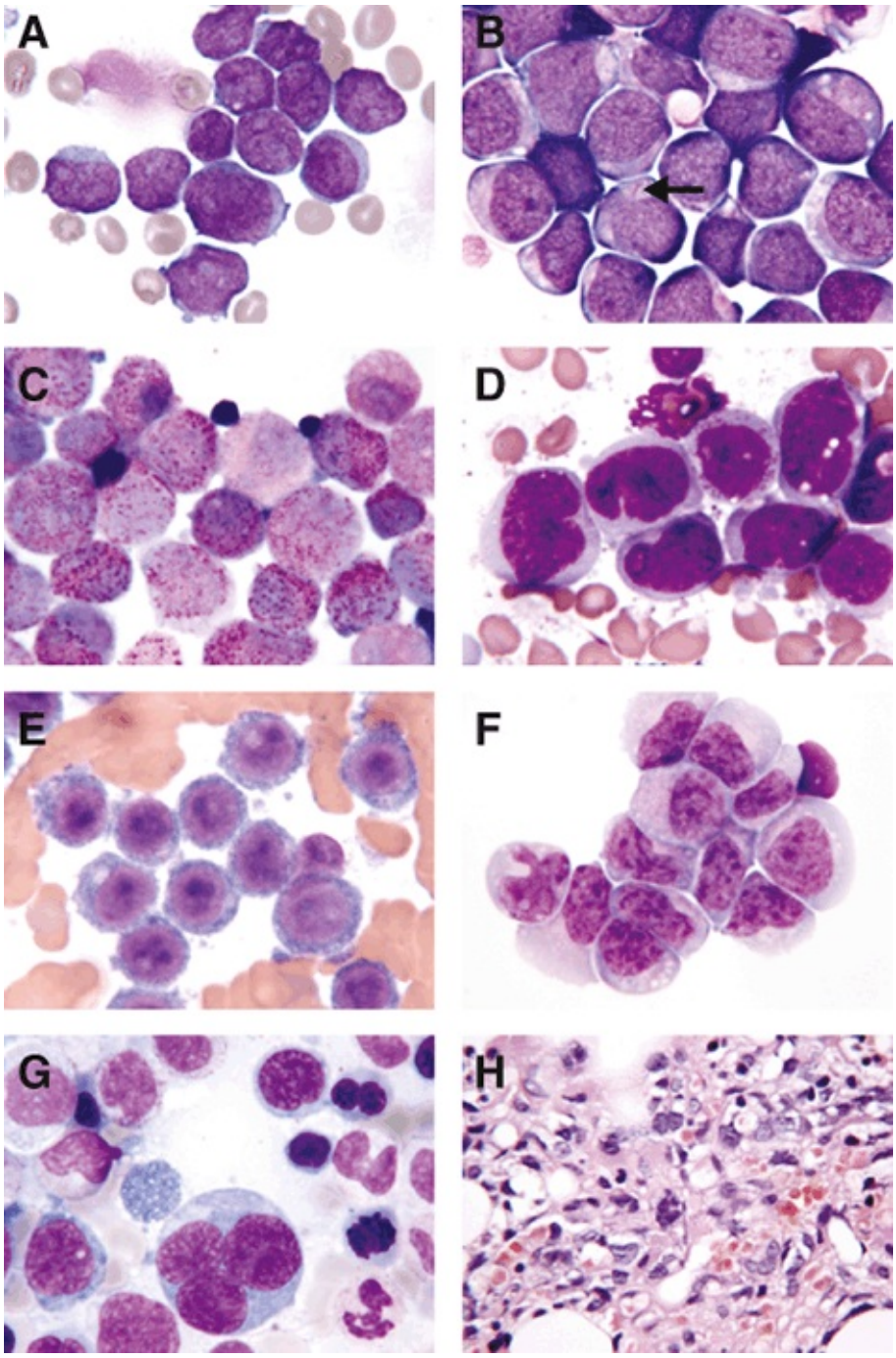

Fig. 16-2 The morphologic spectrum of the acute myeloid leukemias (AML).

(A) Acute myeloblastic leukemia with minimal maturation: the cells are myeloblasts with dispersed chromatin and variable amounts of agranular cytoplasm; some display medium-sized, poorly defined nucleoli. **(B)** Acute myeloblastic leukemia with maturation: some of the blasts contain azurophilic granules, and there are promyelocytes; note the Auer rod (arrow). **(C)** Acute promyelocytic leukemia: all of these cells are promyelocytes containing coarse cytoplasmic granules that sometimes obscure the nuclei. **(D)** Acute myelomonocytic leukemia: promonocytes with indented nuclei are present with myeloblasts; the dense nuclear staining is unusual. **(E)** Acute monoblastic leukemia: these characteristic monoblasts have round nuclei with delicate chromatin, and prominent nucleoli stain intensely with nonspecific esterase (not shown); cytoplasm is abundant. **(F)** Acute monocytic leukemia: most of the cells in this field are promonocytes; monoblasts and an abnormal monocyte are also present. **(G)** Acute erythroid leukemia: dysplastic multinucleated erythroid precursors with megaloblastoid nuclei are present. **(H)** Acute megakaryoblastic leukemia: in this marrow biopsy, there are large and small blasts as well as atypical megakaryocytes.

For risk stratification and treatment decision-making, increasing emphasis in AML is applied to molecular diagnostics either with directed polymerase chain reaction (PCR)–based analyses or, more and more frequently, genomewide high-throughput DNA analyses. At least in patients with cytogenetically normal AML (CN-AML) who plan to undergo curative-intent therapy, a minimum mutational profile for *FLT3, NPM1,* and *CEBPA* should be obtained.[19] Mutations in the

class III receptor tyrosine kinase *FLT3* are among the most frequent mutations observed in AML and are associated with an increased white blood cell (WBC) count at diagnosis. In 20% of AML cases (28 to 34% of CN-AML), an internal tandem duplication (ITD) in either the juxtamembrane domain or the tyrosine kinase domain is found that constitutively activates the tyrosine kinase, leading to enhanced *RAS, MAPK,* and *STAT5* signaling. In 11 to 14% of cases of CN-AML, a point mutation in the activation loop of the kinase domain is found in *FLT3* that similarly leads to constitutive kinase activation. Also associated with AML with an increased WBC count are mutations in *NPM1,* a nucleolar protein that has been implicated in a variety of cellular functions, including ribosome biogenesis, DNA repair, and regulation of apoptosis. *NPM1* mutations have been identified in 25 to 35% of AML cases and are highly associated with CN-AML (45 to 64% of cases). Likewise, mutations in *CEBPA,* a gene encoding a leucine zipper transcription factor that is crucial for myeloid lineage specification, are predominantly found in CN-AML (10 to 18% of cases).[19]

PROGNOSTIC FACTORS

Pretreatment Factors

AML is highly heterogeneous, and responses to AML therapy vary substantially between individual patients. A large number of factors have been independently associated with failure to achieve remission with intensive chemotherapy and/or shortened survival; these include increasing age, poor performance status, prior cytotoxic chemotherapy or radiation therapy or disease evolution from an antecedent hematologic disorder ("secondary" AML), and increased WBC count. In contrast, extramedullary disease, while common, is not an independent prognostic factor.[31] The karyotype of the leukemia is the single most important outcome predictor and provides the framework for contemporary risk-stratification schemes.[32,35] Although slightly divergent schemes are used by individual cooperative study groups or the European LeukemiaNet (ELN), AML is typically divided into favorable-, intermediate-, and adverse-risk groups.[32,35,38] The favorable group includes APL and the CBF AMLs. The adverse group includes inv(3)(q21q26)/t(3;3) (q21;q26), *KMT2A* rearrangements other than t(9;11), monosomy 5, monosomy 7, del(5q), del(7q), abnl(17p), and complex cytogenetics (in the current ELN scheme, defined as three or more unrelated chromosomal abnormalities), among others. The intermediate-risk group encompasses all entities not classified as favorable or adverse. The effect of cytogenetics on complete response rates and survival using this categorization is shown in Table 16-3.[38,39] Any monosomy (not just monosomy 5 or monosomy 7) is associated with a poor prognosis, and having a monosomal karyotype (defined as having two or more distinct monosomies or one monosomy and another structural abnormality) is associated with a very poor prognosis (less than 5% survival at 4 years).[40,41]

Somatic mutations and deregulated expression of certain genes are associated with outcome in AML and enable refinement of cytogenetic risk stratification schemes.[19,32] The presence of biallelic *CEBPA* mutations or an *NPM1* mutation without concomitant *FLT3*/ITD in CN-AML is associated with outcomes comparable to those for CBF AMLs. Conversely, the presence of a *FLT3*/ITD is associated with an increased frequency of relapse and shorter survival, particularly in cases with larger-size ITDs or a higher mutated:wild-type allelic ratio (higher ITD burden). Table 16-4 provides one current example in wide use. It was developed by the ELN and combines cytogenetic and molecular data into a refined risk-stratification scheme.[32] At least in some studies, mutations in another receptor tyrosine kinase gene, *KIT,* are associated with a less favorable outcome in CBF AMLs. More recently, *TP53* mutations—

although rare in AML—have gained importance as they have been found in 70% of AML cases with complex cytogenetic abnormalities and shown to be an independent poor prognostic factor in this AML subset. Prognostic relevance in at least subsets of AML has also been associated with an increasing number of other gene aberrations, including *KMT2A*-partial tandem duplication and mutations in *RUNX1, ASXL1,* and *PHF6* (all unfavorable). Integrating such information has resulted in increasingly complex cytogenetic/molecular risk-stratification schemes, which may come to be used more frequently as molecular profiles are more extensively available.[26,32,42,43] For many other genes (e.g., *DNMT3A* or *IDH1/2*), the prognostic impact or recurrent mutations found in AML is either inconsistent across studies or context-dependent.

Posttreatment Factors

Posttreatment information can improve risk stratification in AML. Early clearance of AML cells from the peripheral blood and bone marrow during induction therapy has been associated with a higher likelihood of achieving complete remission (CR) and better survival independent of pretreatment factors such as cytogenetics.[44,45] For patients who have achieved a morphologic CR, which is defined as the presence of less than 5% blasts in the bone marrow with recovery of blood counts (neutrophil count greater than 1000 per mm^3, platelet count greater than 100,000 per mm^3) in the absence of circulating blasts or evidence of extramedullary leukemia,[32] increasing evidence highlights the prognostic (and perhaps therapeutic) relevance of submicroscopic amounts of measurable ("minimal") residual disease (MRD).[46] Molecular assays (which detect chimeric fusion proteins, somatic mutations, or aberrant gene expression) and multiparameter flow cytometry–based methods (which identify immunophenotypic abnormalities on AML cells) have been developed to quantify MRD. The latter approach is broadly applicable in AML but is currently limited by the lack of standardization/harmonization across laboratories, which complicates data interpretation. Still, numerous studies have demonstrated that the presence of MRD detected at various time points during the treatment course can identify subsets of patients who are at increased risk for AML recurrence and worse survival than similarly treated patients in whom no MRD can be found. MRD assessments may be particularly useful to identify patients with cytogenetically favorable-risk disease but less than optimal response to standard chemotherapy.[47,48]

Table 16-3 Cytogenetic Risk and Treatment Outcomes in Younger Adults with Newly Diagnosed AML[38,39]

	CR Rate		5-Year Relapse Risk		5-Year Survival	
Cytogenetic Risk	**SWOG**	**MRC/NCRI**	**SWOG**	**MRC/NCRI**	**SWOG**	**MRC/NCRI**
Favorable	84%	91%	–	35%	55%	65%
Intermediate	76%	86%	–	51%	38%	41%
Unfavorable	55%	63%	–	76%	11%	14%

Abbreviations: CR, complete remission; MRC/NCRI, Medical Research Council/National Cancer Research Institute; SWOG, Southwest Oncology Group; –, data not available.

TREATMENT OF AML

If untreated, AML typically results in death within several months, primarily because of bone marrow failure (infection, bleeding). Successful treatment for AML can improve quality of life, prolong survival, and cure a significant number of patients. However, with increasing age at

diagnosis, the likelihood of disease features associated with therapeutic resistance, including adverse genetic or epigenetic abnormalities, drug transport activity, or antecedent hematologic disorder or prior chemo/radiotherapy, increases. At the same time, the tolerance to intensive chemotherapy decreases.[49,50] Because of the differences in disease biology and tolerance of intensive therapies, most studies of AML therapy have traditionally targeted either "younger" or "older" patients, with an arbitrary cutoff age of 55 to 65 to distinguish younger from older adults. However, medical fitness for tolerating intensive chemotherapy can be estimated relatively accurately with multiparameter assessment tools that consider factors in addition to age, such as performance status and measures of organ function impairment. The use of such tools should be considered as the basis for the assignment to intensive or nonintensive therapy.[50]

Table 16-4 2017 European LeukemiaNet Cytogenetic/Molecular Risk Stratification of AML[32]

	Subset
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}* Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}* Wild-type *NPM1* and *FLT3-ITD* (normal karyotype) Wild type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}* (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*† Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11)(v;q23.3); *KTM2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM (EVI1)* -5 or del(5q); -7; -17/abnl(17p) Complex karyotype‡, monosomal karyotype Wild-type *NPM1* and *FLT3*-ITD^{high}* Mutated *RUNX1*§ Mutated *ASXL1*§ Mutated *TP53*

*Low, low allelic ratio (< 0.5); high, high allelic ratio (≥ 0.5).
†Takes precedence over rare, concurrent adverse-risk gene mutations.
‡Three or more unrelated chromosomal abnormalities in the absence of one of the WHO-designated recurring translocations or inversions–that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), or inv(3) or t(3;3).
§These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

Initial Intensive Chemotherapeutic Approaches for Medically Fit Patients

Induction Chemotherapy. For four decades, 3 days of an anthracycline in combination with 7 days of continuously infused cytarabine (3+7 regimen) has remained the standard remission-induction therapy in patients with newly diagnosed AML. With this combination, a CR can be expected in 60 to 80% of patients up to age 65 and 45 to 55% in patients older than age 65.[20,32] Randomized trials have demonstrated that outcomes are better with idarubicin (10 to 12 mg/m^2/day for 3 days) or a higher dose of daunorubicin (60 to 90 mg/m^2/day for 3 days) than with the previous conventional daunorubicin dose of 45 mg/m^2/day for 3 days, at least up to age 65.[51-53] A randomized study that was based on a double-induction treatment strategy, however, found no advantage of 90 over 60 mg/m^2/day of daunorubicin in the first treatment cycle except for patients with FLT3/ITD-mutated AML.[54] Approximately 50% of patients will still have more than 5% blasts in their marrow 1 week after the last dose of chemotherapy. Most experts recommend beginning a second cycle of induction in such circumstances.

Aiming to improve results that are achieved with 3+7, one randomized study suggested that the addition of cladribine (5 mg/m^2/day for 5 days) might increase CR rates and survival, but limitations in the study design preclude firm conclusions.[55] The value of higher cytarabine doses during induction remains uncertain. In one randomized study, a combination of fludarabine, high-dose cytarabine, granulocyte colony-stimulating factor, and idarubicin yielded higher CR rates after the first induction course and improved relapse-free (albeit not overall) survival compared with cytarabine/daunorubicin.[56] In another randomized study, however, treatment with high-dose cytarabine and idarubicin was not more effective than 3+7, and outcomes were even inferior in patients with favorable-risk cytogenetics.[57] Several randomized studies have demonstrated that the addition of the CD33 antibody-drug conjugate gemtuzumab ozogamicin reduces relapse risk and improves survival, but these benefits are restricted to patients with favorable- and intermediate-risk disease.[58] Emerging data now also suggest that tyrosine kinase inhibitors can improve event-free and perhaps overall survival (OS) when added to 3+7 therapy in patients with *FLT3*-mutated AML (shown for midostaurin) or all AML regardless of *FLT3* status (shown for sorafenib), although toxicity can be a concern for some of the agents.[59,60] Finally, in patients ages 60 to 75 who have untreated AML and a history of prior cytotoxic treatment, antecedent MDS, or chronic myelomonocytic leukemia (with or without prior exposure to DNA methyltransferase inhibitors), CPX-351—a liposomal formulation of cytarabine and daunorubicin co-encapsulated at a fixed molar ratio (5:1) to maximize synergy between these two agents—at a dose of 100 units/m^2 on days 1, 3, and 5 significantly improved OS, event-free survival, and response rates without an increase in 60-day mortality or adverse events compared to 3+7.[61] Myeloid growth factors can shorten the duration of neutropenia after induction chemotherapy, but there is little evidence that their use alters remission rates or survival.[62]

Postremission Therapy. If no therapy is administered after successful induction, the median duration of remission is only approximately 4 months.[63] Thus, some form of therapy is necessary following the achievement of remission. Based on the results of randomized trials, standard consolidation chemotherapy in medically fit patients less than age 65 who are not candidates for allogeneic HCT usually involves three to four cycles of a regimen that includes high-dose cytarabine (1 to 3 g/m^2/day for 3 to 6 days).[20,32,64] The higher doses of cytarabine that are used in younger patients frequently lead to neurotoxicity in older individuals and probably should be avoided. Low-dose maintenance therapy appears to be generally of little benefit in the treatment of AML. Randomized trials have not found evidence that CNS

prophylaxis improves either disease-free or OS for adults with AML.[65] Whether a subgroup of patients at higher risk for CNS involvement (i.e., those with high blast counts at diagnosis or CD56-positive disease) might benefit from CNS prophylaxis is unknown.

Initial Low-Intensity Chemotherapy Approaches for Medically Less Fit Patients

Medically less fit AML patients[50] should be considered for participation in a clinical trial whenever possible. If such a trial is not available, low-dose cytarabine has been considered for many years as a standard low-intensity chemotherapy regimen after a randomized trial demonstrated superiority over hydroxyurea both in terms of CR rates and survival. However, the benefits were relatively modest and did not extend to the group of patients with adverse-risk AML.[66] The DNA methyltransferase inhibitors (azacitidine and decitabine) are currently probably most commonly used in the United States for medically less fit patients with AML. In randomized studies, primarily older patients with AML assigned to receive azacitidine (75 mg/m^2/day for 7 days every 4 weeks) experienced better OS than those assigned to conventional care regimens (i.e., either supportive care only, low-dose cytarabine, or intensive chemotherapy), with benefits that appeared to extend across the entire risk spectrum of AML.[67,68] Superior survival was also found with decitabine in a similar trial that assigned patients with AML to decitabine (20 mg/m^2/day for 5 days every 4 weeks) or a choice of either supportive care only or low-dose cytarabine.[69] Whether 10-day courses of decitabine[70] have better risk:benefit profiles overall is currently under investigation. Uncontrolled studies suggest that such courses may lead to favorable clinical outcomes and frequent, albeit incomplete, mutation clearance in patients with adverse-risk AML, including those with *TP53* abnormalities.[71]

Treatment of Persistent or Recurrent Disease

Most patients with AML who receive conventional chemotherapy will either not achieve CR (so-called “primary induction failure”) or will experience disease recurrence. Treatment of such patients remains a major challenge.[72,73] The duration of first CR heavily influences outcome after salvage chemotherapy, with second CR rates of 70% or more with an initial CR duration of greater than 2 years, but only 15% for patients with a CR duration of less than 6 months or primary induction failure.[74] Remission duration less than 12 to 18 months, older age, adverse-risk disease at presentation, previous allogeneic HCT, and the presence of a *FLT3*/ITD mutation have been recognized as important predictors of outcome in these patients. Based on such factors, patients can be grouped into those with 5-year survival as high as 40 to 50% and those with 5-year survival as low as 5% or less. There is currently no established standard of care for the treatment of relapsed or treatment-refractory AML. If the initial CR duration was relatively long, retreatment with the initial chemotherapeutic regimen can be considered. For patients with a relatively short first CR, alternative standard regimens or novel therapies, ideally in the setting of a clinical trial, are preferable. Typical intensive salvage regimens encompass intermediate to high doses of cytarabine with or without additional drugs such as anthracyclines, the anthracenedione mitoxantrone, or etoposide. Several novel agents, including clofarabine, vosaroxin, immunomodulatory agents, small-molecule inhibitors (e.g., targeting *FLT3*, mutated *IDH1*, or mutated *IDH2*), DNA methyltransferase inhibitors, histone deacetylase inhibitors, and antibody-based therapeutics, are undergoing active investigation, but their role in relapsed or refractory AML is not yet firmly established. Patients with slowly evolving disease, particularly if they are older or infirm, can sometimes have a reasonable quality of life with supportive care

alone; rapid, intensive cytoreduction is not always warranted for this population.

Hematopoietic Cell Transplantation

Allogeneic HCT offers a strong antileukemic effect, but the benefit of transplantation in terms of survival can be compromised by transplant-related (nonrelapse) mortality. Both disease-related and transplant-related factors should be considered in the decision to proceed to allogeneic HCT or follow a nontransplantation strategy. Based on such benefit:risk assessments, all patients up to ages 70 to 75 in first CR—except those with favorable cytogenetic/molecular risk profile (i.e., APL, CBF AML, double-allelic *CEPBA* mutation, or *NPM1* mutation without *FLT3*/ITD who achieve an early first CR and have no evidence of MRD after induction)—should be considered for allogeneic HCT, particularly if comorbidity scores are low and an HLA-matched donor is available.[75] Suitable alternative donor sources (e.g., haploidentical donors or cord blood) are increasingly considered if no HLA-matched donors are available. For patients with intermediate-risk AML, the absolute benefit of allogeneic HCT in first CR is less marked than for patients with adverse-risk disease, and there is unresolved controversy as to whether equivalent survival may be achieved by delaying transplantation until after the first relapse.[76] Nonmyeloablative or reduced-intensity conditioning regimens have been developed to reduce nonrelapse mortality in older or medically less fit patients.[75,77] Data from one randomized trial show significantly higher rates of relapse and shorter relapse-free survival with reduced intensity as compared with myeloablative conditioning;[78] myeloablative conditioning should therefore be prioritized if the patient is considered a suitable candidate. For patients older than age 40, busulfan plus fludarabine has been shown to be associated with lower transplant-related mortality but retained antileukemic effects compared to busulfan plus cyclophosphamide.[79]

Because of the overall grim prognosis, allogeneic HCT should generally be offered after a second or subsequent CR has been achieved.[72,73] The low likelihood of response to salvage chemotherapy for patients with primary induction failure has led to attempts to use allogeneic HCT as first salvage therapy. Although the posttransplantation relapse rate is high, the 20 to 25% OS with allogeneic HCT for patients with primary induction failure is better than what would be expected with further chemotherapy.[80]

SPECIAL TYPES OF AML

Promyelocytic Leukemia

APL is a distinct subtype of AML with unique clinical, morphologic, and cytogenetic features and, virtually always, the characteristic t(15;17)(q24.1;q21.2) translocation. Compared with most patients with AML, patients with APL tend to be somewhat younger (median age, 30 to 40), rarely have a myelodysplastic prodrome, and usually have a lower WBC count at the time of diagnosis. Among the different subtypes of AML, APL seems to be overrepresented among Hispanic and obese patients. Whereas many of the other clinical and laboratory features are similar to other forms of AML, APL almost always presents with some element of a hemorrhagic syndrome, including hypofibrinogenemia, decreased coagulation factors, elevated fibrin degradation products, and increased platelet consumption. These findings are the result of both disseminated intravascular coagulation and primary fibrinolysis.[81]

A unique feature of APL is its very high sensitivity to treatment with *all-trans* retinoic acid (ATRA) and arsenic trioxide.[82] The robust activity of these agents led to studies combining them with conventional chemotherapy as initial therapy for APL. Randomized trials have

demonstrated that the addition of ATRA to conventional chemotherapy improves CR rates to approximately 90% and, if initiated promptly in patients with suspected APL, decreases the incidence of substantial bleeding complications. Clinical trials conducted before the availability of ATRA demonstrated that APL is particularly sensitive to anthracycline therapy. Thus, substantial doses of anthracyclines were included during the consolidation treatment phase for APL. These trials also demonstrated a clear role for ATRA as maintenance therapy. A large randomized trial demonstrated that the use of arsenic trioxide during consolidation therapy further improves disease-free and OS in both the low-risk group (defined as those presenting with a WBC count of less than 10,000/mm^3) and in high-risk APL (WBC count of more than 10,000/mm^3). With current therapies, survival at 3 years after diagnosis can be expected for more than 85% of low-risk patients and for 75% of those presenting with high-risk disease. Some randomized studies have shown that patients with low-risk APL can be treated with ATRA and arsenic trioxide alone, with more sustained antileukemic efficacy and better survival than that seen with an ATRA/chemotherapy-based regimen.[83,84] When combined with at least one dose of gemtuzumab ozogamicin or perhaps an anthracycline during induction, ATRA and arsenic trioxide are also highly effective in high-risk APL.[83] A small fraction of patients with APL morphology will have a different translocation, such as t(11;17), which is associated with a poor response to ATRA and arsenic trioxide.

During induction therapy with either ATRA or arsenic trioxide, some patients will experience fever, weight gain, respiratory distress, pulmonary infiltrates, episodic hypotension, and renal failure. This condition is thought to be related to the sudden maturation of promyeloblasts (differentiation syndrome) and usually responds to dexamethasone, which should be initiated immediately upon suspicion of this condition. Temporary discontinuation of ATRA or arsenic trioxide may be required for patients in very poor clinical condition as a result of severe renal or pulmonary impairment.[85] Treatment with arsenic trioxide can be complicated by QT-interval prolongation and, rarely, by sudden death.[86] Thus, before initiating treatment, any electrolyte imbalances should be corrected, especially hypomagnesemia and hypocalcemia; other drugs that can prolong the QT interval should be discontinued.

Therapy-Related Myeloid Neoplasms

The current WHO classification of myeloid neoplasms uses the term “therapy-related myeloid neoplasms” to describe AML, MDS, or myeloproliferative disorders that arise after treatment with alkylating agents, radiation, or topoisomerase II inhibitors.[3] As previously noted, the pattern of disease after alkylating agent exposure is somewhat different than with topoisomerase II inhibitors, but most patients are exposed to both agents and a separation is often not practical. In general, the CR rate for treatment-related AML is lower than that seen in de novo leukemias independent of cytogenetic risk group, averaging 35 to 40% in several large series. Furthermore, median disease-free and OS with therapy-related AML is considerably shorter than with de novo AML, and less than 10% of patients can expect to survive disease-free for more than 3 years after the initiation of chemotherapy. Although the number of published studies is limited, allogeneic transplantation leads to long-term disease-free survival for some patients with therapy-related AML[87] and should therefore be considered.

KEY POINTS

- In 60% of AML cases, at least one clonal abnormality in chromosome number or structure can be found. These cytogenetic abnormalities have emerged as the single most important prognostic factor in AML and are indispensable in making therapeutic decisions.
- Genomewide sequencing has identified more than 20 mutations recurrently seen in AML. Of these, testing for mutations in *FLT3, NPM1,* and *CEBPA* is important in determining how patients who enter first remission should be treated.
- Based on cytogenetic and molecular markers, AML can be divided into several categories with distinct disease risk.
- Optimal induction therapy in AML involves the use of an anthracycline and cytarabine.
- All patients up to age 70 to 75 who achieve a complete remission—except those with a favorable cytogenetic/molecular risk profile who achieve an early first complete remission and have no evidence of measurable residual disease after induction—should be considered for allogeneic hematopoietic stem cell transplantation, particularly if comorbidity scores are low and an HLA-matched donor is available.
- The prognosis is poor for patients with recurrent AML, and the likelihood of achieving a second remission is predicted by the length of the first remission. Because of this poor outcome, transplantation should be considered for most patients with recurrent AML who are appropriate candidates.
- The suspicion of APL in a newly diagnosed patient with acute leukemia should trigger the immediate administration of ATRA to reduce the risk of early hemorrhagic death.
- Patients with APL should receive ATRA and arsenic trioxide as part of induction and/or consolidation therapy.

ACUTE LYMPHOBLASTIC LEUKEMIA

ALL occurs both in children and adults, but its incidence peaks between ages 2 and 5. Relative to childhood ALL, in which cure rates are over 80%, the prognosis of adult ALL is significantly worse, particularly in older individuals, with current 5-year relative survival rates of only 10 to 15%.[2,88,89]

PATHOGENESIS

ALL is a clonal disorder that is thought to arise from genetic lesions in hematopoietic progenitor cells committed to differentiate along the B-cell or T-cell pathway. The precise events that lead to ALL are unknown, and only a few cases are associated with genetic predispositions or exposure to exogenous factors such as radiation or chemotherapeutic agents.

CLINICAL PRESENTATION

Approximately 50% of patients with ALL present with enlarged lymph nodes, hepatomegaly, or splenomegaly. Bone pain is commonly reported by patients who have acute disease and those who are younger. Approximately 5% of patients will have involvement of the CNS at the time of diagnosis; this confers a worse prognosis. T-cell ALL is commonly associated with male

gender, a mediastinal mass, and disseminated lymph node involvement.

DIAGNOSIS

ALL can be categorized according to morphology, histochemistry, cell-surface markers, cytogenetics, and molecular biology.

Morphology and Immunohistochemistry

The leukemia cells in ALL are typically smaller than AML blasts and are devoid of granules. The French-American-British Cooperative Group developed a morphology-based classification (Fig. 16-3),[90] which, although once popular, has since been largely replaced by immunology and cytogenetic classification. ALL blasts are typically negative for myeloperoxidase and nonspecific esterase, whereas periodic acid–Schiff staining is more variable.

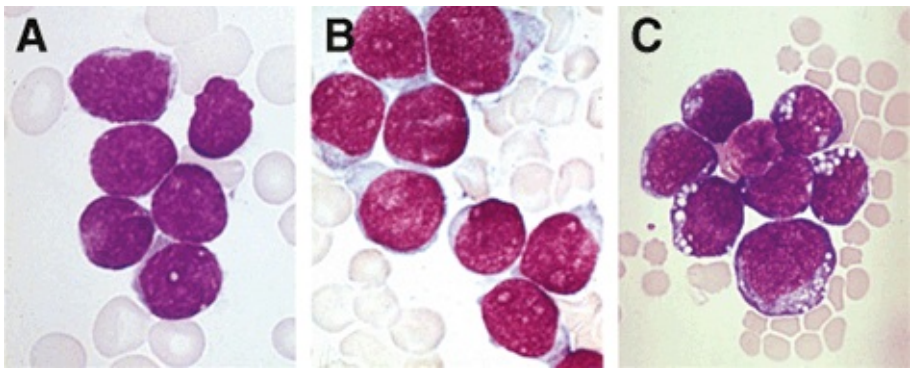

Fig. 16-3 Morphology of acute lymphoblastic leukemia (ALL) in adults.

(A) ALL childhood variant. The cells are small, homogeneous, with inconspicuous nucleoli (FAB-L1). **(B)** ALL adult variant. The cells are pleomorphic, with some cytoplasm and prominent nucleoli (FAB-L2). **(C)** Burkitt-like leukemia. The cells are homogeneous, with multiple nucleoli, deep blue cytoplasm, and sharply defined vacuoles (FAB-L3).

Immunophenotype

Approximately 5 to 10% of all cases of adult ALL express the early B-cell antigens CD19 or CD22 and no other B-cell antigens.[91] In approximately 40 to 50% of adults, the leukemia expresses CD10 (the common ALL antigen). In approximately 10% of cases, B-ALL expresses cytoplasmic immunoglobulin (Ig) but not surface Ig, whereas in 5% of cases surface Ig is present (mature B-cell or Burkitt leukemia). A subset of B-ALLs expresses CD20, a marker that in some, but not all, studies performed without the addition of CD20 antibodies was associated with a worse outcome.[92] Approximately 25% of ALL cases have a T-cell phenotype. In 25% of ALL cases, a nondefinitive (i.e., not myeloperoxidase) myeloid antigen can be detected. Although some studies suggest that such myeloid antigens are a negative prognostic factor, the bulk of evidence suggests no independent significance for their presence. As in AML, discordant combinations of antigens on leukemic blasts allow detection of small numbers of blasts in a morphologically normal marrow using multidimensional flow cytometry. A more sensitive method for the detection of small numbers of ALL blasts involves PCR-based detection of clonally rearranged B-cell immunoglobulin genes or T-cell receptor genes.[93] This technique requires the development of individualized patient-specific probes. More recently, a novel approach based on high-throughput sequencing has been developed; it is as sensitive as PCR-based detection, but it is much less labor-intensive and more easily standardized.

In 2 to 5% of acute leukemias, definition of the disease as either myeloid or lymphoid is

problematic, either because two or more distinct populations of cells exist in the same person (bilineage leukemias) or a single population coexpresses definitive myeloid and lymphoid markers (biphenotypic leukemias). The current WHO classification defines these diseases as mixed-phenotype acute leukemia.[3] Several studies suggest that patients with this type of leukemia have a worse clinical outcome than those with either AML or ALL.[94]

Cytogenetic and Molecular Abnormalities

Cytogenetic and molecular characteristics have important prognostic significance in ALL. In approximately 25% of cases, no cytogenetic abnormalities are found.[95] In approximately 10%, an alteration in chromosome number (usually hyperdiploidy) is present without alteration in chromosome structure.[96] The most common translocation is the Philadelphia (Ph) chromosome, seen in 20 to 30% of adult ALL. The Ph chromosome results from a specific translocation, t(9;22)(q34.1;q11.2), which positions most of the *ABL1* proto-oncogene from chromosome 9 adjacent to the 5′ portion of the *BCR* gene on chromosome 22. The breakpoint on chromosome 9 is highly variable, whereas the breakpoints in the *BCR* gene on chromosome 22 occur within two regions: the major breakpoint cluster region (*M-bcr*), and the minor breakpoint cluster region (*m-bcr*). Rearrangements within the *M-bcr* are transcribed into a chimeric messenger RNA, which produces a hybrid 210-kilodalton protein (p210BCR-ABL1), whereas breaks within the *m-bcr* express a chimeric messenger RNA that gives rise to a smaller 190-kilodalton protein (p190BCR-ABL1). In CML, virtually all breakpoints are mapped to the *M-bcr* (CML-type Ph chromosome). Conversely, in ALL, breakpoints are found within both the *M-bcr* and *m-bcr,* and those within the *m-bcr* are termed the “ALL-type Ph chromosome.”[97] The relative frequency of the two breakpoints in adult ALL has varied among studies, but overall, the two seem to be represented with equal frequency.[98] Ph-positive ALL with the CML-type of the *BCR-ABL1* translocation is not simply the lymphoid blast crisis phase of CML. Patients with this disease rarely have a long prediagnostic prodrome and do not routinely have marked splenomegaly.

The other most common translocations seen in adult B-cell ALL are t(4;11)(q21;q23), which is seen in 7% of B-ALL, involves the *KMT2A* and *AF4* genes, and is associated with a poor prognosis; and the t(8;14)(q24.1;q32), which is seen in 2 to 4% of adult B-ALL, involves *c-MYC* and the Ig heavy chain, and is the translocation associated with Burkitt leukemia. T-ALLs often have translocations involving chromosome 7 or 14 at T-cell receptor enhancer gene sites. The other most common cytogenetic changes seen in adult ALL involve del(9p), seen in 5 to 9% of cases; del(6q), seen in 5 to 7%; and del(13q), seen in 3 to 5%. A newly described poor risk entity found in 20 to 25% of adolescents and young adults is Ph-like ALL, which lacks the classic *BCR-ABL1* translocation but exhibits a gene expression profile that is similar to that of Ph-positive ALL.[99] Kinase-activating genetic rearrangements are characteristic of Ph-like ALL, including rearrangements of cytokine receptor–like factor 2 (*CRLF2*), which are found in about 50% of all Ph-like ALL cases and are often associated with activating mutations in *JAK1/2.*

An increasing number of genes in key signaling pathways (e.g., regulation of lymphoid development, tumor suppression and cell cycle, cytokine receptors, lymphoid signaling, and epigenetic modification) are recognized to be recurrently mutated in ALL.[100] Some of these are associated with a therapeutic response. For example, alterations in *IKAROS* gene family members are selectively found in different subtypes of high-risk ALL, such as Ph-positive ALL or Ph-like ALL, in which *IKZF1* mutations are a hallmark abnormality. T-ALL is characterized by activating mutations in *NOTCH1* (seen in > 50% of cases) and rearrangements of transcriptions factors *TLX1* (also known as *HOX11*), *TLX3* (*HOX11L2*), *LYL1*, *TAL1*, and *KMT2A*.[101]

PROGNOSTIC FACTORS

Pretreatment Factors

Various pretreatment characteristics have been shown to affect CR rates and survival, including increasing age, an elevated WBC count, CNS involvement, and, particularly, cytogenetic and molecular abnormalities (Table 16-5). Based on such factors, investigators generally segregate ALL cases into standard risk and high risk. Although there are inconsistencies in the exact schemas, 5-year disease-free survival averages about 55% for standard risk and 25% for high-risk patients.[102,103] Other factors, such as immunophenotypic characteristics of leukemic blasts (e.g., expression of T-cell or myeloid antigens by ALL blasts), previously associated with a worse prognosis, have lost their independent prognostic importance with modern therapy.

Table 16-5 **Prognostic Risk Factors in ALL**[102,103]

	Unfavorable	**Favorable**
Age (years)	> 35	≤ 35
WBC count	> 30,000/μL*	≤ 30,000/pL
Cytogenetics	t(9;22) t(4;11) Hypodiploidy Near triploidy Complex abnormalities	High hyperdiploidy del(9p)
Mutations (B-ALL)	*KMT2A* gene rearrangement; focal *IKZF1* gene deletion, kinase-activating alterations, *TP53* mutations	
Mutations (T-ALL)	No *NOTCH1/FBXW7* mutation and/or no *NRAS* or *KRAS* mutation and/or no *PTEN* gene alteration (T-ALL)	*NOTCH1/FBXW7* mutation without *N/K-RAS* mutation or *PTEN* gene alteration (T-ALL)
CNS involvement	Yes	No
Time to complete response	> 4 weeks	< 4 weeks
Minimal residual disease	Present	Absent

*> 100,000/μL in T-ALL.
Abbreviations: CNS, central nervous system; WBC, white blood cell.

Cytogenetic characteristics have important prognostic and therapeutic significance (Fig. 16-4).[96] Between 10 and 20% of all cases of ALL are Ph-positive (5% of childhood cases; 20 to

30% of adult cases), with an incidence that increases with age, which may partially explain the importance of age as a prognostic variable. In studies conducted before the availability of imatinib, the likelihood of CR was somewhat lower for patients with Ph-positive ALL and the probability of remaining in CR was much lower. Studies designed to find molecular evidence of the *BCR-ABL1* rearrangement have shown that up to 10% of cases that are Ph-negative or are inadequately assessed by cytogenetic analysis will, nonetheless, have the *BCR-ABL1* rearrangement; their prognosis seems to be the same as that for patients who are Ph-positive by cytogenetic analysis. Although Ph-positive ALL has a very poor prognosis when treated with conventional ALL therapy, results of trials that combined imatinib with standard induction are sufficiently encouraging to warrant inclusion of imatinib or other tyrosine kinase inhibitors (TKIs) in the initial treatment of Ph-positive ALL. The responsiveness of Ph-like ALL to TKIs remains undefined. Other cytogenetic abnormalities of adult ALL that carry a poor prognosis (both in terms of achieving a CR and remaining in CR) include t(4;11), t(8;14), and having complex cytogenetics with five or more abnormalities. In contrast, adults with high hyperdiploidy or del(9p) seem to have a more favorable prognosis.[102-105] A higher risk of relapse is independently associated with *KMT2A* gene rearrangement, focal *IKZF1* gene deletion, or *TP53* mutations in B-ALL and no *NOTCH1/FBXW7* mutation and/or no *NRAS* or *KRAS* mutation and/or no *PTEN* gene alteration in T-ALL.[106,107]

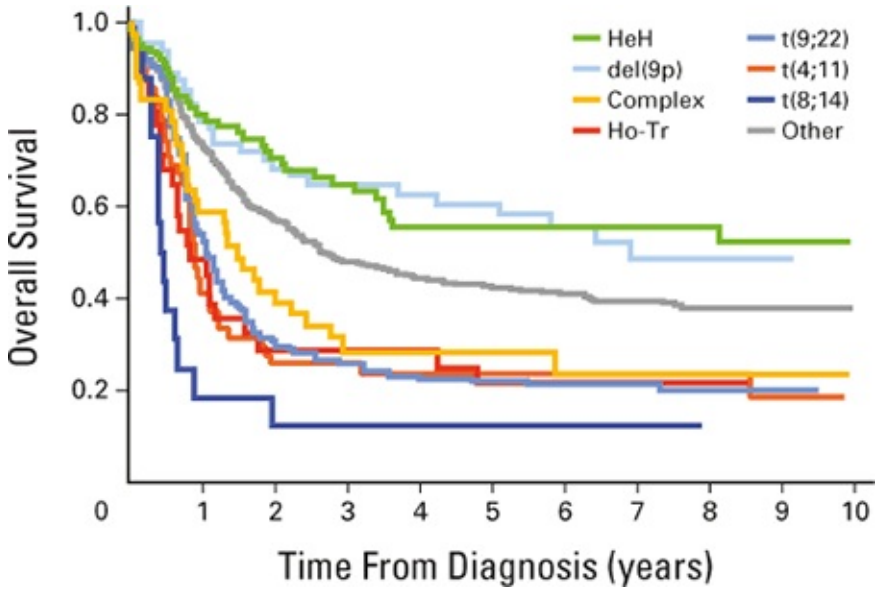

Fig. 16-4 Survival in adult acute lymphoblastic leukemia (ALL) according to cytogenetic abnormality.[96]

Abbreviations: HeH, high hyperdiploidy; Ho-Tr, hypodiploidy/near triploidy.

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Posttreatment Factors

Response to chemotherapy is a primary determinant of outcome in ALL. Several studies have shown that rapid clearance of blasts from the peripheral blood and bone marrow and achievement of a CR during the first chemotherapy course is associated with improved outcomes.[88,103] More recent focus has been on the use of MRD as a prognostic factor. Many studies have demonstrated that the presence of MRD after induction, after consolidation, or prior to HCT can identify patients at high risk for disease recurrence.[93] These studies have

provided the rationale to explore MRD-directed treatment interventions to optimize patient outcomes.

TREATMENT OF ALL

Induction Chemotherapy

Standard induction therapy for adult ALL most commonly involves combination chemotherapy, including vincristine, prednisone, an anthracycline, and asparaginase. With such regimens, 80 to 90% of patients achieve a first CR. Although a number of variations exist, no prospective, randomized trial has identified a clearly superior regimen.[102,103] A number of investigators have explored the use of hematopoietic growth factors immediately after induction chemotherapy. Similar to the findings for AML, the results of such studies demonstrate accelerated myeloid recovery and a decrease in the incidence of febrile neutropenia. In some trials, the CR rate was improved, but no findings have indicated an improvement in disease-free and overall survival.[108] For younger adults with CD20-positive Ph-negative B-ALL, adding the CD20 antibody rituximab to combination chemotherapy improves event-free survival.[109]

Postremission Therapy

If no further therapy is administered after achievement of CR, the duration of remission is invariably short. Therapy after achievement of remission should include CNS prophylaxis, otherwise CNS disease will develop in at least 35% of adults. Patients with a high tumor burden at diagnosis, as evidenced by a high WBC count and elevated lactate dehydrogenase (LDH), are at highest risk. With prophylaxis, the incidence of CNS leukemia as an isolated event is less than 10%. Most trials have included several cycles of intensive consolidation therapy administered over several months after achievement of CR, as well as less intensive maintenance therapy administered over a period of several years. Consolidation frequently includes combinations of high-dose methotrexate, cytarabine, cyclophosphamide, and an anthracycline, whereas maintenance usually comprises low-dose methotrexate, 6-mercaptopurine, vincristine, and prednisone.[102,103] Some but not all data from randomized studies indicate that modification of postremission treatment intensity based on MRD status can optimize treatment outcomes.[110-112] No single optimal regimen for CNS prophylaxis, consolidation therapy, and maintenance has been identified. Current trials are testing whether more intensive regimens, such as those used in pediatric ALL, are tolerable and improve outcomes in adult ALL. Increasing evidence indicates that such regimens are tolerated in patients less than age 40 and appear to improve outcome. With current regimens, approximately 35 to 40% of adult patients with ALL will remain alive in remission at 5 years after diagnosis. With pediatric-inspired therapies, studies have shown 5-year survival rates of 67 to 78% in adolescents and younger adults (up to ages 18 to 30).[102,103]

Treatment of Persistent or Recurrent Disease

Patients who do not achieve CR or subsequently have a relapse have dismal outcomes, with long-term survival generally not exceeding 10%. Therefore, the current strategy is to reduce tumor burdens (if possible) and then to proceed with allogeneic HCT. A variety of chemotherapeutic agents have been utilized in combinations similar to those used during induction such as (liposomal) vincristine, steroids, anthracyclines, asparaginase, methotrexate, and high-dose cytarabine. New drugs for relapsed/refractory ALL include nelarabine, which can

achieve CR rates of 30% or higher in patients with recurrent T-ALL but has significant neurotoxic effects, and clofarabine, forodesine, and rapamycin.[102,103] The bispecific T-cell engaging (BiTE) antibody blinatumomab, a small molecule composed of the single-chain variable fragments of a CD19 and a CD3 antibody, has been approved by the FDA on the basis of the demonstration of a remission rate of 40 to 45% as a single agent in relapsed or refractory B-ALL.[113] Unique toxicities include cytokine release syndrome and neurologic events. A randomized study reported higher remission rates and improved median OS (7.7 vs. 4.0 months) with blinatumomab compared to standard-of-care chemotherapy in adults with relapsed or refractory B-ALL.[114] A randomized study has demonstrated higher CR rates (80% vs. 30%) and longer progression-free and overall survival with a CD22 antibody-drug conjugate, inotuzumab ozogamicin, compared to standard-of-care chemotherapy in adults with relapsed or refractory B-ALL. Inotuzumab ozogamicin is associated with sinusoidal obstruction syndrome (veno-occlusive disease) in approximately 10% of patients, mostly occurring among complete responders who went on to receive allogeneic HCT.[115]

Response rates approaching 100% have been reported with adoptive immunotherapies using T-cells expressing chimeric antigen receptors (CARs) that recognize CD19 in small series of pediatric and adult relapsed ALL cases, even among patients in whom allogeneic HCT failed, but this approach is not yet widely available.[116] Based on early studies, tisagenlecleucel, a CAR T-cell therapy, was approved by the FDA in the fall of 2017 for the treatment of B-ALL in patients up to 25 years of age with B-ALL who haven't responded to standard therapy or who have relapsed at least twice, making it the first gene therapy approved in the United States.[117,118] This type of immunotherapy shows promise in larger patient populations although severe, potentially fatal side effects including cytokine release syndrome and neurological toxicity have been observed.

Hematopoietic Cell Transplantation

Allogeneic HCT is an important postremission treatment modality in ALL, but its curative potential must be balanced against transplant-related morbidity and mortality, late complications, and associated reductions in quality of life.[103] An evidence-based review of available trials led an expert panel to recommend the consideration of myeloablative allogeneic HCT for adults under age 35 with ALL in first CR after multiagent chemotherapy for all disease risk groups because of superior outcomes with regard to postremission chemotherapy.[119] However, while results obtained with transplantation have not yet been compared directly with pediatric-inspired chemotherapy regimens in younger adult ALL patients, retrospective analyses suggest that this chemotherapy approach may yield survival outcomes equal or superior to allogeneic HCT because of lower nonrelapse mortality and no increase in relapse risk.[120] With increasing age, the survival advantage of allogeneic HCT diminishes because of increased nonrelapse mortality. In the absence of a suitable related or unrelated donor, cord blood can be considered as a stem cell source. For patients in second or later CR, allogeneic HCT is recommended over chemotherapy. The superiority of any conditioning regimen is unclear, but some data suggest better outcomes with regimens that include total-body irradiation. More limited data suggest that reduced-intensity conditioning may produce reasonable outcomes in patients who are thought to be unfit for myeloablative regimens.[119] Not surprisingly, the outcomes with HCT depend largely on the disease status of the patient. If allogeneic transplantations are performed during the first CR, long-term survival rates range from about 40% to about 60%. If such transplantations are performed in patients with disease that is

resistant to conventional chemotherapy, long-term survival can be obtained in only 15 to 25% of patients.[119]

Efforts have been undertaken to use a risk-adapted approach to allogeneic HCT in order to spare patients transplant-related toxicities by allocating them to undergo chemotherapy if chemosensitivity was documented (e.g., confirmed MRD-negative status after chemotherapy in standard-risk disease).[121] On the other hand, MRD persistence after induction and consolidation signals a very high risk for subsequent relapse. MRD at the time of transplantation also indicates a higher risk of relapse but outcomes are likely better than with chemotherapy alone. It has not been firmly established whether the use of newer agents such as blinatumomab to convert MRD-positive patients to MRD-negative prior to HCT improves long-term outcomes.

SPECIAL TYPES OF ADULT ALL

Ph-Positive ALL

As noted, ALL associated with t(9;22) translocations has a very poor prognosis when treated with conventional chemotherapy. However, the disease is sensitive to TKIs such as imatinib, dasatinib, nilotinib, or ponatinib. When combined with induction chemotherapy, CR rates have reached 90 to 100%, and OS appears to be improved. In younger adults, less-intensive chemotherapy combined with imatinib over the entire induction period is as effective as, and less toxic than, a more intensive regimen with imatinib given only over the first 2 weeks.[122] Allogeneic HCT is still considered the best curative option, particularly for younger adults, but the degree of improvement in outcome over TKI-containing combination chemotherapy is unclear. One retrospective study of patients with Ph-positive ALL in first molecular remission after chemotherapy with TKI suggests that autologous HCT, while associated with substantially higher posttransplantation relapse risk, may yield similar survival outcomes for matched-sibling and unrelated-donor allogeneic HCT.[123] If an MRD-negative remission is achieved early in Ph-positive ALL, chemotherapy alone may provide an alternative treatment strategy, particularly if patients are thought to be at very high risk for HCT-related mortality.[124] Therapy with dasatinib and prednisone alone results in CRs in a high percentage of older patients with Ph-positive ALL without the need for concomitant chemotherapy, but most patients ultimately have a relapse.[103]

Mature B-ALL

Mature B-ALL is grouped together with Burkitt lymphoma and is treated accordingly (see Chapter 17: Lymphomas).[103]

KEY POINTS

- Induction therapy in adult ALL should generally include vincristine, prednisone, an anthracycline, and asparaginase. With such regimens, complete remission can be achieved in 80 to 90% of patients. Consideration of a pediatric-inspired regimen should be given for all patients up to 40 years of age.
- Patients with CD20-positive B-ALL should receive rituximab during induction and consolidation.
- Patients with Ph chromosome–positive ALL should receive a TKI in combination with

chemotherapy.

- Allogeneic transplantation is an important postremission treatment modality except perhaps in patients who have highly chemosensitive disease.

CHRONIC MYELOID LEUKEMIA

PATHOGENESIS

CML was the first malignant disease found to be consistently associated with a specific cytogenetic abnormality, the Ph chromosome. The abnormal chromosome is the product of a translocation between chromosomes 9 and 22 (t(9;22)(q34.1;q11.2)), which places the *ABL1* proto-oncogene from chromosome 9 contiguous with the 5′ portion of the *BCR* gene on chromosome 22. A molecular rearrangement can still be found in most cases of Ph-negative CML, even though the translocation is masked at the karyotypic level. If no chimeric *BCR-ABL1* gene can be found, the disease should not be considered CML. The transcription of the chimeric *BCR-ABL1* gene results in a hybrid messenger RNA that is translated into a hybrid p210 protein. Both the messenger RNA and the protein, which is a constitutively active form of the ABL1 protein tyrosine kinase, are unique to cells of the leukemic clone. *BCR-ABL1* promotes growth and cellular proliferation through downstream cytoplasmic and nuclear signal transduction pathways such as RAS, RAF, JUN kinase, MYC, and STAT.[125] Consequently, the oncogenic protein transforms hematopoietic cells so that their growth in vitro becomes cytokine-independent, protects cells from apoptotic responses to DNA damage, and increases adhesion of cells to the extracellular matrix.

CLINICAL PRESENTATION AND DIAGNOSIS

The natural history of untreated CML is a relatively benign chronic phase lasting approximately 3 years, followed by an accelerated phase lasting several months and, finally, a rapidly fatal blast crisis. At the time of diagnosis, more than 90% of patients are in the chronic phase, and as many as 50% are diagnosed incidentally during routine blood testing.[125,126] Symptoms include fatigue, night sweats, malaise, weight loss, bone aches, and abdominal discomfort from splenomegaly. Patients typically have leukocytosis, thrombocytosis, and moderate anemia at the time of presentation. The marrow is virtually always hypercellular, and the Ph chromosome is found in more than 90% of cases. In the remaining cases, cryptic or complex translocations can be detected by FISH or PCR assays.

Both the WHO and the ELN have developed criteria to distinguish the chronic phase from the accelerated and blastic phases (Table 16-6).[3,127] The accelerated phase is characterized by fever, night sweats, weight loss, bone pain, difficulty controlling blood counts, increased numbers of blasts, early myeloid cells in the marrow and peripheral blood, and evidence of karyotypic evolution. The most common cytogenetic changes associated with disease evolution are an additional Ph chromosome, trisomy 8, i(17q), and trisomy 19. In more than 60% of cases of blast crisis, the blasts are of myeloid lineage, as determined by morphology and cell-surface markers. In 25 to 30%, the blasts are of lymphoid lineage, and in the remaining cases, blasts may be biphenotypic or undifferentiated. Determination of the blast lineage may be useful for selecting appropriate therapy.

Table 16-6 **Criteria for the Definition of Accelerated-Phase and Blast Phase CML**[125]

Disease Stage	Definition	
	ELN Criteria	**WHO Criteria**
Accelerated Phase	Blasts in blood or marrow 15–29%, or blasts plus promyelocytes in blood or marrow > 30%, with blasts < 30%; basophils in blood ≥ 20%; persistent thrombocytopenia (< 100,000/μL) unrelated to therapy; clonal chromosomal abnormalities on Ph-positive cells, major route*, on treatment	Blasts in blood or marrow 10–19%; basophils in blood ≥ 20%; persistent thrombocytopenia (< 100,000/μL) unrelated to therapy; clonal chromosomal abnormalities on Ph-positive cells on treatment; thrombocytosis (> 1,000,000/μL) unresponsive to therapy; increasing spleen size and increasing WBC count unresponsive to therapy
Blast Phase	Blasts in blood or marrow ≥ 30%; extramedullary blast proliferation, apart from spleen	Blasts in blood or marrow ≥ 20%; extramedullary blast proliferation, apart from spleen; large foci of clusters of blasts in the bone marrow biopsy

*"Major route" abnormalities include trisomy 8, trisomy Ph (+der(22)t(9;22)(q34;q11)), isochromosome 17 (i17(q10)), trisomy 19, and ider(22)(q10)t(9;22)(q34;q11).
Abbreviation: Ph, Philadelphia chromosome.

TREATMENT OF CML

Before the development of specific, highly effective TKIs, therapy for CML included hydroxyurea, interferon-alpha with or without cytarabine, busulfan, and allogeneic HCT. Today, oral TKIs are the treatment of choice for initial therapy of chronic-phase CML.[127] The most mature data are available with imatinib mesylate, a small-molecule inhibitor of several protein tyrosine kinases, including the ABL protein tyrosine kinase. At a dose of 400 mg daily, a complete cytogenetic response (CCyR) and major molecular response (MMR) after 1 year has been achieved in 49 to 77% and 18 to 58% of patients, respectively. OS greater than 85% and progression-free survival (PFS) greater than 80% after 4 to 6 years have been observed in several large studies, with 60 to 80% of patients continuing to receive imatinib therapy after 3 to 5 years. The addition of cytarabine does not improve treatment outcomes, whereas interferon-alpha has been shown in some but not all studies to improve the rates of MMR over imatinib alone. A better early response can also be obtained with higher doses of imatinib (800 mg day).[127]

If TKI therapy is stopped while there is still detectable disease, rapid disease recurrence is the rule. In select patients who respond optimally to TKIs, discontinuation of TKI therapy appears to be safe.[127,128] However, outside of a clinical trial, discontinuation should be considered only after thorough discussion of the potential risks and benefits and only for patients who had a long, stable molecular response on approved TKI therapy for at least 3 years and no history of accelerated- or blast-phase CML and no history of resistance to any TKI.

Imatinib-related toxicities include fatigue, rash, myalgias and arthralgias, bone pain, diarrhea, peripheral edema, elevated lipase and alanine aminotransferase, and cytopenias and are more common at higher doses. Imatinib resistance can result from *BCR-ABL1* mutations in the kinase domain interfering with imatinib binding, *BCR-ABL1* amplification or overexpression, decreased drug bioavailability, or drug efflux. In as many as 50% of cases, the reasons for resistance are unclear. Mutations in *BCR-ABL1* seem to be the most common identifiable reason for resistance and can be detected in samples collected before treatment, suggesting that the delayed imatinib failure may reflect the considerable amount of time required for outgrowth of these selected clones. Not all mutations in *BCR-ABL1* have the same significance; mutations at T315I and those affecting the phosphate-binding loop (P-loop) seem to confer the greatest

degree of imatinib resistance, whereas others can be overcome by a dose increase or are functionally irrelevant.[127]

As compared with imatinib, second-generation TKIs such as nilotinib and dasatinib lead to higher CCyR and MMR rates at least after 1 year and sometimes at later time points and may slightly reduce the rate of progression or failure, whereas no differences in OS have been documented. These drugs can also result in CCyR rates in approximately 50% of patients in the chronic phase in whom resistance to imatinib develops; they are, however, inactive against the T315I mutation. A third-generation oral TKI, bosutinib, has been approved for the treatment of CML in patients with resistance or intolerance to prior therapy and can lead to major cytogenetic responses in approximately 50% of patients in the chronic phase who have experienced treatment failure with imatinib.[127] Ponatinib, a pan-TKI, is approved for the treatment of patients with T315I-positive CML and for adults for whom no other TKI is indicated. The side-effect profiles of these TKIs are similar to that for imatinib, although there are notable distinctions. All second- and third-generation TKIs have cardiac toxicity, and some reports have highlighted vascular safety issues with these agents. Dasatinib and, less so, bosutinib can cause pleural effusions. Dasatinib has also been associated with pulmonary hypertension and expansion of large granular lymphocytes in the peripheral blood, whereas increased serum glucose levels and worsened diabetic control have been observed with nilotinib. Importantly, vascular complications such as arterial and venous thrombosis and embolic events have been seen with nilotinib and ponatinib, and they can occur in 25 to 30% of patients, or more, with ponatinib.[126,129]

The ELN currently recommends initial therapy of chronic-phase CML with imatinib (400 mg daily), nilotinib (300 mg twice daily), or dasatinib (100 mg daily). Although the majority of patients will have an excellent response to initial TKI therapy, careful monitoring (via blood counts, routine cytogenetic analysis of bone marrow, as well as FISH and quantitative PCR analyses of peripheral blood or bone marrow) is critical to identifying failures and changing therapy. The ELN has established milestones for response to TKIs as first-line therapy (Table 16-7).[127] Failure to achieve any of the goals of therapy at 3, 6, or 12 months or beyond is an indication to switch to a different treatment to limit the risk of progression and death. Definitions of expected responses to second-line therapy have also been developed, and they are relatively similar to those for first-line therapy. Failure to have an adequate response to second-line therapy or losing response is an indication to proceed to allogeneic HCT.

Patients with accelerated- or blast-phase CML can respond to TKIs, but responses are generally short-lived and the disease is relatively resistant to most types of therapy. Patients in lymphoid blast crisis with disease resistant to all TKIs sometimes have a response to ALL-type chemotherapy, whereas AML-type induction results in temporary CR for 15 to 20% of patients in myeloid blast crisis.

HEMATOPOIETIC CELL TRANSPLANTATION

With the introduction of TKIs, the rate of allogeneic HCT has greatly declined for patients with chronic-phase CML and is currently reserved primarily for patients who have failed at least 2 TKIs or are intolerant to such therapies, those who have a T315I mutation (particularly if ponatinib therapy fails), or those who have disease progression.[125,126] Three-year survival can be as high as 90% and nonrelapse mortality lower than 10% when allogeneic HCT is used as second-line therapy after imatinib failure.[130] Allogeneic HCT remains the only curative therapy for the accelerated phase—and should be considered early in these patients—and blast crisis

CML and can result in long-term survival in 15 to 40% and 5 to 20% of patients, respectively.[125,126] Results are somewhat better for patients who present in the accelerated phase or blast crisis and respond to TKIs by entering a second chronic phase prior to HCT.

Table 16-7 European LeukemiaNet Definitions of Response to TKIs as First-Line Therapy[127]

	Optimal	Warning	Failure
Baseline	–	High risk or CCA/Ph+, major route	–
3 months	*BCR-ABL1* ≤ 10% and/or Ph+ ≤35%	*BCR-ABL1* > 10% and/or Ph+ 36-95%	Non-CHR and/or Ph+ > 95%
6 months	*BCR-ABL1* < 1% and/or Ph+ 0	*BCR-ABL1* 1-10% and/or Ph+ 1-35%	*BCR-ABL1* < 10% and/or Ph+ > 35%
12 months	*BCR-ABL1* ≤ 0.1%	*BCR-ABL1* > 0.1-1%	*BCR-ABL1* > 1% and/or Ph+ > 0
Then, and at any time	*BCR-ABL1* ≤ 0.1%	CCA/Ph- (-7, 7q-)	Loss of CHR; loss of CCyR; confirmed loss of MMR; new mutations; CCA/Ph+

Abbreviations: CCA/Ph+, clonal chromosomal abnormalities in Ph-positive cells; CCyR, complete cytogenetic response; CHR, complete hematologic response; MMR, major molecular response (i.e., *BCR-ABL1* ≤ 0.1% or ≥ 3 log reduction of *BCR-ABL1*); TKI, tyrosine kinase inhibitor. Em dashes denote not applicable.

KEY POINTS

- TKIs such as imatinib, nilotinib, and dasatinib are remarkably effective in newly diagnosed chronic-phase CML, leading to complete hematologic and cytogenetic responses for most patients. However, continued therapy and careful follow-up are necessary.
- Patients with accelerated- or blast-phase CML can respond to TKIs, but responses are generally short-lived and the disease is relatively resistant to most types of therapy.

CHRONIC LYMPHOCYTIC LEUKEMIA

CLL is the most prevalent adult leukemia in Western countries. The disease is more common in men than in women (ratio, 1.7:1), with a steep age-specific incidence. The incidence is higher is in Jewish people of Russian or eastern European ancestry, but it is rare in Asian countries. There are no known risk factors for CLL; particularly, it is one of the few leukemias that does not seem to be associated with exposure to ionizing radiation, chemicals, or drugs, although data suggest a possible relationship with Agent Orange. However, a strong inherited genetic component is well recognized, and genomewide association studies have identified over 40 susceptibility loci.[131-133]

CLINICAL PRESENTATION

Most patients with CLL are asymptomatic at diagnosis, which is often made incidentally when lymphocytosis is noted during a routine evaluation. The findings on physical examination are normal for 20 to 30% of patients, while lymphadenopathy, hepatosplenomegaly, or both are observed in 40 to 50% of patients. However, as the disease progresses, generalized lymphadenopathy and splenomegaly become common features. Involvement of other organs is unusual and should suggest the possibility of transformation (Richter syndrome).

Infections

Increased susceptibility to infections reflects quantitative and qualitative defects seen within the innate and adaptive immune response (hypogammaglobulinemia, reduced levels of complement, impaired phagocytic killing of nonopsonized bacteria, reduction of functional impairment of T-cell subsets, etc.) that worsen with disease progression.[134] Historically, the most common pathogens have been those that require opsonization for bacteria killing, such as *Streptococcus pneumoniae, Staphylococcus aureus,* and *Haemophilus influenzae.* The increased use of immunosuppressive agents such as fludarabine, cladribine, pentostatin, and alemtuzumab has markedly increased the number of infections with opportunistic organisms such as *Candida, Listeria, Pneumocystis jiroveci,* cytomegalovirus (CMV), *Aspergillus,* herpesviruses, and others. The prophylactic use of intravenous immunoglobulins or antimicrobial agents should be reserved for select patients with documented, repeated infections.

Autoimmunity

Autoimmune hemolytic anemia (AIHA) is noted in 10 to 15% of patients with CLL and has been associated with fludarabine treatment.[135] Many additional patients have a positive direct antiglobulin test (DAT) but no clinical evidence of hemolysis. The frequency of immune thrombocytopenia seems to be approximately 2 to 15%. In most cases, these antibodies are polyclonal and not a product of the malignant B cells. Autoimmune anemia or thrombocytopenia generally responds to corticosteroids such as prednisone at a dose of 60 to 100 mg/day, which may be tapered after 1 or 2 weeks with evidence of response. Patients who do not experience a disease response to corticosteroids may respond to high-dose intravenous immunoglobulins. Rituximab and alternative immunosuppressants such as cyclosporine or cyclophosphamide may also sometimes be useful. Cytotoxic chemotherapy is an option for patients with highly refractory autoimmune hemolytic anemia. CLL-associated immune thrombocytopenia (ITP) may respond to thrombopoietin receptor agonists such as romiplostim and eltrombopag. Splenectomy may be considered when systemic approaches fail. Radiation therapy to the spleen induces only transient responses.

Pure Red Cell Aplasia

Pure red cell aplasia is an uncommon occurrence in CLL (less than 1% of cases).[135,136] It is characterized by normochromic and normocytic anemia with an absolute reticulocyte count of less than 10,000/µL and an absence or near absence of erythroblasts in the bone marrow; the WBC count, WBC differential count, and platelet counts are generally normal. Corticosteroids as well as cyclosporine and rituximab may be effective.[137]

Aggressive Transformation

In about 0.5% per year of patients with CLL, the disease will evolve into a more aggressive lymphoid malignant process termed “Richter syndrome,” which characteristically presents with increasing lymphadenopathy, hepatosplenomegaly, fever, abdominal pain, weight loss, progressive anemia, and thrombocytopenia with a rapid rise in the peripheral-blood lymphocyte count and an increased serum LDH level.[138] This transformation is not clearly related to either the nature or extent of previous therapy. The WHO classification recognizes two distinct pathologic variants of Richter syndrome, namely the diffuse large B-cell lymphoma (DLBCL) variant and the Hodgkin lymphoma (HL) variant. Molecular lesions of tumor suppression (*TP53*), cell cycle (*CDKN2A*), and cell proliferation (*NOTCH1*, *MYC*) account for approximately 90% of

cases of Richter syndrome. Approximately 80% of the variants (and 40 to 50% of the HL variants) are clonally related to the preceding CLL phase. In the other patients, analyses of immunoglobulin heavy chain variable domain (*IGHV*)-D-J genes show different rearrangements compared to the paired CLL, indicating de novo lymphomas arising in a patient with CLL. The prognosis of the DLBCL variant is generally unfavorable but not uniform, with outcomes being better in patients with clonally unrelated Richter syndrome. Outcomes with the HL variant of Richter syndrome are better than with the DLBCL variant but not as good as with *de novo* Hodgkin lymphoma.[138,139]

CLL also may evolve into prolymphocytic leukemia (PLL), which is associated with progressive anemia and thrombocytopenia, with at least 55% prolymphocytes in the peripheral blood. Clinical features include lymphadenopathy, hepatosplenomegaly, wasting syndrome, and increasing resistance to therapy. Transformation to ALL, plasma cell leukemia, or multiple myeloma has been noted anecdotally.

Secondary Malignant Diseases

Secondary malignant diseases occur with increased frequency in patients with CLL, related both to the immune defects of the disease and to the consequences of therapy. The most frequent tumors are skin cancers (including melanomas), colon cancers, lung cancers, and myeloid neoplasms.

DIAGNOSIS

Morphology

The diagnosis of CLL requires a sustained increase in mature-appearing B lymphocytes in the peripheral blood to more than 5000/mm^3; the presence of fewer B cells without palpable lymphadenopathy in an asymptomatic individual is called “monoclonal B lymphocytosis.” In CLL, it is not unusual to find a small percentage of larger atypical cells, cleaved cells, or prolymphocytes. The bone marrow usually is infiltrated by at least 30% lymphocytes. Although a bone marrow aspirate and biopsy are not needed to make the diagnosis, they are useful to evaluate the etiology of cytopenias. Neither lymph node biopsy nor computed tomography scanning is needed in the initial evaluation and should be performed only if clinically indicated.[140,141]

Immunophenotype

The predominant cell population expresses B-cell markers (CD19, CD20, and CD23) and CD5, but not other pan-T-cell markers. The entity formerly described as T-cell CLL is now called “T-cell prolymphocytic leukemia (T-PLL)” and is not considered part of CLL. The B-cells are monoclonal, as evidenced by the presence of either kappa or lambda light chains, and characteristically express surface Ig, CD79b, CD20, and CD22 with low density (as opposed to mantle cell lymphoma, which usually has higher expression of CD20 and surface Ig).[140] Distinguishing CLL from mantle cell lymphoma is essential, as both express CD5. CD23 is often helpful (often negative in mantle cell lymphoma), but absence of cyclin D1 expression is critical for differentiation and confirmation of CLL.

Cytogenetic and Molecular Abnormalities

Conventional banding techniques and FISH detect cytogenetic abnormalities in greater than 50% and greater than 80% of CLL cases, respectively.[142] The most common, either alone or in combination with other abnormalities, is deletion of 13q (55% of cases). The disease course is more benign for patients with 13q14 abnormalities, and such patients often have a normal lifespan. Deletions of 11q are identified in 15 to 20% of cases and are associated with massive lymphadenopathy, often out of proportion to the increase in the peripheral-blood lymphocyte count. Trisomy 12 can be detected in 15 to 20% of cases. Structural abnormalities of chromosome 17 occur in at least 15% of patients when FISH testing is performed. 17p13 deletions lead to disruption of the *TP53* gene and are found more frequently in cases of atypical CLL, which is associated with a higher likelihood of Richter transformation, more prolymphocytes, advanced stage, resistance to chemotherapy, and a poor prognosis. More than one-third of patients have complex genetic abnormalities.

Translocations involving *BCL-2* (t(14;18)(q32;q21)) and *BCL-3* (t(14;19)(q32;q13.1)) have been detected in only 5 to 10% of cases, but overexpression of the *BCL-2* gene is present in more than 70% of cases. The expression ratio of the antiapoptotic gene *BCL-2* to the proapoptotic gene *BAX* is increased in CLL cells, supporting the concept that CLL is more a disorder of prolonged cell survival than a hyperproliferative disease, although both factors probably contribute.

Lymphocytes from approximately half of patients with CLL are naive and have unmutated heavy chain variable domain (*VH)* genes; the other half contain *VH* genes that are mutated, post–germinal-center B cells. The *VH* gene mutation status does not change over the course of the disease. These two populations are characterized by markedly different clinical outcomes, with the survival significantly shorter for the group with unmutated *VH* genes. DNA microarray analyses have shown that ZAP-70 expression distinguishes patients with the unmutated from those with the mutated populations of CLL.[143] Increased ZAP-70 expression is associated with enhanced signal transduction through the BCR complex, which may contribute to an aggressive course.[144] The overall incidence of genomic aberrations is similar in the mutated and unmutated *VH* groups; however, the unfavorable cytogenetic abnormalities (e.g., 17p– and 11q–) occur in the unmutated group, whereas the more favorable mutations (e.g., 13q–) occur in the mutated group.[145] Lymphocytes with trisomy 12 tend to have unmutated *VH* genes. CD38 is expressed more commonly in CLL cells that are ZAP-70–positive and have unmutated *VH* genes. Cytogenetic and molecular markers in CLL may change over time, requiring reassessment if the tempo of disease seems to be changing. Next-generation sequencing technologies have identified recurrent mutations in CLL involving *NOTCH1, SF3B1,* and *BIRC3.*

PROGNOSTIC FACTORS

Several characteristics can stratify patients with CLL into groups according to different clinical outcomes that may require different therapeutic approaches. The five-stage Rai classification[146] is most commonly used in the United States (Table 16-8), and the three-stage Binet system[147] is most often applied in Europe (Table 16-9). The major difference between the two systems is that Rai stages 0 and I are mostly combined into Binet stage A, and Rai stages III and IV are combined into Binet stage C. An internationally applicable prognostic index has been developed that is based on five independent prognostic factors (age, clinical stage, del(17p) and/or *TP53* mutation, unmutated *VH* genes, and β_2-microglobulin)[148] and separates patients with early-stage and from those with advanced-stage CLL into four different prognostic groups with substantially different 5-year OS (Table 16-10).[149]

TREATMENT OF CLL

With the possible exception of allogeneic HCT, CLL is not curable with currently available therapies, and several randomized studies found no improvement in survival with early versus delayed treatment for patients with early-stage disease (Rai 0 to II or Binet A).[150] Therefore, asymptomatic patients with early-stage disease should be monitored, but they should not receive treatment unless enrolled in a clinical trial. Current indications to start therapy include evidence of progressive bone marrow failure (i.e., anemia, thrombocytopenia not associated with autoimmune hemolytic anemia or immune thrombocytopenia), massive or symptomatic or progressive splenomegaly, massive or progressive symptomatic lymphadenopathy, progressive lymphocytosis (with lymphocyte doubling time less than 6 months), steroid-refractory autoimmune anemia or thrombocytopenia, and constitutional ("B") symptoms (weight loss, night sweats, fevers).[151,152]

Table 16-8 **Rai Classification for Clinical Staging of CLL**[146]

Risk	Stage	Description	Median Survival (years)*
Low	0	Lymphocytosis in blood or bone marrow	> 12.5
Intermediate	i	Lymphadenopathy	8.5
	ii	Splenomegaly and/or hepatomegaly with or without lymphadenopathy	6
High	iii	Anemia (hemoglobin, < 11 g/dL)†	1.5
	IV	Thrombocytopenia (platelet count < 100,000/μL)†	1.5

*Of historical significance, as outcomes are changing with newer therapies.
†Anemia and thrombocytopenia cannot be immune-mediated.

Initial Therapy

First-line chemoimmunotherapy prolongs survival in CLL as compared with chemotherapy alone.[153] The exact choice of therapy is generally based on the medical fitness of the patient and the presence or absence of del(17p)/*TP53* mutation. For younger, fit patients without del(17p)/*TP53* mutation, the most commonly used regimen is fludarabine, cyclophosphamide, and rituximab (FCR). Acceptable alternatives include fludarabine and rituximab (FR), substituting pentostatin for fludarabine (PCR), and bendamustine plus rituximab, among others. For patients with significant comorbidities or are over age 65, monotherapy with the oral Bruton tyrosine kinase (BTK) inhibitor ibrutinib has been approved on the basis of results from a randomized trial showing longer PFS and OS, higher response rates, and improvement in hematologic variables as compared with chlorambucil.[154] Possible alternative regimens include

chlorambucil in combination with an anti-CD20 antibody (rituximab, obinutuzumab, ofatumumab) and bendamustine plus rituximab. Patients with CLL with del(17p)/*TP53* mutation have more aggressive disease and generally poor outcomes with chemoimmunotherapy.[153] Ibrutinib is considered first-line therapy of CLL with del(17p)/*TP53* mutation even in young, fit patients,[141,153] but it is associated with bleeding-related adverse events.[155] The oral phosphatidylinositide-3 kinase δ inhibitor idelalisib (GS-1101) has also shown high activity and durable disease control when used together with rituximab in older patients with treatment-naive CLL.[156] However, this drug has the potential for serious side effects, including autoimmune complications, and is therefore not typically used in front-line therapy.

Table 16-9 Binet Classification for Clinical Staging of CLL[147]

Stage	Description	Median Survival (years)*
A	< 2 node-bearing areas†	> 10
B	> 3 node-bearing areas	5
C	Anemia (< 10.0 g/dL) and/or thrombocytopenia (platelet count < 100,000/μL)	2

*Of historical significance, as outcomes are changing with newer therapies.
†Five node-bearing areas are possible: cervical, axillary, inguinal–femoral, spleen, and liver.

Table 16-10 International Prognostic Index for CLL[149]

Score*	Risk Level	5-Year Survival
0–1	Low	93%
2–3	Intermediate	79%
4–6	High	63%
7–10	Very high	23%

*The score is made up of five independent prognostic factors: *TP53* gene mutation with a 17p deletion (4 points), unmutated immunoglobulin heavy-chain variable region (2 points), rising β_2-microglobulin level > 3.5 mg/L (2 points), elevated clinical stage (Binet B/C or Rai I–IV; 1 point), and age > 65 years (1 point).

Patients with CLL who are treated with purine analogs become significantly immunosuppressed.[157] Thus, anti-infective prophylaxis for herpesvirus and *Pneumocystis jiroveci* is recommended. Other expected toxicities of most regimens include moderate myelosuppression. Tumor lysis syndrome occasionally occurs in patients treated for CLL, especially those with high WBC counts or bulky lymphadenopathy. This syndrome may be fatal and is not consistently preventable with the use of prophylactic allopurinol and/or hydration. Fludarabine may be associated with autoimmune hemolytic anemia and thrombocytopenia and should be stopped and switched to alternatives if such complications are seen. Despite the profound immunosuppression associated with single-agent fludarabine, the risk of secondary

malignant disease does not seem to be increased with fludarabine alone, but there may be an increased incidence of myelodysplasia when fludarabine is combined with alkylating-agent therapy.[158]

Treatment of Relapsed or Refractory Disease

The management of relapsed CLL is dependent on several factors, including age, performance status, previous therapy, response to and duration of therapy, and time from last therapy. With many potential treatments available, the exact sequence and timing of salvage therapies is currently being addressed in clinical trials. However, because of the demonstration of remarkable activity with favorable toxicity profiles, monotherapy with ibrutinib or idelalisib together with rituximab are considered standards of care for relapsed or refractory CLL.[141,153] More recently, ibrutinib has also been combined with other chemotherapeutics and shown benefit, for example, when added to bendamustine plus rituximab.[159] More selective inhibitors of BTK (e.g., acalabrutinib) are under clinical study[160] and may provide a better safety profile than ibrutinib. High response rates have been obtained with the BCL-2 inhibitor ABT-199 (venetoclax),[161] which is now approved for patients with 17p deletion who have been treated with at least one prior therapy. Highly encouraging early results have also been reported with CD19-targeted autologous T cells expressing CARs.[115]

Hematopoietic Cell Transplantation

Given the advanced age of most patients with CLL, HCT using high-dose preparative regimens has been limited to a minority of patients. The availability of reduced-intensity transplantation has widened the possible application of transplantation and allows long-term disease control and possible cure for a subset of patients. For standard-risk CLL, allogeneic HCT should be considered in the absence of response or if there is evidence of disease progression after B-cell receptor inhibitors. For high-risk CLL, allogeneic HCT is recommended after two lines of therapy have failed and shown an objective response to B-cell receptor inhibitors or to a clinical trial or after failure to respond or progression after B-cell receptor inhibitors.[162]

Supportive Measures

Splenectomy. Splenectomy may provide important palliation for patients with CLL for whom systemic treatment has failed and who have persistent splenomegaly or cytopenias that preclude chemotherapy. The procedure may also be considered for patients with autoimmune thrombocytopenia or hemolytic anemia whose disease does not respond to corticosteroids, intravenous immunoglobulins, or rituximab.

Leukapheresis. Leukapheresis results in only transient reductions in circulating lymphocytes and is not recommended for general practice. Patients with CLL rarely experience tumor cell aggregates; therefore, regardless of the number of circulating cells, systemic treatment is usually adequate to reduce the number of circulating lymphocytes, when indicated.

KEY POINTS

- Distinguishing CLL from other diseases, notably hairy cell leukemia or the leukemic phases of marginal zone lymphoma or mantle cell lymphoma, is based on the morphologic

appearance of the cells and the distinct immunophenotype of the malignant cells.

- Survival for patients with CLL has improved over the past several years, and a number of novel, highly active agents have become available.

PROLYMPHOCYTIC LEUKEMIAS

B-cell and T-cell prolymphocytic leukemia (B-PLL and T-PLL) are rare lymphoid neoplasms that occur predominantly in older adults, with a slight male predominance.[163] At the time of presentation, the primary clinical features include rapidly increasing lymphocyte counts and splenomegaly. Lymphadenopathy, rashes, peripheral edema, and pleuroperitoneal effusions are relatively common in T-PLL but not B-PLL. The disease presents at an advanced stage for virtually all patients. B-PLL cells are large, with a round nucleus and a prominent nucleolus. In de novo B-PLL, most of the peripheral-blood mononuclear cells tend to be prolymphocytes; in the setting of an aggressive transformation from CLL, there is a dimorphic population in the peripheral blood. The immunophenotype is different from CLL. Cells in B-PLL are positive for CD19 and CD20 and strongly express CD22, surface immunoglobulins, CD79a, and FMC7. Most cases do not express CD5 or CD23. T-PLL typically expresses CD2, CD3, CD5, and CD7, with variable expression of CD4 and CD8. It does not express DNA nucleotidylexotransferase (TdT) or CD1a. Common cytogenetic abnormalities include del(17p) in B-PLL and complex karyotypes typically involving chromosome 14 in T-PLL.

Patients with B-PLL generally receive the same regimens used to treat CLL, but response rates tend to be lower and response durations usually are shorter. Therapeutic activity with alemtuzumab and purine analogs has been noted in both B- and T-PLL, but responses tend to be transient, and allogeneic HCT should be considered in suitable patients in first remission.[163]

HAIRY CELL LEUKEMIA

There are about 1000 new cases of hairy cell leukemia each year in the United States, primarily occurring in middle-aged individuals, with a 4:1 male predominance.[164]

CLINICAL PRESENTATION AND DIAGNOSIS

Patients typically present with symptoms related to pancytopenia (infections, weakness/fatigue, or bleeding) or left upper quadrant abdominal pain related to splenomegaly. Besides cytopenias and splenomegaly, the most common sign includes circulating hairy cells. These cells generally have an eccentric, spongiform kidney-shaped nucleus with characteristic filamentous cytoplasmic projections. A bone marrow biopsy is usually needed to establish the diagnosis because an aspirate often cannot be obtained. The malignant cells in classic hairy cell leukemia are of B-cell origin, have no (or inconspicuous) nucleoli, and express CD19, CD20, CD123, and CD200, as well as the monocyte antigen CD11c and CD25. The most specific marker is CD103. The cells stain positively with tartrate-resistant acid phosphatase. Mutations in BRAF, specifically V600E, have been found in virtually all cases of classic hairy cell leukemia.[165] *BRAF* V600E is thought of as a causal genetic event, leading to the constitutive activation of the RAF–MEK–ERK signaling pathway that represents the key event in the molecular pathogenesis of hairy cell leukemia.[166] Hairy cell variant has a biology and clinical behavior that is distinct from classic hairy cell leukemia and often presents with significant leukocytosis. Cells are characterized by prominent nucleoli and lack of CD200 expression. They also typically do not

express CD25 or CD123, and, molecularly, lack the *BRAF* V600E mutation.[167]

TREATMENT

Treatment is indicated in the setting of massive or progressive splenomegaly, worsening blood counts, recurrent infection, more than 20,000 hairy cells/mm^3 of peripheral blood, or bulky lymphadenopathy. Historically, splenectomy was the standard treatment for hairy cell leukemia. This procedure improves symptoms related to splenomegaly and peripheral blood counts, often for prolonged periods, but it does not affect the disease itself. Splenectomy is now reserved for the rare occasion when a patient has disease that is refractory to treatment and has splenomegaly that is either symptomatic or is resulting in cytopenias.

Classic hairy cell leukemia typically follows an indolent disease course and, today, is highly curable. Over 80% of patients will experience a durable response to treatment with cladribine or pentostatin with or without the addition of an anti-CD20 antibody such as rituximab. The results with cladribine are equivalent to those with pentostatin. The shorter duration of treatment makes the former drug somewhat more attractive, although it may be associated with greater toxicity. While interferon-alpha was the first systemic therapy to demonstrate activity in hairy cell leukemia, its current role is limited, as the purine analogs are superior with regard to response duration, safety, and outcomes. Ultimately, about 30 to 40% of patients will have a relapse. In many cases, relapse is characterized only by an increase in hairy cells in the bone marrow, with no indication for treatment. A second durable response is achieved for most patients who need retreatment, which can be done with the same purine analog that was used for initial therapy. Alternatively, a short course of the oral BRAF inhibitor vemurafenib is highly effective in patients with relapsed or refractory disease.[168] Other treatment options include new anti-CD20 antibodies, an anti-CD22 immunotoxin (moxetumomab pasudotox), or the BTK inhibitor ibrutinib.[164]

Variant hairy cell leukemia has a more aggressive disease course than does classic hairy cell leukemia, and treatment results with purine analog monotherapy are substantially inferior (overall response rate of < 50%, vs. 75 to 100% for the classic version; CR rates of < 10%, vs. > 50 to 70%), but addition of rituximab appears to improve outcomes.[167]

KEY POINTS

- Hairy cell leukemia is highly responsive to treatment with cladribine or pentostatin.
- Patients with relapsed or refractory disease who require treatment may have a response to new anti-CD20 antibodies, an anti-CD22 immunotoxin, a *BRAF* inhibitor, or a Bruton TKI.

CHRONIC T-CELL LEUKEMIAS

Despite considerable effort, the classification of indolent T-cell leukemias remains ambiguous, with many uncommon and imperfectly defined categories.[169] Among the more common forms of chronic T-cell leukemia are T-PLL (see previous discussion), various subtypes of large granular lymphocytosis, adult T-cell leukemia/lymphoma, and NK-cell leukemia.

Large granular lymphocytosis can be divided into two major subsets: those that are CD3-

positive, representing in vivo activated cytotoxic T cells (T-cell large granular lymphocytosis) and NK-cell large granular lymphocytosis, which are CD3-negative. T-cell large granular lymphocytosis tends to occur in older persons, and most patients (60%) are symptomatic at diagnosis. Anemia and recurrent infections associated with neutropenia are common. The phenotype includes CD3, CD8, CD57, with clonal rearrangement of T-cell receptor genes. The NK-cell variety accounts for approximately 15% of large granular lymphocytoses and includes aggressive NK-cell leukemia and a more indolent NK-cell lymphocytosis. The cells are CD3-negative and positive for CD8, CD16, CD56, and they may or may not be positive for CD57. T-cell receptor (TCR) gene rearrangements are absent. In the aggressive form of the disease, patients tend to be younger and do not have rheumatoid arthritis. Infiltration of the gastrointestinal tract and bone marrow are common. Neutropenia is modest compared with the severity of anemia and thrombocytopenia. Patients often die as a result of multiorgan failure with a coagulopathy, generally within a few months of diagnosis, despite aggressive chemotherapy. Approximately 5% of large granular lymphocytosis is a nonclonal expansion of CD3-positive large granular lymphocytosis that is generally unaccompanied by lymphadenopathy or hepatosplenomegaly. The features of the cells are positivity for CD3, CD16, and CD56 and negativity for CD4 and CD8. The disease is indolent, rarely requiring intervention unless accompanied by neutropenia. Prednisone and immunosuppressive agents have been used. It is not clear whether this disorder is actually neoplastic.

Adult T-cell leukemia/lymphoma is endemic in certain geographic areas and linked to human T-cell lymphotropic virus type 1 infection. There are a number of clinical variants that range from a chronic smoldering disorder to an aggressive leukemic disease. The levels of serum calcium and LDH are prognostic for outcome. For aggressive variants, multiagent chemotherapy with or without subsequent allogeneic HCT, or interferon-alpha and zidovudine are recommended. For symptomatic indolent variants, interferon-alpha and zidovudine or watchful waiting should be considered, whereas watchful waiting is appropriate for asymptomatic cases.[10]

MYELODYSPLASTIC SYNDROMES

MDS generally affects older individuals, with a median age at diagnosis of 65 to 70; only 10% of patients are less than age 50.[170]

PATHOGENESIS

The MDSs are a group of clonal, acquired hematopoietic disorders biologically characterized by ineffective hematopoiesis. Multiple steps are required for clinically evident MDS to develop. An early step leads to the expansion of a genetically unstable clone beginning close to, if not at, the level of the stem cell (suggested by the observation that clonal hematopoiesis in MDS is found not only in the myeloid lineage but also, in some cases, in B cells and even T cells). This is followed by acquisition of additional mutations that may confer selective growth advantages to these clones. Links between cytogenetic abnormalities and MDS phenotype are beginning to emerge.[171] For example, patients with deletions in 5q33 (the 5q– syndrome) generally have severe macrocytic anemia, a normal or elevated platelet count, and a relatively low rate of progression to AML. Disease in these patients frequently responds to treatment with lenalidomide. *RPS14* and the casein kinase 1A1 (CK1α) have been identified as likely candidate genes involved in the 5q– syndrome and response to lenalidomide.[172,173]

Sequencing studies have revealed a number of recurrent point mutations beyond those involving cytogenetic abnormalities.[174] Among the most commonly mutated genes are *TET2,*

ASXL1, RUNX1, TP53, EZH2, and *NRAS.* Several of these (*ASXL1, RUNX1, TP53,* and *EZH2*) are associated with shortened survival. *TET2, ASXL1,* and *EZH2* are involved with regulation of DNA methylation. *SF3B1* encodes a core component of RNA splicing machinery and is frequently mutated in MDS cases with ringed sideroblasts.[174]

CLINICAL PRESENTATION AND DIAGNOSIS

Clinical findings in MDS are nonspecific and related to the reduction or dysfunction of blood cells that is present at diagnosis, including fatigue, bleeding diathesis, and infections. Not uncommonly, patients also have immune disorders.[170] The diagnosis is based on the examination of the blood and the bone marrow, which classically shows peripheral cytopenias, a hypercellular marrow with dysplastic features, and in some cases, increased numbers of blasts.[170] Based primarily on the degree of dysplasia and blast percentages in peripheral blood and bone marrow, the WHO recognizes several categories of MDS (Table 16-11).[3] Abnormal cytogenetics are present in 40 to 50% of cases and often demonstrate partial or complete loss or gain of chromosomes rather than balanced translocations (as seen in AML). The most frequent findings are del(5q), del(7), del(7q), +8, del(20q), or del(17p). Chromosomal abnormalities in MDS are of prognostic importance. Abnormalities of chromosome 5 or 7 are associated with the shortest survival, whereas the longest survival is associated with patients with a normal karyotype, –Y, del(11q), del(5q), or del(20q) as the sole abnormality.[170]

PROGNOSTIC FACTORS

Many prognostic factors have been identified in MDS, with the most important independent factors being percentage of bone marrow blasts, karyotype, and number of cytopenias.[170] These factors were used to develop the International Prognostic Scoring System (IPSS), which categorized patients with primary MDS into four risk groups with largely differing survival and risk of progression to AML.[175] Findings from additional studies suggest that, stage for stage, the prognosis is somewhat worse for patients with therapy-related MDS than for patients with primary MDS.

Table 16-11 **2016 World Health Organization Classification of MDS[3]**

Disease	Dysplastic Lineages, Cytopenias, and Ring Sideroblasts*	BM and PB blasts
MDS with single-lineage dysplasia	1 dysplastic lineage; 1–2 cytopenias; < 15%/ < 5% ring sideroblasts†	BM < 5%, PB < 1%, no Auer rods
MDS with ring sideroblasts (MDS-RS) MRD-RS with single-lineage dysplasia (MDS-RS-SLD) MRD-RS with multilineage dysplasia (MDS-RS-MLD)	1–3 dysplastic lineages; 1–3 cytopenias; ≥ 15%/ ≥ 5% ring sideroblasts†	BM < 5%, PB < 1%, no Auer rods
MDS with multilineage dysplasia (MDS-MLD)	2–3 dysplastic lineages; 1–3 cytopenias	BM < 5%, PB < 1%, no Auer rods
MDS with excess blasts (MDS-EB) MDS-EB-1 MDS-EB-2	0–3 dysplastic lineages; 1–3 cytopenias	EB-1: BM 5–9% or PB 2-4%, no Auer rods EB-2: BM 10–19% or PB 5-19%, no Auer rods
MDS with isolated del(5q)	1–3 dysplastic lineages; 1–2 cytopenias; no ring sideroblasts	BM < 5%, PB < 1%, no Auer rods; del(5q) alone or with 1 additional abnormality except –7 or del(7q)
MDS, unclassified (MDS-U) With 1% blood blasts With single-lineage dysplasia and pancytopenia Based on defining cytogenetic abnormality	0–3 dysplastic lineages; 1–3 cytopenias‡	BM < 5%, PB ≤ 1%, no Auer rods§
Provisional entity: refractory cytopenia of childhood	1–3 dysplastic lineages; 1–3 cytopenias; no ring sideroblasts	BM < 5%, PB < 2%

*Cytopenias defined as: hemoglobin < 10 g/dL; platelet count < 100×10^9/L; and absolute neutrophil count < 1.8×10^9/L; peripheral-blood monocyte count must be < 1×10^9/L.
†If *SF3B1* mutation is present.
‡If no dysplastic lineage, must have MDS-defining cytogenetic abnormality by conventional karyotyping.
§Cases with 1% peripheral blood blasts must be documented on at least 2 separate occasions.
Abbreviations: BM, bone marrow; EB, excess blasts; MLD, multilineage dysplasia; PB, peripheral blood; RS, ring sideroblasts; SLD, single-lineage dysplasia; U, unclassified.

Several attempts have been made to refine prognostic scoring in MDS, with the most important systems being the WHO Prognostic Scoring System,[176] which is based on WHO classification, cytogenetics, and red cell transfusion need, and the revised IPSS (IPSS-R) (Table 16-12), which includes a larger number of cytogenetic abnormalities, uses different thresholds for cytopenias and weights for clinical parameters, and divides patients into five rather than four risk groups.[177]

TREATMENT OF MDS

The therapeutic strategy is based primarily on disease risk.[170] The main goals for patients with low/intermediate 1–risk MDS are to reduce the consequences of cytopenias and improve quality of life, whereas for those with intermediate 2/high–risk disease, the focus is on disease modification with prevention of transformation into AML and prolongation of survival. For low/intermediate 1–risk disease or patients who are frail or elderly, supportive care with red blood cell and platelet transfusions as necessary is recommended. Lenalidomide, a 4-amino-glutarimide analog of thalidomide, has been approved for treatment of transfusion-dependent low/intermediate 1–risk MDS associated with the 5q– syndrome and can lead to transfusion independence and cytogenetic response in many patients.[178] Erythropoietin can improve the

anemia associated with MDS in 20 to 30% of cases and is most effective in patients with low endogenous erythropoietin levels.[179] Addition of a myeloid growth factor may result in responses for 20 to 30% of patients who do not experience a response after 4 to 6 weeks, although no randomized study has shown survival improvements. The MDS-associated anemia in some patients may improve with the anabolic steroid danazole. Myeloid growth factors, including granulocyte colony-stimulating factor and granulocyte–macrophage colony-stimulating factor, have been used to treat the neutropenia that sometimes accompanies MDS, but responses have been disappointing, and their routine use as a single agent to prevent granulocytopenia is currently not recommended. Platelet counts have responded to low-dose interleukin-11 and to the thrombopoietin mimetics romiplostim and eltrombopag, but safety concerns with regard to the potential augmentation of myeloblast proliferation remain with the latter class of drugs.[180]

Table 16-12 Revised International Prognostic Scoring System for MDS[177]

IPSS-R Score Values	Score						
Variable	**0 Points**	**0.5 Point**	**1.0 Point**	**1.5 Points**	**2.0 Points**	**3.0 Points**	**4.0 Points**
Cytogenetics*	Very good		Good		Intermediate	Poor	Very poor
Bone marrow blasts (%)	≤ 2		> 2 to < 5		5 to 10	> 10	
Hemoglobin (g/dL)	≥ 10		8 to < 10	< 8			
Platelets (cells/μL)	≥ 100	50 to 100	< 50				
Absolute neutrophil count (cells/μL)	≥ 0.8	< 0.8					
IPSS Categories and Outcomes	Very Low	Low	Intermediate	High	Very High		
IPSS-R score	< 1.5	> 1.5 to 3.0	> 3 to 4.5	> 4.5 to 6	> 6		
Proportion of patients	19%	38%	20%	13%	10%		
Median survival (years)	8.8	5.3	3.0	1.6	0.8		
Time to 25% AML progression (years)	> 14.5	10.8	3.2	1.4	0.7		

*Cytogenetic definitions: very good, -Y, del(11q); good, normal, del(5q), del(12p), del(20q), double including del(5q); intermediate, del(7q), +8, +19, i(17q), any other single or double independent clones; poor, -7, inv(3)t(3q)/del(3q), double including -7/del(7q), complex with three abnormalities; very poor, complex with at least three abnormalities.

Azacitidine and decitabine are both approved for treatment of MDS (azacitidine for all types of MDS, decitabine for intermediate 1–, intermediate 2–, and high-risk disease). Both are thought to have utility in MDS through their DNA demethylating activity, which leads to reexpression of key genes otherwise inactivated in MDS by hypermethylation.[181,182] The effects of azacitidine were documented in a phase III trial that found improved OS compared to conventional care (supportive care alone, low-dose cytarabine, or intensive chemotherapy, as selected by investigators before randomization) for patients with intermediate 2/high–risk disease.[183] Compared to best supportive care, treatment with decitabine was reported to significantly reduce the risk of AML transformation and to improve PFS in a randomized phase III trial in patients with intermediate 1/intermediate 2/high–risk MDS, whereas OS was statistically nonsignificantly prolonged.[182] Neither azacitidine nor decitabine is curative. The presence of *TET2* mutations predicts for better response to hypomethylating agents.[184]

Based on the hypothesis that the pancytopenia seen in MDS may result from T cells'

inhibiting hematopoiesis, trials of immunosuppressive therapy have been conducted using antithymocyte globulin, cyclosporine, or the two agents in combination. Responses, sometimes enduring, have been documented for approximately one-third of patients, particularly those who express HLA-DR15.[185] A variety of biologic response modifiers have been studied in MDS, including agents developed to reduce levels of tumor necrosis factor, as well as antiangiogenesis agents, retinoic acid, amifostine, and interferon. Although responses have been seen with each of these, none have been shown in randomized trials to alter the course of the disease.

Low-dose cytarabine has been studied as a treatment option for MDS, with responses seen in 10 to 20% of cases. Patients with MDS with excess blasts (EB)-1 or EB-2 have, in some cases, been treated with AML-like induction chemotherapy. Although response rates are lower than the rates seen with de novo AML, CRs have been reported in 40 to 60% of patients in some studies,[170] but it is unknown whether this results in an overall improvement in survival.

Hematopoietic Cell Transplantation

Allogeneic HCT is currently the only curative therapy for MDS and can lead to long-term disease-free survival for 35 to 50% of patients, with many patients alive without evidence of disease for more than 5 years after transplantation, and some for as long as 25 years.[170,186] Several mutations (*TP53, TET2,* and *DNMT3A*) have been associated with shorter survival after transplantation.[186] A major question is the appropriate timing of transplantation. Patients with early-stage MDS may live for long periods without any intervention, but after MDS evolves to AML, survival is short and transplantation is less effective than if it had been carried out earlier. Based on an evidence-based review, an expert panel recommended transplantation for patients with an IPSS score of intermediate 2 or high risk and for selected patients with a low or intermediate 1 risk IPSS score who have poor prognostic features not included in the IPSS (e.g., older age, refractory cytopenias).[187] Similarly, a review focused on patients ages 60 to 70 indicated that reduced-intensity allogeneic HCT offered an overall and quality-adjusted survival benefit for IPSS intermediate 2/high–risk MDS.[188]

KEY POINTS

- The three most important factors that predict outcome for patients with MDSs are percentage of marrow blasts, karyotype, and number of peripheral cytopenias.
- The therapeutic strategy is primarily based on the disease risk, with the main goals of reducing consequences of cytopenias and improving quality of life for patients with lower-risk disease, prevention of transformation into AML, and improvement of survival for patients with higher-risk disease.

MYELOPROLIFERATIVE NEOPLASMS

A heterogeneous group of hematologic disorders is currently recognized by the WHO as MPNs, myeloid or lymphoid neoplasms associated with eosinophilia and acquired mutations in growth factor receptors, and myeloid neoplasms with clinical, laboratory, and morphologic features that overlap MDS and MPN (Table 16-13).[3] Here, we will focus on the classical MPNs: PV, ET, and

PMF.

PATHOGENESIS

MPNs are characterized by stem cell–derived clonal myeloproliferation that can evolve into AML or, in the case of PV and ET, myelofibrosis (secondary [post-PV/ET] MF).[6] Over the past decade, multiple recurrent somatic mutations have been identified in these disorders.[6,189] Most prominent among these are the mutually exclusive mutations in *JAK2* (primarily in exon 14; i.e., V617F, and rarely in exon 12), calreticulin (*CALR;* primarily exon 9 deletions and insertions), and myeloproliferative leukemia virus oncogene (*MPL*; primarily exon 10 mutations). *JAK2* mutations are found in almost 100% of PV cases, 50 to 60% of ET cases, and 55 to 65% of PMF cases; 20 to 25% of ET and PMF cases harbor *CALR* mutations, whereas *MPL* mutations are present in 3 to 4% of ET and 6 to 7% of PMF cases, respectively.[6] Increasingly, characteristic differences (e.g., age at diagnosis, blood counts, risk of thrombosis) between these three mutations are recognized.[190] In approximately 10 to 15% of the patients with ET or PMF, neither a *JAK2, CALR,* or *MPL* mutation is found ("triple negative").[6] In addition to these three genes, mutations in many other genes have been described, including *LNK, CBL, DNMT3A, TET2, IDH1/2, EZH2,* and *ASXL1.* Several of these mutations constitutively activate cell-signaling pathways and lead to a clonal growth advantage. Other mutations affect genes involved in epigenetic regulation and are thought to cooperate with the first class of mutations. However, although activation of the JAK-STAT pathway is believed to be central for MPNs, the pathophysiologic role for many of the mutations found in these disorders has yet to be determined.[189] Similarly not fully understood is why a single mutation such as *JAK2V617F* can result in different, clinically distinct disorders, although differences in mutant allele burden, *STAT1* signaling, order of mutation acquisition, and clonal heterogeneity may play a role.[6,191]

Table 16-13 **2016 World Health Organization Classification of Myeloproliferative Neoplasms, Myeloid Neoplasms Associated with Eosinophilia, and Myelodysplastic/Myeloproliferative Neoplasms**[3]

	Classification
Myeloproliferative neoplasms (MPNs)	Chronic myeloid leukemia (CML), *BCR-ABL1*–positive Chronic neutrophilic leukemia (CNL) Polycythemia vera (PV) Primary myelofibrosis (PMF) PMF, prefibrotic/early stage PMF, overt fibrotic stage Essential thrombocytopenia (ET) Chronic eosinophilic leukemia, not otherwise specified MPN, unclassifiable
Mastocytosis	
Myeloid and lymphoid neoplasms associated with eosinophilia and abnormalities of *PDGFRA, PDGFRB,* or *FGFR1*, or with *PCM1-JAK2*	Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement Myeloid and lymphoid neoplasms with *FGFR1* rearrangement Provisional entity: Myeloid/lymphoid neoplasms with *PCM1-JAK2*
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)	Chronic myelomonocytic leukemia (CMML) Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*–negative Juvenile myelomonocytic leukemia (JMML) MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) MDS/MPN, unclassifiable

CLINICAL PRESENTATION AND DIAGNOSIS

Patients may present with fatigue, constitutional symptoms (fever, weight loss, night sweats), microvascular symptoms (headaches, erythromelalgias), itching, bone pain, thromboses at unusual sites (e.g., portal or hepatic vein), early satiety, and abdominal discomfort. Subsets of patients present with a thrombotic event or have a history of thrombosis. On physical examination, palpable splenomegaly or hepatomegaly is common, and evidence for extramedullary hematopoiesis at other sites may be found. Peripheral-blood studies are noticeable for blood counts that exceed the upper limit of normal and changes consistent with hypermetabolism (e.g., elevated LDH and uric acid); leukoerythroblastic changes are characteristic of (P)MF.[6,192] Secondary causes for erythrocytosis and thrombocytosis need to be excluded. Commonly used diagnostic criteria for PV, ET, and PMF are summarized in Table 16-14.[3] Mutational screening is helpful to demonstrate the presence of clonal hematopoiesis. For example, with a *JAK2* mutation screening and a serum erythropoietin level, essentially all patients with PV will be identified. However, the presence of a mutation alone is neither required for, nor proof of, a MPN.[6]

A bone marrow examination is important for accurately diagnosing a MPN.[6] Characteristic findings allow a distinction between PV (trilineage hematopoiesis with pleomorphic megakaryocytes), ET (megakaryocyte proliferation with large and mature morphology), and PMF (megakaryocyte proliferation and atypia as well as reticulin and/or collagen fibrosis) and help identify prefibrotic PMF (bone marrow morphology consistent with PMF but without fibrosis) or masked PV (bone marrow morphology consistent with PV but blood counts not meeting criteria for PV).[6,192]

PROGNOSTIC FACTORS

The median life expectancy varies considerably among ET (20 years), PV (14 years), and PMF (6 years) because of varying risks for thrombosis, bleeding, and clonal evolution. The risk of leukemic transformation is substantially lower for PV or ET (at 20 years: less than 10% for PV and less than 5% for ET) than for PMF.[6] Once leukemic transformation has occurred, median survival is less than 6 months.[193] An increasing number of risk factors have been recognized for shortened survival in the various MPNs. The clinically most widely used ones are:[6]

- **PV:** advanced age, leukocytosis, thrombosis, and abnormal karyotype
- **ET:** advanced age, leukocytosis, and thrombosis
- **PMF:** age, anemia, leukocytosis, circulating blasts greater than 1%, constitutional symptoms, unfavorable karyotype, need for red cell transfusion, and thrombocytopenia; these eight factors are integrated in the Dynamic International Prognostic Scoring System (DIPSS)–plus score, which separates PMF into four risk groups (low, intermediate 1, intermediate 2, and high), with median survivals of 15.4, 6.5, 2.9, and 1.3 years, respectively.[194]

Table 16-14 **2016 World Health Organization Diagnostic Criteria for Polycythemia Vera, Essential Thrombocythemia, and Primary Myelofibrosis**[3]

	Criteria Required for Diagnosis
Polycythemia vera (PV)	▪ Elevated hemoglobin (men, > 16.5 g/dL; women, > 16.0 g/dL) or increased hematocrit (men, 49%; women, 48%) or increased red cell mass ▪ BM hypercellularity, trilineage hematopoiesis with prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes ▪ *JAK2V617F* or *JAK2* exon 12 mutation; if such a mutation is absent, diagnosis of PV is still possible if there is a subnormal erythropoietin level
Essential thrombocythemia (ET)	▪ Persistently elevated platelet count (≥ 450 × 10^9/L) ▪ BM with predominant proliferation of enlarged, mature megakaryocytes with hyperlobulated nuclei ▪ Not meeting diagnostic criteria for classic CML, PV, PMF, MDS, or other myeloid neoplasms ▪ *JAK2V617, CALR, or MPL* mutation, or other clonal marker; if no clonal marker present, no evidence of reactive thrombocytosis
Primary myelofibrosis (PMF)	▪ Megakaryocytic proliferation and atypia. For pre-PMF: no reticulin fibrosis > grade 1, BM hypercellularity, granulocytic proliferation, often decreased erythropoiesis. For overt PMF: grade 2–3 reticulin and/or collagen fibrosis ▪ Not meeting diagnostic criteria for classic CML, PV, ET, MDS, or other myeloid neoplasms ▪ *JAK2V617, CALR, or MPL* mutation or other clonal marker; if no clonal marker present, no evidence of minor reactive BM reticulin fibrosis (for pre-PMF) or reactive myelofibrosis (for overt PMF) ▪ ≥ 1 minor criterion: 1, anemia; 2, leukocytosis ≥ 11 × 10^9/L; 3, palpable splenomegaly; 4, LDH elevation; 5, leukoerythroblastosis (for overt PMF only)

Abbreviations: BM, bone marrow; LDH, lactate dehydrogenase.

TREATMENT OF MYELOPROLIFERATIVE NEOPLASMS

The general goals of therapy for MPNs are the alleviation of symptoms, the prevention of thrombosis or bleeding, minimization of the risk of progression to MF (for PV and ET) and, particularly in MF, reduction of the risk of leukemic transformation and improvement in survival.[6,192]

Therapy of PV

For low-risk patients (younger than age 60, no thrombosis history), low-dose aspirin reduces the risk of thromboembolic events and treats microvascular symptoms.[6,192,195] Likewise, repeated phlebotomies to maintain a hematocrit of less than 45% reduces cardiovascular deaths and major thrombosis.[196] High-risk patients (age 60 or older and/or history of thrombosis) additionally require cytoreductive therapy to lower thrombotic complications. Hydroxyurea, titrated to keep the platelet count in the normal range, is usually considered the first-line treatment in this situation and has shown to be superior over anagrelide. Second-line treatments for individuals whose disease is intolerant or resistant to hydroxyurea include interferon-alpha (for younger patients) and busulfan (restricted to older patients, given its leukemogenic potential).[6,192,195] The JAK inhibitor ruxolitinib is superior to standard therapy in controlling the hematocrit, reducing spleen volume, and improving symptoms in patients with inadequate response to, or unacceptable side effects from, hydroxyurea.[197]

Therapy of ET

For low-risk patients, aspirin is used to treat microvascular symptoms and may reduce the likelihood of vascular events in JAK2-mutated ET; patients with CALR or MPL mutation and triple-negative ET have relatively lower thromboembolic risks, and antiplatelet therapy may not affect the risk of thrombosis. In high-risk patients (age 60 or older or history of vascular complications), hydroxyurea (for older patients) or interferon-alpha (for younger patients) reduces the thrombotic risk.[6,198] Debate remains about whether patients with extreme thrombocytosis (e.g., platelet count > 1000 to 1500 × 10^9/L) without other risk factors should receive cytoreductive therapy.[199]

Therapy of PMF

For low or intermediate 1 DIPSS-plus risk, observation or hydroxyurea (for constitutional symptoms or symptomatic splenomegaly) may be most appropriate. Androgens, prednisone, danazol, immunomodulatory agents (e.g., thalidomide or lenalidomide), or splenectomy may be useful for symptomatic anemia. For intermediate 2 or high DIPSS-plus risk or genetically high-risk disease (i.e., *CALR* mutation–negative and *ASXL1* mutation–positive), allogeneic HCT should be considered, as many patients will experience a durable remission after transplantation with matched-related or matched-unrelated donors.[6,192] In randomized trials, ruxolitinib provided substantial clinical benefits relative to standard therapy in DIPSS-plus intermediate- or high-risk myelofibrosis by reducing spleen size, ameliorating debilitating myelofibrosis-related symptoms, and perhaps improving OS.[200-202] However, ruxolitinib is not a specific inhibitor of the malignant clone and frequently results in myelosuppression. Besides other JAK inhibitors (e.g., momelotinib, pacritinib), efforts are ongoing to develop new classes of drugs such as antianemia medications, antifibrotic agents, and telomerase inhibitors (e.g., imetelstat).[203]

KEY POINTS

- The treatment of PV, ET, and PMF is tailored to the likelihood of the development of venous or arterial thromboses, bleeding, or evolution to AML, the major life-

threatening/limiting complications of these MPNs.

- Besides alleviation of constitutional symptoms, the goal of treatment is to reduce the risk of the development of these complications and to prolong survival.

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LYMPHOMAS

Sonali M. Smith, MD

Recent Updates

- The World Health Organization (WHO) revised the classification of lymphomas; it now recognizes high-grade B-cell lymphoma with dual *MYC* and *BCL2* rearrangements ("double hit lymphoma") as a distinct entity. (Swerdlow SH, *Blood* 2016)
- Response-adapted treatment following interim PET is now routinely used in Hodgkin lymphoma. (Johnson P, *N Engl J Med* 2016)
- Bleomycin can be safely omitted in advanced stage HL patients achieving a negative PET scan after two cycles of ABVD. (Johnson P, *N Engl J Med* 2016)
- PD-1 inhibitors (nivolumab, pembrolizumab) are active in relapsed/refractory Hodgkin lymphoma and are now approved for this indication. (FDA. Nivolumab for Hodgkin lymphoma, 2016; FDA. Pembrolizumab for classical Hodgkin lymphoma, 2017)
- The use of chimeric antigen receptor modified T-cells (CAR-T) was approved in November 2017 for relapsed/refractory large B-cell lymphoma after at least two lines of systemic therapy. (FDA. Axicabtagene Ciloleucel for Large B-cell Lymphoma, 2017)

INTRODUCTION

Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of malignancies derived from mature B, T, and NK cells, encompassing several broad categories and nearly 100 unique biologic subtypes (Fig. 17-1). This chapter covers indolent B-cell lymphomas, aggressive B-cell lymphomas, mantle cell lymphoma, T-cell lymphomas, and Hodgkin lymphoma. In the United States, approximately 85% of NHLs are of B-cell origin, 10 to 15% are T-cell derived, and < 1% are nature killer (NK) cell malignancies.

Hodgkin lymphoma (HL), discussed in the final section of this chapter, is now understood to be a mature B-cell malignancy with a deregulated B-cell program. The initial diagnostic and staging considerations for NHLs and HL are similar and are discussed jointly. However, although biologically related, HL and NHLs have distinct historical and clinical approaches, and management is discussed separately. In this chapter, the term "lymphoma" will be used whenever discussing issues pertinent to both NHLs and HL.

OVERVIEW OF NON-HODGKIN LYMPHOMAS

EPIDEMIOLOGY AND ETIOLOGY

NHL is the sixth most common cause of cancer in men, and the seventh most common cause in women. In 2017, there have been approximately 80,000 new cases of NHL and 22,000

deaths.[1] The incidence of NHL has increased markedly in the past several decades, presumably because of the increasing exposure to carcinogens (e.g., pesticides and herbicides) and the increasing prevalence of immunosuppressed individuals in the United States (including people with AIDS and those receiving immunosuppressive drug therapy). The greatest increases in incidence are in older individuals and in the number of cases of aggressive lymphomas. The median age of patients diagnosed with NHL varies by histologic subtype, although the incidence for most subtypes increases with age. With improved treatment, many patients can expect to be cured of lymphoma or to live with it for prolonged periods of time; there are an estimated 500,000 people living with lymphoma. This is an important consideration when making treatment decisions, since survivors are at increased risk for late toxicity and organ damage related to treatment.

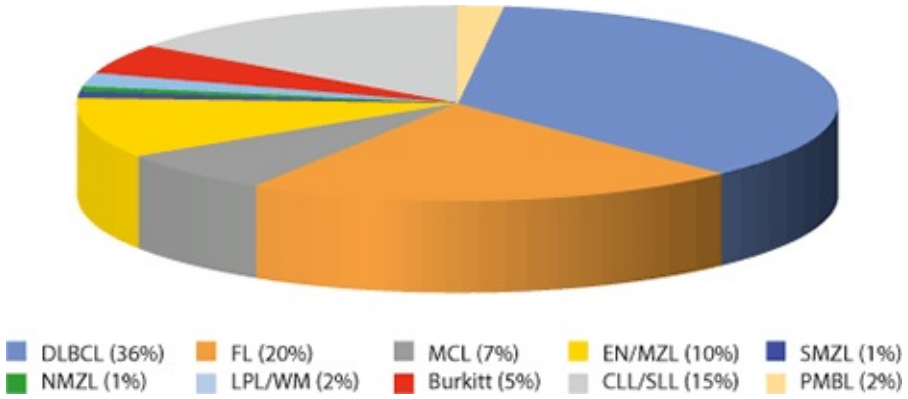

Fig. 17-1 Relative distribution of main non-Hodgkin lymphoma subtypes.

Frequencies based on World Health Organization (WHO) 2008 classification.

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; ENMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; LPL/WM, lymphoplasmacytic lymphoma/Waldendström macroglobulinemia; MCL, mantle cell lymphoma; NMZL, nodal marginal zone lymphoma; PMBL, primary mediastinal B-cell lymphoma; SMZL, splenic marginal zone lymphoma.

The etiology of NHL in most patients is unknown, but there are associations with lymphotropic organisms, innate or acquired immunodeficiency, environmental exposures, and familial predisposition. Several viruses have been linked either directly or indirectly to specific lymphoma subtypes, including Epstein–Barr virus (EBV), hepatitis C, human herpesvirus 8, and HIV. Bacteria, such as *Helicobacter pylori* and *Chlamydia psittaci,* are the etiologic or contributory agents for extranodal gastric and orbital marginal zone lymphomas, respectively. Autoimmune conditions and treatment for autoimmune conditions both appear to increase the risk of lymphoma. NHL was one of the earliest described AIDS-defining malignancies, but the spectrum of lymphomas in the era of antiretroviral therapy has evolved and will be discussed separately. Support for an environmental contribution to lymphoma risk comes from observations that NHL incidence increases in industrialized regions, and there are several pesticides and chemicals that might contribute to lymphoma development.[2] The role of genetics in lymphoma etiology is largely unknown, but there are a number of ongoing studies prompted by families in which multiple members have hematologic malignancies, including lymphoma.[3]

LYMPHOMA DIAGNOSIS AND CLASSIFICATION

The clinical presentation of NHL is variable. Most patients with indolent disease present with incidentally noted asymptomatic adenopathy or organomegaly or, occasionally, with peripheral-

blood lymphocytosis detected during a routine examination. In contrast, patients with aggressive lymphomas often will self-detect a rapidly growing lymph node, experience constitutional symptoms, or note pain associated with a site of disease. Symptoms may be related to compression of anatomic structures and include cough, jaundice, ureteral obstruction, and neurologic compromise. Constitutional symptoms may be the classic "B symptoms" (unexplained fevers, night sweats, ≥ 10% unintentional weight loss) or may be generalized fatigue, asthenia, or weakness. Pruritus, a classic paraneoplastic phenomenon associated with Hodgkin lymphoma, may also occur in other B-cell malignancies.

In terms of pathophysiology, B-cell NHL (B-NHL) develops at various points during normal B-cell ontogeny (Fig. 17-2). The majority of B-cell lymphomas are thought to originate in the germinal center.[4] Because of their function in normal immunity, B cells are exposed to antigenic stimuli in the germinal center and undergo class-switch recombination and somatic hypermutation. These tremendous pressures and associated rapid proliferation likely increase adverse mutations and chromosomal errors leading to malignancy.

The World Health Organization (WHO) lymphoma classification, last published in 2008 and updated in 2016, is the gold standard for defining lymphoma subtypes.[4,5] Confirming a lymphoma diagnosis requires adequate tissue to perform architectural assessment, hematopathology review, immunohistochemistry, and other essential tests based on subtype; an excisional biopsy (≥ 1 cm^3) is the gold standard. Multiple core biopsies can suffice if a lymph node is difficult to access, but fine-needle aspiration is rarely sufficient for diagnostic and prognostic purposes and is a disservice to the patient, who often will need a second biopsy to ensure appropriate therapeutic management.

A reasonably sized specimen allows the hematopathologist to identify whether a lymphoma has retained nodal architecture (i.e., follicular lymphoma) or has a diffuse architecture (i.e., diffuse large B-cell lymphoma [DLBCL], mantle cell lymphoma, small lymphocytic lymphoma, among others). Immunohistochemistry is an essential part of the diagnosis (Table 17-1) and is increasingly important for therapeutic purposes as well. For example, CD20 or CD30 positivity may support the use of specific agents. Cytogenetic analysis is also increasingly used in NHL; chromosomal rearrangements may be diagnostic or supportive of a specific type of lymphoma. For example, the t(11;14) rearrangement is diagnostic for mantle cell lymphoma. However, the t(14;18) rearrangement can be seen in both follicular lymphoma and more aggressive subtypes such as DLBCL or high-grade B-cell lymphoma. Some translocations are prognostic rather than diagnostic. For example, dual t(8;14) and t(14;18) rearrangement involving *MYC* and *BCL2* genes, respectively, in a high-grade B-cell neoplasm leads to an aggressive and chemoresistant phenotype termed "double hit" lymphoma that may require more intense treatment.

STAGING AND INITIAL EVALUATION

The historical staging system for both Hodgkin and non-Hodgkin lymphoma is the Ann Arbor classification, Cottswold revision (Table 17-2).[6] Typical staging involves CT scans of the neck, chest, abdomen, and pelvis along with a bone marrow biopsy. Once the stage is assigned, there is often a subscript indicating whether a patient has the absence (A) or presence (B) of B symptoms. With the advent of functional imaging via positron-emission tomography (PET), the Lugano classification was introduced and has several implications for the modern staging of lymphomas.[6] First, a staging bone marrow biopsy is no longer routinely required for the diagnosis of Hodgkin lymphoma or DLBCL if a PET/computed tomography (CT) has been performed. Second, PET/CT should be used to assess response in fluorodeoxygluose (FDG)-

avid histologies; interpretation of PET scans should be via the 5-point scale,[7] also called the Deauville criteria (Table 17-3). Third, the suffixes A and B are required only for HL, although many practitioners continue to use this as a descriptive element for NHL.

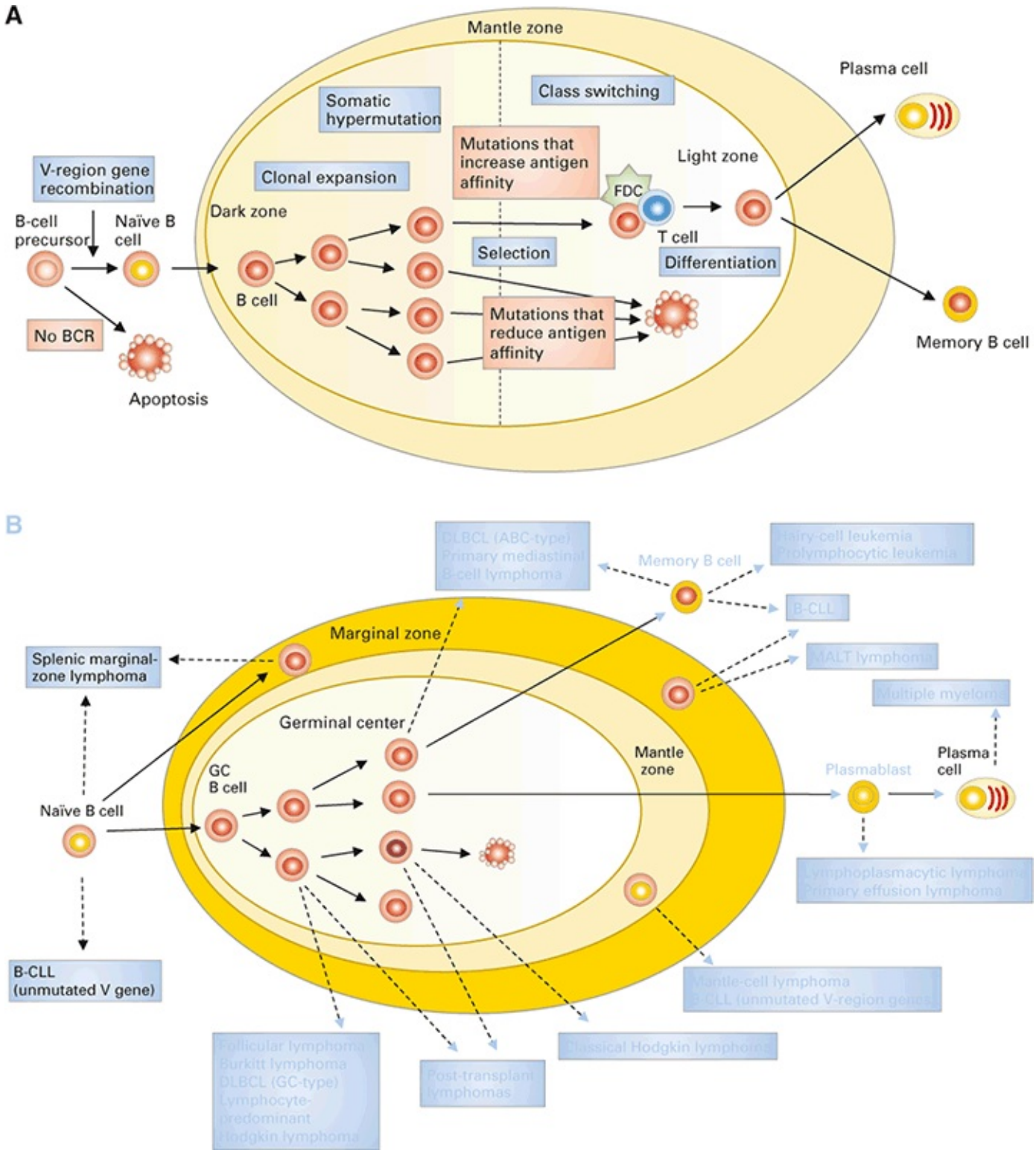

Fig. 17-2 Schematic representation of normal B-cell development (A) and corresponding B-cell lymphomas (B).

Table 17-1 **Key Diagnostic Immunophenotypic and Cytogenetic Features of Non-Hodgkin Lymphomas**

Lymphoma Subtype	CD20	CD10	CD5	CD30	Other	Cytogenetics/FISH	Genes
DLBCL	+++	+/–	Rare	Rare		t(14;18) t(3;14) rare t(8;14) or t(8;22)	*BCL2* *BCL6* *MYC*
FL	+++	+	–	–		t(14;18)	*BCL2*
CLL/SLL	Dim	–	+	–	CD23 +		
MCL	+++	–	+	–	CD23 – Cyclin D1+ SOX11+	t(11;14)	*Cyclin D1*
MZL	+++	–	Rare	–		t(11;18) (ENMZL) trisomy 3, 18 (NMZL) del 7q (SMZL)	*API2-MALT*
LPL/WM	+++	–	Rare	–			*MYD88*
Burkitt lymphoma	+++	+	–	–	TdT -	*t(8;14), t(8;22), t(2;8)*	*MYC*
PMBL	+++	+/–	–	Occasional		*t(16;X)*	*CIITA*
Hairy cell leukemia	+++	–	–	–	CD11c+, CD25+, CD103+		
ALCL, ALK-positive	–	–	–	+++		*t(2;5)*	*ALK*
ALCL, ALK-negative	–	–	–	+++		*t(6;7)*	*DUSP22*
AITL	–	+/–	+/–	–	At least 3 TFH markers: PD1, BCL6, CXCL13, ICOS, SAP, CCR5		*TET2, IDH2, DNMT3A, RHOA, ITK-SYK*
PTCL-NOS	–	+/–	+/–	–	Can have same immunophenotype as AITL; often with dropped CD3 or CD7		

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; ENMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NMZL, nodal marginal zone lymphoma; PMBL (primary mediastinal B-cell lymphoma); PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; SMZL, splenic marginal-zone lymphoma.

Of note, and in stark contrast to many solid tumors, stage by itself rarely dictates treatment or prognosis. The purpose of staging is more descriptive for disease location (nodal vs. extranodal), extent (limited vs. advanced), and bulk (typically ≥ 10 cm). The specific subtype and its associated pathobiologic features are more important than precise stage in determining initial treatment. Clinicians group NHL subtypes into indolent (slow-growing or low-grade), aggressive (fast-growing or intermediate-grade), and highly aggressive (very rapidly growing or high-grade) categories to facilitate clinical decision-making regarding therapy and to estimate disease behavior.

In addition to radiographic staging, a lumbar puncture (LP) should be performed in all patients with Burkitt lymphoma and should be considered for other high-grade lymphomas. The rationale for performing an LP is to detect occult central nervous system (CNS) disease in high-

risk patients and to determine the need for CNS prophylaxis. A CNS-IPI (International Prognostic Index) has been proposed in which greater than three risk factors was associated with a > 10% risk of CNS recurrence after rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) (kidney and/or adrenal gland involvement, age > 60, lactate dehydrogenase (LDH) > normal, Eastern Cooperative Oncology Group [ECOG] performance status [PS] > 1, stage III/IV disease, or extranodal involvement > 1).[8]

Other tests performed at the time of initial evaluation may include cardiac-function assessment (if treatment will include anthracyclines), pulmonary-function testing (if treatment will include bleomycin), HIV, LDH, β_2-microglobulin, uric acid, complete blood count (CBC), and hepatitis B and/or C testing. Testing for hepatitis B is required prior to use of rituximab and other anti-CD20 chemoimmunotherapy because of the risk of viral reactivation and fatal hepatitis. Tests should include those for hepatitis B surface antigen and core antibody for patients without risk factors; patients with risk factors or a history of hepatitis B should be tested for e-antigen as well. Patients who are seropositive for hepatitis B surface antigen or hepatitis core antibody should receive prophylactic therapy, ideally for 12 months.[9,10]

Table 17-2 Staging Systems for Lymphomas[6]

Ann Arbor Staging System*		
I	Involvement of a single lymph node region or lymphoid structure	
II	Involvement of two or more lymph node regions confined to one side of the diaphragm	
III	Involvement of two or more lymph node regions on both sides of the diaphragm	
IV	Disseminated involvement of a deep, visceral organ (bone marrow, liver, etc)	
Revised Staging System for Primary Nodal Lymphomas (Lugano Classification)†		
Stage	**Involvement**	**Extranodal (E) Status**
Limited I II	One node or a group of adjacent nodes Two or more nodal groups on the same side of the diaphragm	Single extranodal lesions without nodal involvement Stage I or II by nodal extent with limited contiguous extranodal involvement
II Bulky	II as above with "bulky" disease	Not applicable
Advanced III IV	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement Additional noncontiguous extralymphatic involvement	 Not applicable Not applicable

*The subscripts used for subtypes are A, absence of B symptoms; B, presence of at least one of the following: unexplained fevers, night sweats, unintentional weight loss > 10% of body weight; X, bulky disease ≥ 10 cm; E, primary extranodal involvement.
†Extent of disease is determined by PET/CT for avid lymphomas and CT for nonavid histologies. Tonsils, Waldeyer ring, and spleen are considered nodal tissue.

SURVIVORSHIP AND SURVEILLANCE

Improved diagnostic and staging methods, treatment options, and supportive care have all translated into tremendous survival benefits for patients with lymphomas. There are more than half a million people with lymphoma who are either cured of their disease or living with chronic

states of this disease in the United States. The success of initial treatment implies that survivorship is an important component of long-term management. The review of late effects of therapy is beyond the scope of this chapter, but several excellent reviews are available.[11,12]

Table 17-3 Five-Point Scale (Deauville Criteria) for PET Assessment in Lymphoma[7]

Score	PET/CT scan result
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

Most patients with HL and the majority of those with DLBCL can expect to enter remission and be cured of their disease. The need to monitor patients for disease recurrence has historically been associated with routine radiographic imaging, often in asymptomatic patients. The risk of recurrence is highest in the first 2 to 3 years following initial therapy and then decreases. Relapses beyond 5 years are rare, and this is usually the point at which patients are considered cured. However, routine radiographic surveillance is no longer the standard of care, based largely on several retrospective analyses. Collectively, these studies found that recurrence was detected in only 2 to 5% of patients who were otherwise clinically and hematologically stable; furthermore, there was no difference in survival if relapse was detected radiographically or after the patient presented with signs or symptoms of disease recurrence.[13,14] Given the increased exposure to radiation and contrast dye, not to mention cost and patient inconvenience, routine surveillance scans following complete remission are no longer recommended in HL and DLBCL. However, all patients should be followed clinically for disease monitoring.

KEY POINTS

- NHLs comprise a group of heterogeneous diseases that vary widely with respect to clinical presentation, therapy, and prognosis.
- Advances in the diagnosis and classification of these diseases are facilitated by immunophenotyping and by newer molecular and genetic approaches.
- Establishing a correct diagnosis at the time of initial presentation is critical to optimal management of NHL. Therefore, an adequately sized biopsy is mandatory to permit rigorous classification. A fine-needle aspirate is virtually never adequate for establishing the initial subtype of NHL.
- Marked advances have been made in the treatment of these diseases in the past decade, largely because of the availability of monoclonal antibodies used either alone or in conjunction with chemotherapy.

OVERVIEW OF INDOLENT NHL

Indolent lymphomas are characterized by slow growth, sometimes spanning decades and by a waxing and waning course and are incurable with standard approaches. The most common indolent lymphomas include follicular lymphoma (FL), marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LPL, includes Waldenström macroglobulinemia), and small lymphocytic lymphoma (SLL). The lifetime risk of transformation of an indolent NHL to an aggressive B-NHL is approximately 30%.

KEY POINT

- Indolent NHLs usually grow very slowly and are also known as low-grade lymphomas. FL, MZL, LPL, and SLL are all indolent lymphomas.

FOLLICULAR LYMPHOMA

FL is the second most common type of lymphoma and represents the paradigm for indolent NHL. This disease is characterized by a follicular growth pattern on lymph node biopsy, although diffuse areas also may be present and should be reported by the pathologist. The characteristic immunophenotype is CD20-positive, CD5-negative, CD23-negative, CD10-positive, and usually BCL6-positive. BCL2 is overexpressed in more than 85% of patients, generally as a result of a t(14;18)(q32;q21) chromosome translocation, which can be detected by fluorescence in situ hybridization or standard cytogenetics.

Most patients with FL have an indolent course. The median life expectancy has increased over the past four decades and is roughly 12 to 15 years based on Surveillance, Epidemiology, and End Results (SEER) data. Single-center studies suggest that it could be even longer; a Stanford analysis found survival after relapse of nearly 20 years.[15] However, not all patients will have a long survival, and identifying patients with more aggressive disease has proved to be challenging in the front-line setting.

At diagnosis, there are several features that could help identify high- versus low-risk patients. First is histologic grade. FL is graded based on the number of large cells (centroblasts) per high-powered field (hpf). Grade 1 has fewer than 5 centroblasts/hpf, grade 2 has 5 to 15, and grade 3 has more than 15. Given a high degree of interobserver variability, grades 1 and 2 were collapsed into one category, now labeled “FL1-2.” In addition, grade 3 FL is divided into FL3A, in which centrocytes are retained, and FL3B, in which centrocytes are no longer present. FL3B is an aggressive lymphoma, and is treated in the same way as for DLBCL. In general, FL1-3A behave similarly and should be approached in the same manner.

Another tool for risk stratification at diagnosis is the Follicular Lymphoma International Prognostic Index (FLIPI), which includes five risk factors (RFs): more than 4 nodal sites, elevated LDH, age > 60, stage 4 disease, and hemoglobin < 11g/dL (useful mnemonic is “NoLASH”) (Table 17-4).[16-23] The FLIPI stratifies patients into three groups with differing 5-year overall survival (OS): low risk (0–1 RFs, 91%), intermediate risk (2 RFs, 78%), and high risk (≥3 RFs, 53%).[22] Although initially developed in the pre–rituximab era, it has been validated in modern clinical trials that FLIPI provides important prognostic information.[24] More recently, there has been an effort to incorporate biologic features into these prognostic tools. The “M7-

FLIPI" is a newly proposed prognostic index that incorporates performance status, FLIPI score, and mutation status of seven key genes in FL pathogenesis.[25] The M7-FLIPI is in the process of being prospectively validated.

It is important to understand that although the FLIPI provides prognostic information and is helpful in defining the population in clinical trials, the FLIPI alone does not direct the timing of treatment initiation. Even patients with high-risk FLIPI scores may not need immediate treatment, and the decision to offer therapy is based on the GELF (Groupe d'Etude des Lymphomes Folliculaires) criteria: involvement of three nodal sites greater than 3 cm, systemic symptoms, splenomegaly, cytopenias, pleural effusions or malignant ascites, any nodal or extranodal tumor mass > 7 cm, or impending organ dysfunction.[26] The general treatment approach to FL is shown in Figure 17-3.

Approximately 10 to 15% of patients with FL have stage I or nonbulky stage II disease at the time of initial presentation. Involved-field or extended-field radiation therapy produces a 10-year failure-free survival (FFS) of 50 to 60% and a median OS of 60 to 80% and has traditionally been considered the standard of care. However, studies of observation alone in early-stage FL have shown similarly favorable outcomes.[27] Furthermore, one large observational study, the National LymphoCare Study,[28] showed that national guidelines endorsing radiotherapy alone for stage I FL were not followed by practicing clinicians in the majority of cases. Among 206 fully staged patients, all treatment approaches evaluated (observation alone, involved-field radiotherapy, rituximab, rituximab plus chemotherapy, and systemic therapy plus radiotherapy) resulted in excellent outcomes, though progression-free survival (PFS) was significantly better in patients treated with either rituximab plus chemotherapy or systemic therapy plus radiotherapy than with radiotherapy alone.

Table 17-4 Prognostic Indices for Non-Hodgkin Lymphomas

RISK FACTORS	RISK GROUP	NO. OF FACTORS	DISTRIBUTION OF PATIENTS	ENDPOINT
IPI (International Prognostic Index) for Aggressive Lymphoma[16]				
Age > 60				5-Year OS
PS > 1	Low	0–1	35%	73%
Serum LDH > ULN	Low intermediate	2	27%	51%
>1 EN site	High intermediate	3	22%	43%
Stage III–IV	High	4–5	16%	26%
Age-Adjusted IPI for Aggressive Lymphoma for Patients ≤ 60[16]				
Age ≤ 60				5-Year OS
PS > 1	Low	0	22%	83%
Serum LDH > ULN	Low intermediate	1	32%	69%
>1 EN site	High intermediate	2	32%	46%
Stage III–IV	High	3	14%	32%
IPI for Patients Treated with R-CHOP[17]				
Age > 60				3-Year OS
PS > 1	Low	0–1	52%	91%
Serum LDH > ULN	Low intermediate	2	21%	81%
>1 EN site	High intermediate	3	17%	65%
Stage III–IV	High	4–5	10%	59%
R-IPI (Revised IPI for Aggressive Lymphoma)[18]				
Age > 60				4-Year OS
PS > 1	Very good	0	10%	94%
Serum LDH > ULN	Good	1, 2	45%	79%
>1 EN site	Poor	3–5	45%	55%
Stage III–IV				
Stage-Modified IPI for Aggressive Lymphoma[19]				
Age > 60				5-year OS
PS > 1		0–1	71%	82%
Serum LDH > ULN		2	22%	71%
Stage II		3	14%	48%
FLIPI (Follicular Lymphoma International Prognostic Index)[20]				
>4 nodal sites				5-Year OS
Serum LDH > ULN	Low	0–1	36%	91%
Age > 60	Intermediate	2	37%	78%
Stage III–IV	High	3–5	27%	36%
Hemoglobin < 12 g/dL				
FLIPI-2[21]				
Age > 60				5-Year PFS
Serum β_2-microglobuline > ULN	Low	0	20%	80%
Hemoglobin < 12 g/dL	Intermediate	1, 2	53%	51%
Bone marrow involvement	High	3–5	27%	19%
Longest diameter of largest involved node > 6 cm				
MIPI (Mantle Cell Lymphoma IPI)[22]				
Age				5-Year OS
Performance status	Low	0–3	44%	60%
LDH: ULN	Intermediate	4, 5	35%	45%
White blood cell (WBC) count	High	6–11	21%	20%
PIT (Prognostic Index for T-Cell Lymphoma)[23]				
Age > 60				5-year OS
PS > 1	Group 1	0	20%	62%
Serum LDH > ULN	Group 2	1	33%	53%
Bone marrow involvement	Group 3	2	26%	33%
	Group 4	3-4	21%	18%

Abbreviations: EN, extranodal; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; PS, performance status; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; ULN, upper limit of normal.

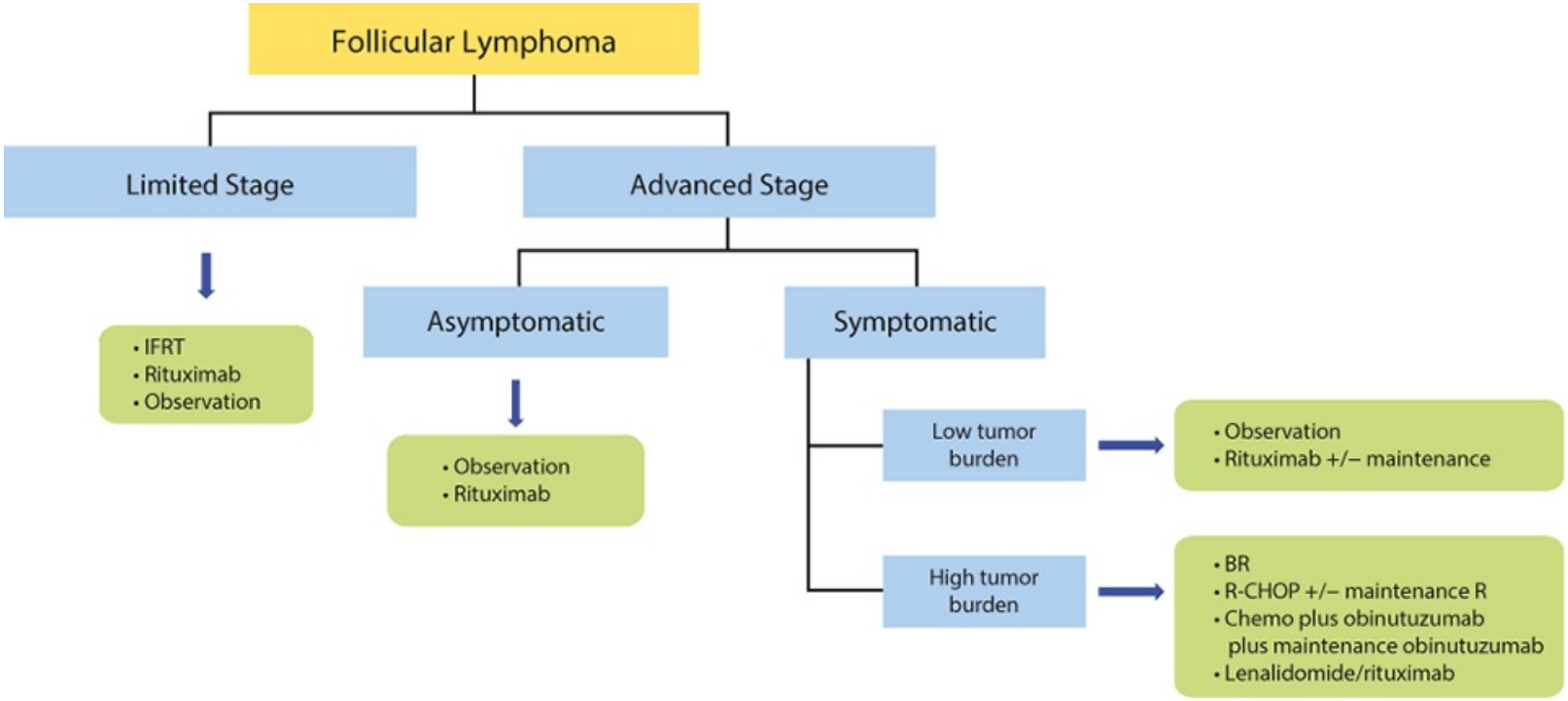

Fig. 17-3 Treatment algorithm for follicular non-Hodgkin lymphoma.

The remaining 85 to 90% of patients with follicular grade 1 or 2 NHL have advanced-stage disease (bulky stage II or stage III or IV) at the time of presentation. The OS reported for such patients was approximately 10 years from the time of diagnosis prior to the availability of antibody-containing regimens[29] and is now estimated by most investigators to be more than 15 years.[15] Despite this relatively long natural history, indolent lymphomas, including FL, are characterized by multiple recurrences. The initial treatment approach to advanced-stage FL depends on the patient's symptoms and assessment of tumor burden. Patients are categorized as "low tumor burden" or "high tumor burden" based on the presence or absence of the GELF criteria discussed earlier. There are several key clinical questions in the initial management of FL: (1) Does the patient need treatment? (2) Does the patient have low tumor burden or high tumor burden disease? (3) Is there a role for maintenance therapy?

MANAGEMENT OF ASYMPTOMATIC DISEASE

It is important to understand that early therapeutic interventions do not prolong survival for patients with asymptomatic FL. There are now several prospective, phase III, randomized trials comparing observation against treatment with alkylating agents, interferon-alpha, or rituximab, and none have found a survival advantage. A three-armed international trial randomly assigned asymptomatic, advanced-stage patients to either watchful waiting, rituximab 375 mg/m^2 weekly for 4 weeks (induction), or induction followed by 12 additional rituximab infusions every 8 weeks for 2 years (maintenance).[30] At 3 years, PFS in patients who did not need therapy was significantly higher in the maintenance group compared to the watchful waiting group (88% vs. 46%, $p < 0.0001$) (Fig. 17-4). However, despite improved time to next treatment and improved PFS, there was no difference in OS.

MANAGEMENT OF SYMPTOMATIC DISEASE

Patients with low tumor burden can be treated with single-agent anti-CD20 therapy. CD20 is a lineage-specific B-cell antigen that is first expressed during the pre-B-cell stage of development

and persists on B cells until terminal plasma cell differentiation. Targeting CD20 has been extremely fruitful, with initial depletion of all mature B cells but eventual reconstitution of normal cells because the pluripotent stem cell does not express CD20 and thus remains intact. Rituximab, approved in 1997, has been extensively studied in CD20-positive B-cell malignancies. When rituximab is used as monotherapy in the initial treatment of patients with FL and low-grade NHL, the response rate ranges from 50 to 70%, with a median duration of response of 1.0 to 2.5 years.[31,32] Other anti-CD20–directed agents include radioimmunotherapy or second-generation monoclonal antibodies (ofatumumab, obinutuzumab).

Patients with high tumor burden are treated with chemoimmunotherapy. The addition of rituximab to chemotherapy has clearly shown improved PFS, event-free survival (EFS), and even OS compared with chemotherapy induction alone.[33-36] The optimal chemotherapy regimen for the initial treatment of FL patients is controversial. Two large phase III clinical trials compared rituximab/cyclophosphamide/vincristine/prednisone (R-CVP), R-CHOP, and rituximab (R) plus fludarabine-containing regimens for treatment of grades 1 to 2 follicular lymphoma.[37,38] Both studies demonstrated superior PFS for patients treated with R-CHOP or R-fludarabine–based therapy compared with R-CVP, although OS did not differ among the three arms. Both studies also showed that regimens with fludarabine and rituximab had significantly more hematologic toxicity and a higher risk of secondary malignancies compared with R-CVP or R-CHOP, making fludarabine-based regimens less desirable than alkylator-based regimens. Some authorities believe these trials established R-CHOP as the preferred regimen for FL, but other lymphoma specialists are reluctant to use doxorubicin-containing regimens such as R-CHOP in patients with indolent lymphomas because of the 1 to 2% risk of cardiomyopathy. Two subsequent trials compared bendamustine, a unique alkylating agent possessing a purine-like moiety, and rituximab (BR) against investigator's choice of R-CVP or R-CHOP.[39,40] These trials were designed as noninferiority trials, and their outcomes seem similar overall. BR has become a preferred regimen because of the absence of treatment-induced alopecia, peripheral neuropathy, and steroid-associated toxicities observed with R-CVP and R-CHOP. There is no improvement in OS for any of these chemoimmunotherapy regimens, although R-CVP seems inferior in nearly all settings, and fludarabine-based treatments have increased toxicity.

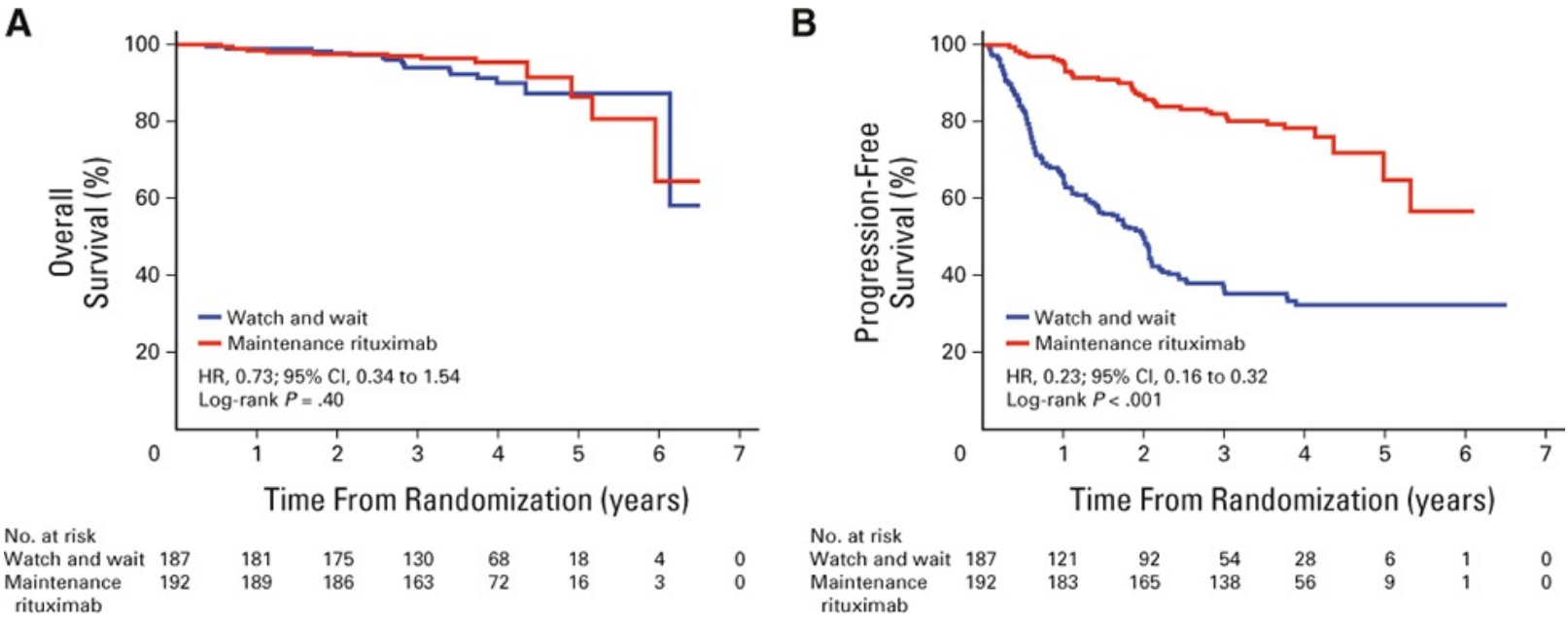

Fig. 17-4 Impact of rituximab treatment in asymptomatic patients with follicular lymphoma showing improved PFS but no impact on OS.

Reprinted from Ardeshna KM, Qian W, Smith P, et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. Lancet Oncol. *2014;15:424–435 with permission from Elsevier.*

Most recently, newer and second-generation anti-CD20 monoclonal antibodies have been tested. Obinutuzumab is a glycoengineered monoclonal antibody targeting CD20 with enhanced antibody-dependent cell-mediated cytotoxicity compared to rituximab. The GALLIUM trial compared obinutuzumab-chemotherapy versus rituximab-chemotherapy in treatment-naive FL and indolent lymphomas; preliminary results suggest a significant PFS advantage, albeit with slightly increased toxicity, and this may become a common option in the future.[41]

A number of trials are testing noncytotoxic agents, including biologic and/or targeted drugs, in an effort to replace chemotherapy. Lenalidomide is an oral immunomodulatory agent that appears clinically synergistic when added to rituximab. Phase II trials show high overall and complete response rates and impressive PFS results.[42,43] An international trial comparing lenalidomide plus rituximab against chemoimmunotherapy is ongoing. Unexpected and severe toxicities have been noted in some combinations of newer nonchemotherapy agents, and ad hoc combinations should not be given outside of a carefully monitored clinical trial.[44]

MAINTENANCE THERAPY

Maintenance strategies have been examined in FL as a way to delay or prevent disease relapse. To further understand the role of maintenance rituximab in patients with FL who have low tumor burdens, ECOG 4402 randomly assigned 289 patients responding to an induction course of 4 weekly doses to either maintenance rituximab (rituximab 375 mg/m^2 every 13 weeks until progression) or to retreatment with rituximab at the time of progression.[45] This study used a novel endpoint of a prespecified time to treatment failure, defined as no response to retreatment rituximab, time to progression < 26 weeks, initiation of alternative therapy, or inability to complete planned therapy. With almost 5 years of follow-up, there was no difference in the primary endpoint or in OS. There were significant cost savings to the retreatment approach compared to the maintenance approach, and there was no difference in health-related quality-of-life parameters. The PRIMA trial randomly assigned patients with FL who had high tumor burden receiving chemoimmunotherapy induction to either 2 years of maintenance rituximab (delivered every 2 months) or observation.[38] Maintenance rituximab improved PFS (75% vs. 58%, p = 0.0001) but did not impact OS, which was greater than 90% in both arms.

There is no consensus on the optimal duration of maintenance rituximab. The SAKK group tested a limited schedule of four additional doses every 2 months and found that 45% of treatment-naive patients still had no events at almost 10 years of follow-up.[46] A subsequent trial of 2 years versus 5 years of maintenance rituximab found improved EFS for longer therapy, but again, no difference in OS and a slight increase in adverse events.[47] Based on the improved disease control but lack of improvement in OS in all of these trials, the use of maintenance rituximab is often based on patient or physician preference.

An alternative to maintenance rituximab is radioimmunotherapy (RIT), which links yttrium-90 (^{90}Y) to an anti-CD20 monoclonal antibody (ibritumomab tiuxetan). With a median follow-up of 7.3 years, an update of the FIT (First-Line Indolent Trial) trial showed that RIT consolidation after chemotherapy has a median time to next treatment of 8.1 years and a 3-year benefit in median PFS as compared to observation.[48] However, only a minority of patients were treated with rituximab-containing induction.

RELAPSED AND REFRACTORY FOLLICULAR AND LOW-GRADE LYMPHOMA

Although FL and other low-grade lymphomas have an indolent natural history, they are incurable malignancies and essentially all patients will experience relapse despite prolonged remissions. At the time of relapse, a similar approach of considering tumor burden and symptoms is applied, since not all patients with progression need immediate therapy.

There are limited prognostic tools at the time of relapse, but a pivotal study has allowed identification of a high-risk subgroup of patients. Based on observations that approximately 15 to 20% of unselected patients with FL experience disease relapse within 2 to 3 years after the end of treatment, the National Lymphocare Study (NLCS) sought to determine whether early relapse was associated with survival.[49] Among 588 patients treated with R-CHOP, patients with progression of disease within 24 months (POD24) had a 5-year overall survival of only 50% (Fig. 17-5). This is in stark contrast to patients without POD24, for whom 5-year survival was 90%. Clinical features associated with overall survival include POD24, age, and poor performance status. The ability to identify a high-risk population in the setting of relapse has spawned a new generation of trials aiming to change these poor outcomes.

For symptomatic patients with progressive disease, there are a number of options. A variety of immunochemotherapy regimens have been used to treat relapsed or refractory disease (e.g., R-bendamustine, R-CVP, R-CHOP), but there is no evidence indicating a major advantage for any specific approach. The GADOLIN trial was a large phase III study comparing the second-generation anti-CD20 monoclonal antibody obinutuzumab plus bendamustine versus bendamustine alone in patients with relapsed indolent NHL[50]; although the combined chemoimmunotherapy trial was superior in terms of PFS and OS, many have argued that the chemotherapy arm of bendamustine alone used a higher than usual dose and had no maintenance component. Furthermore, most patients in North America receive bendamustine as part of initial therapy, and the role of a second exposure to this agent is unclear. Targeted and/or biologic agents with promising activity include lenalidomide, idelalisib, and venetoclax (ABT-199). Other approaches to relapsed or refractory disease include monoclonal antibodies, radioimmunotherapy, biologic therapies, and stem cell transplantation.

Monoclonal Antibodies

Rituximab, a chimeric monoclonal antibody targeting CD20, was initially approved by the U.S. Food and Drug Administration (FDA) for the treatment of relapsed and refractory FL and low-grade NHL based on the results of a pivotal trial that evaluated 166 patients for whom previous treatment had failed.[51] Four weekly infusions of rituximab were administered at a dose of 375 mg/m^2. The response rate was 46%, including a complete response (CR) of 8% and a median time to progression of approximately 1 year. The best responses to rituximab occurred in patients with FL. Only 12% of patients with small lymphocytic lymphoma had a response to a 4-week induction course in the initial pivotal trial. There is no clear advantage to eight weekly infusions compared with the standard four infusions. A second response to rituximab may be achieved in 40% of patients who have a relapse after an initial response to the antibody lasting at least 6 months.[52] Rituximab maintenance also prolongs remission durations in patients treated with a variety of chemotherapy regimens, and a meta-analysis suggested a survival advantage in the setting of relapse.[53]

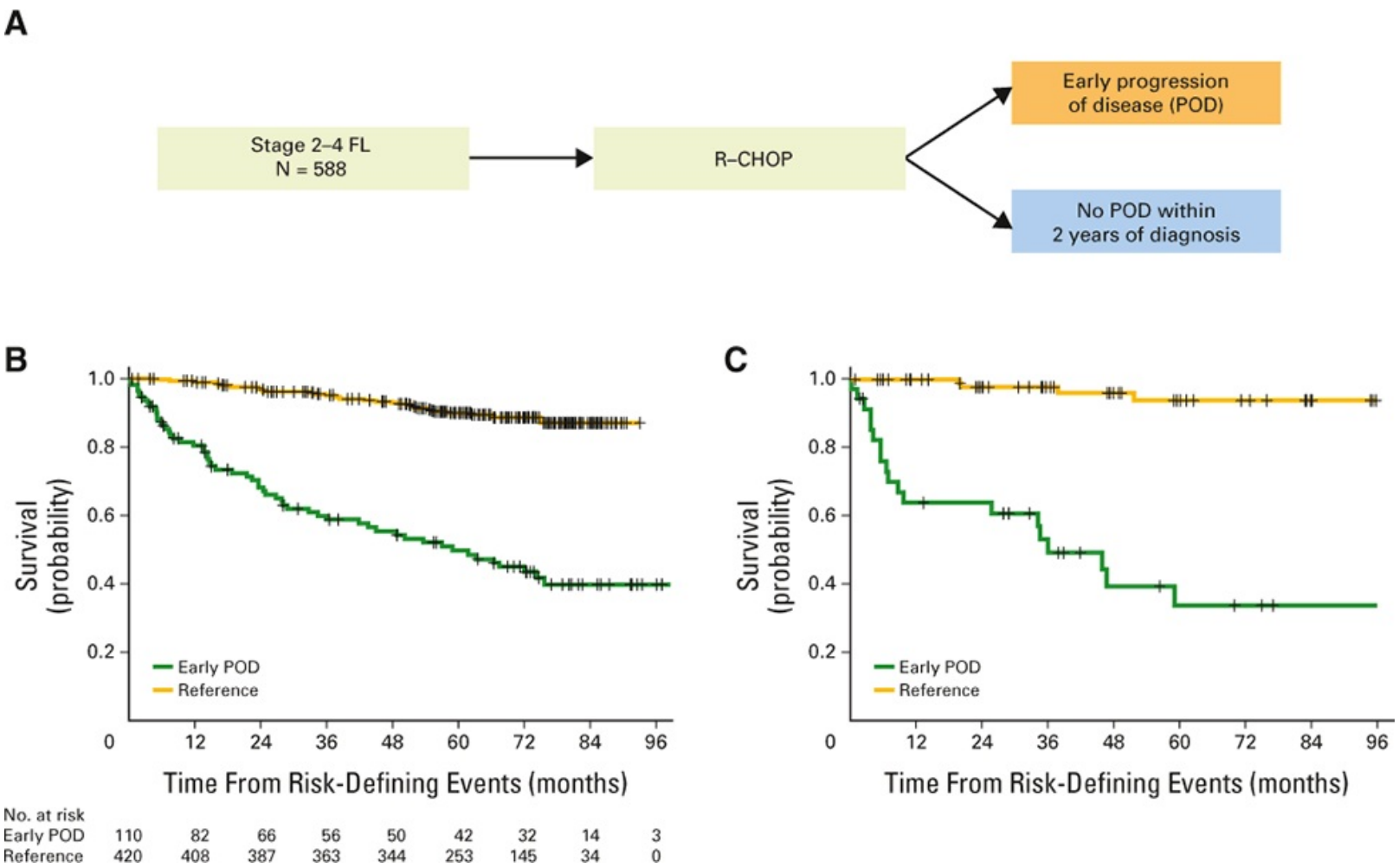

Fig. 17-5 Identification of a high-risk subgroup of follicular lymphoma based on early relapse following initial R-CHOP chemoimmunotherapy.

Abbreviations: FL, follicular lymphoma; POD, progression of disease.

Reproduced with permission from Casulo et al.[49]

Other anti-CD20 monoclonal antibodies, including ofatumumab and obinutuzumab, are being evaluated for relapsed and refractory indolent NHL.

Radioimmunotherapy

Treatment with monoclonal antibodies labeled with isotopes, such as iodine-131 (^{131}I) and yttrium-90 (^{90}Y), has provided promising results. The FDA has approved ^{90}Y-ibritumomab tiuxetan (anti-CD20) for the treatment of relapsed and refractory FL and low-grade NHL, transformed NHL, and disease that has not responded to rituximab and as consolidation therapy for patients following initial chemotherapy. Response rates of more than 80%, with a CR of 26%, were achieved for patients with relapsed and refractory indolent NHL; response rates were lower in rituximab-refractory populations.[54,55] In a randomized study, the rates of complete and overall response were higher with ^{90}Y-ibritumomab tiuxetan than with rituximab, but there was no difference in time to progression.[56]

Toxic effects associated with ^{90}Y-ibritumomab tiuxetan are primarily myelosuppression, with nadirs occurring 6 to 8 weeks after therapy. Patients with baseline thrombocytopenia or greater than 25% marrow involvement by B-NHL should not receive RIT. Secondary acute myeloid leukemia and myelodysplastic syndrome may occur.

^{131}I-tositumomab (anti-CD20) was also approved by the FDA, with response rates for

patients with relapsed or refractory FL or low-grade NHL of 50 to 80%, with a CR of approximately 30%, lasting a median of 9 months.[57] However, ^{131}I-tositumomab is no longer commercially available.

Other Biologic Therapies

Idelalisib is an oral phosphoinositide 3-kinase delta (PI3Kδ) inhibitor approved in 2014 based on a 57% overall response rate (ORR) with a median duration of response of 12.5 months in heavily pretreated indolent lymphomas. Seventy-nine percent of patients had disease that was refractory to at least two prior regimens, and 90% had disease refractory to the most recent regimen.[51] The most common serious adverse side effects of idelalisib were neutropenia, transaminitis, diarrhea, and pneumonitis.[58,59] While most of these toxic effects are early and reversible, some patients have a severe colitis that occurs after several months of therapy and requires treatment cessation. Combination studies of idelalisib are underway, but unexpected and severe toxic effects have occurred.[44] There are a number of second-generation PI3Kδ inhibitors in development, which may be less toxic, and studies are ongoing.

Lenalidomide, an oral immunomodulatory agent, is active in relapsed FL with approximately one-third of patients responding[60]; among responders, durability is long-lasting and over 16 months. When combined with rituximab, there appears to be clinical synergy, with response rates of 76% and CRs of 39%.[42] A number of other agents are in development, including inhibitors of B-cell receptor signaling (Bruton tyrosine kinase [BTK], spleen tyrosine kinase [SYK]) and inhibitors of BCL2.

Stem Cell Transplantation

The use of autologous hematopoietic cell transplantation (ASCT) for treatment of relapsed or refractory indolent NHL is supported primarily by nonrandomized or registry studies with long-term follow-up. In the pre–rituximab era, a collaborative study of 126 adult patients conducted by St. Bartholomew's Hospital and the Dana-Farber Cancer Institute showed an apparent plateau in the remission duration curve of 48% at a median follow-up of 13.5 years.[61] Survival was longer among patients receiving the transplant during second remission compared with that for patients undergoing transplantation later in their disease course. Another retrospective analysis of 100 patients showed no relapses beyond 6 years.[62] A small randomized trial, again prior to rituximab use, showed a marked advantage in PFS and a marginal one for OS for ASCT compared with conventional salvage chemotherapy.[63] More recent trials, which included patients receiving rituximab pre- or posttransplantation, show that approximately 50% of patients achieve long-term PFS even up to 10 years posttransplant.[64-66] Overall, the greatest impact of ASCT appears to be for high-risk patients in first or second relapse.[67]

Short- and long-term complications of ASCT include treatment-related mortality (3 to 5%), prolonged anemia or thrombocytopenia, and a substantial increase in the incidence of secondary myelodysplasia and AML, which ranges from 7 to 19%. The risk of secondary hematopoietic malignancies is increased by the use of total-body irradiation.[68]

Reduced-intensity allogeneic hematopoietic stem cell transplantation (RIC) has also been evaluated in relapsed and refractory FL. A prospective trial of 82 patients who were very heavily pretreated for FL (median, 4 prior regimens, 30% with prior ASCT) showed a 4-year PFS of 76%.[69] A National Clinical Trials Network (NCTN) prospective trial similarly found 3-year PFS of 71% and OS of 82% with a nonrelapse mortality of 16%.[70] There is a consistent increased risk of morbidity and mortality associated with RIC allogeneic transplantation as

compared with ASCT; however, several groups have shown that RIC has improved survival compared to ASCT in patients surviving 24 months posttransplantation.[64,66,71] Overall, the role of transplantation in FL has been controversial in the rituximab era, particularly because targeted agents and less toxic therapies are in active development.

HISTOLOGIC TRANSFORMATION OF FL TO AGGRESSIVE LYMPHOMA

Approximately one-third of patients with FL undergo documented transformation to a more aggressive histology in their lifetime, typically DLBCL. The annual rate of transformation is 2 to 3%, without a clear plateau in the rituximab era.[72] The pathogenesis and drivers of histologic transformation are complex and not clearly defined, but likely include cell cycle aberrations, increased genomic complexity, aberrant somatic hypermutation, and changes in the nodal microenvironment.[73] Although all low-grade lymphomas can transform, most literature focuses on FL.

Confirming a diagnosis of transformed FL can be difficult. The gold standard is a biopsy of a lymph node showing an aggressive B-cell lymphoma that is clonally related to the FL. However, there is a high degree of sampling error because not all biopsy sites will show the histologic transformation. A PET scan is highly useful in this situation. Several studies have shown that higher standardized uptake values (SUV) (above 13 to 17) have high positive predictive value and can be used to determine the biopsy site.[74,75] Clinical features associated with histologic transformation include rapid progression of nodal disease, increased LDH, declining performance status, hypercalcemia, new involvement in extranodal sites, and new-onset B symptoms.[72,76,77] If a biopsy is not safe or not feasible, clinical symptoms and supportive laboratory abnormalities can justify treatment for transformed disease.

Historical data show very poor outcomes for transformed FL. However, this seems to be changing in the rituximab era,[78] although there is a paucity of clinical trials that focus specifically on transformed FL. If patients have not been treated with prior anthracyclines, R-CHOP or a similar regimen is appropriate. In the pre–rituximab era, this would often be consolidated with autologous stem cell transplantation, but this course is more controversial in modern times. If patients have already received anthracycline-based treatment, then they should receive salvage chemotherapy followed by autologous stem cell transplantation. Of note, in some patients, FL can transform in association with a new rearrangement of the *MYC* oncogene, usually with a t(8;14) acquisition. Since the vast majority of FL already has the t(14;18) rearrangement with BCL2 overexpression, this leads to a high-grade double-hit phenotype (see discussion in section on Treatment of Newly Diagnosed Aggressive Lymphomas), and R-CHOP may be insufficient for disease control.

Unfortunately, many patients are elderly or frail at the time of transformation, and there are limited data to support a specific therapy. Radioimmunotherapy, which delivers targeted radioisotopes to CD20 positive disease, is one FDA-approved option. ^{131}I tositumomab is no longer available, but ^{90}Y-ibritumomab tiuxetan offers a 1-week treatment with promising efficacy.[73]

KEY POINTS

- Asymptomatic patients with indolent NHL need not be treated at the time of diagnosis if they have low tumor burden. This is particularly true for elderly patients.

- Indications for initiation of therapy include the development of fever, drenching sweats, weight loss, pain, early satiety, cytopenias as a result of marrow infiltration, malignant pleural effusions or ascites, massive splenomegaly, or large lymph nodes compromising normal organ function (e.g., biliary or ureteral obstruction).
- There is little consensus on the best treatment for indolent lymphomas; options include observation alone, single-agent anti-CD20 monoclonal antibody, and chemoimmunotherapy
- Indolent lymphomas are typically associated with prolonged survival, though multiple relapses are common.
- Approximately 15 to 20% of patients with FL will experience disease progression or relapse within 24 months after undergoing chemoimmunotherapy. These patients have a significantly worse 5-year survival.[79]

MARGINAL ZONE LYMPHOMA

MZLs comprise 10% of B-NHLs and have an indolent course. SEER data show 5-year survival rates of 88.7%, with a median overall survival of 12.6 years.[80] There are three types of MZL, with varying incidences: extranodal marginal zone lymphoma (ENMZL, 70%), splenic marginal zone lymphoma (SMZL, 20%), and primary nodal MZL (NMZL, 10%). ENMZL is further divided into gastric and nongastric types. The clinical presentation depends on the site of involvement, but the most common site of disease is the gastrointestinal tract, which accounts for almost two-thirds of all ENMZLs, and the stomach accounts for 30 to 50% of cases. Ocular adnexa, lung, thyroid gland, and skin are common nongastric sites.[81] Multifocal involvement of a single organ can be seen, and nodal and bone marrow involvement confer a worse prognosis.[82] The median age at presentation is 68 years, and there is a slight female preponderance. Most patients have limited stage disease (stages IE–IIE); however, on complete staging, up to 25% of patients with gastric and 50% with nongastric ENMZL have disseminated disease.[83]

PATHOLOGY AND BIOLOGY

Histopathologically, there is clonal expansion of centrocyte-like and monocytoid-like B cells from the marginal zone with interfollicular expansion, occasional follicular colonization, and increased immunoblasts. These immunoblasts, which are larger than the other B cells, should not be confused with transformation to DLBCL unless they are forming sheets or large clusters. Secondary pathology review can be helpful to aid in treatment decisions. The immunophenotype is that of a mature B cell (CD20-positive, CD79a-positive, CD19-positive, immunoglobulin M [IgM]–positive, IgD-negative) but lacking CD5, CD10, CD23, BCL6, and cyclin D1.[4] Occasionally, CD5 can be positive and distinction from chronic lymphocytic leukemia (CLL) or mantle cell lymphoma (MCL) must be done via other molecular or genetic testing. In addition, it can be difficult to distinguish MZL morphologically from LPL, which is also CD5-negative and CD10-negative; in these cases, molecular testing for *MYD88* supports a diagnosis of LPL and is negative in MZL.[84] Given their extranodal homing, MZL cells can infiltrate epithelial structures, especially in the gastrointestinal tract. This leads to the classic “lymphoepithelial lesion.”

A unique feature of MZL is the association with infectious agents and chronic antigenic stimulation. The concept of lymphoma as an “antigen-driven disease” is best described for gastric ENMZL, formerly called gastric MALT (mucosa-associated lymphoid tissue), in which

Helicobacter pylori (HP) consistently irritates the mucosal T and B cells that line the stomach, causing them to proliferate.[85] At some point, the B cells become autoreactive and develop into an HP-dependent lymphoma. Gastric ENMZL can also be HP-independent, often as a result of the t(11;18) rearrangement, which confers resistance to HP eradication. Other examples of chronic antigenic stimuli leading to MZL include *Chlamydia psittaci* leading to ocular adnexal MZL, hepatitis C to SMZL, and *Borrelia burgdorferi* to cutaneous MZL. Autoimmune conditions associated with MZL include Hashimoto thyroiditis leading to thyroid MZL and Sjögren disease leading to salivary gland MZL.

GASTRIC AND NONGASTRIC EXTRANODAL MARGINAL ZONE LYMPHOMA

The most common MZL is gastric ENMZL in association with HP. Patients typically present with nausea, abdominal discomfort, or gastrointestinal bleeding. Treatment is HP eradication with either triple therapy (proton-pump inhibitor plus two antimicrobials) or quadruple therapy (proton-pump inhibitor, bismuth, tetracycline, metronidazole) for 14 days. A meta-analysis of 32 studies with over 1400 patients showed that this approach leads to nearly 80% HP eradication, although responses are lower for disease greater than stage IE. The t(11;18)(q21;q21) occurs at a high frequency in HP-negative gastric ENMZL, and this rearrangement is associated with resistance to HP eradication and a more aggressive course.[86] Response assessment following HP eradication requires a repeat endoscopy, but this should not be done sooner than 3 months after therapy because responses are often delayed. If a repeat endoscopy is normal but biopsies show lymphoid aggregates, asymptomatic patients may be kept under observation. Surveillance can stop after two sequential negative endoscopies. Patients with HP-negative gastric ENMZL or with resistance to HP eradication should receive second-line options. Several retrospective series done primarily in the pre–rituximab era show that radiotherapy (26 to 40 Gy) to the stomach offers excellent local control and long-term survival of 10 to 15 years; most relapses occur outside the initial treatment field.[87-89] Rituximab monotherapy has an ORR of 77% and CR of 46% in patients with resistant disease; with a median follow-up of 28 months, all 27 patients are alive, 54% of them are disease-free, and there is no difference in response based on t(11;18) status.[90] The decision to pursue radiation versus rituximab is based on patient and physician preference.

Systemic therapy for ENMZL is reserved for patients with symptomatic disease, with rituximab monotherapy being most commonly used. In patients with gastric and nongastric ENMZL the response rate is over 70%, but it is higher in treatment-naive patients (ORR, 87% vs. 45%; $p = 0.03$).[91] While maintenance rituximab improves time to treatment failure (4.8 years versus 1.4 years; $p = 0.012$) and time to first cytotoxic therapy, there is no improvement in OS.[38] One phase III trial compared chlorambucil monotherapy with rituximab monotherapy and with the combination; it is the largest prospective trial in ENMZL.[92] At a median follow-up of 7.4 years, combination chlorambucil and rituximab showed a significant 5-year EFS (68% vs. 50%; $p = 0.0009$) and PFS (72% vs. 57%) benefit compared to rituximab alone. Patients in all arms did well, with approximately 90% 5-year survival. In 2017, ibrutinib monotherapy was approved for relapsed MZL based on an ORR of 46% and good tolerability.[93] Other agents are also being tested, particularly since many underlying pathogenetic lesions in MZL are associated with constitutive activation of nuclear factor kappa B (NF-κB) and aberrant B-cell receptor signaling.

SPLENIC MARGINAL ZONE LYMPHOMA AND NODAL MARGINAL ZONE LYMPHOMA

SMZL presents with symptomatic splenomegaly, lymphocytosis, and marrow infiltration. The clinical presentation is very similar to CLL or hairy cell leukemia, which are the main differential diagnostic considerations. Flow cytometry of peripheral blood with the immunophenotype described above is helpful. In addition, circulating villous lymphocytes with blunt projections at polar ends of the cell can be seen, and they have a different appearance than circulating hairy cells, which have more fine projections in a radial distribution. SMZL is sometimes associated with hepatitis C, and there are reports of lymphoma regression with hepatitis C eradication.[94] However, most symptomatic patients will require lymphoma-specific treatment. Historically, splenectomy has provided good palliation of symptoms. More recently, rituximab monotherapy is also effective and spares the patient a surgical procedure.

Nodal MZL is an uncommon disease and may have a worse prognosis compared to other forms of MZL. This may be because it is at a more advanced stage at diagnosis. The treatment of NMZL follows the paradigm of follicular lymphoma, and there are few studies dedicated to this specific subtype.

KEY POINTS

- There are three types of MZL: EMZL, SMZL, and NMZL.
- MZLs are frequently antigen-driven diseases.
- Initial treatment of *Helicobacter pylori*–associated gastric MZL consists of antimicrobial eradication.

LYMPHOPLASMACYTIC LYMPHOMA/WALDENSTRÖM MACROGLOBULINEMIA

LPL is an uncommon and incurable indolent B-cell lymphoma. The vast majority of LPLs produce an IgM paraprotein, designated Waldenström macroglobulinemia (WM). Since less than 5% of cases produce IgG, IgA, or are nonsecretory, most studies pertain to WM.

LPL/WM is typically diagnosed because of the presence of cytopenias, as the bone marrow is the major site of disease. Less commonly, patients may have adenopathy or organomegaly at the time of diagnosis. Slightly more men than women are afflicted, and the median age is in the 60s.[95] The diagnosis requires a bone marrow biopsy that shows infiltration by small lymphocytes that are CD19-positive, CD20-positive, CD22-positive, CD25-positive, and FMC7-positive and negative for CD10, CD23, and CD103.[4] Approximately 15 to 20% of patients have CD5 positivity, requiring further evaluation to distinguish LPL/WM from other lymphomas, such as mantle cell lymphoma. It has been found that over 90% of WM harbor a point mutation in the *MYD88* gene (*MYD88 L265P*),[84] aiding in diagnosis and the differentiation from other lymphomas.

As with other indolent lymphomas, treatment for LPL/WM is indicated only if there are disease-related symptoms, cytopenias related to marrow infiltration, bulky disease, or IgM-related complications.[96] A number of other symptoms related to the paraprotein may prompt more urgent treatment, including hyperviscosity, cryoglobulinemia, and sensorimotor peripheral neuropathy.

First-line treatment options from the International Workshop on Waldenström macroglobulinemia (IWWM) include rituximab monotherapy, chemoimmunotherapy, ibrutinib, or

bortezomib-based treatment.[96] Several management aspects must be considered. First, an elevated paraprotein level alone is not an indication for therapy in asymptomatic patients. Second, rituximab monotherapy has been associated with a sudden increase in IgM levels, leading to symptomatic hyperviscosity.[97] Third, patients with symptomatic hyperviscosity and very high IgM levels should be considered for plasmapheresis as a bridge to more definitive treatment. Bortezomib is also an excellent option for rapid treatment of symptomatic hyperviscosity.

A number of new agents are in development for LPL/WM. Ibrutinib, an oral and irreversible BTK inhibitor, was approved in 2015 for both treatment-naive and relapsed disease. The pivotal study was a phase II trial of 63 patients with relapsed WM in which an ORR of 90% was observed[98]; of note, this response rate includes both "partial" and "very good partial" responses, and there were no CRs. A *MYD88* mutation predicts for response to ibrutinib; conversely, *CXCR4* mutations are associated with lower response rates. A second trial studying ibrutinib in patients with heavily pretreated, rituximab-refractory disease showed preserved high response rates of 90% and PFS rates of 86% at 18 months.[99]

Although many patients with LPL/WM have initially responsive disease, relapse is inevitable, and most patients die from the disease. In selected patients, allogeneic nonmyeloablative stem cell transplantation offers the chance for cure.

KEY POINTS

- LPL/WM are uncommon indolent lymphomas that usually produce a paraprotein.
- Over 90% of LPL/WM have point mutations in *MYD88*, which can help distinguish this disease from other indolent lymphomas in histologically challenging cases.
- Rituximab monotherapy can lead to transient symptomatic hyperviscosity in patients with high IgM levels.
- Indications for treatment include hyperviscosity, cryoglobulinemia, peripheral neuropathy, cytopenias, or other symptoms.

SMALL LYMPHOCYTIC LYMPHOMA

SLL, the tissue counterpart of CLL, is characterized by an accumulation of small, mature-appearing lymphocytes in the blood, bone marrow, and lymph nodes. The classic immunophenotypic profile of CLL/SLL is expression of CD5, CD19, and CD23, with low-level expression of surface immunoglobulin and CD20. CLL and SLL are usually distinguished arbitrarily by a number of circulating clonal B cells greater than 5000/mm^3 (CLL) or less (SLL). Thus, the diagnosis of SLL can be made in the absence of blood or bone marrow involvement. Although SLL often is included in clinical trials of FL and other low-grade NHLs, its biology and response to various therapies differ enough from those of the other indolent NHLs that it is better treated as CLL (see Chapter 16: Leukemias).

AGGRESSIVE B-CELL LYMPHOMAS

Aggressive lymphomas are characterized by a rapid and usually symptomatic growth phase leading to clinical presentation. DLBCL is the prototype of aggressive B-NHL and comprises

30% of all NHLs. Up to 40% of disease initially presents in extranodal locations, most commonly in the gastrointestinal tract, but also with involvement of the CNS, genitourinary or reproductive tracts, lung, or other sites. Optimal diagnosis requires a tissue specimen sufficiently large to confirm histology and perform important prognostic and predictive tests; fine-needle aspiration is never appropriate as the sole means of diagnosis. The classic morphology is diffuse effacement of the normal lymph node architecture by intermediate- to large-sized cells expressing CD19, CD20, CD79a, and CD45. However, DLBCL is increasingly understood to be a heterogeneous disease with genetic, biologic, and clinical variants that have an important impact on clinical outcomes.

The early observation of heterogeneous outcomes prompted an evaluation for clinical features predictive of outcome. The IPI was a large analysis with multivariate testing of prognostic factors. Five features were most prognostic (Table 17-4) and stratify patients into four risk categories: age > 60, performance status > 1, increased LDH, more than one extranodal site, and stage III–IV disease. Efforts to improve on the original IPI include the R-IPI (revised IPI in the era of rituximab) and the National Comprehensive Cancer Network (NCCN) IPI[100]; however, the original IPI continues to be the most widely used in clinical trials.

The genetic heterogeneity of DLBCL was first described over 15 years ago when gene expression profiling of 20,000 lymphoma-specific genes in frozen tumor specimens identified three unique patterns in otherwise clinically similar patients.[101] The patterns were named after normal B cells at similar stages of development and are referred to as the “cell-of-origin” (COO) model. DLBCL specimens genetically resembling normal germinal center B cells were called germinal center-DLBCL (GCB-DLBCL), whereas those resembling activated B cells were called activated B-cell-DLBCL (ABC-DLBCL). Despite similar clinical risk features, patients with ABC-DLBCL have an inferior survival compared to those with GCB-DLBCL on both CHOP and R-CHOP treatment (Fig. 17-6).[102] GCB- and ABC-DLBCL have different spectrums of gene abnormalities, which may lead to specifically targeted therapies. Testing for COO is difficult in routine clinical practice, since gene expression profiling requires frozen material and is not widely available. A number of immunohistochemical algorithms are used as a surrogate for COO, but there is an approximate 20% error rate. One of the more common algorithms is the Hans method, which stains for CD10, MUM1, and BCL6 to determine COO.[103] NanoString technology is promising, and is being incorporated into prospective trials.

MYC, a proto-oncogene and transcription factor classically rearranged in Burkitt lymphoma (BL), is rearranged in up to 12 to 15% of cases of DLBCL. Because DLBCL is substantially more common than BL, there are many more patients with DLBCL who have *MYC* rearrangements than there are in all BL cases in the United States. Of note, *MYC* rearrangement is *diagnostic* in BL but adversely *prognostic* in DLBCL, likely because of an entirely distinct set of target genes.[104] *MYC* activation delivers a potent proliferative signal. Although *MYC* rearrangement alone was initially thought to be a key adverse prognostic feature, it is more likely that the dual rearrangement of *MYC* with *BCL2* (or less commonly, *BCL6),* occurring in 5 to 7% of cases of DLBCL, is more clinically relevant. The combination of a strong growth signal (*MYC*) and a potent antiapoptotic factor (*BCL2*) leads to an entity dubbed double-hit lymphoma (DHL), a clinically aggressive phenotype with very poor long-term survival following standard chemoimmunotherapy.

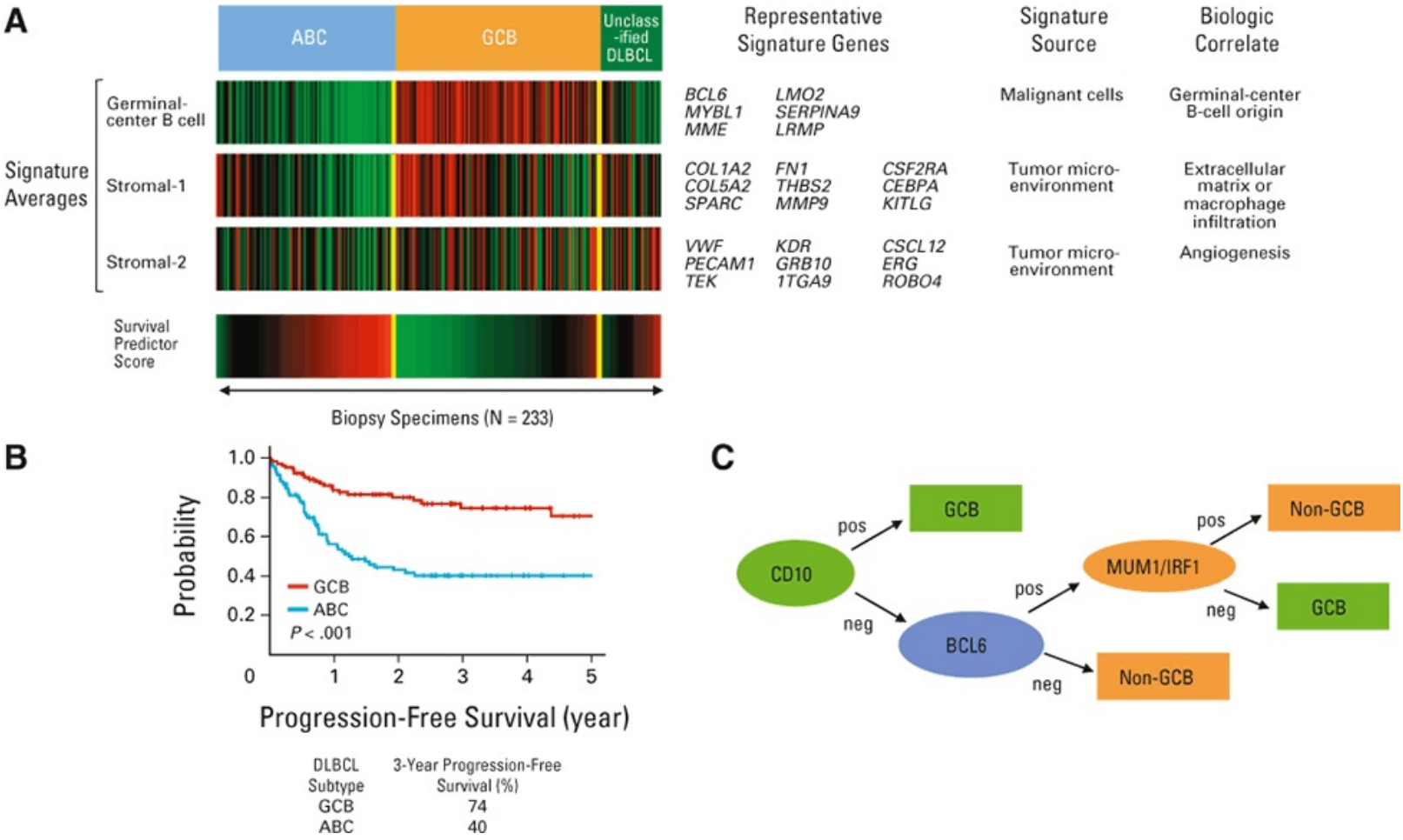

Fig. 17-6 Cell-of-origin (COO) model for DLBCL.

A. Gene expression profiling heat map. B. Survival outcomes by COO in patients treated with R-CHOP. C. Hans algorithm for immunohistochemical determination of COO. See text for details.

Complicating the picture further, both MYC and BCL2 proteins can be overexpressed either with or without the underlying respective rearrangements in up to 30% of patients with DLBCL.[105,106] The double expression of MYC and BCL2 proteins has been acknowledged in the WHO 2016 Update in Classification of Lymphoid Malignancies as an adverse prognostic feature and is termed double expressor lymphoma (DEL). When DEL occurs without underlying DHL, outcomes are still poor but not quite as dismal. As discussed later, it is unknown precisely how these patients should be treated.

It is difficult to know which prognostic feature is most important, but there is clearly overlap between COO, DHL, DEL, and IPI. For example, patients with DHL almost always have a GCB-DLBCL phenotype, whereas most patients with DEL are older and have an ABC-DLBCL phenotype.[105,106]

TREATMENT OF NEWLY DIAGNOSED AGGRESSIVE LYMPHOMAS

Limited-Stage Disease

Approximately 20% of patients with DLBCL have limited disease (stage I or nonbulky stage II) at the time of presentation and have a superior prognosis compared to advanced-stage disease. A stage-modified IPI was developed for risk stratification; it includes age > 60, stage II disease, increased LDH and performance status > 1.[19]

Radiation alone has been supplanted by combined-modality therapy or chemotherapy alone. The Southwest Oncology Group (SWOG) performed a pivotal trial in the pre–rituximab era

comparing CHOP for three cycles plus involved-field radiation therapy (IFRT) with CHOP for eight cycles[19]; at 5 years, the combined-modality arm had improved survival, and this study thus impacted practice patterns. However, the advantage to combined-modality treatment disappears at 7 years, and very-long-term follow-up of almost 20 years shows a pattern of continuous relapse in both arms, suggestive of a unique biology for limited-stage DLBCL.[107]

In the rituximab era, the MINT (MabThera International Trial) trial supports R-CHOP for six cycles without radiation as an excellent option, with 6-year EFS and OS of 84% and 95%, respectively.[108] Preliminary results of a randomized trial show no advantage to radiation after four or six cycles of R-CHOP for patients in metabolic complete remission,[109] and a large Canadian database analysis similarly found that radiation could be safely omitted for patients with a negative PET scan after three cycles.[110] PET-negative patients after three cycles of R-CHOP had a 3-year time to progression (TTP) of 92%, compared to PET-positive patients, who had a 3-year TTP of 60% despite having undergone radiation therapy. Thus, the routine use of radiation is not required in limited-stage DLBCL. An important caveat to the discussion regarding limited-stage DLBCL is that none of these trials fully evaluated the impact of biology (i.e., DHL, DEL, high-grade morphology) or specific extranodal sites (i.e., primary breast). An extension to this latter point is that primary testicular lymphoma, which is often stage I–II, constitutes a distinct clinicopathologic subset of DLBCL and has its own treatment approach.

Advanced-Stage Disease

In the early 2000s, several pivotal studies showed an advantage for not only PFS but also for OS of approximately 15% in both younger and older patients with the addition of rituximab to CHOP chemotherapy.[18,79,108,111] Importantly, most studies show a plateau after 5 years, supporting the curative potential of treatment for DLBCL. However, not all patients are cured, and the preceding discussion highlights the clinical and biologic factors impacting curability. Attempts to improve on R-CHOP have taken several approaches, including dose-dense delivery, addition of etoposide or novel agents to an R-CHOP backbone, the use of consolidative stem cell transplantation, maintenance therapy, or infusional delivery of treatment. (see detailed review in Nowakowski et al.[112])

Although shortening the treatment cycle is feasible, R-CHOP delivered every 14 days (R-CHOP14) is not superior to R-CHOP every 21 days (R-CHOP21).[113,114] The addition of etoposide to either R-CHOP14 or R-CHOP21 increases toxicity without substantial benefit.[115,116] An alternative to R-CHOP is dose-adjusted EPOCH-R (DA-EPOCH-R), which delivers etoposide, vincristine, and doxorubicin by continuous infusion for 96 hours with bolus doses of cyclophosphamide and oral prednisone. The doses of etoposide, doxorubicin, and cyclophosphamide are adjusted by 20% each cycle to achieve a nadir absolute neutrophil count below 0.5×10^9/L. Phase II trials of dose-adjusted EPOCH with rituximab (DA-EPOCH-R) have achieved impressive results both in single-institution and cooperative-group settings.[117,118] However, a recently presented US Intergroup study comparing R-CHOP versus DA-EPOCH-R failed to show an advantage to the more intensive regimen.[119] There are a number of potential explanations, including the lack of details presented regarding biologic subsets. However, even trials that specifically target high-risk populations have not shown an advantage to new regimens, and there is ongoing debate regarding the timing of enrollment, the ability to define high-risk biologic populations in real time, and other factors affecting selection bias.

Postremission strategies have included maintenance rituximab, consolidative oral agents, or consolidative high-dose chemotherapy with autologous stem cell rescue (ASCT). Maintenance

rituximab does not improve PFS or OS following R-CHOP and is not recommended.[120] The role of ASCT in first-line therapy of DLBCL remains controversial, though a recent SWOG trial suggests that patients with high-risk DLBCL (IPI of 4 to 5) have improved survival if consolidated with ASCT in first complete remission.[121] Thus, for now, R-CHOP every 21 days for six cycles remains the standard of care for advanced-stage DLBCL-not otherwise specified (NOS).

Patients with dual rearrangements of *MYC* and *BCL2* and/or *BCL6* (DHL), however, probably need augmented approaches. Large retrospective series have consistently shown less than 20% long-term survival for DHL treated with R-CHOP.[106,122] Several retrospective reviews show that more intensive regimens have better outcomes, and the largest multicenter analysis showed R-CHOP to be inferior to almost any other regimen, with a hazard ratio (HR) of 0.5.[123,124] Prospective data supporting the use of one regimen over another are limited, but a phase II trial spearheaded by the National Cancer Institute shows promising activity of DA-EPOCH-R, although not all patients in this trial have true DHL.[125] Autologous stem cell transplantation as consolidation therapy is controversial, with no clear benefit to date, particularly if patients are in a complete remission after initial chemoimmunotherapy.[126]

Primary Mediastinal B-Cell Lymphoma

Primary mediastinal B-cell lymphoma (PBML) is a distinct aggressive B-cell lymphoma derived from medullary thymic B cells and presents as a large and symptomatic mediastinal mass, often with superior vena cava syndrome and a predilection for extranodal organ involvement. The median age at onset is 30, and there is a slight female predominance. Histopathology shows a diffuse infiltrate of large cells with CD20, CD79a, and PAX5 and usually positive for CD10, BCL6, and CD23.[4] CD30 can be expressed as well and is often weaker in intensity compared to HL. Of interest, there are significant similarities in gene expression between PMBL and classical HL, with deregulation of NFκB, JAK2, and PDL1/PDL2.[127] Cases with intermediate histopathologic features between PMBL and HL are termed “gray zone lymphomas” (GZLs), and these have a worse prognosis.[4,128]

The treatment of PMBL is controversial, and prospective data are limited. Prior to rituximab, several studies suggested improved outcomes with intensified treatments (MACOP-B [methotrexate with leucovorin rescue/doxorubicin/cyclophosphamide/vincristine/prednisone/bleomycin], VACOP-B [etoposide with leucovorin rescue/doxorubicin/cyclophosphamide/vincristine/prednisone/bleomycin], ProMACE-CytaBOM [prednisone/doxorubicin/cyclophosphamide/etoposide/cytarabine/bleomycin/vincristine/methotrex compared to CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone); many of these studies also included consolidative radiation. In the era of chemoimmunotherapy and functional imaging via PET, intensification still seems to have a role, although there is controversy over the ability to omit radiation. A series of 58 patients showed that 21% of PMBL patients have primary induction failure to R-CHOP,[129] and long-term disease control with R-CHOP–like regimens is approximately 60 to 70%.[130] A prospective international trial of rituximab plus various chemotherapy backbones followed by radiation in the majority of patients showed 5-year PFS and OS greater than 90%, with the end-of-treatment PET being the most important discriminant of outcome.[131] Investigators at the National Cancer Institute tested DA-EPOCH-R as a means to obviate the need for radiation and reported 5-year EFS of 93% with no relapses beyond 1 year.[132] An alternative radiation-sparing approach is to deliver intensified R-CHOP

with ICE (ifosfamide/carboplatin/etoposide) chemotherapy.[133] Given the mediastinal location, avoiding radiation is an appealing option.

Primary Testicular Lymphoma

Primary testicular lymphoma is usually an aggressive B-cell lymphoma limited to the testes. It is relatively rare, and occurs in men in the sixth decade of life. Despite being localized (stage I–IIE) in most cases, outcomes are poor as compared with other early-stage DLBCLs. In particular, there is a high risk of CNS recurrence (up to 25%) and a continuous risk of relapse persisting even 10 years after diagnosis.[134] Treatment should include R-CHOP for six cycles, CNS prophylaxis, and radiation to the contralateral testis at the end of systemic therapy.[135]

CNS Prophylaxis

Aggressive B-cell lymphomas can recur in the CNS, with a universally fatal outcome within 1 year. CNS recurrence typically occurs early, within 6 to 12 months after initial treatment, and is often parenchymal. Fortunately, the overall risk of secondary CNS involvement in the rituximab era is low, at approximately 3 to 5% in all patients with DLBCL. Defining patients with a higher risk of recurrence and delivering CNS prophylaxis is essential, but these areas remain incompletely outlined. One international collaboration evaluated 2164 patients with aggressive B-cell lymphomas and proposed a new CNS-IPI comprised of kidney and/or adrenal gland involvement, age > 60, LDH > normal, ECOG PS > 1, stage III–IV disease, or more than one extranodal site.[8] Patients with high-risk disease had a 10 to 12% risk of CNS relapse, and this study facilitates identification of patients who need prophylaxis.

There are several management options for prophylaxis, including intrathecal or systemic approaches. There are no prospective data guiding the best prophylactic regimen, but CNS prophylaxis can be with four to eight doses of intrathecal methotrexate and/or cytarabine, or systemic methotrexate (3 to 3.5 g/m^2) during the course of treatment.[136,137]

Relapsed or Refractory Disease

Despite improved cure rates with chemoimmunotherapy, approximately 30 to 40% of patients with DLBCL will have either primary refractory disease or will experience relapse after a prior response. The treatment approach to relapsed disease is based on the randomized Parma trial conducted more than 20 years ago.[138] The trial randomly assigned 109 patients with relapsed aggressive B-cell lymphomas to either DHAP [dexamethasone/cytarabine (ara-C)/platinum agent] chemotherapy or autologous bone marrow transplantation. Patients undergoing transplantation had a superior EFS and OS of 46% vs. 12% ($p = 0.001$) and 53% vs. 32% ($p = 0.038$), respectively. However, several key caveats to this historic trial include that only chemosensitive patients underwent randomization, marrow involvement was excluded, and the study was conducted prior to the introduction of rituximab.

The modern role of ASCT for relapsed DLBCL is more debated. The CORAL trial randomly assigned patients with relapsed or refractory DLBCL after either CHOP or R-CHOP to one of two salvage regimens prior to ASCT. Among 398 patients, the 3-year EFS was 31% overall, but it was 53% for those with chemosensitive disease who were undergoing transplantation. Patients relapsing within 12 months and having undergone prior R-CHOP therapy had a worse outcome, with 3-year PFS of 23%.[139] A study from the National Cancer Institute of Canada (NCIC) showed similar results,[140] and many interpret the 30% EFS for all patients to suggest a

limited role for ASCT at salvage. However, registry data and analysis of responding patients suggests that chemosensitivity retains an important role, and patients able to proceed to transplantation have durable remissions of 40 to 50%.[141] Furthermore, patients unable to undergo ASCT have extremely poor outcomes, with a 3-year EFS of only 14%. Thus, although ASCT arguably benefits a smaller pool of DLBCL in the rituximab era, some patients with chemosensitive disease continue to derive benefit.

Of note, none of the studies evaluating transplantation have been powered to test the impact of adverse biologic features, and it is unclear whether poor outcomes are driven by patients with DEL, COO, or DHL. A two-institution analysis found that patients with DHL or DEL have worse outcomes with ASCT[142]; conversely, patients lacking these high-risk features have an excellent outcome with ASCT.

Despite the controversy over the benefit of ASCT for relapsed/refractory aggressive B-cell lymphomas, there is no clear alternative. Patients ineligible for transplantation or with recurrence despite transplantation have an abysmal survival of approximately 6 months.[112] While allogeneic stem cell transplantation may help selected patients, new immunotherapy approaches such as modified chimeric antigen receptor T cells hold significant promise.[143]

KEY POINTS

- Aggressive NHLs typically grow rapidly and nearly always require prompt initiation of therapy soon after the diagnosis is established to ameliorate symptoms, avert rapid progression of the disease, and optimize survival.
- Calculation of the IPI for a patient at the time of diagnosis with aggressive NHL permits estimation of projected survival based on individual clinical characteristics.
- Multiagent chemotherapy regimens are nearly always employed in the treatment of aggressive lymphomas. Doxorubicin appears to be the critical drug in curative regimens.
- DLBCL is the most common aggressive NHL and is generally treated with rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone, with a cure rate of approximately 60 to 70%. DLBCL is a heterogeneous disease, with clinical and genomic variants.
- The presence of dual *MYC* and *BCL2* and/or *BCL6* rearrangements in aggressive B-cell lymphomas is called “double-hit lymphoma” and has a poor prognosis with standard R-CHOP treatment.
- CNS prophylaxis is necessary for patients with DLBCL who present with high-risk features and for all patients with BL, lymphoblastic lymphoma, or HIV-associated aggressive lymphomas.

MANTLE CELL LYMPHOMA

Mantle cell lymphoma is an uncommon subtype that occurs in approximately 3000 to 5000 patients per year in the United States. For unclear reasons, there is a strong predilection for male gender, with a 3:1 ratio. The median age at onset is 70 years. The malignant cells characteristically express CD20 and CD5, features shared with CLL. However, MCL does not express CD23 (a feature of CLL) or CD10 (found in most cases of FL). Diagnosis is confirmed

by the presence of mature CD20-positive, CD5-positive B cells with cyclin D1 overexpression due to t(11;14)(q13;q32).[4]

There are three clinicopathologic variants: classic MCL, blastoid MCL, and indolent MCL. SOX11 is positive in classic and blastoid MCL, but is frequently absent in indolent MCL, which presents with splenomegaly and lymphocytosis and has a better initial prognosis. Patients with indolent MCL can be safely observed if there are no symptoms, although essentially all patients will eventually require treatment.[144] Most patients present with adenopathy, but others present with extranodal involvement of the gastrointestinal tract (lymphomatous polyposis) or with peripheral-blood lymphocytosis. The vast majority of patients have bone marrow involvement at diagnosis. CNS involvement has been noted in almost 20% of cases at some stage in the disease course, but this is generally a late feature.

Prognosis in MCL is affected by both clinical and biologic features. The MIPI (Mantle Cell Lymphoma International Prognostic Index) stratifies patients into low-, intermediate-, and high-risk groups based on a calculation that involves age, performance status, LDH, and leukocyte count[22]; the MIPI has been validated in patients undergoing intensive chemoimmunotherapy and ASCT as well.[145] Gene expression profiling shows that the proliferative index is a critical component of prognosis, and a new technique to identify the “proliferation signature” in paraffin-embedded tissue using NanoString platforms is promising.[146] For now, many trials describe proliferation via Ki67 immunohistochemical staining, with ≥ 30% being a high value with associated poor prognosis.[147]

Survival for MCL has substantially improved in the past decade, but it remains an incurable malignancy. Older studies of CHOP or R-CHOP show very high ORRs of 80 to 90%, but PFS is short, at 14 to 21 months.[148,149] This has led to the study and implementation of consolidative high-dose chemotherapy and autologous stem cell rescue for chemosensitive disease following initial induction. Today, there are two approaches to the initial treatment of MCL, primarily based on age (Fig. 17-7). Younger and fit patients are offered intensive induction and ASCT while older and unfit patients are offered less-intensive chemoimmunotherapy regimens. The designations *fit* and *unfit* are not clearly defined, but age is a frequent cut point in clinical trials.

There is controversy over the optimal induction strategy for an aggressive approach. Although R-CHOP has an ORR of 90%, cytarabine-containing regimens induce a higher rate of minimal residual disease (MRD) negativity (47% v. 79%, $p < 0.0001$); MRD negativity is a potent prognostic factor for PFS and is independent of the MIPI score, induction regimen, and quality of remission.[150] Other regimens are also being tested as induction prior to HDC/ASCT, including BR (bendamustine/rituximab) and BRAC (bendamustine/rituximab/cytarabine). ASCT in first remission offers impressive long-term disease control, with median OS and response duration exceeding 10 years, and median EFS of over 7 years.[151] However, late relapses do occur, with baseline MIPI and Ki67 being important prognostic factors. The addition of maintenance rituximab for 3 years improves PFS (82% vs. 65%, $p = 0.0005$), EFS (79% vs. 61; $p = 0.0012$) and OS (89% vs. 81%, $p = 0.0413$) in patients undergoing ASCT.[152]

In addition to induction plus ASCT, the R-HCVAD (methotrexate/cytarabine alternating with cyclophosphamide/vincristine/doxorubicin/dexamethasone; also called Hyper-CVAD) regimen has been developed. Fifteen-year follow-up of the R-HCVAD regimen shows a median FFS and OS of 4.8 years and 10.7 years, respectively.[153] However, the cumulative incidence of therapy-related myelodsyplastic syndrome/acute myeloid leukemia (t-MDS/AML) is 6.2%, and the regimen is not well-tolerated in patients over the age of 60.

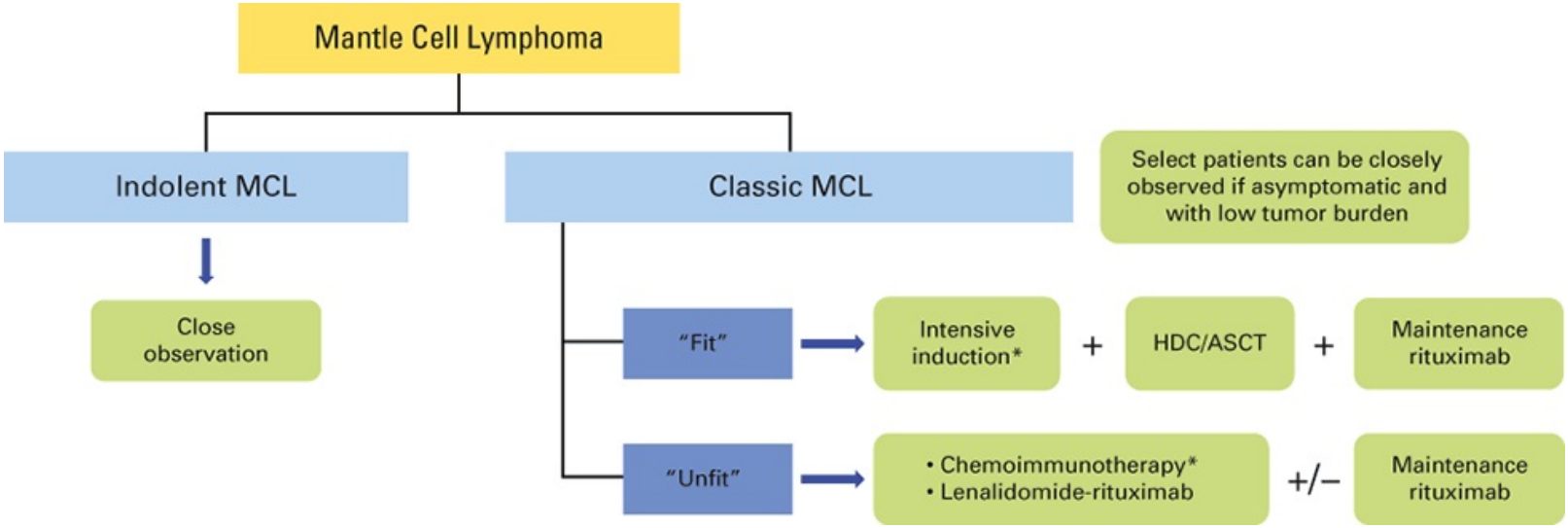

Fig. 17-7 Treatment algorithm for mantle cell lymphoma.

*Intensive induction is usually rituximab plus a cytarabine-containing regimen. Chemoimmunotherapy includes bendamustine and rituximab, R-CHOP, and R-CHP plus bortezomib. Patients with blastoid MCL are treated similarly to fit patients with classic MCL.

For unfit patients, chemoimmunotherapy is the standard of care. As mentioned previously, R-CHOP has high initial response rates—80 to 90%—but complete response rates (approximately 30%) and durable responses are limited. A randomized, phase III trial showed that the addition of maintenance rituximab to R-CHOP reduced the risk of progression or death by 45%. Maintenance rituximab improved the overall survival to 87%, and this is an appropriate option for older patients. However, this trial was conducted prior to the introduction of bendamustine, a uniquely structured alkylating agent with activity in relapsed and refractory disease. There are now two prospective, randomized noninferiority trials comparing BR with R-CHOP/R-CVP in frontline MCL, both showing less toxicity with BR with preserved efficacy.[39,40] Among 94 patients with MCL who were randomly assigned to one of these treatments and followed for 45 months, median PFS had not been reached for BR, compared to 40.9 months for R-CHOP. Compared to R-CHOP, the added value of maintenance rituximab following BR is not clear, and there is a high risk of increased myelosuppression and infection. Other first-line regimens in development are evaluating the roles of bortezomib, lower dose cytarabine, or lenalidomide.[154-156] The combination of lenalidomide and rituximab in this setting is promising, with an ORR greater than 90% and 2-year PFS of 85% in a small prospective trial; larger studies to confirm this activity are ongoing.

Although the approach to MCL has taken these two discrepant approaches, MCL remains incurable. This has led to equipoise between aggressive and nonaggressive therapy and significant debate about the definition of *fit* and *unfit* and whether all eligible patients need a consolidative transplantation. There are several trials prospectively comparing transplant consolidation versus less intensive maintenance strategies, with assessment of minimal residual disease as a key component in direct treatment.

RELAPSED MCL

All patients with MCL will eventually have a relapse, even if there is prolonged remission from initial therapy. At relapse, ASCT offers the potential for cure but is limited to younger patients with appropriate donors and chemosensitive disease. Several agents have been approved in the past few years, including bortezomib, lenalidomide, and ibrutinib.

MCL relies on NFκB signaling for survival, supporting proteasome inhibition as a target.

Bortezomib monotherapy has an ORR of 33% (CR, 8%) and a median TTP of 12.4 months in responders.[157] Neurotoxicity limits bortezomib use, although subcutaneous formulations appear less toxic. Despite excellent rationale and modest activity, other agents have largely supplanted bortezomib use. A large phase II trial of 134 patients with heavily pretreated MCL showed that the immunomodulatory agent, lenalidomide, has an ORR of 28%, with 8% CR[158]; however, responding patients had a duration of response exceeding 16 months, and a subsequent randomized, phase II trial showed superiority of lenalidomide over investigator's choice.[159] The addition of rituximab to lenalidomide increases the ORR and CR rate.[160]

The agent with the highest demonstrated single-agent activity to date in MCL is the oral inhibitor of BTK, ibrutinib, which inhibits tonic B-cell receptor signaling. A pivotal phase II trial in 111 patients with relapsed or refractory MCL found an impressive ORR of 68%, CR rate of 21%, and MRD of 17.5 months.[161] Ibrutinib is generally well tolerated, but there is an increased risk of subdural hematomas in patients who are taking oral anticoagulants, as well as an increased risk of atrial fibrillation and hypertension with prolonged exposure. There are a number of combinations being tested, including the addition of ibrutinib to transplantation strategies and as maintenance following initial treatment. Second-generation BTK inhibitors are also in clinical trials.

KEY POINTS

- MCL is an uncommon, aggressive, and incurable NHL subtype that occurs mainly in older men.
- Diagnostic criteria include clonal CD20-positive cells with coexpression of the T-cell marker CD5 along with t(11;14) and cyclin D1 overexpression.
- Initial treatment is based on the patient's age and comorbidities, often termed *fit* or *unfit.*

LYMPHOBLASTIC LYMPHOMA

Lymphoblastic lymphoma is a very aggressive neoplasm that typically presents in young men (median age, 16) with mediastinal masses. The tumor exhibits an immature T-cell immunophenotype, with expression of CD7, cytoplasmic CD3, and TdT. Rearrangements of the T-cell receptor genes are virtually always present, and activating *Notch* mutations are present in the majority of cases. The clinical distinction between lymphoblastic lymphoma and T-cell acute lymphoblastic leukemia (T-ALL) is based on an arbitrary definition that assigns diagnosis as T-ALL if the bone marrow contains more than 25% lymphoblasts, and lymphoblastic lymphoma if it contains less than 25%. The presence of an elevated serum LDH level and bone marrow or CNS involvement confers an unfavorable prognosis. Complete remission can be achieved in more than 90% of patients treated with intensive, multiagent chemotherapy regimens, such as Hyper-CVAD.[162,163] Involvement of sanctuary sites such as the testes and CNS is common, mandating incorporation of intrathecal chemotherapy into treatment regimens. Patients with clinical evidence of initial testicular involvement that does not resolve following induction should be considered for testicular radiation. The role of mediastinal radiotherapy is controversial. Some series have suggested that intensive leukemia-type chemotherapy regimens produce long-term disease-free survival rates of 73 to 90% in children and 45 to 72%

in adults.[162] A role for high-dose therapy during first complete remission is under investigation for patients with high-risk disease.[164] Long-term survival rates are 63% for patients who undergo ASCT during first complete remission, 31% for patients who undergo transplantation during second complete remission, and only 15% for patients who undergo transplantation with resistant disease.

KEY POINTS

- Lymphoblastic lymphoma is an aggressive lymphoma that expresses immature markers (i.e., TdT) and is treated similarly to acute lymphoblastic leukemia.
- There is a high risk of CNS recurrence; therefore, CNS prophylaxis should be part of treatment for all patients.

BURKITT LYMPHOMA

Classical Burkitt lymphoma is a highly aggressive tumor characterized by an exceptionally high proliferation rate (Ki67 score of approximately 100%), a mature B-cell immunophenotype (monoclonal surface IgM, CD10, CD19, CD20, CD22, BCL6, CD38, and CD43 expression), and a histologic appearance demonstrating diffuse infiltration with a "starry-sky" pattern of macrophages phagocytosing apoptotic tumor cells. All cases of classical Burkitt lymphoma possess a translocation of the *MYC* oncogene at band 8q24, most commonly associated with a t(8;14) translocation, although t(2;8) and t(8;22) translocations involving kappa and lambda loci, respectively, also occur. There are three forms: endemic, sporadic, and HIV-associated. The endemic version occurs in Africa, typically presenting with jaw tumors in children and is almost invariably associated with EBV. Sporadic cases occur elsewhere in the world, often presenting with ileocecal masses and associated with EBV in less than 30% of cases. Burkitt lymphoma is one of the most common types in patients with HIV/AIDS. High-risk features of Burkitt lymphomas include involvement of the CNS and/or bone marrow and a markedly elevated LDH.

Burkitt lymphomas are characterized by a rapid growth rate, and treatment may be associated with a potentially fatal tumor lysis syndrome, renal failure, hyperuricemia, and hyperkalemia. Biochemical abnormalities should be corrected rapidly before treatment, and patients should receive prophylactic rasburicase or xanthine oxidase inhibitors and hydration. Chemotherapy for Burkitt lymphoma has traditionally involved intensive therapy with regimens such as R-HCVAD or cyclophosphamide plus vincristine/doxorubicin/methotrexate alternating with ifosfamide plus etoposide and high-dose cytarabine (CODOX-IVAC), using treatment principles reminiscent of those employed for ALL, including routine CNS prophylaxis.[165-167] The rate of CR with R-HCVAD or R-CODOX-M/IVAC is 85 to 95%, with 47 to 80% FFS at 5 years in various series, depending on patient-selection factors. The OS is 74% for adults treated with aggressive chemotherapy and CNS prophylaxis. Addition of rituximab to aggressive chemotherapy regimens appears to increase the response rate and duration, although randomized clinical trials in this disease are lacking.

Investigators at the National Cancer Institute (NCI) have suggested that less intense regimens may also achieve excellent outcomes in Burkitt lymphoma. Dunleavy et al.[168] treated 30 consecutive patients with infusional EPOCH-R regimens, including 19 HIV-negative patients treated with DA-EPOCH-R and 11 HIV-positive patients treated with a short-course regimen

incorporating a double dose of rituximab (SC-EPOCH-RR). The rates of freedom from progression of disease and OS were 95 and 100%, respectively, with DA-EPOCH-R and 100 and 90% with SC-EPOCH-RR.

Patients with Burkitt lymphoma who have a relapse after initial therapy are generally treated with aggressive salvage chemotherapy regimens followed by attempts at stem cell transplantation, but outcomes are poor in these patients.

KEY POINTS

- Burkitt lymphoma is an aggressive lymphoma characterized by a *MYC* rearrangement, lack of *BCL2* expression, and an extremely high proliferation index.
- Treatment consists of intense regimens with CNS prophylaxis.
- Cure rates are high overall.

PRIMARY CNS LYMPHOMA

Primary central nervous system lymphomas (PCNSLs) are uncommon de novo lymphomas limited to brain structures. including brain parenchyma, leptomeninges, eyes, or spinal cord. Intraocular involvement is seen in 10 to 20% of cases. These are usually aggressive B-cell lymphomas, with DLBCL being the most common. PCNSL can occur in both immunocompromised (mostly HIV-associated) and immunocompetent patients. Among immunocompetent patients, the median age is 60.

Patients typically present with symptoms related to mass effect or infiltration with neurologic compromise and symptoms. The diagnosis requires a tissue diagnosis, usually via a stereotactic biopsy. If possible, it is important to avoid steroids, which are lympholytic, prior to the biopsy because they can lead to a false-negative result or nondiagnostic biopsy with necrosis. If there is concern for irreversible neurologic compromise or impending herniation, avoiding steroids may not be possible. Histopathology shows a dense diffuse infiltrate of large B-cells that are CD20-positive, CD19-positive, PAX5-positive and often of a nongerminal center phenotype with MUM1 positivity.[4] Diagnostic and staging evaluation should also include a lumbar puncture (if safe to perform), slit-lamp eye exam, CT of the chest/abdomen/pelvis, bone marrow biopsy and lab tests to exclude HIV. For men over age 60, a testicular examination and ultrasonography should also be performed.

Treatment for PCNSL has evolved. Whole-brain radiation (WBRT) alone was historically used, with no added benefit from regimens such as CHOP; despite high response rates, 5-year OS was less than 20%.[169] High-dose methotrexate (minimum dose 3 g/m^2) with or without high-dose cytarabine produces superior results compared with radiotherapy alone with a median survival of 51 months.[170-172] However, leukoencephalopathy, particularly in patients over age 60, has led a number of investigators to seek chemotherapy-alone treatments and other groups to test lower doses of radiation. Despite controversy about the optimal dose and timing, WBRT is frequently relegated to the salvage setting.[173]

Radiation-sparing approaches include high-dose methotrexate induction followed by either high-dose chemotherapy and autologous stem cell transplantation[174-176] and induction followed by chemotherapy consolidation.[177] Autologous stem cell transplant consolidation has impressive

results with greater than 90% survival at two years; however, this modality may be limited by age, comorbidities, and chemosensitivity. The addition of intravenous rituximab, particularly in initial cycles of therapy, may also improve outcomes.[177]

The management options for relapsed or refractory PCNSL are limited overall, but there are a number of very exciting agents and approaches in development. If patients have not undergone prior high-dose chemotherapy and autologous stem cell transplantation, this may be an option if salvage regimens can be safely delivered and if there is chemosensitive disease.[178] WBRT is also used, either with or without preceding salvage chemotherapy. Temozolomide, ibrutinib, lenalidomide, and intraventricular rituximab are all in development with promising activity in salvage settings.

KEY POINTS

- Primary CNS lymphoma is a clinical variant of DLBCL occurring exclusively in CNS structures, which may include the brain parenchyma, eyes, leptomeninges, and spinal cord.
- Treatment requires CNS-penetrating agents.
- Consolidation of initial remission can consist of chemotherapy, whole-brain radiotherapy, or high-dose chemotherapy with autologous stem cell transplantation.

LYMPHOMAS ASSOCIATED WITH IMMUNODEFICIENCY

Acquired and iatrogenic immune suppression increase the risk of lymphomas. High-grade B-cell lymphomas, often involving the CNS, were described early in the AIDS epidemic of the 1990s and were considered AIDS-defining illnesses. However, in the era of effective antiretroviral therapy, the incidence of HIV-associated NHL has decreased by over 50%,[179] and the overall prognosis has improved substantially. AIDS-related lymphomas (ARLs) have significantly evolved with the advent and improvement of antiretroviral therapy (ART). Most ARLs in the pre-ART era were high-grade B-cell subtypes, often involving the CNS, and they were highly fatal. However, an analysis of 1456 patients enrolled in clinical trials showed that survival in the contemporary era is approximately 70%.[180] Of interest, the spectrum of ARL is influenced by baseline CD4 count and HIV viral load. Patients with HIV-associated HL and BL have higher CD4 counts and lower HIV RNA compared to other ARLs; in particular, patients with HIV-associated PCNSL had the lowest CD4 counts at diagnosis.[181] Treatment of ARL generally follows treatment of non-HIV NHL. Treatment for HIV-associated DLBCL can be delivered concurrently with ART as long as drug interactions and organ function are carefully monitored. Despite initial concern over increased infectious toxicity with the use of rituximab, a meta-analysis shows improved outcomes[180]; some studies avoid rituximab if the CD4 count at diagnosis is ≤50 cells/mm^3. The NCI has developed a PET-adapted approach to reduce the overall number of chemotherapy cycles (short-course DA-EPOCH-R) associated with a 5-year OS of 68% and acceptable toxicity.[182]

Iatrogenic immunosuppression following solid organ transplantation or hematopoietic stem cell transplantation is associated with an increased risk of subsequent lymphomas, termed “posttransplantation lymphoproliferative disorders” (PTLDs). Iatrogenic T-cell suppression

facilitates EBV-driven B-cell proliferation and consequent PTLD, particularly in cases diagnosed within the first year after transplantation. Thus, the vast majority of PTLDs are of B-cell origin, although other lymphomas can also occur. Risk factors for PTLD include recipient EBV-seronegative status, pediatric populations, coinfection with other viruses (CMV, hepatitis C, human herpesvirus 8) and the duration and intensity of immunosuppressive agents (reviewed in Dharnidharka et al.[183]). There is significant interest in screening for PTLD with serial EBV viral load testing and implementing preventive antiviral prophylaxis in high-risk populations. Early PTLD (less than 1 to 2 years after transplantation) are EBV-positive and may respond to reduced immunosuppression, whereas later PTLDs are more aggressive, are less amenable to reduced immunosuppression, and are EBV-negative.

Confirming a diagnosis of PTLD requires a biopsy. Histopathology can show “early lesions” (plasmacytic hyperplasia, infectious mononucleosis–like lesion), polymorphic PTLD, monomorphic PTLD (includes DLBCL, BL), or classic Hodgkin lymphoma-like PTLD.[4] A rising EBV titer and abrupt-onset adenopathy with constitutional symptoms increase the suspicion for PTLD; a PET scan can be helpful in selecting a lymph node for biopsy. The general treatment approach to PTLD is prompt reduction of immunosuppression and rituximab therapy. Several phase II trials of rituximab monotherapy show response rates of 40 to 60%.[184-186] The sequential addition of CHOP chemotherapy improves the response rate to 90%; however, treatment-related mortality is increased by approximately 10% in these fragile patients.[187]

Finally, both autoimmune diseases (rheumatoid arthritis, Sjögren disease, systemic lupus erythematosus) and treatment for autoimmune conditions have been associated with an increased risk of NHL.[188,189] Both the specific risk and NHL subtype is variable, and may be up to 6-fold higher compared to populations without autoimmune conditions.

KEY POINTS

- Immune suppression (either acquired or iatrogenic or related to underlying autoimmunity) is associated with an increased risk of lymphoma.
- If possible, removing the cause of immune suppression can lead to lymphoma regression.
- In the era of effective antiretroviral therapy, outcomes for HIV-associated lymphomas has dramatically improved.

T- and NK-CELL LYMPHOMAS

Lymphomas arising from mature NK and T cells (NK/TCL) comprise 10 to 15% of NHL in the United States. There is geographic variation, however, and they account for nearly 30% of NHL in Asian countries. The term *peripheral T-cell lymphoma* (PTCL) refers to a diverse group of postthymic T-cell tumors that have a mature T-cell phenotype. Patients tend to have higher scores on the IPI, more B symptoms, advanced-stage disease, and higher serum β_2-microglobulin than comparable patients with DLBCL. Patients with PTCL generally have inferior treatment responses, a high rate of relapse, and few sustained remissions when treated with multiagent chemotherapy regimens such as CHOP. A prognostic index specific for PTCL (known as the PIT) has been devised that includes patient age, LDH level, performance status, and presence of bone marrow involvement.[190] Poor prognosis is also associated with p53

expression, a high Ki67 proliferation index (> 25%), adverse chemokine expression patterns (CXCR3-positive/CCR4-negative), and expression of CD30 and CD56, BCL2, or BCLXL. A full exposition of the details of this diverse group of disorders is beyond the scope of this chapter, but an excellent review is available.[191]

NK/TCLs are diverse and individually relatively rare entities, with approximately 30 defined subtypes. The WHO divides them on the basis of the main site of clinical involvement: primary nodal, primary extranodal, leukemic, or cutaneous.[4] Until recently, there has been a profound paucity of trials dedicated to NK/TCL, and most treatment paradigms are extrapolated from treatment of aggressive B-cell lymphomas. Brief descriptions of the most common entities and general treatment principles follow.

PERIPHERAL T-CELL LYMPHOMA

Primary nodal T-cell lymphomas are aggressive lymphomas and are also called peripheral T-cell lymphomas (PTCLs). There are four major subtypes of PTCLs, including ALK-positive anaplastic large cell lymphoma (ALK+ ALCL), ALK-negative ALCL (ALK– ALCL), angioimmunoblastic T-cell lymphoma (AITL), or peripheral T-cell lymphoma not otherwise specified (PTCL-NOS). This last category is a provisional group encompassing mature aggressive TCLs not included in the other groups. A CD4-positive T-follicular helper cell (T_{FH}) has been identified as the malignant cell of origin in both AITL and in a subset of PTCL-NOS; this discovery may impact the next WHO classification.

Peripheral T-Cell Lymphoma Not Otherwise Specified

The most common PTCL is PTCL-NOS (25 to 30%), and this category is subject to revision as molecular distinctions are clarified. There is an aggressive growth phase with nodal and extranodal involvement and frequent B symptoms. PTCL usually presents with paracortical or diffuse nodal infiltration of malignant lymphoid cells expressing T-cell markers, including CD2, CD3, T-cell receptor (TCR), and usually CD4. Proving clonality can be difficult, as oligoclonal or small clonal TCR populations can occur in nonmalignant tissue; however, a “dropped antigen” (i.e., loss of a typical T-cell antigen) or down regulation of CD5 or CD7 is characteristic of neoplasia.[192] The median age of patients with PTCL is 60 years, with a male-to-female ratio of 1.9:1. The majority of patients present with advanced-stage disease (69%), and two-thirds of the patients have extranodal disease in addition to adenopathy. The treatment approach to PTCL-NOS is extrapolated from DLBCL trials, but the response to CHOP is significantly inferior with ORRs of 60 to 70% but only 25 to 30% PFS.

Angioimmunoblastic T-Cell Lymphoma

AITL accounts for 18% of TCLs worldwide and typically presents with generalized lymphadenopathy, fevers, weight loss, and rash, with autoimmune features, including hypergammaglobulinemia and a positive Coombs test.[193] The disease is derived from follicular helper T-cells (T_{FH}), with malignant cells typically expressing CD10, BCL6, PD1, and CXCL13, in addition to typical T-cell markers (CD2, CD3, CD5, and CD4). The disease course is typically complicated by serious and often fatal infections. EBV-associated B-cell lymphoma often develops during the course of treatment for AITL, apparently derived from EBV-infected B-cell blasts present in the tumor. An important discovery is the strong epigenetic signature associated with AITL; frequently mutated genes include *RHOA* (70%), *TET2* (82%), *IDH2*

(30%), and *DNMT3A* (26%).[194,195]

Anaplastic Large Cell Lymphoma

ALCL is a malignancy of large pleomorphic mature T lymphocytes that express the CD30 antigen (Ki-1) as well as T-cell surface markers such as CD2, CD4, and CD5. Curiously, the pan-T-cell antigen CD3 is negative in more than 75% of cases. There are two subtypes based on the presence or absence of nucleophosmin (NPM)-ALK t(2;5) translocation: ALK+ and ALK– ALCL.[196] Patients with ALK+ ALCL are younger, with a median age at onset of 30, and the disease often occurs in pediatric populations. ALK– ALCL has a median age at onset of 55. ALCL is more common in males, and has advanced stage at presentation with frequent extranodal involvement. ALK+ ALCL has a superior prognosis, with 5-year survival rates of 70 to 90% compared to only 40 to 60% for ALK– ALCL following CHOP or CHOP plus etoposide. However, a subset of patients with ALK– ALCL harboring a *DUSP22* translocation may have good outcomes on par with ALK+ ALCL.[197]

Treatment Approach to PTCL

Treatment of PTCL is challenging. CHOP is associated with long-term disease control of only 25 to 30%,[198] and most of the benefit is in IPI low-risk groups. Despite being a weak regimen in PTCL, most trials are testing the addition of new agents to a CHOP backbone (i.e., romidepsin plus CHOP, alemtuzumab plus CHOP); to date, these have all been negative studies, with two exceptions. First, in a retrospective analysis of patients enrolled on sequential German trials, etoposide added to CHOP (CHOEP) improves PFS in a subset of patients; notably, CHOEP was too toxic for patients over age 60, most of the benefit was in ALCL histology, there was no overall survival difference, and this was not a prospective trial.[199] Second, replacing vincristine in CHOP with the antibody-drug conjugate brentuximab vedotin (BV) is well tolerated and highly active[200]; this is now being tested in a large, international, phase III trial in CD30-positive PTCL.

Patients with disease that is chemosensitive to CHOP-based treatment may be considered for a consolidative stem cell transplantation. A prospective, phase II trial treated 166 patients who had PTCL with CHOEP for six cycles; among 131 responders, 115 underwent consolidative ASCT and had long-term survival of approximately 50%.[201] While there are no directly comparative data, registry studies show 5-year OS of 48% versus 26% in favor of patients undergoing consolidative ASCT.[202] ASCT likely has its biggest impact in the first-line setting and is less effective in relapsed disease.[203]

Aggravating the poor results with first-line treatment is the inability to effectively salvage patients at relapse; population-based data have shown a median OS of less than 6 months for patients who had relapsed.[204] This may be changing in the era of new agents. There are currently four agents approved for use in relapsed PTCL based on large phase II trials: romidepsin, pralatrexate, BV (for CD30-positive disease), and belinostat. Romidepsin and belinostat are histone deacetylase (HDAC) inhibitors and have response rates of 25 to 40%; despite a modest response rate, remissions can be durable. BV, an antibody-drug conjugate against CD30, is highly active with single agent response rates of 85% (CR rates, > 50%) in relapsed/refractory ALCL and other CD30-positive TCL.[205]

PRIMARY EXTRANODAL NATURAL KILLER/T-CELL LYMPHOMA

Enteropathy-Associated T-Cell Lymphoma

Enteropathy-associated T-cell lymphoma (EATL) accounts for approximately 5% of TCLs and is more common in geographic areas with a higher incidence of celiac disease, including North America and Europe. Patients typically present with pain, weight loss, and bowel perforation.[206] Cases associated[206] with celiac disease typically exhibit a pleomorphic histology and express CD3 and CD7, but not CD56, whereas patients without celiac disease often display a monomorphic histology and express CD56. Up to 70% of cases of EATL contain gains at chromosome 9q33-q34. Conventional therapy consists of CHOP, with a median OS of only 10 months in one international series of 62 patients, with a median FFS of only 6 months.[206] The presence of clinical sprue and an adverse PIT score both predicted independently for poor survival. One study suggests that outcomes with EATL may be improved by inducing remission with a novel regimen of ifosfamide plus etoposide and epirubicin alternating with intermediate-dose methotrexate followed by consolidation with ASCT.[207] This approach yielded a 5-year PFS of 52% and OS of 60% among 26 patients who underwent transplantation.

Extranodal Natural Killer/T-Cell Lymphoma

Extranodal NK/TCL is an angioinvasive, necrotizing lymphoma derived from cytotoxic NK or T cells that is almost invariably associated with EBV infection and typically presents in the nasal cavity, nasopharynx, or paranasal sinuses. It is divided into nasal and extranasal types and can affect skin, the gastrointestinal tract, or testes. Nasal obstruction, bleeding, and ulceration are typical; hence, the previous designation of this disease as “lethal midline granuloma.” The malignant lymphoid cells of nasal NK/TCL typically express CD2, CD56, and cytoplasmic CD3ε (but not surface CD3) as well as cytotoxic molecules such as T-cell restricted intracellular antigen (TIA1), granzyme B, and perforin. The disease often presents at an early stage; radiotherapy is a critical therapeutic component of limited-stage disease, either preceding or concurrent with chemotherapy.[208] The disease is relatively resistant to CHOP-type chemotherapy but appears uniquely sensitive to asparaginase-containing regimens such as SMILE, which contains dexamethasone (“steroid”), methotrexate, ifosfamide, L-asparaginase, and etoposide.

Hepatosplenic γδ T-Cell Lymphoma

Hepatosplenic γδ TCL is a rare disease of young males derived from immature or nonactivated γδ T cells possessing an isochromosome 7q abnormality. This lymphoma typically infiltrates the liver, spleen, and marrow sinusoids, with minimal adenopathy. Patients often present with fever, chills, and other systemic symptoms. Cytopenias, especially thrombocytopenia, are typical and often accompanied by a fatal hemophagocytic syndrome. Outcome is poor regardless of management, though many authorities recommend aggressive chemotherapy followed by stem cell transplantation in first remission.

CUTANEOUS T-CELL LYMPHOMA

Cutaneous TCLs (CTCLs) are a heterogeneous group of lymphomas characterized by infiltration of the skin and other organs by malignant but mature T cells. In the WHO classification, these disorders are considered indolent T-cell malignancies. The most common type of CTCL is mycosis fungoides/Sézary syndrome (MF/SS), but there are other subtypes, including primary cutaneous ALCL (not to be confused with systemic ALCL), subcutaneous panniculitis-like T-cell lymphoma, and many others.[4]

In most cases of mycosis fungoides, the diagnosis is made after a prolonged period of ill-defined skin disease or parapsoriasis. Subsequently, patches or plaques characteristic of mycosis fungoides develop. At the time of diagnosis, less than half of patients have limited plaques, one-third have extensive plaques, and 10 to 15% have generalized erythroderma. The spleen, liver, and lymph nodes also may be involved, especially in patients with advanced skin disease and circulating malignant cells. When the peripheral blood becomes extensively involved with the malignant T cells and erythroderma develops, the condition is called Sézary syndrome.

The treatment approach for MF/SS starts with a skin-directed approach, but may eventually require systemic agents.[209] Most patients with CTCLs initially are treated with topical measures, including corticosteroids, photochemotherapy with oral methoxypsoralen therapy followed by ultraviolet light, mechlorethamine, bexarotene, or electron-beam radiation (either localized or total skin). Systemic therapy is needed when these approaches fail or when major organ involvement, diffuse lymphadenopathy, or transformation to large cell NHL develops. Treatment options for advanced CTCL include extracorporeal photopheresis, interferon-alpha, bexarotene, denileukin diftitox, liposomal doxorubicin, nucleoside analogs (e.g., gemcitabine), alemtuzumab, or combination chemotherapy. Histone deacetylate inhibitors such as vorinostat and romidepsin have shown major activity in this condition, as has pralatrexate, and these drugs are being increasingly employed earlier in the disease course. BV is highly active if there is CD30 expression.[210] Patients with CTCL often die from infections, and as such, good skin care and oral antibiotics are important adjuncts to therapy. The only known curative therapy for mycosis fungoides is allogeneic stem cell transplantation, although this approach is appropriate for only a minority of patients.[211]

KEY POINTS

- TCLs are rare, heterogeneous, and aggressive diseases that are frequently chemoresistant.
- Initial treatment of peripheral T-cell lymphomas consists of multiagent chemotherapy with CHOP or CHOEP followed by consolidative autologous stem cell transplant in chemosensitive patients.
- All patients with localized NK/TCL should have radiation therapy as part of their treatment, which improves overall survival.
- Mycosis fungoides is the most common type of CTCL and is an indolent disease in the majority of patients. Treatment is initially skin-directed.

HODGKIN LYMPHOMA

EPIDEMIOLOGY AND ETIOLOGY

HL is a mature B-lymphoid neoplasm that annually is diagnosed in approximately 9050 Americans and with approximately 1150 deaths. HL has a bimodal incidence distribution with respect to age at diagnosis, with an incidence peak in young adulthood and a second peak in the elderly. The etiology of HL is not known. There is an association with EBV, and the likelihood of HL developing is increased 3-fold for people with a history of infectious

mononucleosis. HL nodes show evidence of EBV DNA in the genome of the Reed–Sternberg cell in 30 to 80% of cases. However, because many cases of HL are EBV-negative, controversy remains as to whether there is a causal relationship. There is an increased frequency of the disease in patients with AIDS and patients who have undergone bone marrow transplantation. In patients infected with HIV or AIDS, HL tends to involve extranodal sites and to exhibit an aggressive clinical course with a poor outcome. There are no clear relationships with environmental exposures, although an increase in the incidence of HL has been reported in woodworkers/carpenters, farmers, and meat processors.

CLINICAL PRESENTATION AND CLASSIFICATION OF HL

HL typically presents with painless lymphadenopathy with or without splenomegaly, fevers, drenching night sweats, weight loss and pruritus, or pain in a lymph node–bearing area that is associated with alcohol consumption. The diagnosis is best established by an excisional lymph node biopsy demonstrating large, atypical lymphocytes surrounded by a heterogeneous infiltrate of nonneoplastic inflammatory and accessory cells. The WHO classification of lymphomas distinguishes two major subtypes of HL, namely, classical HL (includes nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted subtypes) and nodular lymphocyte–predominant HL.[4]

CLASSICAL HODGKIN LYMPHOMA

Classical HL (cHL) represents 95% of all cases of HL and is characterized pathologically by the presence of bizarre monoclonal lymphoid cells that may be either mononuclear (Hodgkin cells) or multinucleated (Reed–Sternberg cells). The malignant Hodgkin and Reed–Sternberg (HRS) cells of classical HL express CD15 and CD30 surface antigens, but usually not typical B-cell markers, such as surface immunoglobulin, CD20, CD79a, or the common leukocyte antigen CD45.[3] The B-cell origin of HRS cells is nevertheless demonstrable by the expression of the B-cell–specific activator protein derived from the *PAX5* gene in 90% of cases.[4] Immunoglobulin genes are rearranged in 98% of HRS cells but are not transcribed as a result of the absence of the transcription factor organic cation transporter 2 (Oct-2) and its coactivator B-cell specific octamer binding protein (BOB-1). The malignant (HRS) cells are typically surrounded by a heterogeneous infiltrate of reactive T and B lymphocytes, eosinophils, macrophages, fibroblasts, and variable amounts of collagen deposition (sclerosis). Chromosome 9p24.1 is frequently amplified in cHL, increasing the expression of the programmed cell death 1 (PD-1) ligands, PD-L1, and PD-L2 and promoting their induction through Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signaling.[212]

Four discrete histologic subtypes of cHL are recognized by the WHO classification on the basis of the relative proportions of infiltrating small lymphocytes and of HRS cells and the amount of collagen (sclerosis) in the biopsy. All four subtypes of cHL are evaluated and managed similarly, lessening the importance of subclassification of cHL.

Nodular-Sclerosis Subtype

More than 60% of patients with cHL present with the nodular-sclerosis subtype, which is most common in women, adolescents, and young adults. At the time of presentation, patients characteristically have an anterior mediastinal mass that may produce chest discomfort, dyspnea, or cough. The histologic pattern of nodular-sclerosis HL is at least partially nodular

with fibrous bands. Diffuse areas and necrosis also may be present. HRS cells in nodular-sclerosis HL are typically giant cells with multilobulated nuclei surrounded by a clear area that is an artifact of formalin fixation, leading to their designation as “lacunar variants.” Nucleoli are typically less prominent than in the classical HRS cell. The tumor cells are CD30-positive, CD15-positive or -negative, and CD45-negative. Epithelial membrane antigen expression is rare.

Mixed-Cellularity Hodgkin Lymphoma

Mixed-cellularity HL represents approximately 20% of cases and is more common in men. The histologic appearance is of a diffuse, or vaguely nodular, infiltrate. HRS cells are primarily of the classic variety. The cells are CD30-positive, CD15-positive or -negative, and CD45-negative. In contrast to the other histologic subtypes, EBV genomic DNA is detectable in 60 to 70% of mixed-cellularity HL. Patients tend to present with disseminated disease, and the clinical course may be aggressive; however, this subtype is still curable.

Lymphocyte-Rich Classical Hodgkin Lymphoma

The growth pattern in lymphocyte-rich cHL usually is nodular, but may be diffuse, with a phenotype of CD30-positive, CD15-positive or -negative, and CD20-positive or -negative. This subtype is more common in older males and presents at an early stage of disease. Other findings are similar to nodular lymphocyte-predominant HL, except that patients are slightly older (age 40) at the time of diagnosis, and the presenting mass is more frequently located in the mediastinum. Late relapses are less common, but more often fatal.

Lymphocyte-Depleted Hodgkin Lymphoma

Lymphocyte-depleted HL accounts for less than 5% of cases. It occurs more often in older men and in people who are infected with HIV. It also is more common in nonindustrialized countries. At the time of presentation, patients have a higher incidence of abdominal adenopathy and less peripheral adenopathy than is found with other types of HL. Hepatosplenomegaly may be prominent, and the bone marrow often is infiltrated with lymphoma. The histologic appearance of the lymph nodes is characterized by a diffuse infiltrate, which may appear hypocellular. HRS cells (CD30-positive, CD15-positive or -negative, and CD45-negative) are plentiful and often have a malignant appearance.

NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA

Nodular lymphocyte-predominant HL (NLPHL) is a unique indolent B-cell neoplasm that is distinguished from cHL by histologic and immunophenotypic features, including the presence of large neoplastic cells known as “popcorn” or “lymphocytic and histiocytic” cells (L and H cells) residing in large nodular meshworks of follicular dendritic cell processes filled with nonneoplastic lymphocytes. In marked contrast to the HRS cells of cHL, the malignant L and H cells of NLPHL express typical B-cell surface antigens, including CD20 and CD79a, as well as the common leukocyte antigen CD45, but do not express CD15 or CD30.[213] Fifty percent of NLPHLs harbor *BCL6* rearrangements, in contrast to cHL, in which this is a rare occurrence.[214] NLPHL is responsible for approximately 5% of all cases of HL, typically affects men between ages 30 and 50, usually presents with localized lymphadenopathy (stages I to II), progresses slowly, and is associated with prolonged survival despite frequent relapses.

There is a spectrum of associated pathologic entities (reviewed in Savage et al.[215]) "Progressive transformation of germinal centers" is a benign condition that may precede or occur simultaneously with NLPHL. In addition, up to 15% of patients with NLPHL can have a transformation to aggressive B-cell lymphoma, with advanced-stage and hepatosplenic involvement constituting important risk factors. There is a clonal relationship between NLPHL and the aggressive component, which is frequently a T-cell–rich DLBCL and requires aggressive treatment.

STAGING AND INITIAL EVALUATION OF HL

Recommended diagnostic tests include a history, physical examination, excisional lymph node biopsy with evaluation for histology and immunophenotype, complete blood cell count with differential, chemistry panel including liver-function tests, albumin, LDH, erythrocyte sedimentation rate, chest radiography, CT of the chest, abdomen, and pelvis, FDG-PET, and fertility counseling. Other tests useful in selected cases include pulmonary-function tests (prior to bleomycin therapy), determination of the cardiac ejection fraction (prior to anthracycline therapy), HIV testing, and neck CT scans. Bone marrow biopsies are no longer routinely recommended for staging of HL, provided FDG-PET imaging is performed, as patients with early-stage disease rarely have bone marrow involvement in the absence of PET abnormalities, and those with advanced disease would not have their treatment changed on the basis of bone marrow biopsy findings.[6] After completion of the diagnostic workup, the extent of involvement with HL is designated using the Lugano staging criteria (Table 17-2).

The clinical approach to HL is based on the initial stage and prognostic factors into early stage (IA–IIA, with favorable or unfavorable features) or advanced stage (IIB, III, IV, or bulky disease). Prognostic factors for early-stage HL include a large mediastinal mass, elevated sedimentation rate, involvement of ≥ 3 nodal sites, extranodal disease, age >50 years, or massive splenic disease.[216] Prognostic factors for advanced stage include age > 45 years, stage IV disease, male sex, leukocytosis (WBC > 15,000/mL), lymphopenia (ALC < 600/mL), low albumin, or anemia (hemoglobin < 10.5g/dL).[217] As will be discussed, metabolic response reflected by FDG-PET has emerged as one of the most important prognostic factors for survival, and it forms the rationale for response-adapted therapy.

TREATMENT OF HODGKIN LYMPHOMA

A Historical Note

The treatment approach to cHL relies more heavily on stage and location than do other B-cell lymphomas, partly because of long-standing observations of contiguous patterns of spread when the disease recurs. Precise surgical and pathologic staging in the pre–PET era assessed the sites of known disease and determined the sites with the highest risk of recurrence. Thus, staging laparotomies, splenectomy, extensive lymph node dissection, and lymphangiography allowed the design of radiation fields such as mantle irradiation, inverted Y, para-aortic, extended-field radiation, and others. While highly effective in terms of disease control, morbidity and mortality from toxicity was excessive, and HL is a paradigm disease highlighting the dangers of late effects. Older studies show that, while cure rates are high, HL survivors continue to experience an increased risk of death from second malignancies, cardiovascular compromise, and pulmonary disease from both chemotherapy and radiotherapy. The desire to optimize the risk:benefit ratio in this usually young group of patients is the overriding theme in clinical trial development, and very-long-term follow-up (≥ 10 years) is often needed to

demonstrate the true impact of a therapeutic approach.

Early-Stage Classical Hodgkin Lymphoma

Patients with stage IA–IIA HL have an excellent expected outcome, with long-term survival exceeding 90 to 95%. The historic approach was radiotherapy alone, but the addition of ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine) chemotherapy allowed a reduction in field size and dose with an improved toxicity profile; in the pre–PET era, four cycles of ABVD plus 36 to 40 Gy involved-field radiation therapy (IFRT) achieves a 12-year overall survival of 94% in both favorable and unfavorable disease.[218] A subsequent German trial randomly assigned 1370 patients with favorable prognostic factors to between two and four cycles of ABVD chemotherapy and 20 and 30 Gy IFRT in an effort to reduce both chemotherapy cycles and total radiation dose.[219] There was no difference in response, PFS, or OS among the four arms, and two cycles of ABVD plus 20 Gy IFRT is an appropriate means of limiting both chemotherapy and radiotherapy. Other studies have tested chemotherapy-only regimens. In general, omission of radiation therapy in nonbulky early-stage HL is associated with inferior disease control (EFS, PFS, local relapse) on the order of 3 to 7% (reviewed in Engert et al.[219]); however, very-long-term follow-up shows 12-year overall survival of 94% among those receiving ABVD alone, setting up controversy over the role of combined-modality versus chemotherapy-alone approaches.[221]

Importantly, each of these trials was conducted prior to incorporation of PET and response-adapted approaches. There are now two randomized trials in favorable-risk (UK RAPID and EORTC H10F) and one in unfavorable-risk patients (EORTC H10U)[220,222] testing omission of radiation therapy based on a negative interim PET-CT, usually defined as a Deauville score ≤ 2 after two cycles of chemotherapy. The RAPID trial enrolled over 600 patients with stage IA–IIA HL; patients with a negative PET scan after three cycles of ABVD (426 patients; 74.6%) were randomly assigned to consolidative radiation versus no further therapy.[222] The 3-year PFS was 94.6% versus 90.8% favoring radiotherapy, with no difference in 3-year OS (97.1% vs. 99%; p = 0.27). Given the excellent outcomes, the RAPID approach is now integrated into NCCN guidelines.

Advanced-Stage Classical Hodgkin Lymphoma

HL is highly curable with combination chemotherapy, even in advanced stages. There is a long history of clinical trials refining the optimal systemic therapy (excellent and detailed reviews in Johnson and McKenzie[223] and Lynch and Advani[224]), with important questions revolving around early and late toxicity, role of intensification, role of radiotherapy, and response-adapted treatment. Today, the approach is based on several principles and observations.

First, determining the true impact of a regimen may require very prolonged follow-up. For example, ABVD became the North American treatment of choice based on 7- or 10-year FFS of 70 to 75%, coupled with an excellent toxicity profile.[225-227] The risk of secondary malignancies is extremely low, and fertility is preserved in the majority of patients. More intense regimens, such as the escalated BEACOPP regimen developed in Germany, offer improved disease control, but are associated with increased treatment-related mortality and significant infertility. An Italian intergroup study randomly assigned 331 advanced stage HL patients to ABVD or BEACOPP, and patients with residual or progressive disease were treated with a uniform salvage program.[227] There was more progression in the ABVD arm (45 vs. 20 patients), but the 7-year freedom from second progression and overall survival were similar in the two groups.

Overall, 70% of advanced stage patients are cured with ABVD, and it is difficult to determine who needs escalated BEACOPP (bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisolone) based on baseline features.

Second, response-adapted therapy is an emerging component of treatment. A provocative and influential study of 205 patients showed a 2-year PFS of 95% versus 13% in patients with a negative versus positive PET after two cycles of chemotherapy ($p \leq 0.0001$).[228] Subsequent studies of PET have not recapitulated these massive differences, but it is clear that interim PET has an extremely high negative predictive value. The use of consistent PET interpretation via the 5-point scale (Deauville criteria) is imperative in ensuring comparability between trials. There are two approaches to integrate interim PET in the management of HL: treatment intensification based on positive interim PET versus treatment deescalation based on negative interim PET.[224] The RATHL study used the latter concept to test the ability to eliminate bleomycin from ABVD, a known pulmonary toxin and the cause of pneumonitis and death, particularly in older individuals.[229] The RATHL study enrolled 1214 patients with advanced-stage HL; 84% achieved a PET-negative interim PET after two cycles of ABVD. These patients were randomly assigned to continue ABVD or to change to AVD for four additional cycles. With a median follow-up of 41 months, the 3-year PFS was 85.7% versus 84.4%, and 3-year OS was 97% in both arms. Thus, given increased toxicity from bleomycin, patients with a negative interim PET can safely have this agent omitted for cycles three to six.

When treating with ABVD, it is imperative to deliver treatment on time and without dose reduction to maximize efficacy. Although ABVD is associated with neutropenia, febrile neutropenia is very uncommon in this generally young and healthy population.[223] The use of routine growth factors is not recommended. There is controversy over the interaction between growth factors and bleomycin-induced lung injury, particularly in older patients.[230,231] Prophylactic antimicrobials for pneumocystis jirovecii pneumonia (PJP) and varicella-zoster virus should be considered for patients with prolonged neutropenia.

Bulky Hodgkin Lymphoma

Up to 25% of patients with HL will have bulky disease, currently defined as a mass greater than 10 cm on CT scans or a mediastinal mass greater than 0.33 of the chest diameter on chest x-ray at T5–T6. Bulky disease may or may not be symptomatic, and cough or chest pain are frequently associated symptoms. More abrupt symptoms, such as superior vena cava syndrome, are more likely to be from aggressive lymphomas involving the mediastinum such as primary mediastinal B-cell lymphoma. Bulky disease is connoted with the suffix or postscript “X” in the stage (e.g., II_X or IIX). Bulk is a known adverse prognostic factor. The literature regarding bulky HL is confounded by the general inclusion of bulky disease in early-stage trials in Europe versus inclusion in advanced-stage trials in North America.

Treatment for bulky HL has traditionally been combined-modality therapy, but PET-directed omission of radiation is being evaluated. Given the primarily mediastinal location of bulky HL, RT is associated with secondary malignancies (especially medial breast cancer in young women), cardiovascular disease (which may be aggravated by concurrent use of anthracyclines), and pulmonary toxicity.

Following six cycles of ABVD or Stanford V, 36 Gy consolidative radiation is associated with a 5-year FFS of over 80% in bulky HL.[232] Although retrospective data support the omission of radiation in patients with a negative PET scan, early results from prospective trials are more

complex and controversial. A German trial (HD15) used PET-directed radiation in patients treated with escalated BEACOPP, and it was able to reduce the use of radiation therapy to only 11% of patients[233]; extrapolation to ABVD is controversial. Overall, there is a strong move away from radiation for bulky mediastinal disease, with several trials expected to mature shortly.

Relapsed Classical Hodgkin Lymphoma

While most patients with cHL are cured with initial treatment, approximately 10 to 20% (and up to 50% of high-risk patients) will have disease recurrence. The treatment approach at relapse is influenced by the time to relapse and the nature of the initial treatment, but generally consists of a multistep process of salvage chemotherapy, hematopoietic stem cell mobilization, high-dose chemotherapy with autologous stem cell rescue, and consideration of consolidative BV. In support of autologous stem cell transplantation, two randomized trials showed superiority of high-dose chemotherapy and autologous bone marrow transplantation over conventional chemotherapy.[234,235] The historic British National Lymphoma Investigation (BNLI) randomly assigned 20 patients apiece with nonresponding or relapsed disease to either mini-carmustine/etoposide/cytarabine/melphalan (BEAM) or BEAM (augmented doses of the same agents) followed by autologous bone marrow transplant (ABMT). The 3-year EFS was 53% versus 10% in favor of the transplantation group; the authors concluded a potent dose–response effect. A second trial, the German HD-R1 trial, randomized 161 patients to either dexa-BEAM or BEAM followed by autologous bone marrow transplantation and showed an improved freedom from treatment failure for high-dose chemotherapy (55% vs. 34%, p = 0.019).[235] Of interest, neither of these trials was powered to determine a survival advantage for transplantation, but a meta-analysis confirmed the benefit of transplantation with mature follow-up, and ASCT is now the standard of care.[236]

The most important factors predicting outcome to salvage ASCT are time to relapse and chemosensitivity. The HD-R1 trial defined “early” and “late” relapse at 12 months, and found limited benefit of transplantation for patients with early relapse.[235] Other trials confirm this observation, and patients with refractory disease or who have a relapse within 12 months derive less benefit from ASCT.[237-239] However, chemosensitivity to salvage regimens may supercede time to relapse, and achieving a PET-negative remission prior to ASCT affects outcome. Patients with a positive pre-ASCT PET have an EFS of 33% versus 77% (HR, 4.61; p = 0.00004), and PET negativity overcame other negative prognostic features.[240,241] There are several salvage regimens with high activity, including ICE, DHAP, and gemcitabine-containing regimens; to date, there are no randomized trials showing superiority of a particular salvage regimen. ICE has an ORR of 80% (CR, 50%) and is an excellent bridge to transplantation.[242] Patients with a suboptimal response to ICE who then respond to gemcitabine-based regimens and undergo ASCT seem to have outcomes that are equally as good as those in patients whose disease responds to ICE, with an EFS of 79%; this is proof-of-principle again supporting the importance of chemosensitivity and attaining a negative PET scan prior to ASCT.[241] Newer salvage regimens including the antibody-drug conjugate BV are in development.

While transplantation is an active and appropriate treatment for relapsed HL, the long-term disease control rate is only 50 to 60% in randomized trials and registry analyses,[237,239,243] with relapses occurring mainly in the first 3 years after ASCT. The AETHERA trial randomly assigned 329 patients with high-risk relapsed/refractory HL to BV consolidation or observation. *High risk* was defined as primary refractory disease, relapse within 12 months, or extranodal

disease. BV consolidation was associated with improved PFS (42.9 months vs. 24.1 months; HR 0.57, p = 0.0013),[244] and this is now an approved indication. To date there is no difference in OS.

Not all patients with relapsed HL need ASCT, and there is controversy about how to approach patients with limited relapse or those with minimal therapy in the first-line setting. In particular, patients with a late relapse and limited disease following chemotherapy may be treated with salvage radiation, although this is controversial.[245]

The treatment options for multiply relapsed HL, either after ASCT or in patients who are ineligible for ASCT, has greatly expanded in the past several years. Allogeneic stem cell transplantation, usually with a reduced-intensity conditioning regimen, remains an important and effective option for eligible patients. However, two new treatments have significantly challenged the role and timing of allogeneic transplantation. First, the antibody-drug conjugate BV, which targets CD30 and delivers a toxic payload monomethyl auristatin E (MMAE) has single-agent ORR and CR rate of 75% and 34%, respectively, among 102 patients treated in a pivotal trial.[246] At 5 years, half of patients with a complete remission remain progression-free, raising the possibility of cure for a small portion of patients with relapsed HL. BV is given at 1.8 mg/kg every 3 weeks and is well tolerated overall. The most common toxicity is sensory peripheral neuropathy, which occurs to some degree in most patients; over 80% of patients in the pivotal trial reported eventual resolution of symptoms. A second new option is checkpoint blockade. Amplification of 9p24 in HL leads to PD-L1 overexpression and activation of the JAK-STAT pathway, supporting the use of PD1/PD-L1 axis blockade. Nivolumab and pembrolizumab have emerging data with impressive activity. Nivolumab was FDA-approved in 2017 for relapsed HL based on an 87% response rate in 20 heavily pretreated patients and a subsequent larger phase II trial.[247-249]

Therapy for Nodular Lymphocyte-Predominant Hodgkin Lymphoma

The treatment of NLPHL has traditionally followed general guidelines for cHL, and the rarity of this disease precludes any randomized trials. However, the observation that NLPHL behaves more like an indolent lymphoma and has an overall good prognosis has raised controversy regarding optimal management in order to avoid overtreatment. This latter aspect is emphasized in very-long-term follow-up showing that risk of death from toxicity was 3-fold higher than risk of death from lymphoma in patients with early-stage disease.[250]

Early-stage disease is treated with either radiation alone or abbreviated chemotherapy plus radiation. Patients with stage IA disease with full excision may be observed. The choice of chemotherapy is controversial; most groups recommend ABVD for two to four cycles plus radiation, but retrospective data suggest that alkylating agents are more effective, and CHOP or CVP can be used.[215,251,252] Survival for early-stage disease is excellent and approximates 90% with at least 10 years of follow-up. Patients with advanced-stage disease can be treated with six cycles of ABVD, CHOP, or CVP (reviewed in Savage et al.[215]). Since NLPHL expresses CD20, the addition of rituximab to management strategies has been evaluated. As a single agent, rituximab has a response rate of 94 to 100% and may be palliative in relapsed settings.[253-255] R-CHOP appears very active in a small series of patients with no relapses at 42 months.[256] Patients with asymptomatic, relapsed disease may not need treatment, as prolonged survival is common. The major risk in NLPHL survivors appears to be transformation to DLBCL (or T-cell rich diffuse large B-cell lymphoma, [TCR-DLBCL]), which should be treated as any transformed aggressive B-cell lymphomas.

KEY POINTS

- HL is composed of classical HL (nodular sclerosis, mixed cellularity, lymphocyte-rich, lymphocyte-depleted) and NLPHL, each of which has a distinctive clinical presentation, treatment paradigm, and prognosis.
- Classical HL of any stage is curable in the majority of afflicted patients.
- Combination chemotherapy with ABVD is the standard chemotherapy for classical HL in North America.
- The number of courses of chemotherapy varies with the stage of the disease.
- Low-dose, involved-field radiation therapy is commonly administered following a short course of chemotherapy for the management of early-stage classical HL, although the role of radiotherapy is undergoing reevaluation.
- PET-adapted therapy is now incorporated into treatment, although the ideal way to implement this is still being investigated.
- HL expresses CD30, which can be targeted by the antibody-drug conjugate brentuximab vedotin.
- Amplification of 9p24 is common in classical HL and leads to overexpression of PDL-1.
- NLPHL is a type of HL that behaves similarly to indolent lymphomas and usually expresses CD20. There is a risk of transformation to DLBCL, usually a T-cell rich variant.

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MULTIPLE MYELOMA

S. Vincent Rajkumar, MD

Recent Updates

- In patients who are in complete response, estimation of minimal residual disease (MRD) through next-generation flow cytometry (NGF) or next-generation sequencing (NGS) provides important prognostic information. (Flores-Montero J, *Leukemia* 2017; Martinez-Lopez J, *Blood* 2014)
- Response to therapy is assessed using the Revised International Myeloma Working Group uniform response criteria. (Kumar S, *Lancet Oncol* 2016)
- Bortezomib, lenalidomide, dexamethasone (VRd) has been found to improve overall survival compared with lenalidomide plus dexamethasone (Rd) and is the preferred initial therapy in multiple myeloma. (Durie BGM, *Lancet* 2017)
- Progression-free survival is improved with frontline autologous transplantation (early transplantation) compared with autologous transplantation done at first relapse (delayed transplantation), but overall survival is similar in the context of modern therapy. (Attal M, *N Engl J Med* 2017)
- Lenalidomide maintenance following autologous stem cell transplantation prolongs overall survival in a meta-analysis of randomized trials. (Attal M, *J Clin Oncol* 2016)
- Two daratumumab-based triplet regimens daratumumab/lenalidomide/dexamethasone (DRd) and daratumumab/bortezomib/dexamethasone (DVd) have shown benefit in relapsed multiple myeloma. (Dimopoulos MA, *N Engl J Med* 2016; Palumbo A, *N Engl J Med* 2016)
- A randomized trial showed that administration of zoledronic acid once every 3 months may be as effective as monthly administration for the reduction of skeletal complications of multiple myeloma. (Himelstein AL, *JAMA* 2017)

OVERVIEW

Multiple myeloma is a plasma cell malignancy characterized by osteolytic bone lesions, anemia, hypercalcemia, and renal failure.[1,2] The disease is generally considered incurable, and the clinical course is typically characterized by remissions and relapses, with a decrease in the remission duration with each successive therapy.[3] However, the survival of patients with multiple myeloma has improved dramatically in recent years, with an increase in the 3-year survival rate from approximately 40% with melphalan/prednisone prior to 2000 to more than 80% today. This improvement can be attributed to incorporation of drugs such as thalidomide,[4] bortezomib,[5] lenalidomide,[6,7] carfilzomib,[8] and pomalidomide[9,10] into the overall treatment strategy, as well as the use of autologous stem cell transplantation (ASCT) in selected patients and improvements in supportive care, particularly the use of bisphosphonates.

DISEASE DEFINITION

The definition of *multiple myeloma* was updated by the International Myeloma Working Group

in 2014.[11] The revised definition incorporates specific biomarkers associated with a high risk of progression to symptomatic disease and advanced imaging methods to make the diagnosis of myeloma in patients who do not have standard features of end-organ damage. Multiple myeloma is currently determined by the presence of 10% or more clonal plasma cells on bone marrow examination or biopsy-proven plasmacytoma, plus evidence of one or more of the following myeloma-defining events (MDEs): evidence of hypercalcemia, renal insufficiency, anemia, or bone lesions that can be attributed to the plasma cell proliferative disorder; clonal bone marrow plasma cells 60% or higher; serum free light chain (FLC) ratio 100 or more, provided involved FLC level is 100 mg/L or more; or more than one focal lesion on magnetic resonance imaging (MRI). Patients with multiple myeloma must be differentiated from those with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), and other related plasma cell disorders (Table 18-1).[11-17] Diagnostic criteria provided in the Table replace older criteria that were previously in use.[18,19] MGUS is an asymptomatic premalignant phase of multiple myeloma.[20,21] The risk of progression of MGUS to myeloma or a related disorder is fixed at approximately 1% per year.[21] SMM is a more advanced intermediate stage, defined by the presence of a serum monoclonal protein greater than 3 g/dL or 10 to 60% clonal plasma cells in the marrow but without MDE or amyloidosis. SMM is not a unique biologic stage of disease evolution, but is an intermediate clinical entity that must be differentiated from MGUS and multiple myeloma (Table 18-1), primarily for prognostic and management reasons.[22] In a study of 276 patients with SMM, the risk of progression to multiple myeloma in the first 5 years following diagnosis was 10% per year, 3% per year over the next 5 years, and 1% per year thereafter.[23]

KEY POINTS

- The diagnosis of myeloma requires evidence of one or more MDEs: hypercalcemia, renal insufficiency, anemia, or bone lesions that can be attributed to the plasma cell proliferative disorder; clonal bone marrow plasma cells 60% or higher; serum FLC ratio ≥100, provided involved FLC level is ≥100 mg/L; or more than one focal lesion on MRI.
- MGUS and SMM are asymptomatic plasma cell proliferative disorders that need to be distinguished from myeloma.

EPIDEMIOLOGY AND RISK FACTORS

Multiple myeloma accounts for 1% of all malignant disease and slightly more than 10% of all hematologic malignancies. The annual incidence, age-adjusted to the 2000 U.S. population, is 4.3 per 100,000.[24] In 2017, approximately 30,280 new cases are expected to occur in the United States, and 12,590 deaths are expected to be attributable to myeloma.[25] Myeloma is twice as common in the black population as in the white population.[26] The median age of patients at diagnosis is about 65. There is no known etiology. Exposure to radiation, benzene, and other organic solvents, herbicides, and insecticides may play a role. There is an increased risk of multiple myeloma in first-degree relatives.

KEY POINTS

- Multiple myeloma accounts for 1% of all cancers and approximately 10% of all hematologic cancers.
- Myeloma is twice as common in the black population as in the white population.

PATHOGENESIS

Multiple myeloma is almost always preceded by a premalignant phase, referred to as "MGUS."[27] However, because MGUS is asymptomatic and can be detected only through specific laboratory testing, most patients with multiple myeloma do not have a history of MGUS. The pathogenesis of multiple myeloma involves two initial steps: (1) development of the premalignant MGUS stage; and (2) progression of MGUS to multiple myeloma. The evolution of a normal plasma cell to an MGUS clone is likely triggered by an abnormal response to antigenic stimulation. This results in the development of primary cytogenetic abnormalities in the affected plasma cells. In approximately 40 to 50% of MGUS cases, the primary cytogenetic abnormality is a reciprocal translocation involving the immunoglobulin heavy-chain (IgH) locus on chromosome 14q32 (IgH-translocated MGUS) and one of five recurrent partner chromosome loci: 11q13 *(CCND1* [cyclin D1 gene]), 4p16.3 (*FGFR-3* and *MMSET*), 6p21 (*CCND3* [cyclin D3 gene]), 16q23 (*c-maf*), and 20q11 (*mafB*) (Table 18-2).[28] In most of the remaining patients with MGUS, the primary abnormality is the development of trisomies of one or more of the odd-numbered chromosomes, often resulting in hyperdiploidy (referred to as "hyperdiploid MGUS" or "IgH nontranslocated MGUS").[29] In a small proportion of cases, neither trisomies nor IgH translocations are found, and in some patients both types of abnormalities are found in the same clone.

Table 18-1 Diagnostic Criteria for Plasma Cell Disorders

Disorder	Disease Definition	References
Non-IgM MGUS	All 3 criteria must be met: • Serum monoclonal protein (non-IgM type) < 3g/dL • Clonal bone marrow plasma cells < 10%* • Absence of end-organ damage such as CRAB that can be attributed to the plasma cell proliferative disorder	Rajkumar et al.[11]
Smoldering multiple myeloma	Both criteria must be met: • Serum monoclonal protein (IgG or IgA) ≥ 3g/dL, or urinary monoclonal protein ≥ 500 mg per 24 hr and/or clonal bone marrow plasma cells 10 to 60% • Absence of MDEs or amyloidosis	Rajkumar et al.[11]
Multiple myeloma	Both criteria must be met: • Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma • Any one or more of the following MDEs: ○ Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: ■ Hypercalcemia: serum calcium > 0.25 mmol/L (> 1 mg/dL) more than the upper limit of normal or > 2.75 mmol/L (> 11 mg/dL) ■ Renal insufficiency: creatinine clearance < 40 mL/min or serum creatinine > 177 μmol/L (> 2 mg/dL) ■ Anemia: hemoglobin value of > 2 g/dL below the lower limit of normal, or a hemoglobin value < 10 g/dL ■ Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET/CT ○ Clonal bone marrow plasma cell ≥ 60% ○ Involved:uninvolved serum FLC ratio ≥ 100 (involved FLC level must be ≥ 100 mg/L) ○ > 1 focal lesions on MRI studies ≥ 5 mm	Rajkumar et al.[11]
IgM MGUS	All 3 criteria must be met: • Serum IgM monoclonal protein < 3g/dL • Bone marrow lymphoplasmacytic infiltration < 10% • No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder.	Rajkumar et al.[11]
Smoldering Waldenström macroglobulinemia (also referred to as "indolent or asymptomatic Waldenström macroglobulinemia")	Both criteria must be met: • Serum IgM monoclonal protein ≥ 3g/dL and/or bone marrow lymphoplasmacytic infiltration ≥ 10% • No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder	Rajkumar et al.[11]; Kyle et al.[12]; Gobbi et al.[13]; Baldini et al.[14]; Owen et al.[15]
Waldenström macroglobulinemia	All criteria must be met: • IgM monoclonal gammopathy (regardless of the size of the M protein) • ≥ 10% bone marrow lymphoplasmacytic infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype (e.g., surface IgM+, CD5+/-, CD10-, CD19+, CD20+, CD23-) that satisfactorily excludes other lymphoproliferative disorders, including chronic lymphocytic leukemia and mantle cell lymphoma • Evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder	Rajkumar et al.[11]; Kyle et al.[12]; Gobbi et al.[13]; Baldini et al.[14]; Owen et al.[15]
Light-chain MGUS	All criteria must be met: • Abnormal FLC ratio (< 0.26 or > 1.65) • Increased level of the appropriate involved light chain (increased kappa FLC in patients with ratio > 1.65 and increased lambda FLC in patients with ratio < 0.26) • No immunoglobulin heavy-chain expression on immunofixation • Absence of end-organ damage that can be attributed to the plasma cell proliferative disorder • Clonal bone marrow plasma cells < 10% • Urinary monoclonal protein < 500 mg/24 hr	Rajkumar et al.[11]
Solitary plasmacytoma	All 4 criteria must be met: • Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells • Normal bone marrow with no evidence of clonal plasma cells • Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) • Absence of end-organ damage such as CRAB that can be attributed to a lymphoplasma cell proliferative disorder	Rajkumar et al.[11]
Solitary plasmacytoma with minimal marrow involvement†*	All 4 criteria must be met • Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells • Clonal bone marrow plasma cells < 10% • Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) • Absence of end-organ damage such as CRAB that can be attributed to a lymphoplasma cell proliferative disorder	Rajkumar et al.[11]
Systemic AL amyloidosis‡	All 4 criteria must be met: • Presence of an amyloid-related systemic syndrome (such as renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement) • Positive amyloid staining by Congo red in any tissue (e.g., fat aspirate, bone marrow, or organ biopsy) • Evidence that amyloid is light-chain–related established by direct examination of the amyloid using MS-based proteomic analysis, or immunoelectron microscopy • Evidence of a monoclonal plasma cell proliferative disorder (serum or urine M protein, abnormal FLC ratio, or clonal plasma cells in the bone marrow)	Rajkumar et al.[11]
POEMS syndrome§	All 4 criteria must be met: • Polyneuropathy • Monoclonal plasma cell proliferative disorder (almost always lambda) • Any one of the following 3 other major criteria: 1. Sclerotic bone lesions 2. Castleman disease 3. Elevated levels of VEGF¶ • Any one of the following 6 minor criteria: 1. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) 2. Extravascular volume overload (edema, pleural effusion, or ascites) 3. Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)** 4. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails) 5. Papilledema 6. Thrombocytosis/polycythemia	Rajkumar et al.[11]; Dispenzieri et al.[16]; Dispenzieri[17]

Abbreviations: AL amyloidosis, light-chain amyloidosis; CRAB, hypercalcemia, renal insufficiency, anemia, and bone lesions; CT, computed tomography; FLC, free light chain; MDEs, myeloma-defining events; MGUS, monoclonal gammopathy of undetermined significance; MRI, magnetic resonance imaging; MS, mass spectrometry; PET/CT, positron-emission tomography/CT; POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes; VEGF, vascular endothelial growth factor.
*A bone marrow test can be deferred in patients with low-risk MGUS (IgG type, M protein < 15 g/L, normal free light chain ratio) in whom there are no clinical features of myeloma.
†Solitary plasmacytoma with ≤10% clonal plasma cells is considered to be multiple myeloma.
‡Approximately 2 to 3% of patients with AL amyloidosis will not meet the requirement for evidence of a monoclonal plasma cell disorder listed here; the diagnosis of AL amyloidosis must be made with caution in these patients. Patients with AL amyloidosis who also meet criteria for multiple myeloma are considered to have both diseases.
§Not every patient meeting the listed criteria will have POEMS syndrome; the features should have a temporal relationship to each other and no other attributable cause. Anemia and/or thrombocytopenia are distinctively unusual in this syndrome unless Castleman disease is present.
¶The source data do not define an optimal cutoff value for considering elevated VEGF level as a major criterion. We suggest that VEGF measured in the serum or plasma should be at least 3- to 4-fold higher than the normal reference range for the laboratory that is doing the testing to be considered a major criterion
**In order to consider endocrinopathy as a minor criterion, an endocrine disorder other than diabetes or hypothyroidism is required, since these two disorders are common in the general population.
Reprinted from Lancet Oncol 2014;15:e538-e548, Rajkumar SV, Dimopoulos MA, Palumbo A, et al., International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma, Copyright (2014), with permission from Elsevier. PMID: 25439696.

Once an MGUS clone is established, the second step of progression to multiple myeloma follows a simple, random, two-hit genetic model of malignancy. Although several alterations, such as abnormalities involving the *myc* family of oncogenes, *Ras* mutations, *p16* methylation, and *p53* mutations, have been associated with malignant transformation of MGUS to multiple myeloma, the specific pathogenetic steps are unknown. Studies indicate that there is significant clonal heterogeneity in myeloma, with different dominant clones emerging through the course of various treatments.[30]

Progression of MGUS to myeloma is typically accompanied by an increase in RANKL (receptor activator of nuclear factor kappa B ligand), expression by osteoblasts, and a reduction in the level of its decoy receptor, osteoprotegerin (OPG).[31] This leads to an increased RANKL/OPG ratio, a key factor for osteoclast activation and subsequent bone resorption.

Increased levels of macrophage inflammatory protein 1-alpha (MIP-1α), stromal-derived factor alpha (SDF-α), interleukin (IL)-3, IL-1β, and IL-6 may also play a role in osteoclast activation. At the same time, increased levels of IL-3, IL-7, and dickkopf 1 (DKK1) contribute to inhibition of osteoblast differentiation. This combination of osteoclast activation and osteoblast suppression leads to the pure osteolytic bone disease that is the hallmark of multiple myeloma.

Table 18-2 Cytogenetic categories of MGUS and MM

Cytogenetic Type	Gene(s) Involved	Comment
I. Hyperdiploid MGUS or MM	Unknown; likely many	Characterized by trisomies of one or more odd-numbered chromosomes; in patients with myeloma, hyperdiploidy considered standard risk
II. IgH translocated (nonhyperdiploid) MGUS or MM		Reciprocal translocation involving the *IgH* gene on chromosome 14q32 and a variety of partner chromosomes
t(11;14)	*CCND1* (cyclin D1)	
t(4;14) MM	*FGFR-3* and *MMSET*	
t(14;16) MM	*c-MAF*	Considered to indicate high-risk disease in setting of MM
t(6;14) MM	*CCND3* (cyclin D3)	
t(14;20) MM	*mafB*	Considered to indicate high-risk disease in setting of MM
III. Unclassified MGUS or MM		

Abbreviations: IGH, immunoglobulin heavy-chain; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma.
Permission to reuse given by Dr. SV Rajkumar from Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia *2009;23:3-9. PMID: 18971951.*

KEY POINTS

- Myeloma is preceded by a premalignant phase, clinically referred to as “MGUS.”
- The two principal pathogenetic steps are (1) transition from normal plasma cell to MGUS, and (2) transition from MGUS to myeloma.
- The onset of MGUS is associated with IgH translocations in about 50% of the cases and hyperdiploidy in the remaining 50% of cases.
- Progression of MGUS to multiple myeloma is associated with overexpression of RANKL (receptor activator of nuclear factor kappa B ligand), reduction in the level of its decoy receptor, OPG, and osteoblast inhibition that together lead to bone destruction.

PREVENTION

Prevention of myeloma is hampered by the low likelihood of progression in patients with the premalignant MGUS stage. If deaths due to unrelated competing causes are taken into account, myeloma will develop in only 10% of patients with MGUS. In SMM, the risk of progression in the first 5 years is considerably higher, at approximately 50%. Thus, preventive strategies for multiple myeloma have focused on preventing progression in high-risk patients (≥ 10% bone marrow plasma cells [BMPCs] and either a monoclonal protein level of ≥3 g/dL or the presence on an aberrant plasma cell immunophenotype in > 95% of clonal PCs plus

reduction in the level of normal immunoglobulins) with newly diagnosed SMM. A randomized trial conducted by the Spanish Myeloma Group in patients with high-risk SMM found improved progression-free and overall survival with early use of lenalidomide plus dexamethasone versus observation.[32] However, more data are needed, and for most patients with SMM, observation remains the standard of care.[33]

KEY POINT

- Early intervention with lenalidomide has shown promise in the treatment of SMM, but the standard of care remains observation. Additional clinical trials are ongoing to determine the role of preventive therapy in SMM.

CLINICAL PRESENTATION AND DIAGNOSIS

The most common presenting symptoms of multiple myeloma are fatigue and bone pain.[34] Osteolytic bone lesions and/or compression fractures are hallmarks of the disease and can be detected on routine radiography, MRI, or computed tomography (CT) scans in approximately 70% of patients.[31] Anemia occurs in 70% of patients at diagnosis and is the primary cause of weakness and fatigue. Hypercalcemia is found in 15% of patients. Other symptoms may result from acute renal failure, radiculopathy, or infection.

When multiple myeloma is suspected, patients should be tested for the presence of monoclonal (M) proteins by serum protein electrophoresis (SPEP), serum immunofixation (SIFE), urine protein electrophoresis (UPEP), and urine immunofixation (UIFE). The serum FLC assay can be used for screening in place of these urine studies; however, once a monoclonal plasma cell disorder is identified, urine studies are required at diagnosis in addition to the FLC assay.[35] The serum FLC assay and urine studies help identify the subset of patients with multiple myeloma who lack M protein heavy-chain expression (light-chain multiple myeloma). Only 82% of patients with multiple myeloma have an M protein that is detectable on SPEP, whereas SIFE will identify an M protein in 93% of patients.[34] Combining serum studies with either urine studies or the serum FLC assay will reveal an M protein in 97 to 98% of patients with multiple myeloma.[34,35] Patients with serum M protein less than 1 g/dL and urine M protein less than 200 mg per day are considered to have oligosecretory myeloma. In addition, approximately 2 to 3% of patients with multiple myeloma have true nonsecretory disease with no evidence of an M protein on serum or urine immunofixation; a subset of these patients who also have a normal serum FLC ratio are considered to have true nonsecretory myeloma.[36]

Other tests considered essential are complete blood count (CBC), serum creatinine, calcium, beta-2 microglobulin, albumin, and lactate dehydrogenase (LDH). A unilateral bone marrow aspiration and biopsy is needed for the diagnosis. The monotypic nature of marrow plasma cells must be established by an abnormal kappa:lambda ratio found on immunohistochemistry or flow cytometry. Myeloma cells typically stain positive for CD38, CD56, and CD138. Bone marrow plasma cells should also be studied with fluorescence in situ hybridization (FISH) and/or karyotyping to enable risk stratification (see section on Staging and Risk Stratification).[37] FISH studies do not require dividing cells; hence, they are considerably more informative in myeloma than conventional karyotyping, which requires the presence of metaphases.

Examination of all bones using plain radiography or, preferably, whole-body low-dose CT is

required for detecting lytic bone lesions (Fig. 18-1). MRI and/or fluorodeoxyglucose positron-emission tomography (FDG-PET) combined with CT (PET-CT) may be performed if symptomatic areas show no abnormality on routine radiography (Fig. 18-2). MRI and/or PET-CT or whole-body low-dose CT are required to differentiate SMM and solitary plasmacytoma from MM and are also useful in assessing extramedullary disease, and also whenever there is a concern that the disease assessment may be inadequate with plain radiography and M protein assessments alone.

DIFFERENTIAL DIAGNOSIS

Myeloma should be differentiated from MGUS, SMM, solitary plasmacytoma, Waldenström macroglobulinemia, and light chain (AL) amyloidosis using the criteria listed in Table 18-1.[11] Note that patients with MGUS may have symptoms from unrelated conditions and that to make the diagnosis of multiple myeloma, the observed end-organ damage (anemia, hypercalcemia, renal failure, or bone lesions) must be thought to be attributable to the underlying plasma cell disorder.

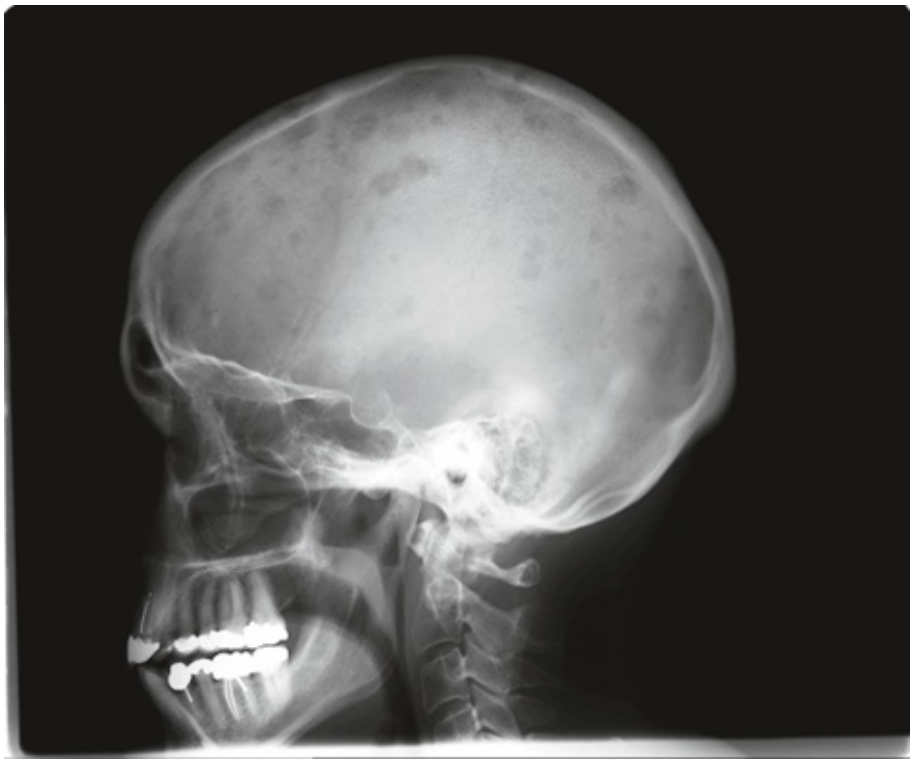

Fig. 18-1 Skull x-ray showing multiple osteolytic lesions.

MONITORING

Once multiple myeloma is diagnosed, patients require periodic measurements of CBC, serum creatinine, serum calcium, and M protein by SPEP and UPEP to assess treatment response and to monitor for relapse. In patients with oligosecretory myeloma (serum M protein <1 g/dL and urine M protein < 200 mg/24 hours) and in some patients with nonsecretory myeloma, the serum FLC assay can be used to monitor response to therapy, provided the FLC ratio is abnormal and the level of the involved FLC is 100 mg/L or higher.[38] In patients with oligosecretory myeloma who have lower levels of FLC and in patients with true nonsecretory myeloma, monitoring is more difficult and requires periodic radiographic studies and bone marrow examinations. Serum and urine tests for monitoring are done monthly during active

therapy and once every 3 to 4 months thereafter. Radiographic tests are done every 6 to 12 months, depending on response to treatment, as well as when symptoms indicate the need for this testing. Bone marrow studies are repeated if needed to confirm complete response or when clinically indicated to assess relapse. In patients who are in complete response, estimation of minimal residual disease (MRD) using next-generation flow cytometry (NGF) or next-generation sequencing (NGS) provides important prognostic information; however, there are no data yet on using MRD results to guide therapy.[39,40] Response to therapy is assessed using the Revised International Myeloma Working Group uniform response criteria (Table 18-3).[41]

STAGING AND RISK STRATIFICATION

The two traditional methods of staging multiple myeloma were the Durie–Salmon stage (DSS),[42] and the International Staging System (ISS).[43] However these staging systems have many limitations, and they do not account for the considerable variation in outcome that is dictated by the underlying cytogenetics of the disease. Patients with del(17p) and translocations t(14;16) and t(14;20) are considered to have high-risk myeloma. Patients with t(4;14) are considered intermediate-risk. Patients who do not have any of these abnormalities, typically those with trisomies or translocations t(11;14) and t(6;14), are considered to have standard-risk myeloma.[37,44] The presence of concomitant trisomies may ameliorate the adverse prognosis associated with intermediate- and high-risk myeloma. The Revised International Staging System (RISS) is the current recommended system for multiple myeloma and incorporates important markers of disease biology, including cytogenetics, in order to provide a more accurate estimation of prognosis than prior staging systems (Table 18-4).[45]

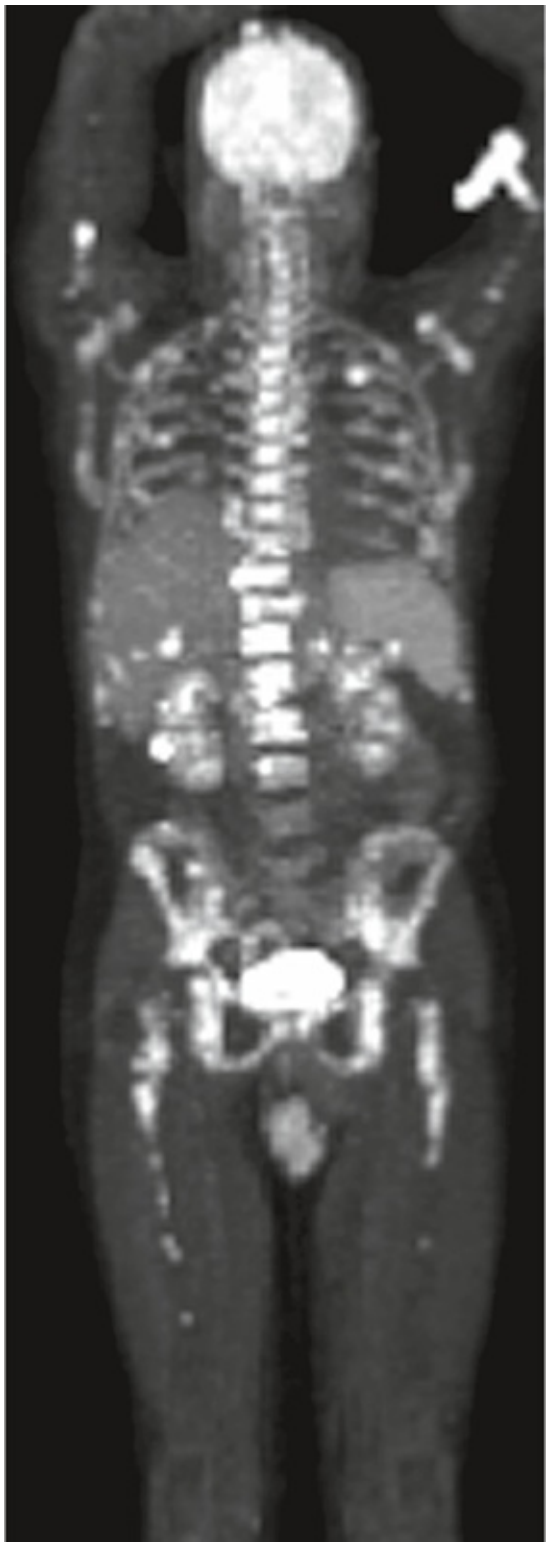

Fig. 18-2 Positron-emission tomographic (PET) scan showing multiple bone lesions with increased uptake of fluorodeoxyglucose (FDG) consistent with active myeloma.

There is also extramedullary involvement within the liver, gallbladder, kidney, and pancreas.

KEY POINTS

- The most common presenting symptoms of multiple myeloma are fatigue and bone pain; other presenting features are hypercalcemia, infection, and acute renal failure.
- When multiple myeloma is suspected, patients should be tested for the presence of M proteins by SPEP, SIFE, and the serum FLC assay.

- Bone imaging studies and a bone marrow biopsy are required if multiple myeloma is suspected.
- Patients are staged using the RISS.
- Patients with *17p* deletion and translocations t(14;16) and t(14;20) are considered to have high-risk myeloma. Patients with t(4;14) are considered intermediate-risk. Patients with trisomies or translocations t(11;14) and t(6;14), are considered to have standard-risk myeloma.
- The presence of concomitant trisomies ameliorates the adverse prognosis associated with intermediate- and high-risk myeloma.

THERAPEUTIC MANAGEMENT

Table 18-5 provides a list of the most commonly used treatment regimens in multiple myeloma.[46-49,51-58] Table 18-6 provides the results of recent randomized trials with these regimens in multiple myeloma.[46,51,52,55-63]

INITIAL THERAPY

The overall approach to therapy in patients with newly diagnosed multiple myeloma is shown on Fig. 18-3.[1] The most commonly used regimen in the United States for the treatment of newly diagnosed multiple myeloma is bortezomib/lenalidomide/dexamethasone (VRd). Other commonly used frontline regimens include bortezomib/cyclophosphamide/dexamethasone (VCd), bortezomib/thalidomide/dexamethasone (VTd), and lenalidomide/low-dose dexamethasone (Rd).

Initial therapy for myeloma must take into account the eligibility of the patient for ASCT. In general, eligibility for stem cell transplantation is determined by age, performance status, and comorbidities. In the United States, the upper age limit for ASCT may be as high as 75, as long as patients are in good functional status without significant comorbidities. In most European countries, patients age 65 or older are not considered candidates for ASCT. Patients who are not candidates for ASCT are treated with a regimen such as VRd for approximately 12 months followed by Rd.[51] Patients who are considered potential candidates for ASCT are first treated with two to four cycles of a triplet regimen such as VRd followed by a stem cell harvest (Fig. 18-3).[37] After stem cell harvest, most patients proceed to ASCT (early ASCT approach), while some may choose to continue the initial treatment regimen and delay ASCT until relapse (delayed ASCT approach).

Table 18-3 **International Myeloma Working Group Criteria for Response Assessment, Including Criteria for Minimal Residual Disease (MRD) in Multiple Myeloma***

Flow MRD–negative	Absence of phenotypically aberrant clonal plasma cells by NGF[4] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of ≥ 1 in 10^5 nucleated cells
Sequencing MRD–negative	Absence of clonal plasma cells by NGS on bone marrow aspirates in which presence of a clone is defined as < 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the Lymphosight platform (or validated equivalent method) with a sensitivity of ≥ 1 in 10^5 nucleated cells[5]
CR	Negative immunofixation on the serum AND urine[11] AND disappearance of any soft-tissue plasmacytomas AND < 5% plasma cells in bone marrow aspiration
VGPR	Serum and urine M protein detectable by immunofixation but not on electrophoresis OR ≥ 90% reduction in serum M protein PLUS urine M-protein level < 100 mg/24 hr
PR	≥ 50% reduction of serum M protein PLUS reduction in 24-hr urinary M protein by ≥ 90% or to < 200 mg/24 hr. If the serum and urine M protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M protein are unmeasurable, and serum FLC is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M protein, provided baseline bone marrow plasma cell ≥ 30%. In addition to the above-listed criteria, if present at baseline, a ≥ 50% reduction in the size (SPD)[12] of soft tissue plasmacytomas is also required
MR	≥ 25% but ≤ 49% reduction of serum M protein AND reduction in 24-hour urine M protein by 50–89% In addition to the above-listed criteria, if present at baseline, a ≥ 50% reduction in the size (SPD) of soft tissue plasmacytomas is also required.
SD	(Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates) Not meeting criteria for CR, VGPR, PR, MR, or PD
PD[8,9]	Any one or more of the following: • Increase of 25% from lowest confirmed response value in one or more of the following: ▪ Serum M protein (absolute increase must be ≥ 0.5 g/dL) ▪ Serum M protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL ▪ Urine M protein (absolute increase must be ≥ 200 mg/24 hr) ▪ In patients without measurable serum and urine M protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) ▪ In patients without measurable serum and urine M protein levels and without measurable involved FLC levels, bone marrow plasma cell percentage irrespective of baseline status (absolute % increase must be ≥ 10%) • Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD of more than one lesion, or ≥ 50% increase in the greatest diameter of a lesion previously > 1 cm in short axis • ≥50% increase in circulating plasma cells (minimum of 200/μL) if this is the only measure of disease

Abbreviations: CR, complete response; FLC, free light chain; MR minimal response; MRD, minimal residual disease; NGF , next-generation flow cytometry; NGS, next-generation sequencing; MM, multiple myeloma; PD, progressive disease; PR, partial response; SD, stable disease; SPD, sum of the products of the maximum perpendicular diameter; VGPR, very good partial response.

*All response categories except MRD require two consecutive assessments made at anytime before the institution of any new therapy.

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TREATMENT FOR PATIENTS NOT CANDIDATES FOR ASCT

For patients who are not candidates for ASCT, melphalan-based regimens are no longer preferred as first-line therapy. In a randomized trial, Rd given until progression improved overall survival in comparison to melphalan/prednisone/thalidomide (MPT) (4-year survival rate 59% and 51%, respectively), leading to the approval of Rd as initial therapy for myeloma in the United States and several other countries.[62] In a more recent trial, progression-free survival (PFS) and overall survival (OS) were superior with VRd compared with Rd.[51] The median PFS was 43 months vs. 30 months ($p = 0.0018$); median OS was 75 months vs. 64 months ($p = 0.025$). Following the results of this trial, VRd is now considered the standard regimen for initial therapy in the United States, except in frail patients, in whom Rd remains an option. VCd and VTd are alternatives to VRd in patients who lack access to lenalidomide and in patients who

present with acute renal failure due to light-chain cast nephropathy.[49,60] The risk of bortezomib-induced neuropathy can be greatly decreased by using a once-weekly schedule of bortezomib[63,65] as well as a subcutaneous route of administration.[66]

Table 18-4 Revised International Staging System for Multiple Myeloma

Stage	Frequency (% of patients)	5-Year Survival Rate (%)
Stage I • ISS Stage I (serum albumin > 3.5, serum beta-2-microglobulin < 3.5) and • No high-risk cytogenetics • Normal LDH	28%	82
Stage II • Neither Stage I or III	62%	62
Stage III • ISS Stage III (serum beta-2-microglobulin > 5.5) and • High-risk cytogenetics [t(4;14), t(14;16), or del(17p)] or elevated LDH	10%	40

Abbreviations: ISS, International Staging System; LDH, lactate dehydrogenase.
Derived from: Palumbo A, Avet-Looiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: a report from International Myeloma Working Group. J Clin Oncol. 2015;33:2863-2869. PMID: 26240224.

The specific regimen used for initial therapy varies across countries, depending on the availability of lenalidomide. In countries with access to lenalidomide, one reasonable treatment approach is VRd for 12 months followed by Rd maintenance for fit patients with standard risk and VRd for 12 months followed by bortezomib-based maintenance for intermediate- and high-risk patients (Fig. 18-3). Rd until progression is a reasonable option for frail, older patients and for patients age 75 or older.

TREATMENT FOR CANDIDATES FOR ASCT

The overall approach to the initial treatment of patients who are candidates for ASCT is shown in Figure 18-3. Three-drug combinations such as VRd, VCd, and bortezomib/thalidomide/dexamethasone (VTd) are the most common regimens used for induction therapy in patients eligible for ASCT.[51,60] VRd was associated with a higher response rate and a greater depth of response compared with Rd in one randomized trial.[51] Although this trial was performed in the nontransplantation setting, the data are interpreted to apply to pretransplantation induction as well. Thus, VRd is the preferred induction regimen for the treatment of newly diagnosed multiple myeloma in patients who are candidates for ASCT.

However, VCd and VTd remain alternatives if there is lack of access to lenalidomide or in the setting of acute renal failure with light-chain cast nephropathy. A randomized trial by the Eastern Cooperative Oncology Group (ECOG) found that lenalidomide plus low-dose dexamethasone (40 mg of dexamethasone once a week) was superior to lenalidomide plus high-dose dexamethasone (40 mg of dexamethasone on days 1 to 4, 9 to 12, and 17 to 20) in terms of OS.[46] Based on this trial, the use of high-dose dexamethasone is no longer recommended in newly diagnosed multiple myeloma, and almost all new regimens including VRd and VCd use the once-weekly schedule of dexamethasone.

The use of lenalidomide for more than six cycles can impair collection of peripheral-blood stem cells in some patients when granulocyte colony-stimulating factor (G-CSF) alone is used for stem cell mobilization.[67] Stem cell mobilization in these patients is usually successful with a chemotherapy-containing mobilization regimen such as cyclophosphamide and G-CSF, or with the use of plerixafor, a CXCR4 inhibitor.

Phase II studies show that the combination of carfilzomib/lenalidomide/dexamethasone (KRd) is highly active in newly diagnosed myeloma.[68] However, carfilzomib is significantly more expensive and cumbersome compared with bortezomib; therefore, KRd is not generally chosen as initial therapy outside the context of clinical trials. An ongoing randomized trial coordinated by ECOG is testing VRd versus KRd in newly diagnosed myeloma (NCT01863550).

In patients with very aggressive disease (plasma-cell leukemia or extramedullary disease) combination chemotherapy such as bortezomib/dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (VDT-PACE) can be used as initial therapy to achieve rapid disease control.[69] Numerous other combinations have been developed, but randomized controlled trials have not shown a clear effect on long-term endpoints compared with the regimens just discussed.

KEY POINTS

- The preferred regimen for initial therapy of multiple myeloma is the triplet regimen VRd.
- VCd and VTd are alternatives, and they are preferred in the setting of acute renal failure with light-chain cast nephropathy.

Table 18-5 **Common Treatment Regimens in Multiple Myeloma**

Regimen	Usual Dosing Schedule*
Lenalidomide (Revlimid)/ dexamethasone (Rd)[46]	Lenalidomide 25 mg PO on days 1-21 every 28 days Dexamethasone 40 mg PO on days 1, 8, 15, and 22 every 28 days Repeated every 4 weeks
Pomalidomide/ dexamethasone (Pom/Dex)[47]	Pomalidomide 4 mg PO on days 1-21 Dexamethasone 40 mg PO on days 1, 8, 15, and 22 Repeated every 4 weeks
Bortezomib (Velcade)/ thalidomide/ dexamethasone (VTD)†[48]	Bortezomib 1.3 mg/m^2 IV on days 1, 8, 15, and 22 Thalidomide 100-200 mg PO on days 1-21 Dexamethasone 20 mg PO on day of and day after bortezomib (or 40 mg on days 1, 8, 15, and 22) Repeated every 4 weeks for 4 cycles as pretransplantation induction therapy
Bortezomib/ cyclophosphamide/ dexamethasone (VCD or CyBorD)†[47,49,50]	Cyclophosphamide 300 mg/m^2 PO on days 1, 8, 15, and 22 Bortezomib 1.3 mg/m^2 IV on days 1, 8, 15, and 22 Dexamethasone 40 mg PO on days on days 1, 8, 15, and 22 Repeated every 4 weeks‡
Bortezomib/lenalidomide/ dexamethasone (VRd)†,[51]	Bortezomib 1.3 mg/m^2 IV on days 1, 8, and 15 Lenalidomide 25 mg PO on days 1-14 Dexamethasone 20 mg PO on day of and day after bortezomib (or 40 mg on days 1, 8, 15, and 22) Repeated every 3 weeks§
Carfilzomib (Kyprolis)/ lenalidomide, dexamethasone (KRD)[52]	Carfilzomib 20 mg/m^2 (cycle 1) and 27 mg/ m^2 (subsequent cycles) IV on days 1, 2, 8, 9, 15, and 16 Lenalidomide 25 mg PO on days 1-21 Dexamethasone 20 mg PO on day of and day after bortezomib (or 40 mg on days 1, 8, 15, and 22) Repeated every 4 weeks
Carfilzomib/ cyclophosphamide/ dexamethasone (KCD) ¶[53]	Carfilzomib 20 mg/m^2 (cycle 1) and 36 mg/m^2 (subsequent cycles) IV on days 1, 2, 8, 9, 15, and 16 Cyclophosphamide 300 mg/m^2 PO on days 1, 8, and 15 Dexamethasone 40 mg PO on days on days 1, 8, and 15 Repeated every 4 weeks
Carfilzomib/pomalidomide/ dexamethasone (KPD)[54]	Carfilzomib 20 mg/m^2 (cycle 1) and 27 mg/ m^2 (subsequent cycles) IV on days 1, 2, 8, 9, 15, and 16 Pomalidomide 4 mg PO on days 1-21 Dexamethasone 40 mg PO on days 1, 8, and 15 Repeated every 4 weeks
Carfilzomib/lenalidomide/ dexamethasone (KRD)[52]	Carfilzomib 20 mg/m^2 (cycle 1) and 27 mg/m^2 (subsequent cycles) IV on days 1, 2, 8, 9, 15, and 16 Lenalidomide 25 mg PO on days 1-21 Dexamethasone 20 mg PO on day of and day after bortezomib (or 40 mg on days 1, 8, 15, and 22) Repeated every 4 weeks
Daratumumab/lenalidomide/ dexamethasone (DRd)[55]	Daratumumab 16 mg/kg IV weekly for 8 weeks, then every 2 weeks for 4 months, and then once a month Lenalidomide 25 mg PO on days 1-21 Dexamethasone 40 mg PO on days 1, 8, 15, and 22 Lenalidomide, dexamethasone repeated in usual schedule every 4 weeks
Elotuzumab/lenalidomide/ dexamethasone (ERd)[56]	Elotuzumab 10 mg/kg IV weekly for 8 weeks, and then every 2 weeks Lenalidomide 25 mg PO on days 1-21 Dexamethasone 40 mg PO on days 1, 8, 15, and 22 Lenalidomide, dexamethasone repeated in usual schedule every 4 weeks
Ixazomib/lenalidomide/ dexamethasone (IRd)[57]	Ixazomib 4 mg PO on days 1, 8, and 15 Lenalidomide 25 mg PO on days 1-21 Dexamethasone 40 mg PO on days 1, 8, 15, and 22 Repeated every 4 weeks
Daratumumab/bortezomib/ dexamethasone (DVd)†[58]	Daratumumab 16 mg/kg IV weekly for 8 weeks, then every 2 weeks for 4 months, and then once a month Bortezomib 1.3 mg/m^2 SC on days 1, 8, 15, and 22 Dexamethasone 20 mg PO on day of and day after bortezomib (or 40 mg on days 1, 8, 15, and 22 Bortezomib/dexamethasone repeated in usual schedule every 4 weeks
Panobinostat/bortezomib†[59]	Panobinostat 20 mg PO three times a week for 2 weeks Bortezomib 1.3 mg/m^2 IV on days 1, 8, and 15 Repeated every 3 weeks

*All doses need to be adjusted for performance status, renal function, blood counts, and other toxic effects.
†Doses of dexamethasone and/or bortezomib reduced based on subsequent data showing lower toxicity and similar efficacy with reduced doses.
‡The day 22 dose of all 3 drugs is omitted if counts are low, after initial response to improve tolerability, or when the regimen is used as maintenance therapy; When used as maintenance therapy for high-risk patients, further delays can be instituted between cycles.
§Omit day 15 dose if counts are low or when the regimen is used as maintenance therapy; When used as maintenance therapy for high-risk patients, lenalidomide dose may be decreased to 10-15 mg per day, and delays can be instituted between cycles as done in total therapy protocols.
¶Dosing based on trial in newly diagnosed patients; in relapsed patients cycle 2 Carfilzomib dose is 27 mg/m2 consistent with approval summary
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AUTOLOGOUS STEM CELL TRANSPLANTATION

ASCT is not curative for multiple myeloma, but prolongs median OS by approximately 12 months.[70,71] The treatment-related mortality rate is very low (1 to 2%), and 40 to 50% of ASCT can be done entirely on an outpatient basis.[72] Melphalan (at a dose of 200 mg/m^2) is used as the standard conditioning regimen, and trials are underway trying to improve the efficacy of the conditioning regimen. ASCT can be done immediately following initial therapy, or it can be delayed until first relapse. In either case, stem cells must be collected early in the disease course. A randomized trial that used VRd as initial therapy found that although PFS is superior with early ASCT (median, 50 months vs. 36 months, $p < 0.001$), OS is similar whether ASCT is performed early (after induction therapy) or late (at first relapse) (4-year OS rate, 83%).[73] In

general, based on superior PFS, early ASCT is preferred. However, patient and physician preferences play an important role in deciding the timing of ASCT, especially in standard-risk patients. Although some earlier randomized trials showed a benefit with two ASCTs done back to back (tandem ASCT),[74] one randomized trial conducted in the United States found no benefit with tandem ASCT in the context of modern therapy.[75]

ALLOGENEIC STEM CELL TRANSPLANTATION

Allogeneic transplantation offers the potential benefit of a graft-versus-myeloma effect. However, conventional myeloablative allogeneic transplantation has a limited role in multiple myeloma because of high treatment-related mortality. One study found a significant OS advantage with ASCT followed by nonmyeloablative allogeneic transplantation compared with ASCT alone.[76,77] However, other trials have not shown such a benefit.[78-80] Although safer, nonmyeloablative transplantation is associated with a greater risk of relapse and has not shown a consistent benefit compared to ASCT alone. At present, allogeneic transplantation is generally not recommended for the treatment of multiple myeloma outside of clinical trials, except in patients under age 60 years with high-risk disease who are experiencing relapse after initial therapy.

MAINTENANCE THERAPY

Maintenance therapy with interferon-alpha, corticosteroids, and thalidomide results in a relatively modest benefit considering its high cost and toxicity.[81] Three randomized studies have shown superior PFS with lenalidomide maintenance post-ASCT.[82-84] In one trial, a significant OS benefit was found with lenalidomide maintenance therapy,[82] and this was confirmed on a subsequent meta-analysis of the three trials.[85] An increased risk of second cancers was seen in two randomized trials with lenalidomide maintenance (approximately 7% in the lenalidomide group compared with 3% in the placebo group; $p < 0.01$), and this needs to be discussed with the patient and monitored during follow-up (Table 18-7).[82,83] Lenalidomide maintenance is recommended for patients with standard-risk multiple myeloma following ASCT. In intermediate- and high-risk patients, the benefit of lenalidomide maintenance is unclear. Bortezomib maintenance (administered twice a month) following ASCT has also shown benefit, and may be considered for patients with high- or intermediate-risk cytogenetics.[86]

KEY POINTS

- Patients who are considered potential candidates for ASCT are first treated with three to four cycles of VRd, followed by a stem cell harvest. After stem cell harvest, patients can either proceed to early ASCT or continue initial treatment regimen and delay ASCT until relapse.
- After ASCT, patients receive maintenance therapy with lenalidomide (standard risk) or bortezomib (intermediate- or high-risk).

Table 18-6 **Results of Selected Randomized Trials in Multiple Myeloma**

Trial	Regimen	No. of Patients	Overall Response Rate (%)	CR plus VGPR (%)	Progression-free Survival (median in months)	p-value for Progression-free Survival	Overall Survival*	p-value for Overall Survival
Newly Diagnosed Myeloma								
Rajkumar et al.[46]	RD	223	81	50	19.1		75% at 3 years	
	Rd	222	70	40	25.3	0.026	74% at 3 years	0.47
Durie et al.[64]	Rd	261	72	32	31.0	0.002	75 (median in months)	0.025
	VRd	264	82	43	43.0		64 (median in months)	
Moreau et al.[60]	VCD	170	84	66	NA		NA	NA
	VTD	170	92	77	NA	NA	NA	
Attal et al.[61]	VRd	350	NA	46% CR	NR; 48% at 3 years		88% at 3 years	0.25
	VRd-ASCT	350	NA	58% CR	NR; 61% at 3 years	< 0.001	88% at 3 years	
Relapsed Myeloma								
Lonial et al.[56]	Rd	325	66	28	14.9		NA	NA
	ERd	321	79	33	19.4	< 0.001	NA	
Stewart et al.[52]	Rd	396	67	14	17.6		65% at 2 years	0.04
	KRd	396	87	32	26.3	0.0001	73% at 2 years	
Moreau et al.[57]	Rd	362	72	7	14.7		NA	NA
	IRd	360	78	12	20.6	0.01	NA	
Dimopoulos et al.[55]	Rd	283	76	44	18.4	<0.001	87% at 1 year	NS
	DRd	286	93	76	NR		92% at 1 year	
San-Miguel et al.[59]	Vd	381	55	6	8.1		30.4 (median in months)	0.26
	Pano-Vd	387	61	11	12.0	<0.0001	33.7 (median in months)	
Palumbo et al.[58]	Vd	247	63	29	7.2	<0.001	70% at 1 year	0.30
	DVd	251	83	59	NR		80% at 1 year	

*Estimated from survival curves when not reported.

Abbreviations: ASCT, autologous stem cell transplantation; CR, complete response; DRd, daratumumab/lenalidomide//dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; ERd, elotuzumab/lenalidomide/dexamethasone; IRd, ixazomib/lenalidomide/dexamethasone; KRd, carfilzomib/lenalidomide/dexamethasone; NA, not available; NR, not reached; NS, not significant; Pano-Vd, panobinostat/bortezomib/dexamethasone; Rd, lenalidomide plus low-dose dexamethasone; RD, lenalidomide plus high-dose dexamethasone; VCD, bortezomib/cyclophosphamide/dexamethasone; Vd, bortezomib/dexamethasone; VGPR, very good partial response; VRd, bortezomib/lenalidomide/dexamethasone; VTD, bortezomib/ thalidomide/dexamethasone.

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TREATMENT OF RELAPSED DISEASE

Almost all patients with MM eventually experience relapse, and with each relapse, the remission duration decreases progressively.[87,88] In general, patients can be retreated with regimens that have been effective in the past, if the initial remission duration was longer than 6 months. Alternatively, regimens that contain active drugs that the patient has not received before can also be tried (Table 18-5). In patients with extramedullary plasmacytomas or plasma cell leukemia, multidrug regimens such as VDT-PACE for 1 to 2 months may be used in an attempt to gain better disease control, but they are associated with greater toxicity. A second ASCT is feasible, although remission durations are approximately 50% of what was achieved with the first ASCT. Since there are no randomized trials, a second ASCT is used in patients who have had a reasonable duration of remission with the first ASCT. Thus, patients who obtain

a remission duration of longer than 36 months with maintenance therapy (or longer than 18 months without maintenance therapy) following the first ASCT are potential candidates for a second ASCT as salvage therapy.

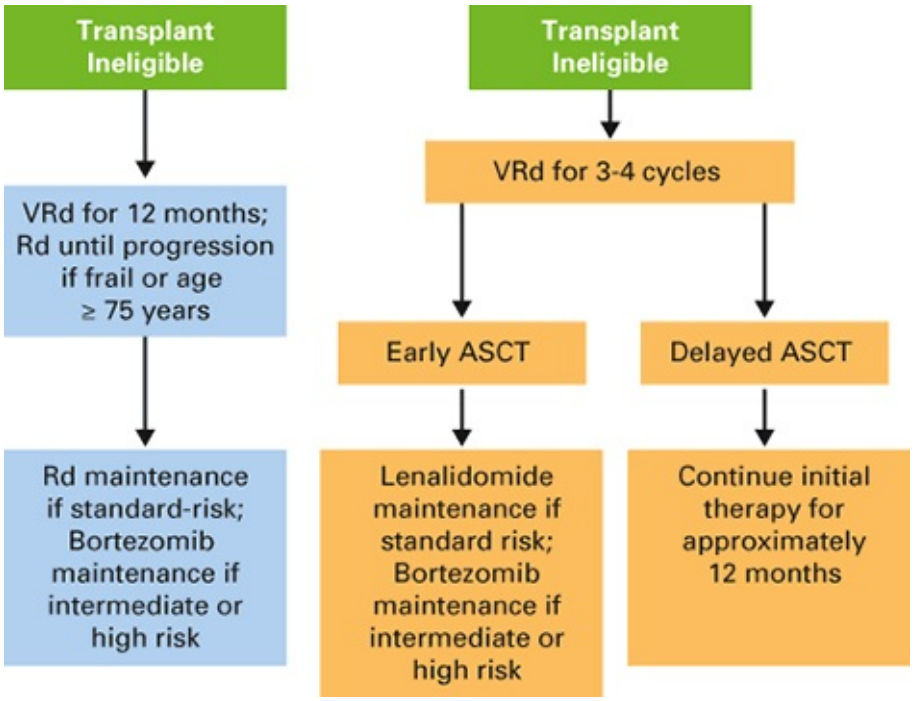

Fig. 18-3 Treatment approach for newly diagnosed patients with myeloma.

Abbreviations: ASCT, autologous stem-cell transplantation; CR, complete response; VGPR, very good partial response; Rd, lenalidomide plus low-dose dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone.

Newer options for patients with relapsed refractory myeloma include the following:

- Pomalidomide (an analog of lenalidomide)[89]
- Carfilzomib (a proteasome inhibitor)[52]
- Panobinostat (a deacetylase inhibitor)[59]
- Ixazomib (an oral proteasome inhibitor)[57]
- Elotuzumab (a monoclonal antibody targeting SLAMF7)[56]
- Daratumumab (a monoclonal antibody targeting CD38)[55,58]

Panobinostat and elotuzumab lack single-agent activity in multiple myeloma but provide clinical benefit in combination with other active agents; in contrast, the other drugs listed have a single-agent activity of approximately 25% in relapsed disease. In recent randomized trials, triplet combinations containing these new drugs have been found to improve response rates and prolong PFS compared with backbone doublet regimens (Table 18-6). However, the newer triplet regimens have not been compared head-to-head in randomized trials, so the choice of a specific regimen at the time of relapse is based on many factors, such as response to prior therapy, aggressiveness of the relapse, patient characteristics, ease of use, and cost. Based on the effect size seen in randomized trials, reasonable options for the treatment of first relapse are daratumumab/lenalidomide/dexamethasone (DRd) for patients whose disease is not refractory to lenalidomide (defined as those who experience a relapse off-therapy or on small doses of single-agent lenalidomide) and daratumumab/bortezomib/dexamethasone (DVd) for patients whose disease is refractory to lenalidomide.[90] Alternatives to the treatment of first

and subsequent relapse include the regimens listed on Table 18-6.

Other combinations that have shown activity in phase II trials incorporate pomalidomide in place of lenalidomide and include regimens such as carfilzomib/pomalidomide/dexamethasone (KPd) and daratumumab/pomalidomide/dexamethasone (DPd). Four-drug combinations that add daratumumab to a standard triplet such as VRd or KRd are also being studied.

Patients with relapsed refractory myeloma should also be considered for clinical trials. Other investigational agents with single-agent activity in myeloma include marizomib and oprozomib (proteasome inhibitors), filanesib (kinesin spindle protein inhibitor), isatuximab (monoclonal antibody to CD38), dinaciclib (cyclin-dependent kinase inhibitor), venetoclax (Bcl-2 inhibitor), LGH447 (PIM kinase inhibitor), and selinexor (XPO-1 inhibitor).[91] Checkpoint inhibitors such as pembrolizumab and cellular therapy using chimeric antigen receptor T cells (CAR-T cells) targeting the B-cell maturation antigen (BCMA) are also showing promise in clinical trials.

KEY POINTS

- Several triplet combinations have been shown to be effective for the treatment of relapsed myeloma.
- Daratumumab (targeting CD38) and elotuzumab (targeting SLAMF7) are the first monoclonal antibodies approved for the treatment of myeloma.

TREATMENT OF COMPLICATIONS AND PALLIATIVE CARE

TREATMENT OF DISEASE COMPLICATIONS

Patients with multiple myeloma should receive bisphosphonates (pamidronate or zoledronic acid) once per month for 1 to 2 years to prevent bone disease.[92-94] In a randomized trial, OS was improved in multiple myeloma with the use of zoledronic acid as prophylactic therapy.[95] A more recent randomized trial suggests that a reduced frequency of administration (once every 3 months) may be as effective as monthly administration.[96] Preliminary data suggest that denosumab is also effective in the prevention of bone disease in multiple myeloma and has shown a benefit in PFS compared with zoledronic acid in a randomized controlled trial. However, more data are needed to determine the optimal patient population who may benefit from this drug.[97] Calcium supplementation and daily vitamin D supplementation is needed for patients receiving bisphosphonates. Surgical fixation of fractures or impending fractures of long bones can be performed as needed. Palliative local radiation should be limited to patients with disabling pain that has not responded to analgesics and systemic therapy. Vertebroplasty and kyphoplasty may be useful to decrease pain.[98] Severe hypercalcemia can develop in some patients with multiple myeloma. This is a medical emergency and requires treatment with hydration, corticosteroids, and either pamidronate (60 to 90 mg IV over 2 to 4 hours) or zoledronic acid (4 mg IV over 15 minutes).

Table 18-7 **Results of Randomized Phase III Trials of Lenalidomide Maintenance in Myeloma after Autologous Stem Cell Transplantation**

Trial	Regimen	No. of Patients	Median PFS (months)	p-value for PFS	3-Year Overall Survival Rate (%)*	Median Overall Survival (months)	p-value for OS	Second Cancers (%)†	Reported p-value for Second Cancer Incidence
McCarthy et al.[82]	Placebo Lenalidomide maintenance	229 231	27 46	< 0.001	80 88	NR NR	0.03‡	2.6 7.7	0.008
Attal et al.[83]	Placebo Lenalidomide maintenance	307 307	23 41	< 0.001	84 80	NR NR	0.70	3.0 7.5	0.002

*Estimated from survival curves when not reported.
†Excludes nonmelanoma skin cancers.
‡Derived from Cox proportional-hazard models; not clear whether two-tailed or whether or not adjustment for covariates was done. Abbreviations: NR, not reported; OS, overall survival; PFS, progression-free survival.
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Renal failure is common in multiple myeloma and can be multifactorial. Volume depletion, nonsteroidal anti-inflammatory agents, infection, hypercalcemia, and radiographic contrast media may also contribute to renal failure. The most common cause of acute renal failure is light-chain cast nephropathy, which requires prompt therapy to lower serum light-chain levels. The role of plasmapheresis is controversial, but may be incorporated in conjunction with VCd to treat patients with myeloma who present with proven or suspected acute light-chain cast nephropathy with a goal of reducing the involved FLC level to less than 500 mg/L.[99,100]

Other disease-related complications include anemia, infections, and hyperviscosity syndrome. Anemia usually improves with treatment of the underlying multiple myeloma, but some patients may require transfusions or erythropoietin. Intravenous gamma globulin is indicated only if patients have recurrent serious infections associated with severe hypogammaglobulinemia. Hyperviscosity syndrome manifests with symptoms such as epistaxis, mucosal bleeding, headache, and blurred vision. Hyperviscosity syndrome requires emergent plasmapheresis.

MANAGEMENT OF DRUG TOXICITY

The major side effects with thalidomide are sedation, constipation, and peripheral neuropathy. In contrast, the major side effects of lenalidomide are anemia, neutropenia, and thrombocytopenia. Both drugs cause fatigue. Because of the risk of teratogenicity, the use of any of the immunomodulatory agents (thalidomide, lenalidomide, and pomalidomide) in pregnant patients is absolutely contraindicated. Further, to prevent teratogenicity, there are strict requirements that must be met before these drugs can be prescribed. Patients receiving thalidomide, lenalidomide, and pomalidomide are also at significant risk of venous and arterial thrombotic events and require thromboprophylaxis with aspirin, low-molecular-weight heparin, or warfarin.[101,102] Thalidomide, lenalidomide, and pomalidomide can cause a skin rash that can be serious in a small proportion of patients. Medications such as sulfonamides and allopurinol may increase the risk and severity of skin toxicity and should be avoided if possible. Treatment with thalidomide, lenalidomide, and pomalidomide can lead to thyroiditis and subsequent hypothyroidism. Thyroid-function tests should be performed at baseline and every 3 to 4

months thereafter while a patient is on this therapy. Severe diarrhea can develop in approximately 10 to 15% of patients taking lenalidomide for a prolonged time. The treatment is cessation of therapy, standard antimotility agents, and a bile acid sequestrant such as colestipol. Lenalidomide requires dose reduction in patients with renal failure; the starting dose should be reduced to 10 mg per day in patients with creatinine clearances of 30 to 60 mL/min, 15 mg every other day with creatinine clearances less than 30 mL/min, and 5 mg per day for patients who are on dialysis.

The major side effects of bortezomib are gastrointestinal toxicity, thrombocytopenia, and neuropathy. The best way to reduce the risk of neuropathy is to use bortezomib in the once-weekly schedule instead of the twice-weekly schedule, and SC instead of IV administration. Patients who are being treated with bortezomib (and other proteasome inhibitors) are at high risk for reactivation of herpes zoster, and routine prophylaxis with acyclovir is recommended. Neuropathy is less of a risk with ixazomib and carfilzomib compared with bortezomib. The main side effects of ixazomib are nausea and diarrhea. Major side effects of carfilzomib include fatigue, nausea, cytopenias, and shortness of breath.[103] Carfilzomib can also cause significant cardiac dysfunction in approximately 5% of patients; this must be considered carefully in the treatment of elderly patients.

The main adverse reactions with daratumumab and elotuzumab are infusion-related reactions, which are mostly seen with the first dose. With daratumumab, approximately 50% of patients may have a grade 3 or higher infusion reaction with the first dose; but this decreases to less than 5% with subsequent doses. Panobinostat is associated with grade 3 or higher diarrhea in more than 20% of patients; further study is needed to determine the optimal role of this agent.

Because steroids play a major role in the treatment of multiple myeloma, patients often have major steroid-related side effects. These are best prevented by using the lowest possible dose of steroids. During the first few months of therapy, dexamethasone 40 mg once a week is sufficient.[46] Some patients require a lower dose even at the outset. After the first few months, an attempt should be made to rapidly reduce the dose of steroids.

Bisphosphonate therapy is associated with a risk of osteonecrosis of the jaw, and dental hygiene should be assessed prior to initiation of bisphosphonate therapy. Other drug-induced complications include myelodysplastic syndrome and a risk of second primary malignancies.

KEY POINTS

- Patients with multiple myeloma should receive bisphosphonates prophylactically to prevent skeletal-related events.
- Severe hypercalcemia is a medical emergency and requires treatment with hydration, corticosteroids, and intravenous bisphosphonates.
- The most common cause of acute renal failure is light-chain cast nephropathy, which requires prompt therapy to lower serum light-chain levels.
- Patients receiving thalidomide, lenalidomide, and pomalidomide are at significant risk for venous and arterial thrombotic events and require routine thromboprophylaxis.
- The best way to reduce the risk of neuropathy is to use bortezomib in the once-weekly schedule instead of the twice-weekly schedule, and SC instead of IV administration.

- The standard dose of steroids to be used in myeloma therapy usually should not exceed dexamethasone 40 mg once per week (or equivalent) unless there is an emergent need.

RELATED DISORDERS

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

MGUS is a premalignant precursor of multiple myeloma.[20,21] It is defined by a serum M protein concentration lower than 3 g/dL, less than 10% clonal plasma cells in the bone marrow, and absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency that can be attributed to a plasma cell disorder.[104] The three subtypes of MGUS are non-IgM MGUS, IgM MGUS, and light-chain MGUS (Table 18-1). MGUS is present in more than 3 to 4% of the population older than age 50.[20] The risk of MGUS is significantly higher in the black population compared with the white population.[105,106] The risk of MGUS is also higher in first-degree relatives of patients with MGUS or multiple myeloma[107] and in those exposed to certain pesticides.[108]

MGUS is asymptomatic, but in a small subset of patients it may be associated with sensorimotor peripheral neuropathy (MGUS neuropathy), membranoproliferative glomerulonephritis (MPGN), lichen myxedematosus (papular mucinosis, scleromyxedema), pyoderma gangrenosum, or necrobiotic xanthogranuloma. The main clinical significance of MGUS is its lifelong risk of transformation to multiple myeloma or related malignancy at a rate of 1% per year.[21] The size and type of the M protein at diagnosis of MGUS and an abnormal serum FLC ratio are prognostic factors for progression (Table 18-8).[109] The baseline bone marrow evaluation can be deferred in patients with low-risk MGUS and patients with IgM MGUS who have a normal FLC ratio and no anemia, lymphadenopathy, or organomegaly.[110] Similarly, bone imaging at diagnosis can be deferred in patients with low-risk MGUS or IgM MGUS if there are no clinical concerns for multiple myeloma or related disorder. There is no treatment needed for MGUS. Patients with low risk MGUS should be followed at 6 months, and subsequently at the time of symptoms that may indicate progression. All other patients with MGUS should be followed at 6 months and if stable, yearly thereafter.

SMOLDERING MULTIPLE MYELOMA

Smoldering (asymptomatic) multiple myeloma (SMM) is defined by the presence of an M protein level ≥ 3 g/dL in the serum, or an M protein level ≥ 500 mg per 24 hours in the urine, and/or 10% or more plasma cells in bone marrow in the absence of MDE or amyloidosis (Table 18-1).[11,23,104,111] It is differentiated from MGUS and light-chain MGUS based on the size of the M protein and the level of marrow involvement. The risk of progression to multiple myeloma or related plasma cell disorder is 10-fold higher than with MGUS. The risk stratification of SMM is shown in Table 18-9.[112] The current standard of care for most patients with SMM is observation every 3 to 4 months. One randomized trial found improved PFS and OS with early use of lenalidomide plus dexamethasone versus observation in patients with high-risk SMM, but more data are needed before this regimen can be considered a standard approach in this setting.[32]

Table 18-8 **Risk-Stratification Model to Predict Progression of Monoclonal Gammopathy of Undetermined Significance to Myeloma or Related Disorders**

Risk Group	No. of Patients	Relative Risk	Absolute Risk of Progression at 20 Years	Absolute Risk of Progression at 20 Years Accounting for Death as a Competing Risk
Low risk (serum M protein < 1.5 g/dL, IgG subtype, normal FLC ratio (0.26–1.65)	449	1	5%	2%
Low-intermediate risk (any one factor abnormal)	420	5.4	21%	10%
High-intermediate risk (any two factors abnormal)	226	10.1	37%	18%
High risk (all three factors abnormal)	53	20.8	58%	27%

Abbreviation: FLC, free light chain.

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SOLITARY PLASMACYTOMA

Solitary plasmacytoma is an early-stage plasma cell malignancy that is in between MGUS/SMM and multiple myeloma along the spectrum of plasma cell disorders. It is defined by the presence of a single biopsy-proven plasmacytoma (bony or extramedullary) and a normal bone marrow examination.[104] An M protein may be present in serum or urine at diagnosis, but usually disappears with therapy. Treatment consists of radiation therapy 40 to 50 Gy to the involved site. Patients with an apparent solitary plasmacytoma who have limited (< 10%) clonal marrow involvement are considered to have solitary plasmacytoma with minimal marrow involvement (Table 18-1); these patients are also treated similarly to patients with solitary plasmacytoma. The risk of recurrence or progression to myeloma within 3 years is approximately 10% in patients with solitary plasmacytoma versus 20 to 60% in patients with solitary plasmacytoma and minimal marrow involvement.

PLASMA CELL LEUKEMIA

Plasma cell leukemia is an aggressive form of multiple myeloma characterized by circulating clonal plasma cells in the peripheral blood and extramedullary disease. Treatment of plasma cell leukemia is unsatisfactory. Initial treatment with VRd or a multidrug regimen such as VDT-PACE for two to three cycles followed by ASCT and subsequent maintenance therapy is a reasonable strategy.

IMMUNOGLOBULIN LIGHT CHAIN (AL) AMYLOIDOSIS

Amyloid is a proteinaceous substance that consists of rigid, linear, nonbranching fibrils, 7.5 to 10 nm in width, aggregated in a beta-pleated sheet conformation.[113] It is detected on Congo red staining based on the classic apple-green birefringence. The several types of amyloidosis are classified on the basis of the major protein component of the amyloid. In AL amyloidosis, the fibrils consist of the variable portion of a monoclonal light chain. AL amyloidosis is an infrequent consequence of clonal plasma cell disorders and may be seen with MGUS, SMM, or multiple myeloma (Table 18-1). It is a systemic disease that can affect numerous organs such as the tongue (macroglossia), heart, liver, kidney, peripheral nerves, and lungs. The standard treatment is a bortezomib-based regimen (e.g., VCD) for approximately 1 year. Eligible patients can also be considered for ASCT.[114] The goal of therapy is to achieve an involved FLC level of

less than 40 mg/L.

Table 18-9 **Definition of High-Risk Smoldering Multiple Myeloma***
Bone marrow clonal plasma cells ≥ 10% and any one or more of the following:
Serum M protein ≥ 30 g/L
IgA SMM
Immunoparesis with reduction of two uninvolved immunoglobulin isotypes
Serum involved/uninvolved FLC ratio ≥ 8 (but < 100)
Progressive increase in M-protein level (evolving type of SMM)†
Bone marrow clonal plasma cells 50–60%
Abnormal plasma cell immunophenotype (≥95% of bone marrow plasma cells are clonal) and reduction of one or more uninvolved immunoglobulin isotypes
t (4;14) or del 17p or 1q gain
Increased circulating plasma cells
MRI with diffuse abnormalities or 1 focal lesion
PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction

Abbreviations: FLC, free light chain; M, monoclonal; MRI, magnetic resonance imaging; PET-CT, positron-emission tomography/computed tomography; SMM, smoldering multiple myeloma.

*Note that the term "smoldering multiple myeloma" excludes patients without end-organ damage who meet the revised definition of *multiple myeloma*, namely clonal bone marrow plasma cells ≥ 60% or FLC ratio ≥100 (plus measurable involved FLC level ≥ 100 mg/L) or more than one focal lesion on magnetic resonance imaging. The risk factors listed in here are not meant to be indications for therapy; they are variables associated with a high risk of progression of SMM and identify patients who need close follow-up and consideration for clinical trials

†Increase in serum monoclonal protein by ≥25% on two successive evaluations within a 6-month period.

WALDENSTRÖM MACROGLOBULINEMIA

Waldenström macroglobulinemia is a malignancy of plasma cells that have not yet undergone switch recombination.[115] It might better be considered a lymphoproliferative disorder pathologically and clinically similar to low-grade lymphomas, in which an IgM paraprotein is present. The neoplastic cells in Waldenström macroglobulinemia secrete IgM M protein, and have a morphologic appearance that is in between lymphocytes and true plasma cells, commonly referred to as "lymphoplasmacytic." The disease definition requires presence of an IgM M protein, 10% or greater bone marrow involvement, and a typical immunophenotype (e.g., surface IgM+, CD10−, CD19+, CD20+, CD23−) that would exclude other

lymphoproliferative disorders (Table 18-1).[104] Most patients with Waldenström macroglobulinemia have a recurrent mutation of the MYD88 gene (MYD88 L265P).[116] The main symptoms are weakness, fatigue, and hyperviscosity. Unlike in multiple myeloma, lytic bone lesions are not seen. Indications for therapy include symptomatic anemia, hyperviscosity, organomegaly, or other cytopenias. Initial treatment is typically with either bendamustine plus rituximab (BR) or dexamethasone/rituximab/cyclophosphamide (DRC).[117,118] In selected patients with limited disease, single-agent rituximab may be an option, but there is a risk of a "tumor flare" if single-agent rituximab is used, resulting in a rapid rise in IgM levels. Therefore, combination therapy is preferred for patients with high IgM monoclonal protein levels. Other active regimens for the treatment of Waldenström macroglobulinemia include bortezomib/rituximab/dexamethasone (BRD), cladribine, or fludarabine alone or in combination with rituximab, and Rd. Ibrutinib has shown remarkable activity in Waldenström macroglobulinemia and is rapidly becoming a preferred agent for the treatment of the disease.[119]

POEMS SYNDROME

This syndrome is characterized by polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS).[120] Patients with POEMS syndrome usually have osteosclerotic bone lesions or Castleman disease (a rare polyclonal lymphoproliferative disorder). The major clinical problem in POEMS is a severe chronic inflammatory–demyelinating polyneuropathy with predominantly motor features. Other abnormalities seem in POEMS syndrome are listed in Table 18-1. If the osteosclerotic lesions are in a limited area, radiation therapy is the treatment of choice. If there are widespread osteosclerotic lesions, treatment is similar to that for multiple myeloma.

KEY POINTS

- MGUS can progress to myeloma or a related malignancy at a rate of 1% per year.
- The risk of progression to myeloma or related plasma cell disorder in SMM is 10-fold higher than with MGUS.
- Solitary plasmacytoma is defined by the presence of a single biopsy-proven plasmacytoma (bony or extramedullary) and a normal bone marrow examination. Treatment consists of radiation therapy (40 to 50 Gy) to the involved site.
- Plasma cell leukemia is an aggressive form of myeloma characterized by circulating clonal plasma cells in the peripheral blood and extramedullary disease.
- AL amyloidosis is a systemic plasma cell proliferative disorder that can affect numerous organs such as the tongue (macroglossia), heart, liver, kidney, peripheral nerves, and lungs.
- Waldenström macroglobulinemia is a malignancy of plasma cells that secrete IgM M protein.
- POEMS syndrome is a rare plasma cell disorder characterized by polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes.

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HEMATOPOIETIC CELL TRANSPLANTATION

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Recent Updates

- Methods have been developed allowing for the identification of "permissive" HLA-C and HLA-DPB1 single antigen mismatched donors resulting in transplantation outcomes identical to those seen with completely matched unrelated donors. (Petersdorf EW, *N Engl J Med* 2015)
- For patients with acute leukemia, survival following myeloablative HCT using cord blood as the source of stem cells is at least as good as that seen using matched unrelated donors and may be advantageous for those with measurable residual disease. (Milano F, *N Engl J Med* 2016)
- A randomized trial comparing reduced-intensity versus myeloablative conditioning for treatment of AML showed decreased relapse rates and improved overall survival (OS) with the use of myeloablative conditioning. (Scott BL, *J Clin Oncol* 2017)
- The addition of antilymphocyte globulin to standard GVHD prophylaxis was shown to reduce the incidence of chronic GVHD without affecting OS. (Kroger N, *N Engl J Med* 2016)
- Based on the results of a phase 3 trial, defibrotide was approved by the FDA as treatment for severe sinusoidal obstruction syndrome. (Richardson PG, *Blood* 2016)

OVERVIEW

The term "bone marrow transplantation" was originally used to describe the process of transferring the lymphohematopoietic system from one individual to another. With the demonstration that peripheral blood and umbilical cord blood also can serve as sources of hematopoietic stem cells, the term "hematopoietic cell transplantation" (HCT) is now more appropriate. HCT can be used to replace an abnormal but nonmalignant hematopoietic system with one from a normal donor. HCT is also used to treat a variety of malignancies because it allows for the administration of higher doses of chemotherapy and radiotherapy than would otherwise be possible. And in the setting of allogeneic transplantation, it confers an immunologic graft-versus-tumor effect. Worldwide, more than 70,000 patients received HCTs in 2016 (http://www.cibmtr.org). The frequency of transplantation varied widely from country to country, with a close association of transplantation rates with gross national income (GNI) per capita.[1] However, substantial differences exist among countries with similar GNI per capita with regard to transplantation frequency, disease indication, and choice of donor. This chapter focuses on general principles of HCT, including stem cell source, preparative regimens, and complications. The role of transplantation in the treatment of specific diseases is discussed in greater detail in the chapters focused on those illnesses.

INDICATIONS

IMMUNODEFICIENCY STATES

Allogeneic transplantation can successfully establish a normal immune system for patients with severe combined immunodeficiency disorders; it also can correct the abnormalities associated with Wiskott–Aldrich syndrome and other immunodeficiency states.[2,3]

NONMALIGNANT DISORDERS OF HEMATOPOIESIS

The most data about and the best outcomes of transplantation for nonmalignant disorders of hematopoiesis are reported for severe aplastic anemia and thalassemia, with a growing experience for sickle cell anemia. A total of 90% of patients with severe aplastic anemia can be cured with allogeneic HCT from a matched sibling[4]; results are slightly less favorable if a matched unrelated donor is used.[5] Allogeneic HCT cures 70 to 90% of patients with thalassemia major, with the best results seen among patients who received the transplant before the development of hepatomegaly or portal fibrosis.[6] Although data for sickle cell disease are more limited, current reports document 5-year survival and disease-free survival of 93% and 84%, respectively.[6-8] Cures also have been obtained for other nonmalignant disorders of hematopoiesis, including Fanconi anemia,[9-11] Blackfan–Diamond syndrome, chronic granulomatous disease,[12] Kostmann syndrome, and leukocyte adhesion deficiency. However, because allogeneic transplantation still has significant and unpredictable complications, treatment recommendations should be based on identifying patients at high risk from their underlying diseases for whom the risk of HCT is justified.

INBORN ERRORS OF METABOLISM

Allogeneic HCT can replace the abnormal enzyme systems and result in cure for patients with mucopolysaccharidosis and Gaucher disease. Prior damage caused by the enzyme abnormality may not be reversible, arguing for early transplantation for the more severe syndromes.

MALIGNANT DISEASES

The most frequent use of HCT has been for the treatment of malignant diseases. In the United States, the leading indications for allogeneic transplantation are acute myeloid leukemia (AML; approximately 50%), followed by myelodysplasia (MDS) and acute lymphoblastic leukemia (ALL). Transplantation consistently achieves 5-year disease-free survival rates of 50 to 70% when performed for AML and ALL in first remission.[13] Meta-analyses of studies comparing the outcome of matched sibling allogeneic HCT compared with conventional chemotherapy for adult patients with these disorders show improved survival with HCT.[14-16] The advantages of transplantation are most apparent for patients with higher-risk leukemia and less for those with lower-risk disease. If transplantation is withheld until second remission, results are less favorable, with cure rates of 25 to 40%. Cure rates of 30 to 60% have been reported for patients with MDS who are treated with allogeneic HCT.[17] Because patients with early-stage MDS often live for long periods without treatment, HCT is generally reserved for patients with advanced-stage disease.[18,19] Although more than 70% of patients with chronic myeloid leukemia (CML) in the chronic phase can be cured with allogeneic HCT, transplantation is usually restricted to patients whose disease has progressed following initial therapy with a tyrosine kinase inhibitor.[20] Allogeneic HCT can reverse the marrow fibrosis and cure patients with primary myelofibrosis.[21] Allogeneic transplantation is also used in the treatment of patients with recurrent chronic lymphocytic leukemia and non-Hodgkin lymphoma with marrow involvement.[22]

The leading indication for autologous transplantation in the United States is multiple myeloma, followed by non-Hodgkin lymphoma and Hodgkin lymphoma. Prospective, randomized trials have shown that autologous transplantation, when used as part of initial therapy, prolongs life for patients with multiple myeloma, particularly when followed by lenalidomide maintenance therapy.[23,24] Autologous HCT is curative for 40 to 50% of patients with non-Hodgkin lymphoma or Hodgkin lymphoma that recurred following first-line therapy; these results are superior to what would be expected with additional chemotherapy.[25,26] Debate persists about the role of high-dose chemotherapy with autologous transplantation as part of initial therapy for patients with high-risk non-Hodgkin lymphoma and mantle cell lymphoma.[27] Autologous HCT also is used to treat chemosensitive solid tumors; the greatest experience is with testicular cancer and neuroblastoma.[28]

KEY POINT

- All diseases of hematopoiesis, both nonmalignant and malignant, are potentially curable with HCT.

SOURCE OF STEM CELLS

Hematopoietic stem cells used for transplantation can be categorized according to the relationship between the donor and the recipient or according to anatomic source. In the rare cases in which the patient has an identical (syngeneic) twin, HCT can be conducted without the risks of graft rejection or graft-versus-host disease (GVHD) because the individuals are genetically identical throughout the genome.

ALLOGENEIC TRANSPLANTATION

When the marrow of a patient is clearly abnormal (as in aplastic anemia and in most cases of leukemia), allogeneic rather than autologous transplantation is preferred. The best source of allogeneic hematopoietic stem cells is from an HLA-identical sibling. HLA molecules display both exogenous peptides (e.g., from an infecting organism) and endogenous peptides, presenting them to T cells to initiate an immune response. If two persons are HLA nonidentical, T cells from one person will react vigorously to the mismatched HLA molecules on the surface of cells from the second individual. The HLA molecules themselves are termed “major HLA determinants.” Even though nontwin siblings may be HLA-matched, the endogenous peptides presented by the HLA antigens will differ, resulting in T-cell responses against minor HLA determinants. The genes encoding HLA class I (*HLA-A, HLA-B,* and *HLA-C*) and class II (*HLA-DP, HLA-DQ,* and *HLA-DR*) are located on chromosome 6, are tightly linked, are codominantly expressed, and tend to be inherited as haplotypes with low recombination frequency (Fig. 19-1).[29] Thus, for any given patient, the likelihood that a full sibling will be HLA-matched with the patient is 25%. The likelihood of finding a matched sibling for a patient can be calculated by the formula $x = 1 - 0.75^n$, where x equals the probability of finding a matched sibling, and n equals the number of siblings. Given the size of families in the United States, the chance that a matched sibling can be identified for any patient is approximately 30%. Since hematopoietic stem cells do not express ABO, HCT can be carried out across ABO blood group barriers by removing incompatible red blood cells (RBCs) and/or isoagglutinins from the donor graft.[30]

However, even with appropriate manipulation of the donor graft, a major ABO mismatch (e.g., recipient O, donor A) can result in immediate or delayed hemolysis of donor RBCs by persistent recipient isohemagglutinins, and a minor mismatch (e.g., recipient B, donor O) can result in immediate hemolysis of recipient RBCs by donor-derived isohemagglutinins in the graft or delayed hemolysis of recipient RBCs by newly generated isohemagglutinins from donor lymphocytes (i.e., passenger lymphocytes).

Family members who are genotypically identical to the patient for one HLA haplotype and are either phenotypically identical or partially matched on the other HLA haplotype have been used as donors. Use of one-antigen–mismatched related donors results in a marginal increase in graft rejection, GVHD, and transplantation-related mortality.[31] If patients are undergoing transplantation for leukemia that is in remission, this degree of mismatching appears to result in a slightly worse outcome. However, if patients are undergoing transplantation for higher-risk leukemia, the increased graft-versus-tumor effect associated with a single mismatch appears to balance the negative effect.[32] Historically, when conventional forms of GVHD prophylaxis were used, results using donors mismatched for two or three major HLA determinants resulted in high rates of graft rejection or GVHD. However, newer techniques, including the use of post-transplantation high-dose cyclophosphamide, have been developed that allow the safe use of haploidentical donors who share one haplotype with the patient but are mismatched for two or more antigens on the nonshared haplotype.[33-35]

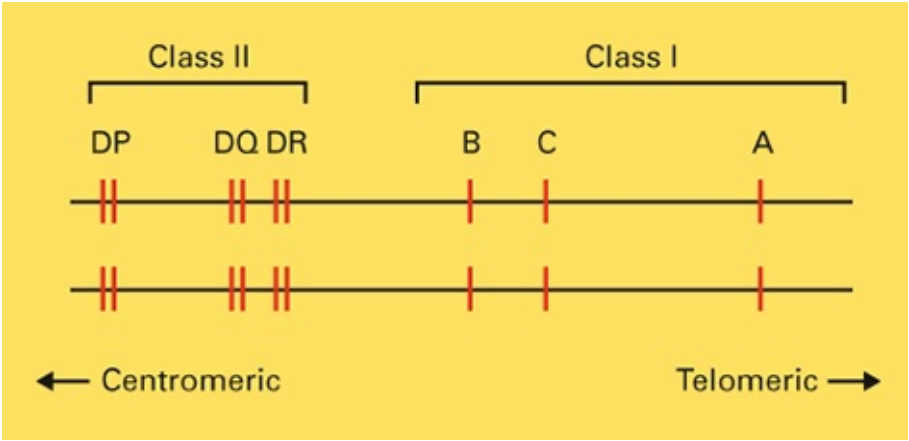

Fig. 19-1 Genes associated with human leukocyte antigen (HLA) typing.

The genes encoding HLA class I (*HLA-A, HLA-B,* and *HLA-C*) and class II (*HLA-DP, HLA-DQ,* and *HLA-DR*) are located on chromosome 6, are tightly linked, are codominantly expressed, and tend to be inherited as haplotypes with low recombination frequency. Thus, for any given patient, the likelihood that a full sibling will be HLA-matched with the patient is 25%.

Donors who are completely unrelated to the patient but are matched for *HLA-A, B*, *HLA*, and *DRB1* have been used in an increasing number of cases with promising results. Since the formation of the National Marrow Donor Program and other, international, registries, more than 25 million healthy individuals have volunteered to serve as stem cell donors. The likelihood of finding a fully matched unrelated donor varies among racial and ethnic groups from 75% for whites of European decent to a low of 16% for blacks of South and Central American descent. When compared with the outcome of matched sibling transplantation, transplants from unrelated donors matched with the patient at *HLA-A, B, C,* and *DRB1* are associated with greater morbidity, mostly from GVHD, but survival at 3 to 5 years posttransplantation is very similar.[36] A single-antigen mismatch is associated with more GVHD, higher treatment-related mortality, and lower survival.[37] In a study of 3857 unrelated transplantations, which largely

involved bone marrow as the source of stem cells, mismatches at *A* or *DRB1* were less well tolerated than mismatches at *B* or *C*. Mismatching at two loci was associated with greater risk.[38] Although HLA is the dominant factor affecting outcome, other donor factors, including age, sex, parity, and cytomegalovirus (CMV) serology, have a small but measurable impact.[39] If peripheral blood rather than marrow is the source of unrelated stem cells, mismatching for *HLA-C* appears to be less well tolerated.[40] It may be possible to identify "permissible" *HLA-C* mismatches with no greater risk than seen with fully matched unrelated donors.[41] More recently, mismatching at *HLA-DPB1* has been shown to increase the risk of transplant-related mortality and methods to identify permissive *HLA-DPB1* mismatches have been developed.[42]

Umbilical cord blood also is rich in hematopoietic stem cells, and studies have shown that cord blood can serve as a source of stem cells for transplantation. Because cord blood has relatively few mature T cells, the risk of GVHD with cord blood appears to be somewhat less than the risk associated with similarly matched marrow, although the risk of graft rejection or failure may be greater. Cord blood is sometimes used as a source of stem cells to treat family members suffering from hematologic disorders; survival is essentially equivalent to that seen following matched sibling bone marrow transplantation.[43] By far the most common use of cord blood has been in the treatment of unrelated recipients who lack matched related or unrelated donors. Because of the paucity of mature T cells in cord blood, matching criteria can be less stringent, allowing treatment for patients with one- or two-antigen mismatches. In an analysis of 1061 recipients of transplants from unrelated cord blood, the number of cells per kilogram infused was found to have a considerable influence on the outcome, as did patient age and degree of match with donors, with improved survival associated with higher cell dose, younger patient age, and greater degree of matching.[44] Low cord-blood-cell dose increased the risk of graft failure, delayed hematopoietic engraftment, and delayed immune recovery, which previously limited cord-blood transplantation to children and smaller adults.[45] Trials exploring the use of double-cord transplants (which serves to provide a greater cord-blood-cell dose) demonstrate that even though only one cord ultimately engrafts, the use of two cords reduces the risk of graft failure and is associated with an enhanced graft-versus-tumor effect.[46,47] There does not appear to be an advantage to the use of two cords in cases in which a single cord provides a sufficient number of cells, at least in children and young adults.[48]

With the availability of matched related, matched unrelated, single-antigen–mismatched related, haploidentical, and cord-blood donors, a source of allogeneic stem cells can be found for the vast majority of patients in need (Table 19-1). Although matched related donors are generally preferred, limited prospective randomized trials have compared alternative donors. Emerging data suggest relatively similar survival following matched unrelated, unrelated cord-blood, and haploidentical donor transplantation.[35,49,50] However, time to engraftment, graft failures rates, GVHD, transplant-related mortality, and relapse risk vary by donor source, and all must be taken into consideration when choosing an alternative donor.[51] For example, the increased graft-versus-tumor effects seen following cord-blood transplantation may favor its use for patients at high risk for relapse.[52]

On average, the time between initiating the search for an alternative donor and performing the transplantation is 3 to 4 months; however, in urgent circumstances, donors can be identified and grafts procured within 6 weeks.

KEY POINTS

- Although GVHD is more common following transplantation from matched unrelated donors than from matched siblings, survival rates appear similar.
- Methods have been developed that allow for the selection of "permissive" single-antigen–mismatched donors.
- Transplantation using either cord blood or haploidentical donors is feasible, meaning that an allogeneic donor can be found for the large majority of patients in need.

AUTOLOGOUS TRANSPLANTATION

The use of a patient's own (autologous) stem cells for transplantation also is possible. The most common indications for autologous transplantation are in the treatment of non-Hodgkin lymphoma and multiple myeloma. Autologous transplantation is also sometimes used to treat malignancies of nonhematopoietic origin, including neuroblastoma and germ cell tumors. The technique also has been explored as a treatment option for patients with AML and ALL, using stem cells collected during remission. In the cases of AML and ALL, enough patients have received transplants with either allogeneic or autologous marrow to allow for comparisons of the two therapies. In general, autologous transplantation is associated with fewer complications. GVHD does not occur, and the incidence of infectious complications, idiopathic pneumonia syndrome, and sinusoidal obstruction syndrome (formerly termed "veno-occlusive hepatic disease") are lower. However, the risk of tumor recurrence is higher with autologous transplantation, likely because of a lack of a graft-versus-tumor effect and tumor contamination of the reinfused stem cell product. Gene-marking studies have demonstrated that tumor cells within the transplanted marrow can contribute to relapse.[53] Ex vivo treatment of autologous stem cell collections to remove contaminating cells—although based on sound preclinical models—has not been adequately tested in prospective, randomized clinical studies.

BONE MARROW

Because bone marrow is rich in hematopoietic stem cells, it was used first as the source of stem cells for transplantation. Marrow for transplantation usually is obtained through multiple aspirations from the posterior and sometimes from the anterior iliac crests. To obtain as many marrow cells with as little peripheral-blood contamination as possible, the collection from each aspiration site is normally limited to 5 to 10 mL, and a total collection usually comprises approximately 1 to 1.5 L of marrow from a healthy adult donor.[54] The marrow is heparinized and filtered through screens to remove osseous spicules and fat globules before either being infused into the patient or cryopreserved for later transplantation. In some studies, the marrow has been treated before infusion or cryopreservation to test whether removal of T cells, or T-cell subsets, from allogeneic marrow can improve outcome by reducing GVHD, or whether tumor cells can be removed prior to autologous transplantation.[55]

PERIPHERAL BLOOD

Hematopoietic stem cells circulate in the peripheral blood, albeit in small numbers. During recovery from drug-induced cytopenias or after exposure to a hematopoietic growth factor, such as granulocyte–macrophage colony-stimulating factor or granulocyte colony-stimulating factor (G-CSF), the number of hematopoietic progenitor cells in the peripheral blood increases

considerably. With the use of these mobilizing techniques, followed by leukapheresis, it is possible to collect sufficient stem cells from the peripheral blood to permit successful transplantation. Because peripheral blood has a higher proportion of T cells than marrow, the first trials of peripheral blood stem cell transplantation were performed in the autologous setting, in which GVHD is not a concern. These studies demonstrated that such transplantation is not only feasible but also results in faster engraftment than is seen with autologous marrow.[56] When more than 5.0×10^6 CD34+ cells/kg are infused, recovery to 0.5×10^3 granulocytes/μL and 20×10^3 platelets/μL is generally seen less than 2 weeks after transplantation. Because of the rapid engraftment and decreased costs associated with peripheral-blood stem cell transplantation, it has largely replaced marrow as the source of stem cells for autologous transplantation.

Table 19-1 Probability of Finding an Allogeneic Donor for Hematopoietic Cell Transplantation

Matched sibling: 30%				
One-antigen–mismatched related donor: 3%				
	Unrelated Donor			
	8/8	**7/8**	**Cord Blood**	**Haploidentical**
White	70%	90%	> 95%	> 95%
Hispanic	35%	75%	95%	> 95%
Black	18%	70%	90%	> 95%

Given the rapid recovery associated with the use of autologous peripheral-blood stem cells, pilot studies of allogeneic peripheral-blood stem cell transplantation using HLA-identical sibling donors were performed.[57] The results of these studies demonstrated rapid engraftment without an increase in the incidence of acute GVHD. Randomized trials have confirmed these findings.[58] In most studies, the incidence of chronic GVHD associated with allogeneic peripheral-blood stem cell transplantation is higher, but both disease-free survival and OS rates appear to be improved, particularly for patients who received transplants for more advanced-stage disease.[59] In the unrelated donor setting, a large randomized study comparing marrow with peripheral blood after myeloablative conditioning showed faster engraftment but more chronic GVHD with peripheral blood. Overall survival was equivalent, thus favoring the use of marrow in the unrelated allogeneic transplantation setting unless there is a specific concern with slower engraftment.[60]

Stromal cell–derived factor 1 (CXCL12) produced by marrow stromal cells is a key regulator of hematopoietic stem cell homing and retention in the marrow by interacting with the alpha-chemokine receptor CXCR4 found on stem cells. Plerixafor, an antagonist of CXCR4, results in mobilization of CD34+ cells into the peripheral blood and may be useful when added to G-CSF in the 10 to 20% of patients in whom the mobilization of adequate numbers of cells fails when treated with G-CSF alone.[61]

The incidence of serious adverse events after bone marrow donation is 2.4% compared with 0.6% after peripheral-blood stem cell donation. There is no evidence for an increased risk of cancer, autoimmune illness, or stroke in donors receiving G-CSF for stem cell mobilization.[62,63] Guidelines have been developed to determine medical suitability of unrelated adult donors and for the hematopoietic cell collection process.[64,65]

KEY POINTS

- In the matched unrelated donor setting, a comparison of mobilized peripheral blood versus bone marrow after myeloablative conditioning showed faster engraftment but more chronic GVHD and equivalent survival with peripheral blood.
- Plerixafor, an antagonist of CXCR4, results in mobilization of CD34+ cells into the peripheral blood and may be useful when added to G-CSF in the 10 to 20% of patients who experience failure in the mobilization of adequate numbers of cells when treated with G-CSF alone.

PREPARATIVE REGIMEN

The form of treatment administered to patients directly before transplantation depends on the disease being treated, the source of the stem cells, and the health of the patient. Patients with severe combined immunodeficiency diseases often require no preparative regimen before transplantation because there is no abnormal cell population that must be eradicated and because their immune system is so severely compromised that the infused hematopoietic cells are rarely rejected if the donor is an HLA-matched sibling. In contrast, patients with aplastic anemia are sufficiently immunocompetent to reject allogeneic marrow if no pretransplantation immunosuppression is given. Thus, high-dose cyclophosphamide alone or combined with antithymocyte globulin often is used as the preparative regimen for allogeneic transplantation in aplastic anemia. When transplantation is applied to the treatment of leukemia or other malignant diseases, the regimen must be immunosuppressive (in the setting of allogeneic transplantation) and contribute to the eradication of the malignant disease.

Although high-dose myeloablative preparative regimens were the initial approach to transplantation for malignant diseases, the observation that some of the antitumor effects following allogeneic transplantation are the result of a graft-versus-tumor response led to investigations of whether reduced-intensity regimens might be as effective and less toxic. Evidence for the existence of a graft-versus-tumor effect includes the finding that relapse rates following allogeneic marrow transplantation are the lowest when acute and chronic GVHD develops, greater if no GVHD develops, and greater still if syngeneic or T-cell–depleted allogeneic marrow is used.[66,67] Additional evidence of a potent graft-versus-tumor effect comes from the use of viable donor lymphocyte infusions. The simple transfusion of as few as 1×10^7 viable donor lymphocytes per kilogram as treatment for patients whose disease relapsed after allogeneic transplantation can result in complete remission for as many as 70% of patients with CML and for a smaller but still substantial portion of patients with AML, MDS, or multiple myeloma.

Currently used preparative regimens for allogeneic transplantation can be placed in three general categories. The myeloablative regimen causes irreversible marrow aplasia and requires replacement of the hematopoietic system; the nonmyeloablative causes minimal marrow suppression; and reduced-intensity conditioning causes cytopenias of intermediate duration.[69] Compared with high-dose preparative regimens, nonmyeloablative and reduced-intensity regimens result in a shorter duration of pancytopenias with reduced transfusion needs, fewer bacterial infections, and a lower incidence of direct toxicities to the lung and liver.[70] Relapse rates are generally higher with reduced-dose regimens.[71] A prospective, randomized trial

demonstrated increased relapse rates and diminished survival with the use of reduced-intensity conditioning compared to myeloablative conditioning in patients with AML and MDS.[72] Thus, reduced-intensity conditioning is generally restricted to older patients and those with significant comorbidities, while high-dose regimens are preferred for younger, fit patients. Suggested dose adjustments for patients with renal or hepatic impairment have been published.[73,74]

KEY POINTS

- The purpose of the preparative regimen used prior to HCT is to help eliminate the underlying disease and, in the case of allogeneic transplantation, to provide sufficient immunosuppression to allow the donor cells to engraft.
- Evaluation of a patient's comorbidities can be used to help select the most appropriate preparative regimen.
- In general, myeloablative conditioning is preferred in patients who are able to tolerate the procedure.

ENGRAFTMENT

Following the administration of a myeloablative preparative regimen and the infusion of stem cells, a period of profound myelosuppression ensues. Within 1 to 2 weeks after transplantation, the peripheral leukocyte count begins to increase, signifying engraftment. When stem cells are procured from marrow and no hematopoietic growth factors are used after transplantation, the granulocyte count reaches $0.1 \times 10^3/\mu L$ by approximately day 16 and $0.5 \times 10^3/\mu L$ by day 25, and platelets reach $20 \times 10^3/\mu L$ by day 19. Administration of G-CSF can accelerate the recovery of peripheral granulocyte counts by as much as 1 week. The platelet count recovers simultaneously with or shortly after recovery of granulocytes.

When peripheral blood is the source of stem cells, engraftment is more rapid, with a granulocyte count of $0.5 \times 10^3/\mu L$ and a platelet count of $20 \times 10^3/\mu L$ achieved by day 12, on average. Engraftment following cord-blood transplantation is typically delayed by approximately 1 week compared with that following marrow transplantation. Engraftment of allogeneic stem cells can be documented using fluorescence in situ hybridization of sex chromosomes if the donor and recipients are of opposite sexes, or DNA-based assays of short tandem repeat loci. With these techniques, the donor-versus-recipient origin of populations of cells can now be determined in virtually all cases.

KEY POINT

- Using in situ hybridization with sex chromosome–specific probes or typing of the variable number of tandem repeat polymorphisms, the donor-versus-recipient origin of populations of cells can be determined in virtually all cases.

COMPLICATIONS OF MARROW TRANSPLANTATION

Both the nature and the degree of complications associated with HCT depend on the age and health of the patient, the specific preparative regimen used, and the source of stem cells. The frequency of complications is higher and the rate of survival is lower for patients with a Karnofsky performance score of less than 80% and for patients with significant comorbidities.[75] GVHD is normally seen only after allogeneic transplantation and is associated with an increased incidence of infection. The extent of other specific organ toxicities is largely dependent on the specific preparative regimen used. Figure 19-2 illustrates the approximate timing of possible toxicities after allogeneic transplantation using a typical intensive preparative regimen. Transplantation-specific scoring systems have been developed that can predict the overall likelihood of GVHD and overall mortality following allogeneic HCT. Such systems are useful in the selection of preparative regimens for individual patients, allowing those with few comorbidities to have the benefit of more intense regimens while selecting safer, less intense regimens for those with significant comorbidities.[76,77] The following sections discuss the major complications of HCT.

GRAFT FAILURE

In some instances, the transplanted graft functions briefly, but after a period of days or weeks, marrow function is lost and myeloid elements are absent on evaluation of marrow obtained by biopsy. In the setting of allogeneic transplantation, failure of the graft usually is the result of residual host immune elements rejecting the donor marrow, a phenomenon termed “graft rejection.” Following transplantation involving an HLA-identical donor, graft rejection occurs most commonly when the patient has received multiple transfusions prior to transplantation and little prior chemotherapy and when the preparative regimen is less immunosuppressive, such as with the use of cyclophosphamide monotherapy before transplantation for aplastic anemia. In general, the greater the disparity in HLA antigens between donor and recipient, the higher the chance of rejection. In the setting of partially matched cord-blood transplantation, the presence of donor-specific anti-HLA antibodies in the patient prior to transplantation, found in perhaps 10% of cases, predicts a high rate of graft rejection, so use of such cord units should be avoided.[78]

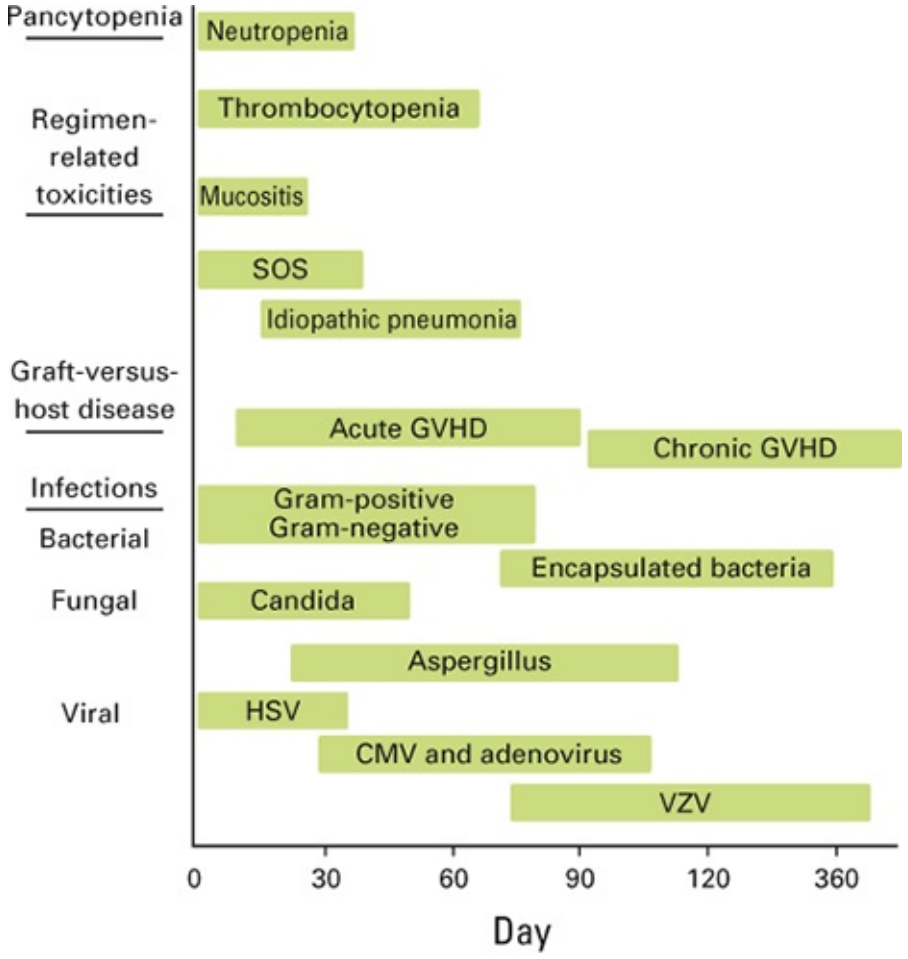

Fig. 19-2 The approximate timing of possible toxicities after allogeneic transplantation using a typical intensive preparative regimen.

Abbreviations: CMV, cytomegalovirus; GVHD, graft-versus-host disease; HSV, herpes simplex virus; SOS, sinusoidal obstruction syndrome; VZV, varicella zoster virus.

Also, because donor T cells react with and help eliminate host immunocompetent cells not eradicated by the preparative regimen, T-cell depletion of donor marrow prior to transplantation can lead to persistence of host immunity, resulting in an increased chance of graft rejection.

Graft failure occurs rarely in recipients of autologous transplants. A single cause is often difficult to identify, but several have been implicated, including prior exposure to stem cell poisons, marrow damage during in vitro processing and cryopreservation, drug toxicity after transplantation, and viral infections.

Patients with graft failure—but not immunologically mediated graft rejection—sometimes have a response to treatment with a hematopoietic growth factor, such as G-CSF, with an increase in the granulocyte count that may be sustained even after discontinuation of the growth factor. If persistent host lymphocytes are detected, which documents graft rejection, a second marrow transplant following an immunosuppressive preparative regimen may be successful.[79]

GRAFT-VERSUS-HOST DISEASE

GVHD is a complication usually restricted to allogeneic transplants and is the result of allogeneic T cells, which were transfused with the graft, reacting against targets on the genetically different host.[80-82] A National Institutes of Health (NIH) Consensus Report recognized two categories of GVHD, each with two subcategories (Table 19-2).[83] Acute GVHD usually develops within the first 3 months after allogeneic HCT and typically presents with an

erythematous or maculopapular rash, nausea, vomiting, anorexia, diarrhea (sometimes profuse), ileus, or cholestatic jaundice. Symptoms of acute GVHD sometimes occur beyond 3 months after transplantation (late-onset GVHD) or only when immunosuppression is withdrawn.

The most commonly used regimens to prevent GVHD include a combination of an antimetabolite (methotrexate or mycophenolate mofetil) and a calcineurin inhibitor (cyclosporine or tacrolimus). A combination of tacrolimus plus sirolimus may be equally effective.[84] A prospective, randomized trial reported that the addition of antilymphocyte globulin to standard prophylaxis led to a lower rate of chronic GVHD without affecting OS.[85] Other approaches to preventing GVHD include the removal of T cells from the donor marrow and the use of high-dose cyclophosphamide posttransplantation.[86,87] Prospective, randomized trials comparing these approaches are under way.

With standard regimens, such as methotrexate plus tacrolimus, moderate acute GVHD requiring therapy occurs in approximately 30% of patients who have undergone transplantation from a matched sibling donor. Acute GVHD usually is staged and graded using a modification of the original Seattle system (Tables 19-3 and 19-4).

Factors associated with an increased risk of moderate or severe acute GVHD include HLA mismatching, older age of patient and donor, a multiparous woman as the donor, and exposure to more intensive conditioning regimens. More recently, biomarkers have been identified, including TNF R1, ST2, and REG32 that can distinguish patients with acute GVHD who are likely to have a low incidence of nonrelapse mortality from those likely to do worse.[88] The appropriate clinical use of these biomarkers has not yet been established.

Table 19-2 Categories of Acute and Chronic GVHD[83]

Category	Time of Symptoms after HCT	Presence of Acute GVHD Features	Presence of Chronic GVHD Features
Acute GVHD			
Classic acute	≤ 100 days	Yes	No
Late-onset	> 100 days	Yes	No
Chronic GVHD			
Classic chronic	No time limit	No	Yes
Overlap	No time limit	Yes	Yes

Abbreviations: GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation.

Table 19-3 **Clinical Staging of Acute Graft-versus-Host Disease**[31]

Clinical Stage	Skin (Erythematous Rash)	Liver (Serum Bilirubin)	Gut (Diarrhea)
1	25% of body surface	2–3 mg/dL	500–1000 mL per day
2	25–50% of body surface	3–6 mg/dL	1000–1500 mL per day
3	Generalized	6–15 mg/dL	> 1500 mL per day
4	Desquamation and bullae	> 15 mg/dL	(Pain or ileus)

Standard treatment of acute GVHD is prednisone at a daily dose of 2 mg/kg, although a lower dose of 1 mg/kg may be used for grades 1 to 2 acute GVHD.[89] The optimal duration of steroid therapy is unknown but should be as limited as possible to avoid side effects of prolonged therapy. Patients who fail to respond to steroids sometimes respond to alternative therapies such as antithymocyte globulin or extracorporeal photopheresis, but there is no standard second-line treatment for acute GVHD.[90]

Chronic GVHD affects 20 to 40% of matched sibling transplant recipients and resembles a collagen vascular disease involving skin, liver, eyes, mouth, upper respiratory tract, esophagus, and less frequently, serosal surfaces, female genitalia, and fascia (Fig. 19-3). An NIH Consensus project developed a detailed staging system for chronic GVHD in which 12 organ systems are graded from 0 (no symptoms) to 3 (severe involvement) and these 12 scores are then combined into an NIH Global Severity Score of chronic GVHD as shown in Table 19-5.[91]

Chronic GVHD is seen more frequently with HLA mismatching, with the use of peripheral-blood stem cells instead of marrow, among older patients and among patients who have had prior episodes of acute GVHD. If chronic GVHD develops while the calcineurin inhibitor is being tapered, increasing the inhibitor to therapeutic levels may be effective. Mild chronic GVHD can sometimes be managed using local therapies alone (e.g., topical steroids to the skin and cyclosporine eye drops). More severe disease is usually treated with prednisone alone or in combination with a calcineurin inhibitor, which can control chronic GVHD in 50 to 70% of cases. Randomized trials exploring alternative approaches to primary therapy have so far failed to identify a better approach.[82] Patients for whom primary treatment of chronic GVHD fails are sometimes treated with mycophenolate mofetil, sirolimus, extracorporeal photopheresis, or low-dose interleukin-2.[90,92] Eventually, immunosuppression can be tapered and discontinued in 80 to 90% of patients, but it may require many months to several years of immunosuppression before tolerance develops. The median duration of treatment is 2 to 3 years. Bacterial infection frequently occurs among patients with chronic GVHD, and prophylactic treatment with antibiotics should be administered while patients are receiving immunosuppressive therapy. A commonly used regimen includes trimethoprim/sulfamethoxazole plus penicillin, which provides protection against both *Pneumocystis jirovecii* and encapsulated organisms.

Table 19-4 Clinical Grading of Acute Graft-versus-Host Disease[31]			
Clinical Grade	**Skin**	**Liver**	**Gut**
I (Mild)	1 or 2	0	0
II (Moderate)	3	1	1
III (Severe)	1, 2, or 3	2 or 3	2, 3, or 4
IV (Life-threatening)	4	4	

As noted earlier, the incidence of both acute and chronic GVHD is increased in recipients of transplants from mismatched or unrelated allogeneic donors (Table 19-1). A mild syndrome, similar to GVHD, that involves the skin and gastrointestinal system develops in some patients after autologous transplantation. The syndrome nearly always resolves with a short course of prednisone, does not appear to have an antitumor effect, and does not affect overall transplantation outcome.

Following allogeneic transplantation, in 3 to 5% of cases, an autoimmune disorder will develop, most commonly autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura. Unrelated donor source and chronic GVHD are risk factors. Treatment is with cyclosporine, prednisone, or rituximab.[93]

KEY POINT

- GVHD results from T cells in the donor graft reacting with allogeneic targets on the genetically different host. The standard approach to GVHD prophylaxis is administration of a calcineurin inhibitor and an antimetabolite. Removal of T cells from the donor graft, treatment with cyclophosphamide posttransplantation, and the addition of antilymphocyte globulin are encouraging new approaches.

INFECTIOUS COMPLICATIONS

Infection is a major risk for nearly all transplant recipients. Recipients of autologous transplants are at risk for the early bacterial and fungal infections common to all patients with granulocytopenia. Recipients of allogeneic hematopoietic grafts, particularly patients in whom GVHD develops, also are at risk for late-onset bacterial, fungal, and viral diseases.

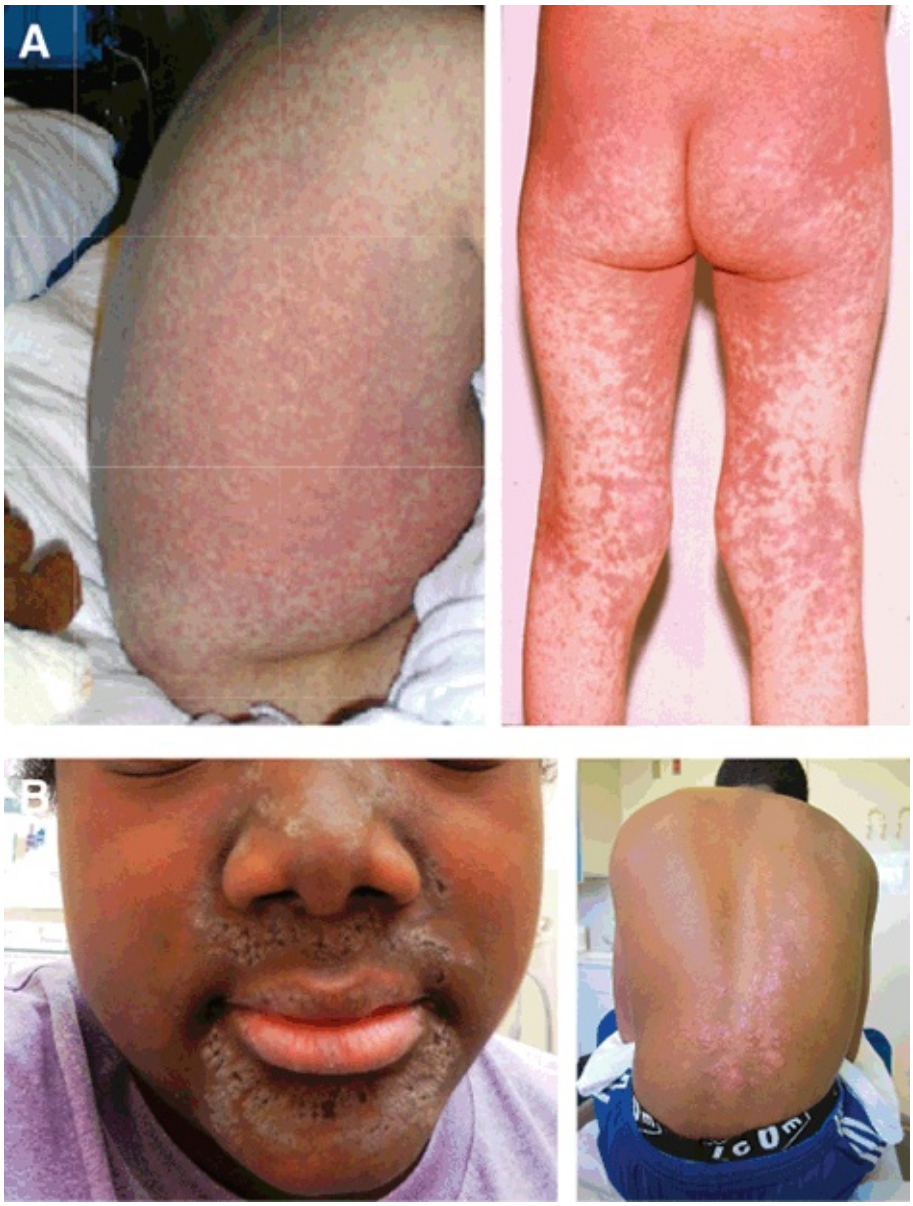

Fig. 19-3 Acute and chronic graft versus host disease of the skin.

Acute GVHD classically develops within the first 3 months after allogeneic hematopoietic cell transplantation and typically presents with an erythematous or maculopapular rash (panel A). Chronic GVHD develops sometime after the first 3 months, often presenting with cutaneous manifestations, including atrophic changes with depigmentation, lichen-planus–like lesions, and development of sclerotic features (panel B).

During the early neutropenic period following transplantation, patients are likely to become febrile, and in approximately 50% of patients who are febrile neutropenic, a bacterial source can be identified. Therefore, at most transplantation centers, antibiotic treatment is initiated once patients become granulocytopenic, even if they are afebrile. Prophylaxis against fungal pathogens has been shown to reduce rates of fungal infection and improve OS.[94] Prophylaxis with fluconazole is generally recommended for patients at standard risk, while prophylaxis with a mold-active agent (voriconazole, posaconazole) should be considered for patients with higher-risk disease, including patients with a prior fungal infection or recipients of a cord-blood or unrelated donor transplant.[95] While approaches vary, one standard approach is to continue fungal prophylaxis for 75 days after allogeneic HCT and until resolution of neutropenia after autologous HCT. Although having a prior invasive fungal infection increases transplant risk, with current methods of prophylaxis, it should not be considered a contraindication for HCT.[96] Patients who become or remain febrile despite treatment with broad-spectrum antibiotics and who have no obvious source of infection usually are treated with additional antifungal agents

(voriconazole, micafungin, or amphotericin, depending on the clinical situation). Recipients of cord-blood transplants sometime have “cord colitis,” a syndrome of diarrhea responsive to metronidazole, alone or in combination with a fluoroquinolone.[97] Molecular studies suggest *Bradyrhizobium enterica* as the causative agent.[98]

Although laminar airflow isolation and prophylactic granulocyte transfusions can prevent early infection, neither action influences OS and, thus, neither approach is recommended. With current methods of supportive care, the risk of death as a result of infection during the early granulocytopenic period after transplantation is less than 3% for recipients of either allogeneic or autologous transplants.

Herpes simplex infection, which can contribute to the severity of oral mucositis, can be prevented with the use of systemic acyclovir 250 mg/m^2 every 8 hours intravenously, beginning 1 week before and continuing for 1 month after transplantation.[99] At many centers, acyclovir is continued for up to 1 year to prevent late infection or reactivation with varicella zoster virus (VZV).

In the past, symptomatic CMV infection, which typically involves either the gastrointestinal tract or the lungs, occurred in approximately 25% of patients who received allogeneic transplants and led to death (typically from CMV pneumonia) in 10 to 15% of patients. Primary CMV infection in the setting in which both donor and recipient are without latent CMV infection (as evidenced by having no detectable antibodies to CMV before transplantation) can be prevented by using only blood products that come from donors without latent CMV or by using blood products that have been filtered to remove all leukocytes. For patients with evidence of latent CMV before transplantation, the use of prophylactic ganciclovir, starting either at the time of initial engraftment or at the time of CMV reactivation, can substantially reduce the risk of CMV disease. Prophylactic ganciclovir is not without toxicities, however, and granulocytopenia is more common for patients receiving prophylactic ganciclovir than for patients in control groups.[100] The granulocytopenia seen with ganciclovir usually responds to G-CSF treatment. Prophylactic ganciclovir generally is not recommended for patients who have an autologous transplant, except for cases in which T cells are removed from the stem cell inoculum. Foscarnet is effective for some patients in whom CMV infection develops despite the use of ganciclovir as well as for patients who cannot tolerate ganciclovir. Foscarnet can, however, be associated with severe electrolyte wasting. A new oral agent, letermovir, appears to be safe and effective in reducing the incidence of CMV infection.[101]

Table 19-5 **NIH Global Severity of Chronic Graft-versus-Host Disease**[91]

Mild Chronic GVHD	Moderate Chronic GVHD	Severe Chronic GVHD
One or two organs involved with no more than a score of 1+	Three or more organs involved with no more than a score of 1	At least one organ with a score of 3
Lung score of 0	OR	OR
	At least one organ (not lung) with a score of 2	Lung score of 2 or 3
	OR	
	Lung score of 1	

Abbreviations: NIH, National Institutes of Health; GVHD, graft-versus-host disease.

Pneumonia result from infection with *Pneumocystis jirovecii*, previously seen in 5 to 10% of transplant recipients, can be prevented by treatment with oral trimethoprim/sulfamethoxazole

for 1 week before transplantation and resuming prophylaxis once the granulocyte count exceeds 0.5 × 10^3/μL. Treatment 2 days per week while patients are receiving immunosuppressive drugs after transplantation usually is sufficient to prevent pneumocystis disease. Allergic reactions to trimethoprim/sulfamethoxazole are common but usually can be managed with desensitization. Additionally, dapsone or atovaquone can serve as a substitute for trimethoprim/sulfamethoxazole.

Community-acquired viral infections, including respiratory syncytial virus (RSV), influenza virus, and parainfluenza virus, can cause lethal pneumonias in the transplant patient. Patients with upper respiratory symptoms before transplantation should be screened by nasopharyngeal lavage for viral infections before proceeding to HCT. If RSV, influenza virus, or parainfluenza virus is found, transplantation should be delayed. Ribavirin and anti-RSV antibody may be effective in treating established RSV infection in the transplant patient.

Late infections, occurring more than 3 months after transplantation, usually are restricted to VZV or, for patients with chronic GVHD, to recurrent bacterial or fungal infections. The use of prophylactic trimethoprim/sulfamethoxazole, penicillin, or other agents can reduce the incidence of late-onset bacterial infections for patients with chronic GVHD. Reactivation of VZV can be prevented by the use of prophylactic acyclovir.

Antibody titers to vaccine-preventable diseases decline after allogeneic or autologous HCT if the recipient is not revaccinated. Therefore, posttransplantation revaccination against influenza, *Haemophilus influenzae,* menningococccus, pneumococcus, polio, diphtheria, tetanus, pertussis, hepatitis A and B, and human papillomavirus is generally recommended.[102] The choice of vaccine and schedule may vary depending on patient age, underlying diagnosis, and amount of continuing immunosuppression. Therefore, although a number of guidelines have been written, the decisions of who, when, and how to vaccinate should be made in consultation with infectious-disease experts.

KEY POINTS

- Fungal infections can be prevented and survival improved with the use of antifungal prophylaxis during the first few months after transplantation.
- For patients without latent CMV infection, death from CMV can be prevented by using only blood products from donors without latent CMV infection or depleting blood products of white blood cells. For patients with latent CMV infection, death from CMV can be substantially reduced by administering ganciclovir at the time of reactivation.

CHEMORADIOTHERAPY TOXICITIES

Following most standard preparative regimens, immediate toxic effects, such as nausea, vomiting, fever, and mild skin erythema, are common. Unusual toxic effects associated with high-dose cyclophosphamide include hemorrhagic cystitis and, rarely, acute hemorrhagic carditis. Parotiditis commonly is seen among patients undergoing total-body irradiation therapy.

Oral mucositis requiring narcotic analgesia typically develops 5 to 7 days following transplantation using high-dose preparative regimens. Patient-controlled analgesia provides the greatest patient satisfaction and results in lower cumulative doses of narcotics. Keratinocyte growth factor (palifermin) significantly shortens the duration of severe mucositis following high-

dose autologous transplantation regimens and is recommended for use in this setting.[103,104]

Sinusoidal obstruction syndrome (SOS), previously termed “veno-occlusive hepatic disease,” can develop within 1 to 4 weeks after treatment with many high-dose preparative regimens, and its symptoms include weight gain, ascites, tender hepatomegaly, and jaundice. The overall incidence of SOS is approximately 5%, but the incidence and grade vary according to the preparative regimen. In general, the incidence is higher for patients with abnormal results of liver-function tests before transplantation and for patients with an active infection at the time of transplantation.[105] Defibrotide, a mixture of single-stranded oligonucleotides that functions as an anticoagulant, has been approved by the FDA for treatment of SOS on basis of retrospective, controlled trials.[106] Results of a randomized trial suggest that defibrotide may also be effective if used prophylactically.[107] Prophylaxis with ursodeoxycholic acid may decrease the incidence of SOS, and randomized studies have shown decreased rates of acute GVHD and better survival.

Idiopathic pneumonia syndrome (IPS), which is thought to be a toxicity directly related to chemoradiotherapy, occurs 30 to 90 days after transplantation in up to 5% of patients. As with other toxicities, the incidence of IPS is dependent, in part, on the preparative regimen, occurring more frequently following administration of regimens that include high doses of total-body irradiation. Preexisting lung disease, prior radiation therapy to the thorax, and increased age also seem to be associated with an increased risk of IPS, whereas fractionated radiation instead of single-dose radiation appears to decrease this risk. The mortality rate associated with IPS is approximately 50%, and no available treatments are clearly effective, although early results with tumor necrosis factor blockade may be favorable.[108]

Two categories of chronic pulmonary dysfunction are seen among patients who survive longer than 3 months after allogeneic transplantation: restrictive lung disease and obstructive lung disease. The most common cause of restrictive disease is cryptogenic organizing pneumonia, which is characterized by a dry cough, shortness of breath, fever, and radiographic findings showing a diffuse, fluffy infiltrate. Histology shows patchy fibrosis, granulation tissue within alveolar spaces and small airways, and absence of an infectious agent. The disease is quite responsive to corticosteroids and may reverse completely.[109] Bronchiolitis obliterans is an obstructive defect characterized by progressive dyspnea, nonproductive cough, and radiologic evidence of airway trapping.[110] Histology shows enhanced deposition of collagen and granulation tissue in and around bronchial structures and eventual obliteration of small airways.[109] The disease is highly associated with chronic GVHD. Management generally involves increasing immunosuppression. Preliminary results with a combination of fluticasone, azithromycin, and montelukast appear encouraging.[111] However, complete reversal is uncommon.

Delayed complications attributable to the preparative regimen include decreased growth velocity in children and delayed development of secondary sexual characteristics. Most postpubescent women will experience ovarian failure, and few men regain spermatogenesis following HCT using high-dose preparative regimens. However, occasional patients will regain fertility following even myeloablative conditioning regimens, and patients should be counseled about this possibility.[112] Cataracts occur for as many as one-third of patients, with an increased risk among patients receiving high doses of total-body irradiation and patients requiring steroids for treatment of GVHD. Thyroid dysfunction, usually well compensated, also may occur. Patients treated with high-dose chemoradiotherapy and HCT are at an increased risk for the development of second cancers and posttransplantation lymphoproliferative disorders (PTLD). The risk for Epstein–Barr virus–associated PTLD is highest for patients receiving T-cell–depleted allogeneic transplants and for patients who receive multiple cycles of highly

immunosuppressive drugs to treat GVHD.[113] An increase in solid tumors has been reported after transplantation, with a 3% 10-year cumulative rate, which is two to three times the age-adjusted rate in the general population. A high incidence of MDS (nearly 10%) has been reported following autologous transplantation for lymphoma, but whether MDS is a complication of transplantation or is the long-term effect of chemotherapy used before transplantation is unknown.[114]

LATE EFFECTS AND LONG-TERM SURVIVORSHIP

Late nonmalignant complications are common after transplantation, with at least one late effect occurring in almost 50% of long-term survivors.[115] Among a cohort of 1087 survivors, 2.5% of autologous and 25% of allogeneic transplantation survivors noted three or more late effects. The most commonly noted effects were pulmonary complications, osteoporosis, and diabetes mellitus. Without a control group of nontransplanted cancer survivors, the precise causation of these late effects is uncertain.

Case–control studies of patients who survive more than 5 years after undergoing transplantation show that survivors have more physical limitations than controls based on Medical Outcomes Study 36-Item Short Form Survey (SF-36) scores, but they report approximately equal rates of osteoporosis, hypothyroidism, employment, marital satisfaction, divorce, and psychologic conditions. Transplantation survivors do report an increased incidence of musculoskeletal problems and sexual dysfunction.[116] Among those surviving more than 5 years after transplantation, mortality rates remain higher than expected, yielding an estimated 30% lower life expectancy compared with that of the general population.[117] The leading causes of excess deaths in 5-year survivors are, in order, recurrent disease, second malignancy, chronic GVHD, respiratory ailments, and cardiovascular events.

KEY POINTS

- Patients in whom graft failure develops following transplantation who have recovery of host lymphocytes can sometimes be cured with a second allogeneic transplantation.
- Defibrotide has been approved by the FDA for treatment of SOS on the basis of retrospective, controlled trials.
- Among those surviving more than 5 years after transplantation, mortality rates remain higher than expected, yielding an estimated 30% lower life expectancy compared with that of the general population. The leading causes of excess deaths in 5-year survivors are, in order, recurrent disease, second malignancy, chronic GVHD, respiratory ailments, and cardiovascular events.

RELAPSE AFTER TRANSPLANTATION

There is a substantial risk of recurrent malignant disease after transplantation, particularly when transplantation is performed after failure of conventional therapy rather than earlier in the course of the disease. A number of clinical trials are currently testing whether the use of novel targeted therapies can prevent or delay posttransplantation relapse. The appropriate management of patients who do have a relapse after transplantation depends on the disease

and type of transplant. Patients whose disease recurs after autologous transplantation may have a response to subsequent chemotherapy, and occasionally, such responses are surprisingly complete and prolonged, particularly if the duration of remission after transplantation was long. Reduced-intensity allogeneic HCT has been found to be tolerable (and sometimes effective) for patients whose disease relapsed following an autologous transplantation.[118]

Patients taking immunosuppressive drugs who have recurrent disease after allogeneic transplantation will, on occasion, have a second complete remission after discontinuation of immunosuppressive therapy. Infusions of viable lymphocytes from the original stem cell donors can result in complete remission for many patients. In a European study involving 135 patients, the rate of complete response was 70% for patients with chronic-phase CML, 12% for patients with advanced-phase CML, 29% for patients with AML or MDS, and 0% for patients with ALL.[68] Occasionally, patients with myeloma and non-Hodgkin lymphoma also have a response. Most experts recommend that patients with recurrent acute leukemia undergo reinduction chemotherapy prior to donor lymphocyte infusions to decrease the leukemia cell burden and provide sufficient time for a graft-versus-tumor effect to develop. Some form of GVHD develops in approximately 60% of patients after infusion of donor lymphocytes; of those patients, 50% require therapy for GVHD and 15% experience life-threatening GVHD. In addition, marrow aplasia occurs in 35% of patients, and the overall mortality associated with infusion of donor lymphocytes is 20%. Limiting the dose of CD3+ lymphocytes to less than 10×10^7 can decrease the risk of GVHD and life-threatening complications without impairing the graft-versus-leukemia effect.[119] Chimeric antigen receptor T cells targeting CD19 have been shown to be effective in the treatment of patients with ALL who have experienced a relapse after transplantation.[120] Responses have also been seen following treatment with ipilimumab, but immune-mediated toxicity and GVHD flares were also seen.[121]

A number of patients have had a second allogeneic transplantation as treatment for relapse after the first transplantation. Such transplantations, if performed within 1 year of the original transplantation, have been associated with a high risk of severe or fatal transplant-related toxicities, including SOS and idiopathic interstitial pneumonia. However, the results are better when the second transplantation is performed more than 1 year after the original transplantation, with prolonged subsequent remissions reported for as many as 25% of patients.[118] Retrospective studies show similar outcomes whether one uses the same donor as for the first transplantation or switches to a different donor.[122]

KEY POINT

- Patients who experience a relapse following allogeneic HCT often respond to subsequent immunologic manipulation, including withdrawal of immunosuppression, donor lymphocyte infusions, and treatment with checkpoint inhibitors.

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CANCER IN ELDERLY PATIENTS

Ravindran Kanesvaran, MD, and Harvey Jay Cohen, MD

Recent Updates

- Age-related immune dysfunction (ARID) may affect immunotherapy use in elderly cancer patients. (Hurez V, *Clin Exp Immunol* 2017)
- A systemetic review and update found that screening tools do not replace geriatric assessment, but they are recommended to identify patients in need of a full assessment. (Decoster L, *Ann Oncol* 2015)
- The first phase III randomized controlled trial of the use of a comprehensive geriatric assessment (CGA) in elderly patients with advanced non-small cell lung cancer reported treatment allocation on basis of CGA did not show improvement in treatment failure free survival (TFFS) or overall survival (OS), but slightly reduced treatment toxicity. (Corre R, *J Clin Oncol* 2016)
- A new method to better define frailty in elderly cancer patients who receive chemotherapy is based on a deficit-accumulation index. (Cohen HJ, *Cancer* 2016)

OVERVIEW

Geriatric medicine is a subspecialty that deals with care of older adults. Although there is no consensus on the specific chronologic age that defines the geriatric patient population, in developed countries the age of 65 or older is generally accepted.[1] The International Society of Geriatric Oncology (SIOG) defines a geriatric oncology patient as a cancer patient older than 70 years of age. Cancer, a major problem for the elderly, is the second leading cause of death in the United States following heart disease. Age is the single most important risk factor for developing cancer with approximately 60% of all newly diagnosed malignant tumors and 70% of all cancer deaths occurring among people at least 65 years of age.[2] It has been estimated that by 2030, 20% of the U.S. population (70 million people) will be older than age 65. The median age range for diagnosis for most major tumors, common to both men and women, is 68 to 74, and the median age range at death is 70 to 79.[3,4] For most malignancies, the death rate is disproportionately higher in the elderly population. Possible explanations include an altered natural history of some cancers, competing comorbidities, decreased physiologic reserve compromising the ability to tolerate therapy, physicians' reluctance to provide aggressive therapy, and barriers to accessing care. Communication between health care providers and elderly patients may be hampered by deficits in hearing, vision, and cognition. The elderly patient with cancer often has an elderly caregiver, and the diagnosis of cancer often affects the health-related quality of life (QOL) of both individuals. These challenges contribute to defining "geriatric oncology" as a true subspecialty, leading to the development of the National Comprehensive Cancer Network guidelines that address special considerations for older adults

with cancer.[5]

LIFE EXPECTANCY AND THE COST OF CANCER CARE

Life expectancy at age 65 is of substantial relevance when considering the cancer burden in the older population.[6] Over the past four decades, the average life expectancy has increased by 3 years for older men and by 6 years for older women. Determination of life expectancy is important in decisions regarding cancer screening and treatment planning. In a population-based study of community-dwelling U.S. adults older than age 50, a prognostic index was developed using data from 11,701 individuals and validated in 8,009 individuals.[7] Twelve percent of the study population and 11% of the validation cohort had a cancer diagnosis, with a 4-year mortality of 22%. Data were collected on participants' demographics (age, gender), specific diseases and behaviors (such as smoking), and difficulties with a series of functional measures. Points were assigned to 12 predictor variables and the subsequent risk score was strongly associated with 4-year mortality in the validation cohort. Individuals with 0 to 5 points had ≤ 4% risk of death at 4 years, 6 to 9 points a 15% risk, 10 to 13 points a 42% risk, and 14 or more points a 64% risk for dying at 4 years. There are several tools to estimate a patient's life expectancy, including the University of California, San Francisco's ePrognosis (eprognosis.ucsf.edu), although these tools are not specific to older patients with cancer. Thus, more data and tools such as these are needed for older adults with cancer.

The costs of cancer care to Medicare are substantial and vary by tumor site, stage at diagnosis, phase of care, and survival. In the 2008 Surveillance, Epidemiology, and End Results database review, the mean net costs of care were highest in the initial and last year-of-life phases of care and lowest in the continuing phase. Mean 5-year net costs varied widely, from < $20,000 for patients with breast cancer or melanoma of the skin to > $40,000 for patients with central nervous system, esophageal, gastric, or ovarian cancers or lymphoma. For patients with acute myeloid leukemia (AML), 80% of the costs are related to inpatient hospitalization.[8] However, with the advent of new targeted agents, the cost of anticancer agents has more than doubled in the past decade, from $4500 to more than $10,000 per month.[9] Of the seven anticancer drugs approved by the U.S. Food and Drug Administration in 2016, three were immuno-oncology drugs that cost more than $12,000 per month of therapy. Many targeted agents have been priced between $6000 and $12,000 per month, or approximately $70,000 to $115,000 per patient annually. This high cost may prevent elderly patients from being able to procure their medications.[10] This, in turn, results in costs nationally of over $100 billion annually, because of increased health services utilization, hospital admission, and adverse drug events.[11] The economic impact of cancer survivorship is considerable, remains high years after a cancer diagnosis, and is approximately the same for young and older patients.[12] Financial toxicity can have varying degrees of severity and can increase if the treatment approach is not adjusted or appropriate supportive measures are not initiated in a timely manner.[13] Some have advocated the inclusion of financial issues when discussing benefits and risks of therapies.

Older adults with cancer are a heterogeneous group, ranging from fit, active, and robust individuals to those who are frail with physical and cognitive impairments and increased risk for disease and therapy-related complications. A knowledge of the biology of aging, impact of comorbidities, the costs of cancer care, use of a comprehensive geriatric assessment (CGA), and a willingness to spend time with the patient and his or her family members are essential to providing care for older patients. This chapter discusses many of the general relationships of oncology and aging. It focuses on the epidemiologic, etiologic, and biologic relationships

between the processes of aging and neoplasia. It also underscores the importance of a CGA in treatment decision making and prediction of chemotherapy toxicity for older adults with cancer. The clinical management of individual malignancies is discussed only as an example of general principles, and the approach to specific malignancies is covered in chapters related to the appropriate organ system.

KEY POINTS

- Cancer is predominantly a disease of older adults.
- Cancer-related mortality rates for patients 65 years of age or older are disproportionally higher than the incidence.
- The cost of cancer care for the elderly is significant and is expected to increase, especially with the advent of new targeted therapies and immuno-oncology agents.

RELATIONSHIP BETWEEN AGING AND NEOPLASIA

The molecular, cellular, and physiologic changes that are a part of the aging process also predispose patients to cancer. While the landmark paper by Hanahan and Weinberg (please refer to Chapter 2: Molecular Biology) was recently updated to delineate ten hallmarks of cancer, there are nine hallmarks that represent common denominators of aging as well.[14,15] Carcinogenesis is a multistep process that includes initiation, followed by promotion and progression to disease. The various theories that link aging and cancer include[16-20]:

- **Longer duration of carcinogenic exposure:** Aging allows the time necessary for the accumulation of cellular events to result in neoplasm. Somatic mutations are believed to occur at the rate of approximately 1 in 10 cell divisions, with approximately 10 cell divisions occurring in a human's lifetime.
- **Altered susceptibility of aging cells to carcinogens:** Aging may increase or decrease the susceptibility of normal cells/ tissue to become cancerous cells.
- **Decreased ability to repair DNA:** It is possible that damage is more difficult to repair in older cells.
- **Oncogene activation or amplification or decrease in tumor suppressor gene activity:** These processes may be altered in the older host, resulting either in increased action, promotion, or differential clonal evolution.
- **Telomere shortening and genetic instability:** The function of telomeres and telomerase are intimately involved in senescence and neoplastic processes. Telomeres, the terminal end of all chromosomes, shorten progressively as cells age, beginning at age 30, with a loss of approximately 1% per year. This shortening appears to be causally related to controlled cell proliferation. Each time a cell divides, 30 to 200 base pairs are lost from that cell's telomeres. Because the major function of telomeres is to protect the stability of the more internal coding sequences (i.e., allow cells to divide without losing genes), this loss may lead to genetic instability, which may promote mutations in oncogenic or tumor-suppressor gene sequences. Without telomeres, chromosome ends

could fuse together and degrade the cell's genetic blueprint, making the cell malfunction, become malignant, or potentially die. Telomere length is a predictor of mortality in people age 60 or older. Telomerase is responsible for adding back telomeric repeats to the ends of chromosomes (i.e., regenerate the telomeres). It is generally not expressed in normal cells, but it is activated in malignant cells. Although telomerase can reverse replicative cell senescence, indiscriminate activity of this enzyme may increase the likelihood of tumor formation.

- **Microenvironment alterations:** Older people accumulate senescent cells and have higher levels of interleukin-6 (IL-6), the "geriatric cytokine," which is one of the causes of frailty. Senescent cells can compromise tissue renewal capacity and secrete multiple factors (e.g., IL-1, matrix metalloproteinase 3 [MMP-3]) that alter tissue homeostasis and create a tissue environment that synergizes with mutation accumulation to facilitate malignant transformation.
- **Decreased immune surveillance:** Loss of tumor-specific immunity occurs with progressive age.

Interactions of these factors—resulting in initiation and cumulative promoting events, including mutations and other alterations in critical genes, which may exceed host resistance factors—occur during the aging process. Cellular senescence suppresses cancer by arresting cells at risk of malignant transformation.[21] However, senescent cells also secrete molecules that can stimulate premalignant cells to proliferate and form tumors. Thus, cellular senescence-induced suppression of malignant transformation, a function important for the organism in early life (through the reproductive period), may be selected for, although such senescence may be deleterious in later life.

AGE-RELATED PHYSIOLOGIC CHANGES

A decline in physiologic functioning begins at age 30 and continues at a rate of approximately 1% per year. The aging process occurs at a different rate in each person, as does loss of individual organ reserve.[22,23] In most cases, these physiologic changes are clinically imperceptible. However, illness and subsequent medical interventions also impact physiologic processes, which may not return to baseline levels. Changes of aging include thinning skin, increased bruising, decreased cardiac reserve, reduction in cardiac myocytes, increased vascular stiffness, and decreased gastrointestinal motility and absorption. As blood flow and liver mass decrease, hepatic function declines. Metabolism through the cytochrome P450 microsomal enzyme system also decreases, impacting drug metabolism and elimination.[24] In the kidney, renal blood flow decreases, and both kidney mass and glomeruli are lost and replaced by fat and fibrotic tissue. The kidneys' ability to concentrate urine, excrete water, and eliminate toxins decreases.

The senescent brain undergoes a number of changes. Brain weight, blood flow, and neurotransmitter production all decline with age. The latter may be related to the presence of Parkinson's disease in 30% of individuals older than age 70. Both walking speed and truncal stability correlate with longevity and development of geriatric problems, including depression and dementia.[25,26] With increasing age, gait speed slows, stride length shortens, and individuals increasingly lean forward, perhaps related to a decline in the number of Purkinje cells within the cerebellum.

Neuronal loss may also lead to decreased levels of neuroreceptors, such as mu and delta, which may be the mechanism for enhanced sensitivity to opioid analgesics in older individuals. This loss also results in a decreased ability to perceive pain and also may contribute to compromised wound healing.

Immunologic "dysregulation" occurs in older adults. Declines in thymic mass and hormones result in a decrease in naive lymphocytes and an increase in memory T cells with maintenance of a normal total lymphocyte count but decreased response to mitogens.[17] Levels of inflammatory cytokines (IL-6 and IL-1-beta), C-reactive protein (CRP), and transforming growth factor-beta increase with age. Elevations of IL-6 and D-dimer have been associated with shorter survival and increased functional dependency.[27] Interleukin-2 levels decrease with age, contributing to a loss of lymphocyte proliferation. Although the etiology of increased cytokine levels is uncertain, it has been proposed that inflammatory reactions throughout a lifetime result in an accumulation of certain cytokines. These cytokines contribute to a catabolic state and to sarcopenia. Immunoglobulin levels increase, but antibody response decreases.[28] Such immunologic changes result in increased susceptibility to infection and may be responsible for the altered natural history of certain malignant diseases.

In older adults, the complete blood count (CBC) is generally within the normal range, despite an increased fat/cell ratio in the bone marrow.[29] The marrow reserve is compromised by illness or oncologic treatment, with greater decline in blood counts compared with counts in younger patients.[30] Anemia is more common with age, occurring in 10% of patients > 65 years of age and 20% of patients >age 85, according to the National Health and Nutrition Examination Survey.[31]

KEY POINTS

- Physiologic changes of aging begin at age 30.
- The rate of physiologic change with aging varies by organ system and individual.
- Immunologic changes from aging result in increased susceptibility to infection and the risk of cancer.
- Marrow reserve is compromised in the elderly, leading to greater decline in blood counts compared to younger patients.

COMPREHENSIVE GERIATRIC ASSESSMENT

Aging is a heterogeneous process that is impacted by more than chronologic age. The comprehensive geriatric assessment (CGA) is designed to capture the functional age of older adults to identify those who have diminished life expectancy and/or are at increased risk for hospitalization and functional decline (Table 20-1).[32] Traditionally in oncology, the Eastern Cooperative Oncology Group (ECOG) performance status (PS) has been used to quantify patient well-being and to determine whether patients can tolerate chemotherapy. However, this measure does not reflect functional status of these patients. The CGA assesses functional status, comorbidities that may impact cancer therapy, nutritional status, polypharmacy, psychologic and cognitive status, socioeconomic issues, and geriatric syndromes. These CGA measures are reliable and valid, can be obtained in a brief time (median 22 minutes), and are

prognostic for morbidity and mortality in older patients. Abbreviated screening instruments designed to determine who might need a full assessment, which can be used as stratifiers and predictors, are outlined in Table 20-2.[33] Due to the lengthy nature of doing a CGA, a recent paper published by a SIOG task force provided an update on all the geriatric assessment (GA) screening instruments available and the data supporting their use in clinical practice.[34] This time-saving step may enable clinicians to select the appropriate patient for a CGA.

USES OF GERIATRIC ASSESSMENT IN ONCOLOGY

Various instruments for GA have been used for over a decade in oncology, for a variety of malignancies, to examine multiple endpoints, including chemotherapy toxicity. In a study by the Cancer and Aging Research Group (CARG), geriatric assessment variables, sociodemographics, tumor/treatment variables, and laboratory results were incorporated into a model that was predictive for chemotherapy toxicity in 500 older adults.[35] A scoring system in which the median risk score was 7 (range 0 to 19) was utilized to risk-stratify patients, with the risk score being the percent incidence of grades 3 to 5 toxicity. This identified older adults at low (0 to 5 points; 30%), intermediate (6 to 9 points; 52%), or high risk (10 to 19 points; 83%) for chemotherapy toxicities ($p < 0.001$). This was recently validated in an external cohort of 250 older adults with cancer.[36] In another study of 518 elderly patients with cancer, 24 parameters, including GA, were incorporated to create the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score to predict grade 4 hematologic or grade 3/4 nonhematologic toxicities.[37] In their risk categories, patients with low-risk scores had a 7% chance of hematologic and 33% chance of nonhematologic toxicity compared to high-risk patients with corresponding toxicity risks of 100% and 93% respectively. A limitation of both these studies was the small numbers of patients with hematologic malignancies (who tend to have less bone marrow reserve, making them more vulnerable to hematologic toxicities) and the studies not being designed to predict grade 2 toxicities, which also impact quality of life.

Age-based reduction of first cycle chemotherapy doses (primary dose reduction) is not routinely recommended by most guidelines. A CARG study demonstrated that primary dose reductions were more common for older patients receiving chemotherapy with palliative, rather than curative, intent.[38] Increasing age and comorbidities, but not Karnofsky Performance Scale Index status, were independently associated with primary dose reductions.

CGA has also been used to aid decision-making. In the ELCAPA01 study, geriatricians conducted CGAs in 375 elderly patients with cancer to identify factors associated with dose intensification, decrease, or delay of more than 2 weeks.[39] In multivariate analysis, functional status as assessed by the activities of daily living (ADL) score and the presence of malnutrition were independently associated with changes in cancer treatment. CGA interventions have also been shown to be associated with improved chemotherapy tolerance. In a British study, two cohorts of older patients (age ≥ 70) receiving cancer chemotherapy were studied.[40] The observational control group (70 patients) received standard oncology care, while the intervention group (65 patients) underwent risk stratification using a patient-completed screening questionnaire, and patients at high risk received a CGA. The impact of CGA interventions on chemotherapy tolerance outcomes and grade 3 or higher toxicities were evaluated with outcomes adjusted for age, comorbidity, metastatic disease, and initial dose reduction. Intervention participants undergoing CGA received a mean of 6.2 ± 2.6 (range, 0 to 15) CGA intervention plans each. They were more likely to complete cancer treatment as planned (odds ratio [OR], 4.14; 95% CI; 1.50, 11.42; $p = 0.006$), with fewer required treatment

modifications (OR, 0.34; 95% CI; 0.16, 0.73; p = 0.006). The overall grade 3 and higher toxicity rate was 43.8% in the intervention group and 52.9% in the control (p = 0.292). In a recent prospective phase III trial on elderly patients with advanced non-small cell lung cancer examining the impact of CGAs in improving survival outcomes found that CGA-based treatment allocation did not improve treatment failure free survival and overall survival (OS) when compared to standard treatment allocation based on PS and age.[41] Patients undergoing CGA had significantly fewer toxicities of all grades and fewer toxicity-related treatment failures. At present, this data set is being analyzed to identify other factors that help define frailty and predict toxicities.

Table 20-1 Domains for Cancer-Specific Comprehensive Geriatric Assessment (CGA)

Domain with Measure	Number of Items	Description
Functional Status		
MOS physical health	10	Measures limitations in a wide range of physical functions (from bathing/dressing to vigorous activities such as running)
Instrumental activities of daily living (IADL, subscale of the OARS)	7	Measures ability to complete activities required to maintain independence in the community (i.e., meal preparation, shopping, making telephone calls, money management)
Karnofsky performance status*	1	Global indicator of patient function determined by the health care professional on a scale of 0 to 100
Numbers of falls in past 6 months	1	Number of times patient has fallen in the past 6 months
Timed Up and Go*	1	Performance-based measure of functional status: Amount of time it takes for seated patient to rise from a chair, walk 10 feet, walk back, and sit down
MOS social activities	4	Measures ability to participate in social activities and degree to which health status limits normal social activities
Comorbid Medical Conditions		
Physical health section (subscale of the OARS)	15	List of comorbid illnesses and the degree to which they impair daily activities; patient can add additional comorbid illnesses not listed; rating of eyesight and hearing
Psychological State		
Hospital Anxiety and Depression Scale	14	Measures of anxiety and depression
Social Support		
MOS social support survey: Emotional/informational and tangible subscales	12	Perceived availability of social support
Nutritional Status		
Body mass index	1	Weight/height
Percent unintentional weight loss in past 6 months	1	Unintentional weight loss in the past 6 months/baseline body weight x 100
Cognition		
Blessed Orientation-Memory-Concentration Test*	6	Gross measure of cognitive function
Medications		
Comprehensive list of medications	1	List of medications, including prescribed, herbal, and over-the-counter medications

*Items completed by the health care professional.
Abbreviations: MOS, Medical Outcomes Study; OARS, Older American Resources and Services.
Source: Hurria A, Cirrincione CT, Muss HB, et al. Implementing a geriatric assessment in cooperative group clinical cancer trials: CALGB 360401. *J Clin Oncol*. 2011;29:1290–1296. PMID: 21357782.

In the Pre-operative Assessment of Cancer in the Elderly (PACE) trial, validated instruments

including the CGA, Brief Fatigue Inventory, ECOG PS, and American Society of Anesthesiologists' grade were used to ascertain suitability for surgery of 460 elderly patients with cancer.[42] Of these, 83% had at least one comorbidity, the most common being hypertension (53.5%). In a multivariate analysis, moderate-to-severe fatigue, a dependent ADL, and poor PS were identified as independent predictors of postoperative complications. In another study of 74 elderly patients (median age 70) with acute myelogenous leukemia undergoing induction chemotherapy, OS was significantly shorter in patients whose CGA identified cognitive impairment and impaired physical function.[43] A recent large pooled analysis of 869 newly diagnosed older adults with myeloma found that a GA-based frailty score could predict mortality- and treatment-related toxicity.[44]

CONCEPT OF FRAILTY

A position statement from the American Medical Association defined the term "frailty" as characterizing "the group of patients that presents the most complex and challenging problems to the physician and all health care professionals," because these are the individuals who have a higher susceptibility to adverse outcomes, such as mortality and institutionalization. Currently, two main models of frailty exist: the phenotype model and the cumulative deficit model.[45]

Table 20-2 **Comparisons of Geriatric Assessment (CGA) Methodologies**

Instrument	Method	Scoring	Interpretation	Remarks
G8	Interview	Total score: 17	▪ Score 0 to 14: Presence of geriatric risk profile ▪ Score > 14: Absence of geriatric risk profile	Takes 2 to 3 minutes to complete screening
Groningen Frailty Indicator (GFI)	Conducting screening tests on patient	Total score: 15	▪ Score 0 to 3: Absence of geriatric risk profile ▪ Score 4 to 15: Presence of geriatric risk profile	Circle answers and use specific scoring rules set by the test
Vulnerable Elders Survey-13 (VES-13)	Self-report and interview	Total score: 10	▪ Score 0 to 2: Absence of vulnerability ▪ Score 3 to 10: Presence of vulnerability	Takes less than 5 minutes to complete
Senior Adult Oncology Program 2 (SAOP2)	Self-report and interview	N/A	▪ If one item is positive: Respective specialist consulted ▪ If several items impaired: Geriatric referral for MDT	Clinic staff administers last page of interview
Abbreviated CGA (aCGA)	Interview: ▪ Four questions from the GDS		▪ GDS score ≥ 2: Complete full 15-item GDS	
	▪ Three questions about ADL		▪ Any impairment of ADL: Complete full ADL	
	▪ Four questions about IADL		▪ Any impairment of IADL: Complete full IADL	
	▪ Four questions from the MMSE		▪ Cognitive screening score ≤ 6: Complete full MMSE	

Abbreviations: ADL, activities of daily living; GDS, Geriatric Depression Scale; IADL, instrumental activities of daily living; MDT, multidisciplinary team; MMSE, Mini Mental State Examination.

Source: Extermann M, Aapro M, Bernabei R, et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). *Crit Rev Oncol Hematol*. 2005;55:241-252. PMID: 16084735.

PHENOTYPE MODEL

The phenotype model was based on a landmark study of 5210 patients age 65 or older within the large prospective Cardiovascular Health Study.[46] A frailty phenotype was established with five variables: (1) unintentional weight loss, (2) self-reported exhaustion, (3) low energy expenditure, (4) slow gait speed, and (5) weak grip strength. Those with three or more of the five factors were judged to be frail, those with one or two factors as pre-frail, and those with no factors as robust (or not frail). At a 3- and 5-year follow-up, those categorized as frail were reported to have more adverse outcomes in terms of disability and mortality than the other two groups. Mortality at 7 years was 12%, 23%, and 43% for the not frail, pre-frail, and frail groups, respectively.

CUMULATIVE DEFICIT MODEL

This frailty index was developed as part of the Canadian Study on Health and Aging, which was a large 5-year prospective cohort study of 10,263 patients designed to investigate the epidemiology and burdens of dementia among older adults in Canada (mean age 82).[47] Ninety-two baseline variables of symptoms, signs, and abnormal laboratory values, disease states, and disabilities (collectively referred to as “deficits”) were used to define frailty. The frailty index was a calculation of the presence or absence of each variable as a proportion of the total (e.g., 20 of 92 deficits present gives a frailty index of 20/92 = 0.22). Frailty was defined as the cumulative effect of individual deficits or simply, “the more individuals have wrong with them, the more likely they are to be frail.” A recent study using the deficit accumulation principle described earlier demonstrated that a CGA-based deficit accumulation frailty index (DAFI) of 51 items applied to cancer patients was predictive of outcomes such as chemotherapy toxicity and hospitalizations.[48]

FRAILTY IN CANCER

Although frailty models provide important prognostic information for the geriatric population at large, data applicable to patients with cancer are limited. In a national sample of 12,480 community-based older adults using the 2003 Medicare Current Beneficiary Survey, 18% reported a history of cancer.[49] Among those with cancer, 60.3% reported one or more geriatric syndromes, compared to 53.2% of those without cancer ($p < 0.001$). Those with cancer had a statistically significantly higher prevalence of hearing trouble, urinary incontinence, falls, depression, and osteoporosis than those without cancer. Among specific cancer subtypes, lung cancer was associated with vision, hearing, and eating troubles; prostate cancer was associated with incontinence and falls; cervical/uterine cancer was associated with falls and osteoporosis; and colon cancer was associated with depression and osteoporosis.

BIOLOGIC MARKERS OF FRAILTY

Aging is associated with increased levels of circulating cytokines and proinflammatory markers. Aged-related changes in the immune system (e.g., immunosenescence, increased secretion of cytokines by adipose tissue) can lead to a state of chronic inflammation or “inflammaging.” High levels of IL-6, IL-1, tumor necrosis factor α (TNF-α), and C-reactive protein (CRP) in the elderly are associated with increased risk of morbidity and mortality. In particular, cohort studies of elderly participants have indicated that increased TNF-α and IL-6 levels are associated with frailty.[28] These biomarkers of frailty have now been evaluated in patients of all ages with many

tumor types (e.g., colon cancer, AML, multiple myeloma) with all demonstrating increased levels of proinflammatory cytokines. These frailty cytokines not only have been thought to play a role in carcinogenesis (e.g., AML and multiple myeloma) but also are in fact responsible for several cancer-related symptom complexes, including cancer cachexia, fatigue, poor PS, and cognitive issues. Factors contributing to the development of frailty are summarized in Figure 20-1.

In a recent review incorporating biomarkers of aging into cancer research, potential biomarkers were divided into three groups: (1) markers of systemic inflammation (e.g., IL-6, CRP, D-dimer); (2) markers of cellular senescence (e.g., telomere length); and (3) imaging for sarcopenia. These biomarkers had shown associations with frailty and mortality in numerous studies.[50] It will be important to incorporate biomarkers into future oncology clinical trials to assist oncologists in choosing appropriate treatment regiments and supportive care measures.[50]

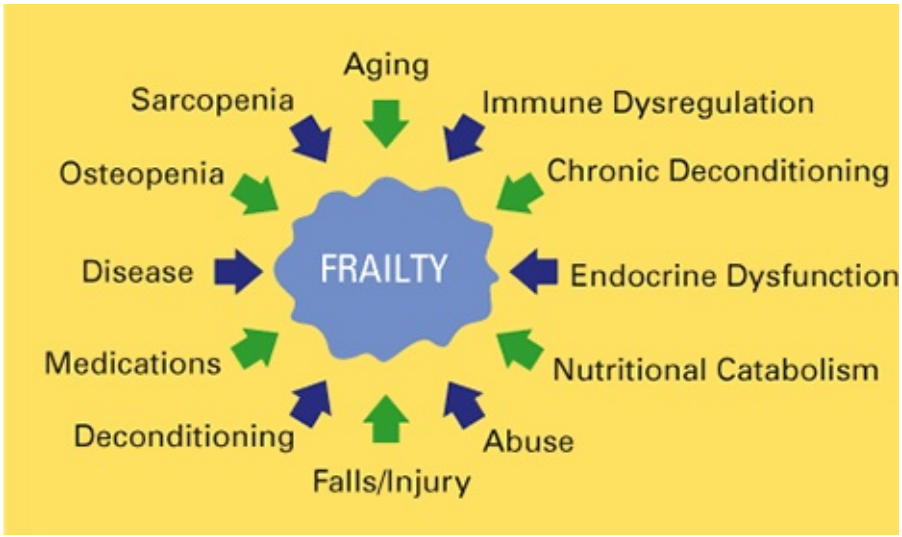

Fig. 20-1 Factors contributing to the development of frailty.
Many factors contribute to the development of frailty, which is determined by the clinical assessment of the elderly patient.

KEY POINTS

- CGA assists in defining physiologic reserve.
- Comorbid medical conditions increase the physiologic age.
- Aging is associated with an increase in proinflammatory cytokines such as TNF-α and IL-6, which contribute to frailty.
- Frailty is correlated with a severe loss of functional reserve and lack of tolerance to intervention.
- ECOG or Karnofsky PS alone may not provide an accurate measure of the functional status of an older patient with cancer.
- CGA can be used to predict survival and risk of chemotherapy tocixity in older adults with cancer.

TREATMENT APPROACHES

SURGERY

Surgery and other invasive procedures are frequently part of the care of the elderly patient with cancer. Concomitant comorbidities, impaired wound healing, and decreased physiologic reserve contribute to prolonged hospital stay and rehabilitation following surgical and other procedures. With regard to wound healing, inflammatory and proliferative responses are decreased, remodeling occurs to a lesser degree, and collagen formation is qualitatively different from that of younger individuals.[51] The normal repair process initiated by inflammation requires intact sensory nerves that stimulate increased blood flow and growth factor production. Loss of sensory neurons and co-occurring morbidities, such as diabetes and vascular disease, contribute to delayed wound healing. Complications are more common with emergent surgical procedures. Some procedures may be used as preventive measures, such as hemicolectomy, performed to prevent the need for an emergency operation to treat bowel perforation or obstruction. The American Geriatrics Society Task Force and the American College of Surgeons provide general guidelines for older adults undergoing surgery, which are applicable to older patients with cancer undergoing surgery.[52,53]

RADIATION THERAPY

Radiation therapy (RT) may be used with either curative or palliative intent, as well as an effective adjunct to surgery and/or chemotherapy. The International Society of Geriatric Oncology (SIOG) Task Force developed guidelines for best practices in radiation oncology for elderly patients with cancer.[54] For elderly patients with breast cancer, shorter courses of hypofractionated whole-breast RT are safe and effective. For patients with non-small cell lung cancer (NSCLC), conformal radiotherapy and involved field techniques without elective nodal irradiation have improved outcomes without increasing toxicity. If comorbidities preclude surgery, stereotactic body radiotherapy (SBRT) is an option for early-stage NSCLC[55] and pancreatic cancer. For patients with intermediate-risk prostate cancer, 4 to 6 months of hormonal therapy combined with external beam radiotherapy (EBRT) is an option. Short-course EBRT is an alternative to combined modality therapy for older patients with rectal cancer without significant comorbidities, and endorectal RT may be an option for early disease. For primary brain tumors, short courses of postoperative RT following maximal debulking provide comparable survival to longer treatment schedules. SBRT also is alternative to whole-brain RT for patients with limited brain metastases.[56] Intensity modulated radiotherapy (IMRT) is beneficial in reducing radiation doses to the carotids in head and neck cancer and improves locoregional control in esophageal cancer. Radiation to the oral pharynx and oral cavity can produce a loss of taste, dryness of mucous membranes, and salivary gland involution, which can lead to decreased nutritional intake in frail and elderly patients with concomitant morbidity. Age is associated with a decline in pulmonary reserve and morbidity may be expected at lower cumulative doses in older patients. However studies do not show that increasing age as a predictor of pneumonitits in patients who have radiotherapy to the thoracic area.[57] Depression and cognitive decline are side effects of whole-brain RT.

SYSTEMIC THERAPY: CHEMOTHERAPY AND TARGETED AGENTS

Older patients are consistently underrepresented in clinical trials, and therefore much of the treatment data for this population are extrapolated from studies of predominantly younger

patients.[58] There is a clear lack of prospective data for patients > 80 years of age. Overall survival is a primary endpoint in many clinical trials, but in the elderly may be compromised more by comorbidities than the cancer itself. A recent SIOG and European Organisation for Research and Treatment of Cancer task force has put forth suggestions for clinical trial design and endpoints in geriatric oncology research, suggesting that oncology trials should be without an upper age limit, include measures of QOL, and note decreases in cancer-related symptoms.[59] A recent study found that older patients enrolled in phase I clinical trials had similar survival outcomes and toxicity profiles compared with younger patients.[60] Although elderly participants had more comorbidities and lower albumin levels at baseline, there was no significant difference in survival (8.8 months versus 9.9 months; $p = 0.68$) and clinical benefit rate (69% versus 56%; $p = 0.07$) compared with younger patients. Age ($p = 0.23$) did not impact the frequency of grade 3/4 toxicities.

Chemotherapy

The SIOG task force has published guidelines for dose modification of chemotherapy agents for elderly patients with renal insufficiency, as well as those with cancer.[61,62] With oral agents absorption is adequate despite gastric emptying, but may be affected by concomitant medications such as H2 blockers, antacids, and proton pump inhibitors. Caution must be used with cytotoxic drugs such as methotrexate, bleomycin, cisplatin, and ifosfamide. Declines in the glomerular filtration rate may contribute to excess toxicity. As lean body mass decreases in the elderly, it is very important to adjust the dose based on a creatinine clearance and not merely the creatinine. Concomitant administration of drugs such as nonsteroidal anti-inflammatory drugs may compromise renal function. Acute toxicities such as nausea and vomiting occur less frequently in older patients; however, the lack of functional reserve can readily lead to dehydration and renal insufficiency.[63] Neurotoxicity related to taxanes, platinum agents, vincristine, high-dose cytarabine, and bortezomib; cardiotoxicity from doxorubicin; and mucositis from 5-fluorouracil are all more common and severe in older patients.[61] Whether the risk of myelotoxicity increases with age remains a controversial issue, but studies indicate longer duration of neutropenia in the elderly.[61] Pretreatment CGA is useful to predict the risk of toxicity for elderly patients.

Targeted Agents

Targeted therapeutic agents, including tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors, human epidermal growth factor receptor 2 and *BRAF*-mutation targeted drugs, antiepidermal growth factor receptor inhibitors, and antivascular endothelial growth factor products have been increasingly used in all cancer patients in the past decade.[64] As with chemotherapy trials, data for older patients have been extrapolated from trials of predominantly younger patients. A study of older adults with chronic myeloid leukemia found that comorbidities and polypharmacy may affect cytogenetic response. In this study it was observed that patients with fewer comorbidities who were only on tyrosine kinase inhibitors (no polypharmacy) had a better chance of a complete response.[65] In addition, many targeted agents are metabolized by the cytochrome P450 system, increasing the risk for significant drug interactions. Patient selection and geriatric evaluation are critical for appropriate drug selection, dosing, and monitoring of these agents. Table 20-3 provides recommendations for the use of targeted therapy in solid tumors in elderly patients.[64]

Immuno-oncology Agents

Immune checkpoint inhibitors, which impact immune function, are a new class of oncologic agents used in the treatment of a variety of malignancies. Expression of immune checkpoints on T cells increases with age, making immune checkpoint blockade a promising option for older cancer patients.[66] However, the impact of immunosenesence on these agents is not clear. The term “age-related immune dysfunction (ARID)” may be used to describe immune-related changes of aging and their potential interaction with immune-oncology agents.[67] Use in older patients is enhanced by a relatively low toxicity profile as compared to conventional chemotherapy.[68] However, more data regarding clinical benefit in elderly patients are needed.

HEMATOPOIETIC CELL TRANSPLANTATION

Historically, the associated morbidity and mortality limited the use of allogeneic hematopoietic cell transplantation (HCT) to individuals younger than age 50. However, autologous HCT has been used for patients up to age 70. As there are no guidelines for using HCT in older adults, patient selection, choice of conditioning regimen, immunosuppression, and cell source are arbitrary and are generally based on cardiopulmonary and hepatorenal function. Risk-assessment tools such as CGA and comorbidity measures have recently been applied to delineate potential elderly candidates for HCT therapy. Reduced-intensity conditioning (RIC) for allogeneic HCT has led to a more favorable toxicity profile and decreased transplanted- related mortality compared to myeloablative approaches, thus impacting traditional age barriers.[69] Donor selection for older recipients is an additional issue. Older patients may have older human leukocyte antigen-matched siblings, with diminished hematopoietic cell yields, and potential health limitations to be donors. Important geriatric issues such as nutrition, caregiver support, and cognitive assessment have not been extensively evaluated in the setting of HCT. For example, acute delirium occurs in up to 50% of allogeneic HCT recipients and may be more common in the elderly.[70] More specific details of hematopoietic cell transplantation are covered in Chapter 19.

Table 20-3 **Recommendations for Use of Selected Targeted Therapy in Solid Tumors in Elderly Patients**

Drug	Disease Setting	Efficacy Data	Safety Data	Data Source	Specific Considerations in Older Adults
Imatinib	GIST	Limited	Limited	Pivotal adjuvant trials	Potential toxicity concerns: myelosuppression, fluid retention, diarrhea, rash
Gefitinib	Advanced NSCLC	Available; effective	Available; favorable toxicity profile in elderly patients	Elderly-specific data	Well tolerated; monitor for rash and diarrhea
Erlotinib	Advanced NSCLC	Available; effective	Available; increased toxicity	Pivotal trials and elderly-specific data	Extreme caution; close monitoring for toxicity: rash, stomatitis, dehydration, anorexia, and fatigue
Crizotinib	Advanced NSCLC	Limited	Limited	Pivotal trials	Likely reasonable option, although data are limited
Sorafenib	Advanced HCC	Limited; appears effective	Limited; appears safe	Elderly-specific data	Monitor for GI and skin toxicity
Everolimus	ER-positive MBC; HER2-positive	Effective	Caution; higher incidence of treatment-related deaths in elderly patients	Elderly-specific data	Close monitoring for stomatitis, diarrhea, and anemia
Trastuzumab	Breast cancer; HER2-positive	Limited	Limited	Retrospective data	Use in elderly patients without cardiac risk factors; regular cardiac monitoring
Pertuzumab	MBC; HER2-positive	Available; effective	Limited; increased toxicity in all patients	Pivotal trial	Use in elderly patients without cardiac risk factors
T-DM1	HER2-positive MBC	Limited	Limited	Pivotal trial	Favorable safety profile
Vemurafenib	*BRAF*-mutant advanced melanoma	Limited	Limited	Pivotal trial	Monitor for skin toxicity, fatigue, arthralgia
Dabrafenib	*BRAF*-mutant advanced melanoma	Limited	Limited	Pivotal trial	Monitor for skin toxicity, fever, fatigue, arthralgia
Ipilimumab	Advanced melanoma	Available	Available	Pivotal trial; elderly-specific data	Immune-related adverse events: dermatologic, endocrine, GI
Sunitinib	mRCC	Available	Available; increased toxicity	Elderly-specific data	Monitor for GI toxicity, HFS, HTN, fatigue; first-line dose modification may be appropriate
Pazopanib	mRCC	Available	Available; favorable toxicity profile in elderly patients	Pivotal trial	Monitor for GI toxicity, HTN, anorexia
Sorafenib	mRCC	Available	Available	Pivotal trial	Monitor for skin toxicity, diarrhea, fatigue, and rare serious AEs (HTN, cardiac ischemia)
Everolimus	mRCC	Available	Available; well tolerated	Elderly-specific data	Monitor for stomatitis, rash, fatigue

Temsirolimus	mRCC	Available	Available; well tolerated	Pivotal trial	Monitor for rash, fluid retention, hyperlipidemia, hyperglycemia
Axitinib	mRCC	Available	Limited	Pivotal trial	Monitor for HTN, diarrhea, fatigue
Cabozantinib	mRCC	Available	Limited	Pivotal trial	Monitor for HTN, diarrhea, mouth ulcers, HFS
Cetuximab	mCRC	Available; effective	Limited	Pivotal trial	Monitor for rash, GI toxicity
Pantiumumab	mCRC	Available; effective	Limited	Pivotal trial	Well tolerated; monitor for skin toxicity, diarrhea, hypomagnesemia
Bevacizumab	mCRC	Available; effective	Available; increased risk for HTN	Elderly-specific data	Monitor for HTN; screen for vascular risk factors
Aflibercept	mCRC	Available; effective	Available; increased risk of toxicity	Pivotal trial	Cautious use in elderly patients, given toxicity profile
Regorafenib	mCRC	Available; effective; smaller benefit than in younger patients	Available; increased toxicity	Pivotal trial	Cautious use in elderly patients, given toxicity profile and small benefit
Bevacizumab	Advanced ovarian cancer	Available	Limited	Pivotal trials	Monitor for HTN
Trastuzumab	Advanced gastric cancer	Limited	Limited	Pivotal trial	Use in elderly patients without cardiac risk factors
Ramucirumab	Advanced gastric cancer	Limited	Limited	Pivotal trial	Lack of data to support use

Abbreviations: AEs, adverse events; ER, estrogen receptor; GI, gastrointestinal; GIST, GI stromal tumors; HCC, hepatocellular carcinoma; HFS, hand-foot syndrome; HTN, hypertension; MBC, metastatic breast cancer; mCRC, metastatic colorectal cancer; mRCC, metastatic renal cell carcinoma; NSCLC, non-small cell lung cancer; T-DM1, trastuzumab emtansine.

SUPPORTIVE CARE MEASURES

Supportive care measures are especially important for elderly patients as they help improve treatment tolerability and minimize dose reductions and delays in therapy. Many of the specific aspects of supportive care are covered in Chapter 21 and are mentioned here to stress their importance for the management of the elderly patient with cancer. There are established guidelines on the prevention and treatment of mucositis, use of antiemetics, and growth factor utilization. Chemotherapy-induced neutropenia is reduced by 60 to 75% with myeloid growth factor use, thus reducing the occurrence of febrile neutropenia and infections. These agents also prevent dose reductions that can compromise the effectiveness of the therapy. The American Society of Clinical Oncology (ASCO) guidelines recommend prophylactic use of colony-stimulating factors (CSFs) to reduce the occurrence of febrile neutropenia when the risk of febrile neutropenia is 20% or higher and when no other equally effective and safe regimen that does not require CSFs is available.[71] Primary CSF prophylaxis is recommended for patients who are at high risk for febrile neutropenia based on age, medical history, disease characteristics, and myelotoxicity of the treatment regimen. The guidelines do not address recommendations for the use of CSFs in AML or myelodysplastic syndromes.

Antiemetic prophylaxis with a 5-HT3-receptor antagonist in combination with corticosteroids is recommended for patients receiving moderately to highly emetogenic chemotherapy or

radiotherapy.[72] A 2017 ASCO update recommends that all patients receiving highly emetogenic chemotherapy regimens should be given a four-drug combination that includes an NK1receptor antagonist, a 5-HT3 receptor antagonist, dexamethasone, and olanzapine. Netupitant and palonosetron plus dexamethasone is an additional treatment option in this setting.

Other symptoms can affect an elderly patient's QOL. The use of stool softeners to prevent constipation from vinca-alkaloid-induced bowel neuropathy and opioid use is important. Fatigue is one of the most common symptoms, affecting 40 to 90% of patients during treatment and 19 to 80% following completion of therapy.[73] The etiology of fatigue is multifactorial, ranging from immobility and deconditioning to anemia, depression, pain, poor nutrition, drugs, and metabolic causes. Treatment of fatigue generally requires treatment of the underlying causes (e.g., treat anemia with hematinics, iron, B12, and folate). Exercise programs can have a positive role in the treatment of cancer-related fatigue. Drugs such as methylphenidate and modafinil have been used to treat cancer-related fatigue but have not been well studied in the elderly.[73]

PALLIATIVE CARE AND END-OF-LIFE ISSUES

Many older patients are realistic with regard to nearing the end of life and are open to discussion about their disease and its potential consequences. Patients' individual goals, independence, and physical, emotional, and spiritual health are priorities. In a landmark study of patients age 60 or older who were terminally ill, it was found that if the outcome was survival but with severe functional impairment or cognitive impairment, 74.4 and 88.8% of participants, respectively, would not choose treatment.[74] Palliative care is an essential component of care throughout the disease process, and not just in the terminal stages. (These issues are discussed in further detail in Chapter 22: Palliative Medicine for Cancer.)

An interdisciplinary palliative care team focuses on preventing and relieving suffering, regardless of the disease, stage, or need for other therapies. The goals of palliative care for the elderly are the same as those for younger individuals, and an accurate identification of all symptoms is particularly useful. Simplified instruments, such as the Edmonton Symptom Assessment Scale—which assesses nine symptoms common for patients with cancer: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath—are useful in providing a profile of symptom severity over time.[75]

KEY POINTS

- The American Geriatrics Society Task Force and the American College of Surgeons provide general guidelines for older adults undergoing surgery, which are applicable to older patients with cancer.
- Delivery, duration, and dosage of radiotherapy must be carefully planned, based on organ function, comorbidities, and geriatric evaluation, as side effects may be more pronounced for elderly patients.
- Chemotherapy should be dosed based on creatinine clearance, with use of CSFs as indicated.
- Targeted agents may have several drug interactions for the older patient with polypharmacy.
- Immuno-oncology drugs appear safe for use in older adults, although data on benefits to

elderly patients are still limited.

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SYMPTOM MANAGEMENT

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Recent Updates

Vaginal Dryness

- New data support that a topical vaginal lidocaine product decreases dyspareunia. (Goetsch MF, *J Clin Oncol* 2015)
- Newly published data also support that vaginal laser treatments can help resolve symptoms associated with vaginal dryness. (Salvatore S, *Climacteric* 2015)

Nausea and Vomiting

- The addition of olanzapine to a serotonin receptor antagonist, dexamethasone, and a neurokinin kinase 1 receptor antagonist improved the control of nausea in patients receiving highly emetogenic chemotherapy. (Navari R, *N Engl J Med* 2016)
- Rolapitant, a new NK-1 receptor antagonist, has been shown to decrease chemotherapy-induced vomiting and is now available. (Rapoport BL, *Lancet Oncol* 2015)

Chemotherapy-Induced Neuropathy

- New pilot data support that topical cryotherapy might help prevent paclitaxel-associated neuropathy, but more definitive data are needed. (Hanai A, *J Clin Oncol* 2016; Sundar R, *J Clin Oncol* 2016; Eckhoff L, *Breast Cancer Res Treat* 2013)

Mucositis

- New data from two relatively large phase II clinical trials strongly support the utility of oral corticosteroid swish-and-spit preparations for markedly decreasing everolimus-associated oral mucositis. (Rugo H, *J Clin Oncol* 2016; Jones VL, *Cancer Res* 2016)

Bone Health

- Published results support that bisphosphonates can be given at 3-month intervals for 2 years, as opposed to 1-month intervals, for prevention of bone-related events in patients with breast cancer, prostate cancer, and multiple myeloma. (Himelstein AL, *JAMA* 2017)

Hot Flashes

- New data from a randomized, placebo-controlled study support that oxybutynin can decrease hot flashes more than a placebo. (Simon JA, *Menopause* 2016)

OVERVIEW

Efforts to alleviate the common symptoms related to cancer and/or cancer therapy are important aspects of ideal oncologic care. The following symptoms are discussed in this chapter:

- Nausea and vomiting associated with cytotoxic agents
- Management of estrogen-deprivation symptoms
- Oral mucositis and esophagitis associated with treatment

- Malignant ascites
- Anorexia and cachexia
- Diarrhea associated with cancer or cancer therapy
- Cancer fatigue
- Skin rashes
- Chemotherapy-induced peripheral neuropathy
- Sexual health
- Bone health
- Anemia
- Prevention and treatment of thromboembolic complications
- Alopecia

Although these symptoms do not encompass all toxicities of cancer and cancer therapy, others such as pain, dyspnea, and constipation are discussed in Chapter 22: Palliative Medicine for Cancer.

NAUSEA AND VOMITING ASSOCIATED WITH CYTOTOXIC AGENTS

Vomiting is a natural protective mechanism to rid the body of toxic substances. However, in the setting of cancer chemotherapy and radiation therapy, nausea and vomiting become toxic effects of major concern. For patients, nausea and vomiting are one of the most feared toxic effects related to cancer treatment—an observation described in surveys conducted in the 1980s and confirmed in the 1990s—even after the introduction of antiemetic agents that are considered highly effective. Protracted emesis can lead to dehydration, electrolyte imbalance, and other metabolic derangements, as well as early discontinuation of chemotherapy. Appropriate and aggressive prophylaxis against and effective management of chemotherapy-associated nausea and vomiting continues to be of major importance.

The emetic response can be conceptualized as a brainstem-based reflex arc. The final common pathway begins in the emetic center, a diffuse neural complex located in the brainstem near the nucleus tractus solitarius. Efferent neuronal pathways from the emetic center activate and coordinate the many muscle groups necessary for an effective vomiting response. This reflex arc has multiple afferent pathways that lead to the vomiting center. The chemoreceptor trigger zone with its porous blood–brain barrier is located in the area postrema adjacent to the fourth ventricle and can be activated by humoral mediators that enter the cerebrospinal fluid. Activation signals are then transmitted to the emetic center. Corticosteroids help to decrease the transfer of emetogenic substances across the blood–brain barrier and thus help to prevent chemotherapy-associated emesis. The peripheral pathways begin at nerve endings in the upper gastrointestinal tract itself. Vagal pathways, which terminate in the brainstem, allow activation of the emetic center. Other afferent pathways include cerebral cortical-signaling pathways (learned emesis) and vestibular pathways related to motion sickness.

The emetic reflex arc includes synaptic sites through which signals are relayed to receptors by various neurotransmitters. Identification and blockade of these key neurotransmitter receptors have been the major strategies for the development of effective antiemetic agents. Dopaminergic, serotonergic, and neurokinin receptors have been considered to be of major

importance in acute vomiting. Other receptors, such as cannabinoid and opiate receptors, also may have a role in emetic pathways.

Emetic potential can be affected by patient characteristics; nausea and emesis with prior chemotherapy is particularly important. Emesis also tends to be more severe for younger patients and for women. A history of motion sickness and/or a history of morning sickness during pregnancy also appear to directly correlate with chemotherapy-induced nausea and vomiting. Findings from several retrospective and prospective studies have suggested that the risk of emesis is lower for patients with a history of excessive alcohol intake than for patients with no such history.

There are three different types of nausea and vomiting related to chemotherapy: acute, delayed, and anticipatory.

ACUTE NAUSEA AND VOMITING

Acute nausea and vomiting induced by chemotherapy has been defined as that which occurs within the first 24 hours after administration of a chemotherapy agent.

DELAYED NAUSEA AND VOMITING

Some chemotherapy drugs, such as cisplatin and cyclophosphamide, may cause delayed nausea and vomiting, defined as occurring 2 to 5 days after the administration of chemotherapy. This delayed emesis is often of lesser intensity and occurs in fewer patients, but it can be of longer duration than acute emesis. While it may appear to be independent of the acute emetic response, acute emesis is a risk factor for the development of delayed emesis. The antiemetic agents that are effective for managing delayed vomiting differ from those that are effective for managing acute vomiting; this suggests that different neurotransmitter mechanisms—if not different physical sites—are involved in these two forms of emesis. Delayed nausea and emesis remains a challenge to manage. Currently available regimens have improved the incidence of delayed vomiting, but until recently, delayed nausea has been a difficult problem to treat. Olanzapine has been shown to prevent delayed nausea associated with moderate and highly emetogenic chemotherapy.[1] The risk factors for delayed nausea and vomiting are similar to those for acute nausea and vomiting; they include chemotherapy-related factors and patient characteristics.

ANTICIPATORY NAUSEA AND VOMITING

Anticipatory (learned) emesis is a conditioned reflex that can be rapidly established by poor antiemetic protection during an earlier course of chemotherapy. It can be triggered by numerous stimuli that are associated with chemotherapy and can occur at any time. Anticipatory emesis is similar to conditioned taste aversions that also can be seen among patients with cancer.

TREATMENT ACCORDING TO EMETOGENIC POTENTIAL OF CHEMOTHERAPY

In 1999, the American Society of Clinical Oncology (ASCO) convened a multidisciplinary panel to classify the emetogenic potential of chemotherapy agents and to provide recommendations to manage nausea and vomiting.[2] Following an extensive review of the literature and guided by clinical experience, the panel categorized agents based on the incidence with which each chemotherapy regimen caused emesis.[3,4] Currently, regimens that cause vomiting in greater

than 90% of patients, without the use of antiemetic drugs, are considered as being highly emetogenic chemotherapy (HEC). Moderately emetogenic chemotherapy regimens (MEC) cause emesis in 30 to 90% of patients. Lowly emetogenic chemotherapy is expected to produce emesis in 10 to 30% of patients; a minimal-risk category is for expected emesis in less than 10% of patients. Of note, combination doxorubicin/cyclophosphamide chemotherapy was initially considered to be a moderately emetogenic regimen but now is commonly identified as a highly emetogenic regimen.

TREATMENT OF NAUSEA AND VOMITING

The best strategy for managing emesis is prevention, which should begin with the first course of chemotherapy, because once emesis occurs, it is far more difficult to control. Effective management of emesis reduces medical complications that can result from protracted vomiting. Added benefits are that control of emesis decreases the possibility premature discontinuation of chemotherapy and/or the development of anticipatory nausea/vomiting.

Most of the antiemetic agents developed in the 1960s and 1970s were antidopaminergic drugs specifically targeted at the dopamine-2 receptor. These agents include the phenothiazines (e.g., prochlorperazine), the butyrophenones (e.g., haloperidol), and the substituted benzamides (e.g., metoclopramide).

A dose–response curve for efficacy for phenothiazines and butyrophenones indicates that these two classes of agents have a low therapeutic index. Antidopaminergic toxicity, including extrapyramidal reactions, agitation, and depression, is dose-dependent and can be limiting for the use of these agents. Therefore, phenothiazines and butyrophenones generally are used only to control mildly emetogenic chemotherapy and in relatively low doses.

The substituted benzamide metoclopramide blocks the dopamine-2 receptor and, at high doses, the serotonin-3 (5-HT3) receptor as well. The development in 1981 of the high-dose metoclopramide regimen (2 mg/kg intravenously every 2 hours for five doses) was a breakthrough in antiemetic therapy and provided the first effective treatment for control of emesis induced by high-dose cisplatin. However, antidopaminergic toxicity is a major limiting factor with high-dose metoclopramide. In general, metoclopramide has been replaced with the 5-HT3 receptor antagonists because of their improved toxicity profiles. In 2013, the European Medicines Agency's Committee on Medical Products for Human Use recommended that metoclopramide be curtailed because of serious neurologic side effects.[5]

Antiemetic agents with a high therapeutic index include the 5-HT3 receptor antagonists and corticosteroids (Table 21-1). The 5-HT3 receptor antagonists became available in the 1990s and have become a cornerstone of modern antiemetic therapy for highly emetogenic and moderately emetogenic chemotherapy regimens.

Table 21-1 **Antiemetic Agents**	
Therapeutic Index	**Agents**
High	5-HT3 receptor antagonists (ondansetron, granisetron, dolasetron, and palonosetron); corticosteroids (dexamethasone and methylprednisolone); neurokinin-1 receptor antagonists (aprepitant and netupitant), and olanzapine
Limited	Dopamine-2 receptor antagonist (metoclopramide); phenothiazines (chlorpromazine and prochlorperazine); butyrophenones (haloperidol)
Adjunctive	Benzodiazepines (anxiolytics); antihistamines

Clinical trials have shown that efficacy is similar for the first three clinically available 5-HT3 receptor antagonists: ondansetron, granisetron, and dolasetron. The classic dose–response curve of 5-HT3 receptor antagonists approximates a logarithmic shape; that is, a steep and linear dose response is present until a threshold (shoulder) value is reached, after which, increasing the dose does not further increase efficacy (plateau effect). Although the modest side-effect profile of the 5-HT3 receptor antagonists allows for dose escalation without a substantial increase in side effects, the most cost-effective dose will be one close to the threshold value; that is, the lowest dose that provides maximum antiemetic protection. However, this value is affected by the emetic potential of the chemotherapy administered; therefore, the threshold value varies for different classes of chemotherapy agents and for high-dose (compared with standard-dose) regimens. As a group, the 5-HT3 receptor antagonists have a mild side-effect profile, including mild headache, transient and asymptomatic elevation of transaminase levels, and constipation. Additionally, they can cause prolongation of the QTc interval, which may be important if used with other newer oral anticancer agents such as pazopanib, which may exacerbate this risk. The newest 5-HT3 receptor antagonist, palonosetron, has a longer half-life and a higher receptor-binding affinity than the other three agents. It is now established that this drug is more effective than the other 5-HT3 receptor antagonists.[6]

Corticosteroids can be useful either as a single agent or in combination with a 5-HT3 receptor antagonist or a dopamine-receptor antagonist. Generally, a corticosteroid (e.g., dexamethasone) is recommended whenever a 5-HT3 receptor antagonist is given. Two small randomized, placebo-controlled clinical trials looked at day 1 alone versus days 1 through 3 dexamethasone in addition to 5-HT3 and neurokinin-1 receptor (NK-1) antagonists in highly emetogenic chemotherapy.[7,8] Both trials concluded that significant differences were not found in patient preference, quality of life, or symptoms between the study arms. These results support the opportunity to stop the dexamethasone in subsequent chemotherapy courses if too many side effects develop from this drug (e.g., glucose intolerance or insomnia).

The NK-1 antagonist aprepitant was a major advance in the prevention of both acute and delayed nausea and vomiting, especially delayed.[9] Although initially it was most commonly

prescribed as a 3-day oral treatment, it has now been demonstrated that a single day of intravenous fosaprepitant controls nausea and vomiting equally as well as 3 days of oral aprepitant.[10] Guidelines recommend an NK-1 receptor antagonist for patients receiving highly emetogenic chemotherapy.[11] Reports have supported that intravenous fosaprepitant causes substantial venous toxicity when administered through peripheral veins, especially with doxorubicin-based chemotherapy.[12,13] A combination product consisting of palonosetron and the NK-1 receptor antagonist netupitant has become available as an option for the treatment of highly emetogenic chemotherapy regimens.[14,15]

Two randomized, placebo-controlled trials looked at a new NK-1 inhibitor, rolapitant, in patients receiving highly emetogenic chemotherapy.[16] These two studies enrolled 1087 patients undergoing highly emetogenic chemotherapy regimens. All patients received granisetron and dexamethasone and then were randomly assigned to receive either rolapitant or placebo. Complete relief from delayed emesis was significantly better in the rolapitant group (71%), as compared with the placebo group (60%) ($p = 0.0426$). Of note, post-marketing reports of substantial allergic reactions during rolapitant infusions led to labeling changes regarding this potential toxicity.

Another treatment option for the prevention of nausea and vomiting is olanzapine.[1] Olanzapine 10 mg orally on days 1 to 4 of chemotherapy was compared to placebo in a randomized, phase III trial in chemotherapy-naive patients receiving a highly emetogenic regimen. All patients also received a 5-HT3 and an NK-1 antagonist, as well as dexamethasone. Patients receiving olanzapine had significantly less nausea and vomiting following chemotherapy in both the acute and delayed time frame. The most common side effect in those receiving olanzapine was sedation, which was most prominent on day 2 after chemotherapy.

The 2014 version of the National Comprehensive Cancer Network (NCCN) guidelines recommend that an olanzapine-containing regimen is an option for preventing nausea and vomiting for patients receiving moderate to highly emetogenic chemotherapy, based on a series of trials supporting its use.[17-20] This regimen consists of olanzapine 10 mg orally on days 1 to 4 along with palonosetron 0.25 mg and dexamethasone 20 mg, both intravenously on day 1. The guidelines also recommend olanzapine as a breakthrough medication for patients in whom nausea/vomiting develops after chemotherapy.

Marijuana has become available for medical use in a number of states in the United States. While there are reports that marijuana is helpful for controlling nausea/vomiting, the best product, dose, and associated toxicities have not been identified. Dronabinol is a cannabinoid approved by the U.S. Food and Drug Administration (FDA) in 1985 for patients who have chemotherapy-induced nausea and vomiting in spite of receiving standard antiemetic therapy.[21] May and Glode have published an excellent review of the studies involving the use of dronabinol for chemotherapy induced nausea and vomiting.[22] Studies show that cannabinoids have a low therapeutic index. In addition, their role is limited by side effects such as dizziness, sedation, hypotension, and dysphoria, especially in older adults.

Occasionally, adjunctive agents, such as benzodiazepines and antihistamines, are a helpful addition to the antiemetic regimen. If the patient is particularly anxious, an anxiolytic agent such as a benzodiazepine may be helpful, especially within the 1 to 12 hours prior to therapy. Of the benzodiazepines, lorazepam is used most often. Its greatest contribution is probably its anxiolytic properties.

Regarding the treatment of anticipatory nausea and vomiting, management options include the following:

- Prevention by the appropriate use of prophylactic antiemetic use
- Behavioral desensitization
- Distraction
- Focusing on enjoyable things
- Benzodiazepines
- Relaxation

GUIDELINES

Perhaps the best way to ensure the appropriate use of antiemetic agents for patients receiving chemotherapy is to apply guidelines in clinical practice. In addition to ASCO guidelines, last updated in 2017,[6] several other guidelines are available.[23-26] One very effective way of making antiemetic guidelines work is to have them electronically linked to the ordering of specific chemotherapy regimens.[27]

RADIATION THERAPY–INDUCED NAUSEA AND VOMITING

As with chemotherapy, radiation therapy can cause nausea and vomiting, with the treatment field being one of the major determinants of risk. The dose of radiation therapy administered per fraction and the pattern of fractionation are also important risk factors but are less well defined. As with chemotherapy, the risk can be classified as high, moderate, or low.

The 2012 ASCO antiemetic guidelines recommend the use of both a 5-HT3 antagonist and dexamethasone for prevention of radiation-induced nausea.[6] Nonetheless, there is a dearth of data regarding this subject, and more information is desired. In practice, many radiation oncologists do not treat all patients with prophylactic therapy; rather, they treat patients if nausea/vomiting becomes an issue.

For patients receiving radiation with low emetogenic risk, either a 5-HT3 receptor antagonist or a dopamine-receptor antagonist (e.g., prochlorperazine) can be used as needed and continued prophylactically for each remaining day of radiation treatment. Because the difference in efficacy between dopamine receptor antagonists and 5-HT3 receptor antagonists is smaller in this setting, dopamine receptor antagonists are commonly recommended (based on expense), and 5-HT3 receptor antagonists are reserved for rescue.

KEY POINTS

- There are three types of chemotherapy-induced nausea and vomiting: acute, delayed, and anticipatory.
- 5-HT3 receptor antagonists are helpful medications for patients receiving emetogenic chemotherapy. When 5-HT3 receptor antagonists are used, corticosteroids also are recommended.
- NK-1 inhibitors, including oral aprepitant, netupitant, and rolapitant or intravenous fosaprepitant are particularly efficacious for preventing delayed nausea and vomiting and are recommended for patients receiving highly emetogenic, and some moderately emetogenic, chemotherapy regimens.

- Olanzapine has been shown to significantly reduce nausea and emesis in highly emetogenic regimens when combined with 5-HT3 receptor antagonists, dexamethasone, and NK-1 inhibitors.
- Knowledge of the emetogenic potential of chemotherapy agents and the use of antiemetic guidelines is critical in treating patients.

ESTROGEN-DEPRIVATION SYMPTOMS

HOT FLASHES

Menopausal symptoms, including hot flashes, are highly prevalent among patients with breast cancer and in other premenopausal women who undergo ovarian function suppression. Additionally, approximately 75% of men undergoing androgen-deprivation therapy will have substantial discomfort because of hot flashes. Many times, these hot flashes are severe and may last for a considerable time.[28]

Estrogens and androgens can alleviate hot flashes for women and men, respectively. Clearly, there is concern about giving estrogen to women who have had breast cancer.[23] Similarly, the administration of androgens to men with prostate cancer defeats the purpose of androgen-deprivation therapy. A consensus among many experts is that estrogen-replacement therapy should not generally be recommended for women with a history of breast cancer. In contrast to this recommendation, some data suggest that estrogen therapy is not associated with adverse events for most survivors.[29,30] This means that estrogen can be used by select women for relief of symptoms, provided they understand the potential risks associated with treatment. Nonetheless, alternative agents are available to control hot flashes for this patient population (Table 21-2).

Table 21-2 Pharmacologic Treatment of Hot Flashes (Agents Other Than Estrogen)

Progesterone Analogs	Megestrol acetate: 20 to 40 mg PO per day
	Medroxyprogesterone acetate: 400 to 500 mg IM injection (once)
Nonhormonal Agents	Venlafaxine: 37.5 mg PO per day for 1 week, then 75 mg PO per day
	Paroxetine: 10 mg PO per day
	Citalopram: 10 mg to 20 mg PO per day
	Desvenlafaxine: 50 mg PO per day for 1 week, then 100 mg PO per day
	Escitalopram: 10 to 20 mg PO per day
	Gabapentin: titrate PO doses up to 900 mg per day
	Pregabalin: titrate PO doses up to 75 mg per day
	Clonidine: 0.1 mg PO per day

Progesterone analogs appear to alleviate hot flashes about as effectively as estrogen, with low doses of megestrol acetate decreasing hot flashes by approximately 80%.[31] Despite this efficacy, there is concern regarding the use of any hormone for patients with breast or prostate cancer. Although megestrol acetate is used at times to manage metastatic prostate cancer, men who receive low doses of megestrol acetate may have a marked and prolonged decrease in prostate-specific antigen levels when low doses of the drug are withdrawn. This effect is somewhat akin to the withdrawal of flutamide causing a reduction of prostate cancer activity. Although other side effects from megestrol acetate include increased appetite, weight gain, and venous thrombosis, these have been largely seen with drug doses that are manyfold higher than the doses used for the treatment of hot flashes. It is not clear that the same side effects are seen with the low doses used for the management of hot flashes.

An alternative way to give a progesterone analog is to use IM medroxyprogesterone acetate (MPA). The results of randomized studies show that IM MPA injections of 400 to 500 mg control hot flashes for a prolonged period in breast cancer survivors.[32,33] Because this modality can control hot flashes for a prolonged period, relatively short-term progesterone analog therapy is possible, alleviating the concern about long-term, continuous hormone therapy.

Given the desire to find nonhormonal agents to treat hot flashes, a number of clinical studies have been conducted to explore this possibility. Selective serotonin receptor reuptake inhibitors and serotonin and norepinephrine receptor reuptake inhibitors—antidepressant medications—have been found to be effective for the treatment of hot flashes (Table 21-2). Results of pilot studies[34, 35] support that low doses of venlafaxine decreased hot flash intensity and frequency, both for breast cancer survivors and for men receiving androgen-deprivation therapy. The results of a randomized, placebo-controlled trial confirmed these findings among women, demonstrating a dose-response effect up to the target dose of 75 mg daily of venlafaxine (noting that patients should be started on a dose of 37.5 mg/day for a week). This dose resulted in a 60% reduction of hot flashes, compared with a 27% reduction for the placebo.[36]

The next reported antidepressant drug, paroxetine (10 to 20 mg daily) was associated with a similar reduction in the number of hot flashes in a randomized, placebo-controlled trial.[37] Subsequently, in randomized, double-blind, placebo-controlled trials, citalopram,[38] escitalopram,[39] and desvenlafaxine[40] decreased hot flashes to a similar degree. Fluoxetine (20 mg daily) and sertraline (50 mg daily) appear to reduce hot flashes slightly more than does a placebo, but they seem to be less effective than the other antidepressants noted above.[41,42] Paroxetine, fluoxetine, and sertraline decrease the metabolism of tamoxifen, to its active metabolite, endoxifen, by the enzyme CYP2D6. Therefore, it is recommended that these agents should be avoided for patients receiving tamoxifen. Venlafaxine and citalopram do not alter tamoxifen metabolism as much as some other antidepressants.[43] A meta-analysis has confirmed that multiple antidepressants moderately decrease hot flashes.[44]

Data from pilot and randomized clinical trials demonstrate that relatively low doses of gabapentin decrease the frequency of hot flashes to a degree similar to that of the newer antidepressant agents.[45-48] Gabapentin should be started at 100 to 300 mg daily. After 3 days, the dosing frequency can be titrated upward. Doses of 900 mg daily decrease hot flashes by approximately 50 to 60%. Although some data suggest that higher doses may be more efficacious, this has not been proven.

One clinical trial did look at the efficacy of gabapentin compared with that of venlafaxine, utilizing patient preference as its primary endpoint. Patients were randomly assigned to receive venlafaxine or gabapentin in doses recommended by previous placebo-controlled clinical studies of hot flashes. Patients were treated for 4 weeks followed by a 2-week washout period before

being crossed over to the alternative treatment. Although the two agents appeared to reduce hot flashes to a similar extent (approximately a 65% reduction) and had similar amounts of toxic effects, 68% of patients preferred venlafaxine, while only 32% preferred gabapentin (p = 0.01).[49] Since a third of patients preferred gabapentin as an initial treatment, a trial period for this medication is reasonable if venlafaxine was not sufficiently efficacious.

The results from well-powered, randomized, placebo-controlled trials indicate that the antihypertensive medication clonidine inhibits hot flashes more than placebo (p = 0.0006).[50] However, clonidine causes substantially more toxicity (e.g., hypotension, drowsiness, dry mouth, and constipation) than placebo. Because patients were just as likely to choose a placebo as compared with clonidine in a randomized, double-blind, crossover clinical trial, enthusiasm for this agent is tempered.

Pilot data, published in 2007, [51] supported that oxybutynin was helpful for decreasing hot flashes. These findings were confirmed in a placebo-controlled randomized, double-blinded trial[53] that demonstrated that 15 mg of oxybutynin decreased hot flashes to what appears to be a similar degree as is seen with several antidepressants and gabapentinoids. The main toxic effect was mouth dryness. The authors suggested that lower doses be studied; such a trial is accruing patients.[52]

Although the findings from a number of pilot studies have suggested that soy products could alleviate hot flashes, the majority of results from large, placebo-controlled clinical trials do not demonstrate any benefit from a phytoestrogen product for breast cancer survivors.[54,55] Likewise, well-conducted studies have not demonstrated any benefit from black cohosh,[56] flaxseed,[57] or magnesium oxide.[58] Limited data support that vitamin E is more effective than a placebo[59,60] for decreasing menopausal hot flashes.

Several nonpharmacologic options to prevent hot flashes have been studied for otherwise healthy postmenopausal women. Although pilot information supports the use of paced respirations[46] and cognitive behavioral therapy,[61] the more established of these approaches to date is hypnosis; randomized trials of clinical hypnosis versus a structured attention control arm have demonstrated a decrease in hot flashes by both patient diary and physiologic measurements of hot flashes,[62,63] supporting the use of this approach by experienced personnel.

Electroacupuncture has been compared to gabapentin in a four-arm, randomized, placebo- and nocebo-controlled trial.[64] In this small pilot study of 120 patients with 30 patients in each arm, there was a statistically significant decrease in the hot flash composite score in women assigned to electroacupuncture as compared with those assigned to gabapentin, placebo, or sham acupuncture. The results of this study suggest that this modality deserves further study in larger controlled trials.

VAGINAL DRYNESS

Vaginal dryness from urogenital atrophy is another major symptom of estrogen depletion for some women. It can contribute to pain with intercourse, as well as itching and irritation. Non–estrogen-containing vaginal lubricants are helpful for alleviating symptoms.[65] Nonetheless, these products appear to be less efficacious than topical estrogen therapy.[66]

Given that women with estrogen receptor–positive breast cancer benefit from the use of aromatase inhibitors, which lower postmenopausal estrogen levels, and that all vaginal preparations appear to be absorbed to some degree, there is concern about administering vaginal estrogen. Patients must be informed of the risks of this therapy, and they should be

allowed to balance the desire for controlled symptoms against presumably small potential risks. However, it does not make much sense to use vaginal estrogens for women who are taking aromatase inhibitors, given that the goal of the latter is to lower estrogen levels as much as possible. There is less theoretical concern for patients taking tamoxifen, since tamoxifen works for premenopausal women, who can have markedly elevated estrogen concentrations.

There are intriguing data that dehydroepiandrosterone (DHEA) can decrease vaginal dryness and reduce discomfort during sexual activity without leading to increased systemic estrogen levels in women with vaginal dryness who do not have a history of breast cancer.[67,68] A randomized, double-blind, placebo-controlled clinical trial involving patients with a history of cancer supports that DHEA is safe and useful for women with vaginal dryness and/or dyspareunia.[69] A commercial preparation of vaginal DHEA was approved by the FDA in 2016.

Data from a 46-patient randomized, placebo-controlled study support that a 4% aqueous lidocaine preparation, used topically at the introitus 3 minutes before sexual activity, can decrease dyspareunia.[70] Additionally, data support that vaginal laser therapy can alleviate vaginal symptoms associated with estrogen depletion.[71,72] Further data regarding its efficacy and toxicity are needed.

KEY POINTS

- Nonhormonal therapies to decrease hot flashes include the following:
  - SSRI /SNRIs (caution with paroxetine and tamoxifen)
  - Gabapentin
  - Acupuncture
- Hormonal therapy for hot flashes can include the use of progesterone analogs.
- Topical lidocaine applied to the introitus can ease dyspareunia.
- DHEA and vaginal laser therapy can help alleviate vaginal dryness.

ORAL MUCOSITIS AND ESOPHAGITIS ASSOCIATED WITH TREATMENT

Oral mucositis and esophagitis are common complications of chemotherapy and radiation therapy. The overall incidence of oral mucositis is approximately 40% for patients who receive standard-dose chemotherapy. The incidence varies with the chemotherapy agents used and increases substantially for patients who receive dose-intensified regimens. Mucositis and esophagitis are common for patients receiving radiation to susceptible areas, and both can be exacerbated by concomitant chemotherapy. Dental evaluation prior to therapy should be encouraged if poor oral hygiene is seen on exam. Mucositis may occur as a result of direct injury from cytotoxic chemotherapy or radiation therapy, secondary infections from treatment-induced myelosuppression, or graft-versus-host disease.

The severity of mucositis is dose- and treatment-specific. Mucositis typically starts 5 to 7 days after the initiation of chemotherapy. It often presents first as erythema on the soft palate, the buccal mucosa, the ventral surface of the tongue, and the floor of the mouth. These symptoms may progress to a generalized desquamation. More than 90% of ulcerations are localized on nonkeratinized mucosa. Mucositis that results from chemotherapy can resolve within a few days or last up to 2 to 3 weeks; oral mucositis caused by radiation therapy

typically lasts an average of 6 weeks.

Chemotherapy agents frequently associated with mucositis include the antimetabolites fluorouracil (5-FU) and methotrexate and high-dose or prolonged infusions of chemotherapy. In addition, newer targeted agents, including many of the tyrosine kinase inhibitors, such as everolimus, as well as new immune checkpoint inhibitors, can also cause mucositis. Radiation therapy to the oral cavity frequently causes a host of oral complications, including mucositis, xerostomia, dental caries, tissue necrosis, and taste alterations.

PREVENTION OF MUCOSITIS ASSOCIATED WITH CHEMOTHERAPY OR TARGETED THERAPY

The Multinational Association of Supportive Care of Cancer (MASCC) and the International Society for Oral Oncology (ISOO) has developed clinical practice guidelines for the prevention and treatment of cancer therapy–induced oral and gastrointestinal mucositis. MASCC/ISOO has issued clinical practice guidelines for the management of mucositis secondary to cancer therapy.[73] The prevention of oral mucositis is an important goal because, once present, it can make ingestion of fluids, nutrition, and medications difficult. Two general approaches, oral cryotherapy and treatment with palifermin, have been shown to have a role in preventing mucositis (Table 21-3). Numerous other agents have been proposed for the prevention chemotherapy-induced mucositis, but most have not been shown to be effective, when compared with a placebo. Such agents include sucralfate, allopurinol, chamomile tea, glutamine, and vitamin E.

Table 21-3 Steps to Prevent Oral Mucositis

Step	Rationale	Example
Alter the mucosal delivery and excretion of individual chemotherapy agents	Mucous membranes have less exposure to the cytotoxic agent.	Oral cryotherapy
Modify the epithelial proliferative capabilities of the mucosa	Rate of basal epithelial cell proliferation correlates with the susceptibility of mucosal tissues to the toxic effects of chemotherapy.	Palifermin
Decrease local inflammatory response	Diminish an immune-mediated response	Oral corticosteroid rinse

One treatment that has been shown in clinical trials to effectively prevent mucositis is oral cryotherapy: sucking on ice chips during administration of chemotherapy. This treatment produces temporary vasoconstriction and appears to reduce the delivery of bolus-dose 5-FU

chemotherapy to the oral mucosa. Results from several controlled clinical trials indicated that oral cryotherapy reduces oral mucositis resulting from such treatment by approximately 50%.[74,75] Phase II evidence suggests that oral cryotherapy also decreases edatrexate-associated mucositis.[76-78] MASCC guidelines also suggest cryotherapy for patients receiving high doses of melphalan.

ASCO and MASCC guidelines recommend palifermin,[79-81] a keratinocyte growth factor, to decrease severe mucositis for patients undergoing autologous stem cell transplantation with total-body–irradiation conditioning regimens. Palifermin also has been studied in a placebo-controlled trial for patients receiving 5-FU; results suggest that it decreased mucositis more than placebo. The results, however, were not overly promising, and the patients enrolled in this trial were not given oral cryotherapy to alleviate mucositis. This, and the expense of the drug, precludes its use for preventing 5-FU–induced mucositis.[82]

MASCC guidelines now recommend low-level laser therapy for the prevention of oral mucositis in adults receiving high-dose chemotherapy in preparation for hematopoietic stem cell transplantation, with or without irradiation;[83] the guidelines are applicable only for institutions that are very familiar with this treatment.

Data from two phase II trials strongly support that oral corticosteroid swish-and-spit preparations markedly decrease everolimus-associated mucositis. In one trial, patients were instructed to swish 10 ml of a solution of alcohol-free dexamethasone (0.5 mg/5 mL oral solution) for 2 minutes and then spit four times daily for 8 weeks.[84] They were also instructed to fast for 1 hour afterward. A total of 79% of these patients did not have any reported mucositis in the first 8 weeks of therapy, compared to only 33% in the historical control group. The incidence of grade 2 or greater mucositis was 2.4%, as compared to 33% in a large prior clinical trial. Hyperglycemia was reported in some patients, but the rate was not different from results presented in the BOLERO-2 trial of everolimus, in which this therapy was not used. Another trial supported that two other corticosteroid preparations produced similar results.[85] A prospective clinical trial using a dexamethasone swish-and–spit preparation is in development to confirm these promising results.[86]

PREVENTION OF RADIATION-ASSOCIATED ORAL MUCOSITIS

A dental evaluation before the initiation of radiation therapy to the oral cavity is recommended. Fluoride carriers can provide fluoride for maintaining tooth integrity and, if worn during treatments, may help prevent radiation scatter from metal dental work, decreasing the inappropriately high radiation dose to buccal mucosa near metal dental work.

Effective management of established oral mucositis includes general measures, such as oral hygiene and dietary modification, topical local anesthetics, and systemic analgesics. MASCC guidelines recommend low-level laser treatment for the prevention of radiotherapy-induced oral mucositis for patients not receiving concomitant chemotherapy.[83]

For the prevention of oral mucositis in patients with head and neck cancer who are receiving moderate-dose radiation therapy, MASCC/ISOO guidelines[73] also recommend the use of a benzydamine mouthwash.

PREVENTION OF RADIATION-ASSOCIATED ESOPHAGITIS

The results of a placebo-controlled trial showed no benefit from the use of sucralfate for the prevention of radiation-associated esophagitis.[87] Some evidence suggests that amifostine can mildly decrease radiation-induced esophagitis but at the cost of moderate toxicity,

inconvenience, and expense.[88,89] These data do not support the routine use of amifostine.

TREATMENT OF ESTABLISHED MUCOSITIS

General measures to treat oral mucositis include good oral hygiene and dietary modification. Patients should brush gently with a soft-bristled toothbrush and fluoride toothpaste two to three times daily. Gentle flossing daily is encouraged to remove food and bacteria buildup. The mouth can be rinsed every 4 hours with a saline and baking soda solution (one-half teaspoon of salt plus one-half teaspoon of baking soda in a cup of warm water). This treatment has been reported to be soothing (and is thought to be cleansing). Also, dentures should be removed, particularly at night. Note that these recommendations have not been validated by controlled clinical trials but intuitively appear reasonable.

The maintenance of adequate caloric intake in the presence of mucositis can be a challenge. The length of time food is allowed to come in contact with the oral mucosa should be limited. The diet should consist of food that requires little or no chewing. Foods that irritate the mucosa (chemically or mechanically) should be avoided, including foods that are acidic, spicy, salty, coarse, or dry.

Adequate relief of pain associated with mucositis should be sought with pharmacologic agents, as outlined by MASCC/ISOO mucositis guidelines.[90] Transdermal fentanyl is one option. A 2% morphine mouthwash has also been recommended for patients with mucosal pain related to chemoradiation for head and neck cancer. MASCC/ISOO guidelines[73] also recommend a doxepin mouthwash, based on double-blind, placebo-controlled trial data that supported that a liquid doxepin preparation decreased radiation therapy–associated oral mucosal pain.[91] These data were replicated in a recently reported placebo-controlled trial,[92] which also reported that a “magic mouthwash” preparation (diphenhydramine, lidocaine, and an antacid) also decreased mucosal pain more than did a placebo. MASCC/ISOO[73] guidelines also endorse the use of a benzydamine mouthwash for patients with head and neck cancer who are receiving concomitant chemotherapy and radiation.

KEY POINTS

- There are multiple causes of mucositis related to cancer therapy.
- Oral cryotherapy is a useful prevention strategy for patients receiving bolus-dose 5-FU therapy.
- Palifermin decreased oral mucositis for patients receiving a bone marrow–ablative chemotherapy regimen associated with a high incidence of mucositis.
- Treatment of established mucositis involves the use of analgesics, a saline and baking soda solution mouthwash, and modification of food consistency.
- A doxepin mouthwash and a topical “magic mouthwash” preparation decrease mucosal pain associated with radiation therapy–induced mucositis.
- Oral corticosteroid mouth rinses appear to decrease everolimus-associated mucositis.
- Low-dose laser therapy can help prevent mucositis associated with stem cell transplantation or chemoradiotherapy for head and neck cancers.

MALIGNANT ASCITES

ETIOLOGY AND DIAGNOSIS

Ascites, the accumulation of fluid in the abdominal cavity, is a common cause of distress for patients with advanced cancer. Less than 10% of cases of ascites in the United States are associated with malignancies, and more than 80% of these develop in patients with epithelial cancers, particularly of the ovaries, endometrium, breast, colon, gastrointestinal tract, and pancreas.

Ascites indicates conditions that elevate hydrostatic pressure (e.g., congestive heart failure or cirrhosis), conditions that decrease osmotic pressure (e.g., nephrotic syndrome or malnutrition), or conditions in which fluid production exceeds resorptive capacity (e.g., infections and malignant diseases). Around 50% of cases of malignant ascites are associated with peritoneal carcinomatosis, while the rest are associated with liver dysfunction (e.g., from massive hepatic metastases and/or from cirrhosis), the Budd–Chiari syndrome, or chylous ascites.

Because the pathophysiologic features and treatments for them differ, physicians must first distinguish between malignant and nonmalignant ascites. It should not be assumed that cancer is the cause until other common etiologies, such as cirrhosis, heart failure, and peritonitis, have been considered.

Clinical determination of the presence or absence of ascites has the advantages of speed, convenience, and cost savings. A focused history and physical examination may identify the signs and symptoms of ascites. The clinical history can distinguish patients at high and low risk for ascites. For example, the development of ascites is unlikely for patients who report no increase in abdominal girth and for male patients who report no history of ankle swelling.

Physical exam findings include bulging flanks, dullness over the flanks on percussion, shifting dullness, and the presence of a fluid wave. Diagnostic imaging may be helpful if the physical examination is equivocal or when there is a relatively small amount of fluid, or when loculation is present. Ultrasound or computed tomography (CT) of the abdomen may identify even small amounts of free fluid.[93] Fluid obtained by paracentesis can help determine the cause. Ultrasound guidance is helpful if the fluid is difficult to obtain or loculation is suspected. The most specific test to determine whether the ascites is the result of a malignant process is cytologic analysis; however, the absence of malignant cells does not exclude cancer. The fluid should be evaluated for color, cell count, and total protein concentration; a serum-ascites albumin gradient (SAAG) also should be determined (Table 21-4).

Table 21-4 **Analysis of Fluid Obtained by Paracentesis**		
Characteristics	**Interpretation**	**Comment**
White, milky color	Chylous ascites	
Reddish (bloody) color	Malignant disease	The presence of blood also may be the result of abdominal tuberculosis.
Cytologic analysis	Malignant cells indicate cancer	Absence of malignant cells does not exclude cancer.
Absolute neutrophil count of greater than 250/μL	Bacterial peritonitis	
Total protein concentration ≤ 2.5 g/dL	Transudative ascites (less likely to have malignant cells)	
Serum-ascites albumin gradient (SAAG) ≥ 1.1 g/dL	Portal hypertension	

Although the laboratory findings from malignant ascitic fluid can be quite variable, the following findings do support a likely malignant etiology:

- Blood
- Malignant cells on cytologic analysis
- Low (negligible) absolute neutrophil count
- Total protein concentration of ≥ 2.5 g/dL

TREATMENT

Once a diagnosis of malignant ascites is established, treatment is directed at relieving symptoms such as dyspnea, abdominal pain, fatigue, anorexia or early satiety, and reduced exercise tolerance. Before making a treatment plan, each treatment's adverse effects must be taken into account as well as the prognosis, expected response to treatment, and patient preferences (Table 21-5).

Table 21-5 **Treatment Options for Ascites**	
Therapeutic Approach	**Comment**
Sodium restriction	Potential benefits and burdens of sodium restriction, as well as other treatment options, should first be discussed with the patient.
Chemotherapy	For patients with cancers that are responsive to chemotherapy, such as lymphoma, breast, or ovarian cancer
Diuretics	Well-tolerated and particularly useful for patients with cancer in whom ascites arises at least partially from nonmalignant causes; must be used carefully (see text)
Paracentesis	For ascites that is associated with respiratory distress or for symptomatic ascites that is resistant to diuretics
Intraperitoneal catheters	For patients who need repeated paracenteses

Chemotherapy can be considered for patients with chemotherapy-sensitive diseases. In select patients, diuretics can be used judiciously to remove only enough fluid to ensure the patient's comfort. Diuresis should be slow and gradual, not to exceed the patient's capacity to mobilize ascitic fluid. Overly aggressive management of ascites with diuretics may lead to more adverse effects rather than symptom relief.

It is usually best to start with a diuretic that works to block the effect of increased aldosterone activity at the distal nephron. Spironolactone often is used as first-line treatment, starting with a daily dose of 25 to 50 mg in the morning. Spironolactone may be associated with painful gynecomastia, and as such, amiloride 5 mg daily is an alternative. If the response is suboptimal despite maximal use of distal diuretics, a low dose of a loop diuretic may be added, such as 20 mg of furosemide daily.

The initial dose of the diuretic may be gradually increased over days to weeks until the desired symptom relief is achieved. It may take several weeks for a given dose of diuretic to achieve its ultimate effect. Sometimes, very large doses of diuretics are needed to produce an adequate effect.

Diuretic therapy is likely to be burdensome for patients who have limited mobility or urinary tract outflow symptoms, such as hesitancy or frequency, poor appetite or poor oral intake, or difficulties related to polypharmacy. Diuretic therapy is frequently associated with more disadvantages than benefits for patients with advanced cancer and a poor performance status. In these situations, therapy can result in incontinence, lead to sleep deprivation, and cause problems related to self-esteem, skin care, safety, fatigue, hyponatremia, hypokalemia, or symptomatic postural hypotension.

Therapeutic paracentesis provides the most rapid symptomatic relief with minimal morbidity and mortality and is the favored first-line therapy for ascites in most patients who have cancer.

It may be the only therapeutic modality that is effective for patients with malignant ascites. As much as 5 to 10 L of fluid may safely be removed during a single session. Paracentesis can be performed either in the outpatient clinic setting or in the individual's home. Ascitic fluid, however, may reaccumulate, sometimes relatively rapidly, depending on the underlying disease process. The frequency of the subsequent drainage depends on the patient's subjective reports of distressing symptoms. In general, for patients with cancer who have malignant ascites, there is no role for albumin or colloid infusions after paracentesis, unless the patient becomes symptomatic because of intravenous volume depletion.[94]

A variety of intraperitoneal catheters have been used for patients for whom repeated large-volume paracentesis is needed for comfort and for whom the prognosis warrants a minor surgical procedure.[95] This allows the patient and family to drain the fluid at home on an as-needed basis without having to come to the medical facility. Surgical treatment of malignant ascites, with a peritoneovenous shunt, is associated with risks and, therefore, is rarely recommended.

Anecdotal information suggests that octreotide may be helpful for patients with malignant ascites.[96] A small randomized, placebo-controlled clinical trial of this subject was not able to confirm benefit, but had low power.[97]

Having reviewed all the treatment options for malignant ascites, it should be noted that ascites often can be a marker of disease progression. It may be appropriate to have a discussion with these patients that focuses on realistic goals and options, such as palliative care and hospice.

KEY POINTS

- Therapeutic paracentesis is the primary treatment of choice for most patients with cancer who have symptomatic ascites.
- Permanent indwelling peritoneal catheters can provide relief for patients who require repeated paracentesis.
- Colloid or albumin infusions are generally not required unless a patient is symptomatic after large-volume paracentesis.
- Diuretics can be useful therapeutic modalities for selected patients with ascites. Spironolactone is the initial diuretic to consider, with furosemide added after treatment with spironolactone is started.
- For patients with far-advanced cancer, the use of diuretics for malignant ascites may be associated with more disadvantages than benefits.

ANOREXIA AND CACHEXIA

ETIOLOGY AND DIAGNOSIS

Involuntary weight loss, long recognized as an adverse prognostic factor for patients with cancer, has been reported to occur in 15 to 40% of patients at the time of cancer presentation and in as many as 80% of patients with advanced cancer. Anorexia contributes to the wasting seen in cancer-related cachexia, but it is not the only cause. The etiology of involuntary weight

loss for patients with cancer is believed to be multifactorial.

In 1980, Dewys et al. reported that decreased survival was a consequence of cancer-associated cachexia.[98] This retrospective analysis of 3047 patients with 11 different tumor types demonstrated a relationship between tumor type and incidence, as well as between tumor type and degree of weight loss. For each tumor type, survival times were shorter for patients who lost weight compared with patients who had not. In addition to survival, several other consequences of involuntary weight loss include decreased response to and tolerance of radiation therapy and chemotherapy, increased frequency of surgical complications, weakness, fatigue, loss of energy, and inability to perform everyday tasks.

In 2011, a consensus opinion was reported regarding the definition of cancer cachexia and defining three clinical stages of cachexia: precachexia, cachexia, and refractory cachexia.[99] Precachexia includes early metabolic alterations such as anorexia and impaired glucose tolerance and typically precedes any significant weight loss. Cachexia includes cases in which patients have lost more than 5% of their body weight in the preceding 6 months, have a body mass index (BMI; the weight in kilograms divided by the square of the height in meters) of less than 20 along with sarcopenia, and have continued weight loss. Patients who have active catabolism, a low World Health Organization (WHO) performance status (grade 3 to 4), and a life expectancy of less than 3 months are considered to have refractory cachexia. All phases of cachexia are accompanied by anorexia, early satiety, chronic nausea, asthenia, changes in body image, involuntary weight loss, impaired immune function, poor performance status, and fatigue. Cancer-related cachexia differs from simple starvation because there is a disproportionate loss of lean body mass as opposed to adipose tissue among patients with cancer-induced cachexia. Data support that measurement of lean muscle mass by abdominal CT scans can be helpful for identifying patients with cancer cachexia; CT scan data illustrate that some obese patients have low lean muscle mass and are suffering from cancer cachexia. A host of metabolic alterations are thought to play an important role, including tumor products, such as lipolytic and proteolytic factors; humoral factors, such as serotonin and bombesin; and cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, and interferon-alpha. The end result is a reduction in the synthesis of lipids and proteins and an increase in lipolysis.[100]

A 2015 report proposed a means for classification of cancer-associated weight loss.[101] This system was based on BMI and percentage of weight change over the previous 6 months. It illustrated that patients who lived longest had a BMI greater than 25 and no weight loss (21 months' survival), while the patients who lived the shortest time (4.6 months) had lower body weight and more weight loss. This clarifies that cancer-associated weight loss can develop in obese patients, and this can lead to sarcopenia and poor prognosis. Unfortunately, it does not provide data to support that nutritional interventions will improve quality or quantity of life for patients with advanced cancer.

Anorexia is a multidimensional symptom that usually results from multiple contributing factors, some of which are directly related to the presence of the tumor and some of which are related to reversible comorbid factors. The potential causes of anorexia include constipation, emesis, mucositis, depression, decreased gastric emptying, dysphagia, food aversions, and fat malabsorption. One of the challenges in the clinical assessment of patients with anorexia is to characterize all of the different contributors so that a targeted treatment approach can be implemented.

The intensity of symptoms of anorexia varies among patients. Although it may be a major problem for many patients, it is not a major concern for all of them, even if cachexia is

prominent. The lack of eating is often a bigger problem for the family than for the patient, because the patient may not be bothered by a lack of appetite. When patients abstain from eating, the family loses a chance to nurture their loved ones. Teaching the family to substitute other nurturing activities (e.g., help with bathing, massage) may help to relieve their concerns about the patient's lack of appetite. For some patients, it may be best not to offer medications; anorexia may be one of many symptoms that will promote discussion of the goals of care and lead to a greater focus on defining life priorities, setting appropriate life goals, providing symptom management, and/or considering a hospice approach.

TREATMENT

Numerous prospective, randomized clinical trials have been conducted to ascertain whether nutritional support would improve outcomes for patients with cancer. In general, the results of these studies have shown that if there is such an effect, it is likely a small one or it is confined to a small subset of patients. Nutritional counseling alone can improve daily caloric intake by approximately 450 calories. However, this advantage is generally short-lived and does not appear to translate into improved patient weight, quality of life, or survival.

The use of parenteral nutrition does not have a major role for most patients with advanced cancer.[102] However, it may provide some benefit for selected patients with cancer, such as patients who are unable to maintain adequate nutrition because of bowel obstruction but who do not have another life-threatening problem. Parenteral nutrition also may benefit patients with cachexia who have a potentially curable tumor and who require short-term nutritional support. In addition, parenteral nutrition may be useful preoperatively for patients who will have tumor resection. In this latter indication, parenteral nutrition has been shown—in some situations—to decrease surgical complications and, possibly, to increase survival.

Enteral nutrition, usually through a gastrostomy tube that has been placed endoscopically or by an interventional radiologist, may be considered when food intake is inadequate but the gastrointestinal tract is functionally intact. This technique often is used for patients with upper aerodigestive tract cancer who may have temporary disruption of eating and swallowing while undergoing radiation therapy. Enteral nutrition offers several advantages compared with parenteral nutrition (Table 21-6). The major serious complication associated with enteral nutrition is aspiration, and the risk of this complication increases for patients with delayed gastric emptying. The risk may be reduced by frequent aspiration of the gastric contents during the first days of infusion, in order to decrease stasis. If stasis is found, metoclopramide or domperidone can be given to increase gastric emptying, understanding that, in 2013, the European Medicines Agency's Committee on Medical Products for Human Use recommended that metoclopramide use be curtailed because of serious neurologic side effects.[5] Alternatively, a duodenal tube can be inserted as an alternative route of nutritional support; however, there is no good evidence that placing a tube in the duodenum or jejunum (rather than in the stomach) helps prevent aspiration. All are associated with an increased risk for aspiration pneumonia (as evidenced in dementia studies).[103] Other side effects associated with enteral nutrition include diarrhea, constipation, nausea/vomiting, abdominal cramping, bloating, distention, and expense.

Table 21-6 **Advantages of Enteral Nutrition Compared with Parenteral Nutrition**
Fewer risks and complications
Less expensive
More easily carried out at home by most patients
Delivers nutrients in a more physiologic manner

Fat malabsorption may occur in patients with pancreatic disease, in patients who have undergone gastric resection or bone marrow transplantations, or in patients who have short-bowel syndrome or chronic radiation enteritis. If there is increased stool odor, an empiric trial of exogenous pancreatic enzyme can be considered. A total of 8000 units of lipase should be administered for every 5 to 7 g of fat in a meal.

Drugs that have been demonstrated to be helpful for the treatment of cancer anorexia/cachexia are listed in Table 21-7. Megestrol acetate is the drug most widely studied in cancer-related anorexia and cachexia, with at least 12 controlled clinical trials completed. [104] In these studies, megestrol acetate was administered daily over periods ranging from 1 week to more than 12 weeks. Increases in appetite and/or body weight were documented in the vast majority of the studies.[105] Megestrol acetate, 160 to 1600 mg daily, provides benefits for appetite, caloric intake, and weight gain. In one clinical trial, the effect appeared to plateau at 800 mg, suggesting that this amount should be the maximum dose. The weight gained with the use of megestrol is predominantly adipose tissue, not lean body mass.[106]

Table 21-7 **Treatment of Cancer-Related Anorexia**

Drug	Function	Dosing
Megestrol acetate	Improves appetite, increases caloric intake, decreases nausea and vomiting	Activity seen with range of 160 to 1600 mg/day; recommended maximum dose, 800 mg/day
Medroxyprogesterone acetate	Stimulates appetite	Activity seen with range of 300 to 1000 mg/day; generally well tolerated, with a side-effect profile similar to that of megestrol acetate
Dexamethasone	Increases appetite and food intake and improves the sense of well-being and performance status, generally only for a short period of time	2 to 4 mg per day

The benefits of megestrol acetate should not be overestimated. Although randomized, placebo-controlled trials have shown that up to 70% of patients assigned to the megestrol arm gained weight, so did 44% of those assigned to some placebo groups. In addition, megestrol had no effect on either survival or quality of life in these studies. The North Central Cancer Treatment Group (NCCTG) conducted a randomized, placebo-controlled trial of megestrol compared with placebo in 243 patients with non-small cell lung cancer and found that those receiving megestrol had a median survival of 8.2 months compared with the 10.2-month median survival for those taking placebo. Jatoi et al. estimate that only about 20% of patients receiving megestrol for treatment of anorexia/cachexia will derive benefit.[107-109]

Megestrol acetate is commercially available in the United States as 20-mg and 40-mg tablets

and as a 40-mg/mL oral suspension. A 160-mg tablet is available in Canada. Several factors should be considered in dose selection:

- Side effects may be dose-related.
- High doses are expensive. The suspension is the preferred delivery mode, as it is less expensive, at least in the United States, and more bioavailable than the tablets.
- Lower doses are effective in stimulating appetite; therefore, it is reasonable to start with a daily dose of 400 mg, with the dose titrated to clinical response.
- There is a micronized megestrol acetate formulation that reportedly allows for better drug absorption in the fasting state, but it may be more expensive than other forms of this drug.[110]

Megestrol acetate is generally well tolerated, with side effects occurring infrequently and likely in relation to the size of the dose administered. In clinical trials, patients receiving megestrol acetate generally are no more likely to discontinue treatment because of side effects than patients receiving placebo. The side effect of greatest concern is thromboembolic complications, and because of this possibility, megestrol acetate is relatively contraindicated for patients with a history of thromboembolic disease. Also, because the drug can cause adrenal-axis suppression, adrenal insufficiency may occur either while a patient is using the medication or shortly after discontinuing treatment. Thus, in the event of infection, surgery, or trauma, stress doses of corticosteroids should be given. Furthermore, anecdotal experience suggests that megestrol acetate may alter glucose control for patients with diabetes mellitus who require insulin. Of note, this agent has antiemetic efficacy; the findings from randomized, placebo-controlled clinical trials have demonstrated less nausea and vomiting for patients receiving the drug, compared with patients receiving placebo preparations.[108,111]

MPA is another progesterone analog that stimulates appetite, but it has been less widely studied than megestrol acetate. It is generally well tolerated, with a side-effect profile similar to that of megestrol acetate.

At least five randomized clinical trials have been conducted with various corticosteroids. The results of the trials have indicated that these drugs increase appetite and food intake and enhance the patient's sense of well-being and performance status.[105,112]

To compare the activity and tolerability of megestrol acetate and a corticosteroid, a randomized, controlled study was conducted in which patients with cancer-related anorexia and cachexia were randomly assigned to receive 800 mg of megestrol acetate daily or 0.75 mg of dexamethasone four times daily. Patients were followed at monthly intervals. The two drugs produced similar appetite enhancement and changes in nonfluid weight, with a trend favoring megestrol acetate. Drug discontinuation because of toxicity or patient refusal was significantly higher with dexamethasone than with megestrol acetate (36% vs. 25%; $p = 0.03$). However, deep vein thrombosis was more common with megestrol acetate (5% vs. 1%; $p = 0.06$).[113]

Several factors should be considered when deciding whether to use megestrol acetate or corticosteroids for the treatment of cancer-related cachexia. Megestrol acetate is favored when cachexia is the main symptom, whereas corticosteroids may be useful when other symptoms, such as pain, also are present. Megestrol acetate is preferable for long-term use or when weight gain is desired. Corticosteroids are particularly useful for patients with limited survival expectancy, especially when weight gain is not the principle desired outcome. Corticosteroids, ideally, should not be used longer than several weeks because longer-term use is associated

with unacceptable side effects, such as edema, muscle weakness, dysphoria, hypokalemia, hyperglycemia, and immunosuppression. There is no known advantage to using corticosteroids and megestrol acetate concomitantly.

Cyproheptadine is a serotonin antagonist that has been available for more than 30 years. It has been used in Latin America and Europe as an appetite stimulant for patients with cancer. In a large, randomized, controlled study, oral cyproheptadine 8 mg three times daily produced a mild increase in appetite and food intake but had no effect on progressive weight loss.[114] As a result of its side effects (notably sedation) and limited efficacy, cyproheptadine is not recommended for patients with cancer-related cachexia.

Two newer agents have reported data that appear positive but are not yet established for recommendation in routine clinical practice. One of these is the selective androgen receptor modulator enobosarm.[115,116] The other is a ghrelin mimetic, anamorelin, which can result in the release of growth hormone by binding to a growth hormone secretagogue receptor. Two double-blind, placebo-controlled trials evaluated the use of anamorelin in patients with cachexia related to advanced lung cancer.[117] Lean body mass measurements and appetites were better with the active drug than with placebo; however, grip strength was not significantly different between the study groups.[118]

An older drug, olanzapine, may also be helpful for treating cancer anorexia. When olanzapine was used in combination with megestrol acetate, as opposed to megestrol acetate alone, one trial supported that this drug improved appetite and led to increased weight gain.[119] Ideally, this drug should be further studied for the treatment of cancer anorexia/cachexia.

Many other agents have been suggested for the treatment of cancer-related anorexia and cachexia, but none of these agents has shown benefit when tested in controlled clinical trials. These drugs include hydrazine sulfate, eicosapentaenoic acid, pentoxifylline, fluoxymesterone, oxandrolone, and dronabinol.[120-123] Reports of trials involving antibodies against TNF (otherwise known as “cachectin”), such as etanercept and infliximab, suggest that these drugs also are not helpful.[124] However, the relatively newer agents myostatin inhibitors are being tested as a potential therapy for cancer cachexia.

KEY POINTS

- Anorexia is a prominent clinical problem for many patients with advanced cancer. For patients with far-advanced cancer who are not undergoing therapy, anorexia needs to be treated only if the patient considers it to be a substantially bothersome symptom.
- The two classes of clinically available medications that have been demonstrated to be helpful for cancer-related anorexia and cachexia are corticosteroids and progesterone analogs. Progesterone analogs (e.g., megestrol acetate) are generally better tolerated than corticosteroids when given for substantial periods of time.
- Deep vein thrombosis and adrenal suppression are two notable side effects of megestrol acetate.
- Total parenteral nutrition should be used only for carefully selected patients.
- Anorexia may cause emotional problems for family members because of a perception of a lost nurturing opportunity. Teaching the family to substitute other nurturing activities (e.g., help with bathing, massage) may be beneficial.

DIARRHEA ASSOCIATED WITH CANCER OR CANCER THERAPY

Cancer and cancer therapy can cause diarrhea from any one of a large number of mechanisms. Careful evaluation is required to determine the most effective therapy for an individual patient. Nonpharmacologic and pharmacologic steps often are required for the management of acute treatment-related diarrhea, and several nonpharmacologic measures can be carried out in clinical practice to manage subacute diarrhea (Table 21-8).[125] Rehydration is important for patients with diarrhea severe enough to cause volume depletion. Usually, an increased intake of clear liquids will suffice, but intermittent parenteral administration of fluids and electrolytes may be necessary for some patients.

Table 21-8 Steps in the Evaluation and Management of Patients with Diarrhea

Conduct a comprehensive evaluation of the patient at the first report of diarrhea.
Obtain information about the onset and duration of diarrhea and the number and characteristics of the stool.
Ask the patient about other symptoms, such as fever, abdominal pain, dizziness, and weakness that could indicate the cause of diarrhea and the risk of dehydration and infection.
Review the patient's diet and medication usage to identify any foods or medicines that may be causing or contributing to the diarrhea.
Advise the patient to eat frequent small meals and to avoid foods that irritate the intestines or stimulate its motility.
Encourage the patient to drink 8 to 10 large glasses of clear liquid per day in order to maintain adequate hydration and to prevent potential dehydration.
Taper or eliminate medications that may cause or exacerbate diarrhea, if medically possible.

CHEMOTHERAPY-INDUCED DIARRHEA

Etiology and Incidence

Chemotherapy can cause diarrhea by irritating or damaging the crypt and villous cells of the intestinal mucosa. The incidence and severity of chemotherapy-induced diarrhea depends on many factors, including the treatment regimen and drug doses. In general, diarrhea is most common with regimens that include antimetabolites. The most studied of these agents is 5-FU. The risk of diarrhea from 5-FU increases when leucovorin is given as a modulating agent. Capecitabine provides long-term exposure to 5-FU, similar to infusional 5-FU, and has similar toxicities.

Diarrhea also is common with other antimetabolites, such as irinotecan and topotecan. With irinotecan, diarrhea may occur immediately after administration through a cholinergic

mechanism (early-onset diarrhea), or a more severe, potentially life-threatening, form of diarrhea may develop days after administration (late-onset diarrhea). The severity of late-onset diarrhea correlates with peak plasma levels of the irinotecan metabolite SN38. The incidence of diarrhea associated with these two drugs for patients with metastatic cancer of the colon are noted in Table 21-9.[109] It is important to note that patients who have received antibiotics or cisplatin-based therapy may have a *Clostridium difficile* infection and that patients with neutropenia are at risk for typhlitis.

Table 21-9 Incidence of Diarrhea for Irinotecan and Topotecan

Drug	Diarrhea	
	Any Grade (%)	Grade 3 or 4 (%)
Irinotecan		
Early-onset diarrhea	50	10
Late-onset diarrhea	90	30
Topotecan	30	5

Targeted Therapies and Diarrhea

Diarrhea is a common side effect of many of the new targeted therapies. Studies of small-molecule inhibitors of epidermal growth factor receptor (EGFR), such as erlotinib, gefitinib, or afatinib, report up to 90% incidence of diarrhea, but only 15% of cases are severe.[126] The monoclonal antibodies directed against EGFR, cetuximab and panitumumab, have reported rates of diarrhea in the 20% range, but the incidence of severe diarrhea is typically 3% or less.[127,128] Drugs that inhibit the vascular endothelial growth factor (VEGF) pathway (sorafenib, sunitinib, axitinib, regorafenib, ponatinib, pazopanib, cabozantinib, lenvatinib, bevacizumab, and vandetanib) have reported incidences of diarrhea ranging from 30 to 80%, but only 3 to 17% are grade 3 or 4.[129-132] Treatment is generally nonspecific, using antimotility agents and withdrawing the offending drug until symptoms resolve. The HER-2–directed drugs lapatinib[133] and pertuzumab[134] are both known to cause diarrhea (up to 80% with 20 to 30% severe and 48% with 3% severe, respectively), but generally can be managed with nonspecific therapy and withholding or dose adjustment of therapy. The mammalian target of rapamycin (mTOR) inhibitors everolimus and temsirolimus both are reported to cause diarrhea, but less commonly than other targeted treatments.[135] Trametinib and cobimetinib are mitogen-activated protein kinase kinase (MEK) pathway inhibitors for use in patients with *BRAF*-mutated melanoma. These produce significant diarrhea in less than 5% of cases.[136]

Checkpoint inhibitors are an exciting new wave of drugs that produce an immune response against the cancer. While efficacious in certain malignancies, a wide variety of toxicities have been noted. Among these is diarrhea, with a reported incidence of 30% with ipilimumab (10% severe).[137] Programmed cell death protein 1 (PD-1) blockade produces less frequent diarrhea at 1-3%.[138] Patients receiving either the cytotoxic T-lymphocyte antigen 4 (CTLA-4), PD-1, or programmed cell death ligand (PDL-1) inhibitors need to be educated about the potential life-threatening side effect of severe colitis about the need to report symptoms early.

Treatment

Checkpoint inhibitor–induced diarrhea is handled differently than most other types, with treatment largely based on corticosteroids.[139] It has been recommended that other antidiarrheal medications (e.g., loperamide) not be used because they can mask the underlying autoimmune pathology that needs to be treated. In severe cases, administration of high-dose IV corticosteroids is indicated, with anti-TNF antibody infliximab being used in refractory cases.[140]

Atropine can be used to treat the acute-onset diarrhea that results with irinotecan therapy. Opioid-like medications often are useful for other types of therapy-related diarrhea, although they are contraindicated with infectious causes of diarrhea. Of these agents, loperamide and diphenoxylate are most commonly used for treating acute diarrhea caused by a variety of conditions. Octreotide also is effective and is generally well tolerated but carries significant financial cost. Loperamide has been compared with octreotide for the treatment of 5-FU–induced diarrhea. In one clinical trial, 41 patients with grade 2 or greater diarrhea (according to the National Cancer Institute Common Terminology Criteria for Adverse Events) resulting from 5-FU–containing chemotherapy were randomly assigned to receive 0.1 mg of subcutaneous octreotide twice daily for 3 days or 4 mg of oral loperamide initially and then 2 mg every 6 hours for 3 days. Diarrhea resolved for 19 (91%) of the 21 patients in the octreotide arm compared with 3 (15%) of the 20 patients in the loperamide arm ($p = 0.005$). No side effects were observed in either treatment arm.[141] An alternative to starting octreotide after the doses of loperamide used in this randomized trial failed is to give higher doses of loperamide (i.e., 4 mg initially and then 2 mg every 2 hours) until the patient has been diarrhea-free for 12 hours.

A randomized, double-blind clinical trial of octreotide was conducted with patients receiving cisplatin. All the patients enrolled in the study had experienced diarrhea as a result of a prior course of cisplatin therapy; 43 of these patients were randomly assigned to receive either octreotide (0.1 mg) or placebo (1 mL of saline solution) by subcutaneous injection 15 minutes before and 6 hours after cisplatin therapy. Diarrhea, defined as more than two loose bowel movements per day, occurred in 75% of patients who received placebo and in 5% of patients who received octreotide ($p = 0.01$). Side effects were minimal. These findings suggest that octreotide is useful for the secondary prevention of cisplatin-induced diarrhea for patients with a history of diarrhea during prior courses of cisplatin.[142]

Treatment of chemotherapy-induced diarrhea can follow an algorithmic approach, as detailed in Table 21-8 and Fig. 21-1.[109]

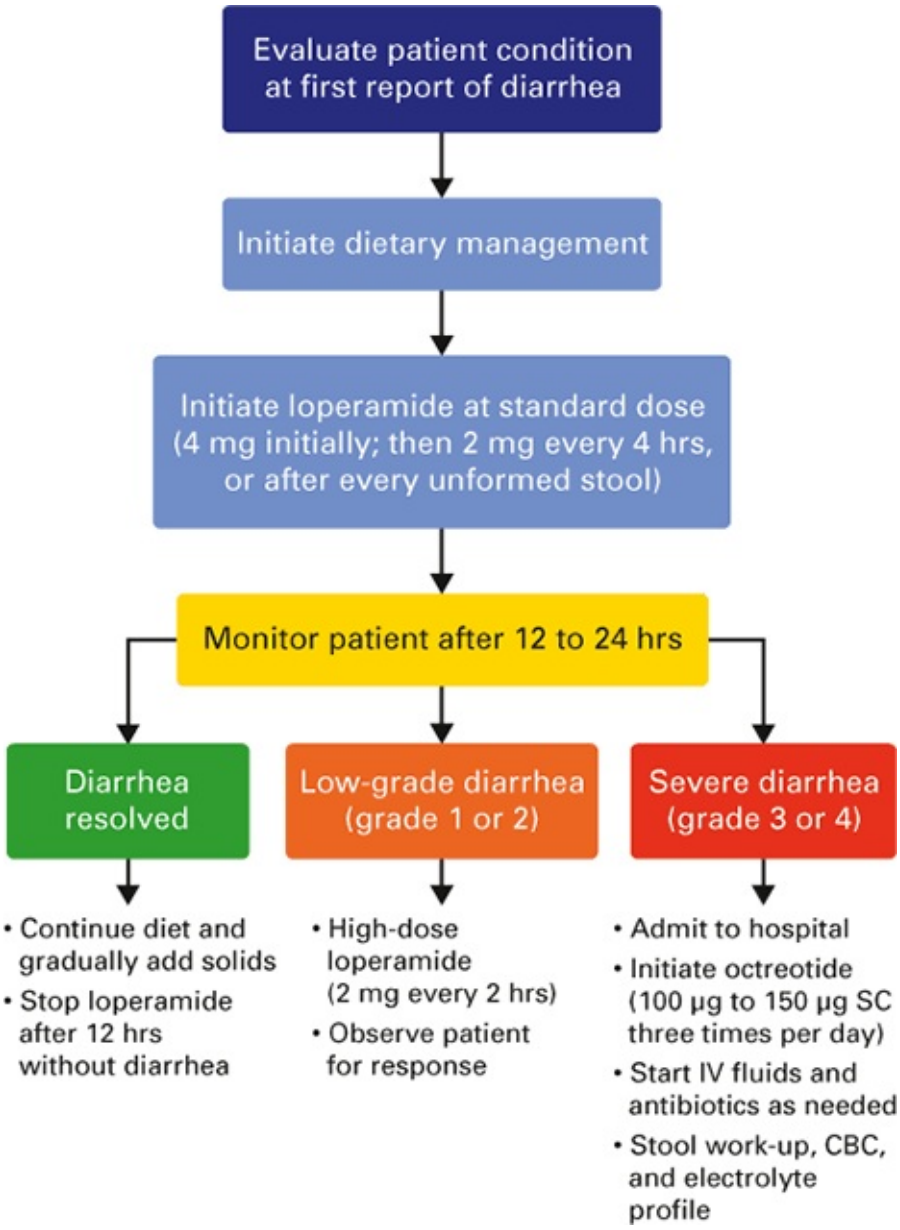

Fig. 21-1 Diarrhea management algorithm.

Note that this figure does not apply to checkpoint inhibitor associated–diarrhea, which is mainly managed by steroids, after other etiologies are excluded.

Abbreviations: hrs, hours; SC, subcutaneously; IV, intravenous; CBC, complete blood count.

RADIATION-INDUCED DIARRHEA

Etiology and Incidence

Diarrhea is the most common adverse effect of pelvic radiation therapy. Such therapy damages the mucosa of the small and large intestines and thereby can produce secretory diarrhea. The incidence and severity increases with the addition of 5-FU. For example, in one study, the combination of 5-FU and radiation therapy produced a significantly higher rate of acute diarrhea at any time during treatment than radiation therapy alone (79% vs. 41%; $p = 0.001$). The difference between the two groups was also observed for grades 3 and 4 diarrhea (22% vs. 4%; $p = 0.001$).[143]

Treatment

Several placebo-controlled clinical trials have tried to identify a drug that can be used to prevent diarrhea induced by pelvic radiation therapy. The findings from one trial suggested that the use

of olsalazine agent actually increased diarrhea.[144] Similar findings were also seen with sulfasalazine.[146]

Another trial demonstrated that cholestyramine decreased diarrhea, but at the cost of other toxicities that negated the benefit.[147] Trials of sucralfate have provided mixed results that preclude its recommendation for use in clinical practice.[148,149] Glutamine did not improve diarrhea in a double-blind clinical trial.[150] A randomized, double-blind, placebo-controlled clinical trial was unable to demonstrate any benefit for octreotide as an agent to prevent radiation-induced diarrhea.[151]

Preliminary evidence suggests, however, that octreotide may have a role in the treatment of diarrhea induced by pelvic radiation therapy. Thirty-two patients with grade 2 or 3 diarrhea associated with pelvic radiation therapy were randomly assigned to receive either 0.1 mg of subcutaneous octreotide three times daily or 10 mg of oral diphenoxylate (with atropine) daily. Diarrhea resolved within 3 days for 13 of the 16 patients in the octreotide arm and for 3 of the 16 patients in the diphenoxylate arm (81% vs. 19%; $p = 0.005$).[152]

An important lesson to be learned from clinical trials designed to evaluate diarrhea prevention for patients receiving pelvic radiation therapy is that the use of pharmacologic agents, on an ad hoc basis outside of a clinical trial, may be inappropriate. Most of the various categories of agents evaluated in clinical trials consistently failed to show a benefit with an acceptable safety profile. Thus, using seemingly benign drugs to prevent diarrhea during pelvic radiation therapy may expose patients to toxicity without any corresponding benefit.

GRAFT-VERSUS-HOST DISEASE–ASSOCIATED DIARRHEA

For patients who have received a bone marrow transplant, diarrhea may result from graft-versus-host disease (GVHD) or from infections related to the use of immunosuppressive therapy. The epithelial damage caused by high-dose chemotherapy can serve as a stimulus for activation of alloreactive cytotoxic T cells, which release a cascade of inflammatory cytokines that contribute to necrosis of epithelial crypt cells.

At the first sign of acute gastrointestinal symptoms that may signify a graft-versus-host reaction, a stool specimen should be evaluated for bacterial, fungal, and viral pathogens and supportive management should be initiated. In addition, the general measures for managing diarrhea should be used (Table 21-8). Consultation with a gastroenterologist should be considered.

If the findings on stool evaluation are positive for pathologic bacteria, a course of appropriate antibiotics should be started. For patients with a diagnosis of GVHD (established by biopsy), corticosteroids should be used, and prophylactic immunosuppressive therapy should be continued. Octreotide should be considered at an intravenous dose of 500 µg three times daily. If the patient has a response within 4 days, octreotide should be discontinued in order to avoid ileus. However, if there is no response to octreotide, second-line therapy with antithymocyte globulin or with infliximab should be considered. Alternatively, participation in a clinical trial studying this problem is reasonable, as there is no uniform agreement on the ideal treatment for this problem.

CANCER-ASSOCIATED DIARRHEA

Cancer itself, rather than its treatment, may cause diarrhea. For example, in pancreatic cancer, the presence of inadequate digestive enzymes may lead to osmotic diarrhea. For patients who have an increased stool odor, an empirical trial of exogenous pancreatic enzyme should be

considered. There are various forms of pancreatic enzymes that contain various amounts of lipase, protease, and amylase. Doses need to be individualized for patients and modified based on results.

Secretory diarrhea may occur in medullary thyroid cancer as a result of the overproduction of calcitonin and prostaglandins, in carcinoid syndrome as a result of the increased secretion of prostaglandins and serotonin, and with pancreatic islet cell cancers. In these situations, octreotide generally is the best option for controlling diarrhea. Cyproheptadine also may be helpful for carcinoid syndrome–related diarrhea.

KEY POINTS

- 5-FU, irinotecan, and topotecan commonly cause diarrhea. Irinotecan causes two types of diarrhea: an early-onset diarrhea after administration through a cholinergic mechanism and a more severe diarrhea that generally begins a few days after irinotecan administration.
- Diarrhea is common with many of the new targeted therapies.
- Checkpoint inhibitors can cause severe life-threatening enterocolitis, which should be recognized and treated early with steroids.
- Radiation to the pelvis causes diarrhea for a substantial number of patients.
- GVHD also can cause diarrhea that can be treated with steroids and octreotide.
- Loperamide should be prescribed for patients with chemotherapy-induced diarrhea. Octreotide can be helpful for patients in whom loperamide does not control chemotherapy-induced diarrhea. Octreotide also can be helpful for treating radiation-induced diarrhea.
- For diarrhea associated with pancreatic insufficiency, pancreatic enzyme replacement may be helpful.

CANCER FATIGUE

Fatigue is one of the most bothersome symptoms for patients with cancer.[153,154] It affects patients receiving adjuvant chemotherapy or radiation therapy and those with advanced disease. Fatigue has been noted to occur for anywhere from 60 to 90% of patients receiving chemotherapy and for 65 to 100% of patients receiving radiation therapy. The NCCN has defined cancer fatigue as “a distressing persistent subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.”[150] This problem is often not relieved with rest. In 2014, the first ASCO guidelines were published regarding cancer-related fatigue.[155] These guidelines were actually an adaptation of data from three other guidelines: the pan-Canadian guideline on screening, assessment, and care of cancer-related fatigue in adults with cancer, the NCCN Clinical Practice Guidelines in Oncology for Cancer-Related Fatigue, and the NCCN Guidelines for Survivorship. These ASCO-adapted guidelines reiterated that fatigue is prevalent among patients with a history of cancer and that it negatively affects life quality and functioning.

Evaluation of cancer fatigue should consist of a history, physical examination, and screening blood work, including a complete blood count and chemistry evaluation of renal function, thyroid function, liver function, calcium, and electrolytes. Adrenal function tests may be indicated in selected situations, and screening for depression also is appropriate. If the screening evaluation detects any abnormalities, reasonable attempts to correct them are recommended.

Complicating the evaluation and management of cancer-related fatigue is distinguishing the etiology of the fatigue and managing the side effects of the cancer and cancer treatments that contribute to fatigue. One trial looked at 152 patients with advanced cancer who reported baseline fatigue and were randomly assigned to standard care or a nurse-led symptom intervention clinic. Those in the treatment arm did show a trend toward lower fatigue scores on the Multidimensional Fatigue Inventory scale.[156] Control of specific causes of fatigue such as anemia, nausea, pain, sleep disturbances, and depression can help to alleviate fatigue.

Exercise is a commonly recommended therapy for cancer-related fatigue.[157-165] The 2014 ASCO fatigue guidelines[166] favored the use of nonpharmacologic treatment approaches, such as exercise. Multiple randomized clinical trials have looked at a supervised exercise program compared to routine care to decrease cancer-related fatigue. Meta-analysis of these trials does show a preponderance of breast cancer patients enrolled, and most trials used aerobic activities with a few trials also incorporating resistance training.[167] Exercise trials have examined patients actively undergoing cancer therapies as well as those who have completed treatments. Benefits were seen in both groups, along with improved quality-of-life measures. A Cochrane review of 56 trials concluded that aerobic exercise had a more substantial effect on cancer related fatigue than routine therapy.[168]

Psychostimulants such as methylphenidate and modafinil have been studied, but the bulk of evidence suggests that they are not very helpful.[169-172] The 2014 ASCO fatigue guidelines confirmed the thought that pharmacologic management with psychostimulants does not currently appear to be beneficial. Studies of ginseng, another pharmacologic agent, have provided preliminary clinical information and animal data.[173-177] Two randomized, placebo-controlled trials support that ginseng is helpful for alleviating cancer-related fatigue.[178,179] The recommended dose from these studies is 2000 mg per day, divided into two doses of 1000 mg each with breakfast and lunch. It is probably best to take both doses before noon to better ensure that it does not negatively affect sleep. The two studies evaluated American ginseng and used a pure ground root product. It may be important to use pure ground root as opposed to extracted ginseng, which could have ethanol. The use of ethanol-derived extracts has been found in preclinical studies to exhibit estrogenic characteristics and would therefore be contraindicated for most breast cancer survivors and patients with other estrogen-sensitive cancers. If American ginseng is purchased in a store or over the internet, it is important to buy pure ground root, preferably 5% ginsenoside content, as opposed to ginseng extract, because, under most circumstances, it will not be obvious what was used to make the extract. It might be best to obtain the manufactured product that was used in the actual clinical trials,[178,179] given the unregulated status of herbal preparations in most countries.

KEY POINTS

- Cancer fatigue is very common and often multifactorial.
- Patients with cancer-associated fatigue should be evaluated and treated for coexisting

conditions, such as depression, anemia, thyroid dysfunction, and electrolyte disorders.

- In patients with cancer fatigue, exercise during and after therapy appears to improve fatigue.
- Data support a trial of ginseng in clinical practice.

SKIN RASHES FROM TARGETED AGENTS AND CHEMOTHERAPY DRUGS

EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS

EGFR inhibitors are approved by the FDA for use in various cancers.[180-183] One of the most common toxic effects of EGFR inhibitors is a prominent skin rash, affecting up to 50% of patients treated with these drugs.[183-186] This rash has acnelike characteristics but is not considered acne (Fig. 21-2). Other targeted drugs that are associated with a similar rash include inhibitors of mTOR, such as everolimus and temsirolimus, and multikinase inhibitors, such as sorafenib and sunitinib.

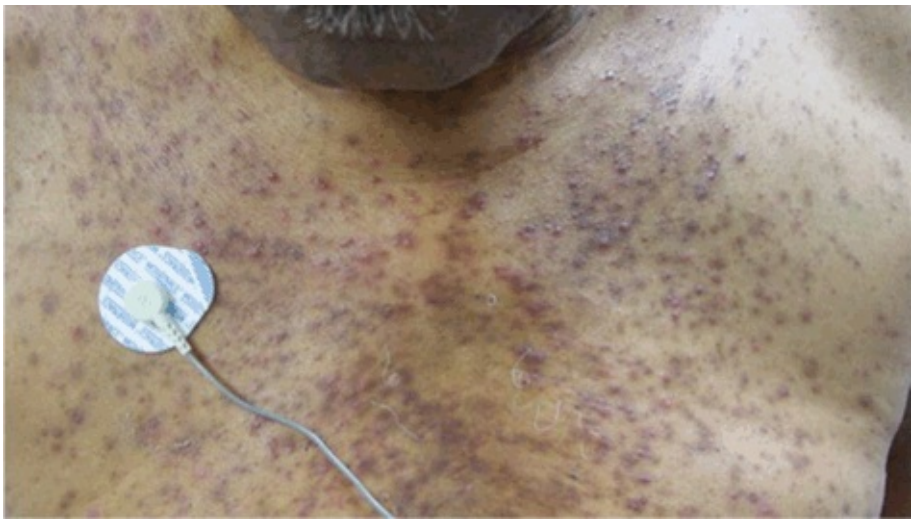

Fig. 21-2 Representative papular rash in a patient receiving an EGFR antagonist.

Although there are many anecdotal therapies that may be useful in this situation, there is a paucity of clinical trial data to appropriately guide therapeutic choices. Three randomized, double-blind, placebo-controlled clinical trials have looked at tetracycline or a tetracycline derivative as a potential means for preventing this rash for patients initiating EGFR inhibitor therapy. Two of these trials suggested that tetracycline or minocycline use moderately decreases rash severity,[187,188] although the third trial did not support this finding.[189] A publication regarding an open-label, randomized trial, did support that tetracycline decreased skin toxicity associated with afatinib.[190]

One study[191] has reported that a combination therapy approach decreased EGFR inhibitor (i.e., panitumumab) skin toxicity when compared with a control group. The treatment consisted of skin moisturizers, sunscreen, a topical steroid preparation (1% hydrocortisone cream), and doxycycline (100 mg twice daily). Despite the treatment groups being randomly assigned, the control arm did not receive placebo preparations, so there was no attempt to blind the patients or their attending physicians. Although the data from this randomized pilot trial are not definitive, they did reveal a markedly decreased incidence in reported grade 2 or worse skin toxicity (62% vs. 29%).

Given the paucity of definitive clinical trials regarding the management of this rash, the therapeutic options are based on clinical experience and expert opinions. Consultation with a dermatologist is recommended for patients with moderate to severe rashes. Agents that have been recommended for use include sunscreen (despite a placebo-controlled trial that was unable to prove benefit),[192] skin moisturizers, steroid creams, topical clindamycin, and oral doxycycline. For severe rashes, investigation of potential infections is appropriate.

In addition to the acneiform rash, these drugs can also cause a large number of other dermatologic problems, including periungual disease, photosensitivity, pruritus, xerosis, Stevens–Johnson syndrome, and skin cancers. Of note, there are extensive data supporting that patients in whom a rash develops appear to have more antitumor activity with the EGFR inhibitor than do patients with no rash.[193-196] This may be related to pharmacogenetic factors.

CAPECITABINE AND LIPOSOMAL DOXORUBICIN RASHES

One of capecitabine's dose-limiting toxicities is a prominent rash called "palmar–plantar erythrodysesthesia," also known as "hand–foot syndrome." This problem can also be seen, usually to a lesser extent, with other chemotherapy agents, such as infusional 5-FU. Symptoms from this problem usually begin with erythema and proceed to pain and then to desquamation. If the drug is used for too long, this syndrome can lead to substantial morbidity, to the point that patients may be incapacitated, are unable to use their hands well, and/or are unable to walk. Also, ulcers that are slow to heal may develop.

Anecdotal information had suggested that vitamin B_6 was helpful for alleviating this problem, but a large placebo-controlled study was unable to show any benefit for this approach.[197] Another proposed antidote consisted of a urea–lactic acid cream, but a placebo-controlled NCCTG trial suggested that it actually caused more skin troubles than did a placebo.[198]

At this time, it is recommended that patients should be carefully educated to immediately stop taking their planned multiday cycle of capecitabine if tenderness of the palms or soles develops. Doses from the next cycle should be appropriately attenuated.

Liposomal doxorubicin also causes palmar–plantar erythrodysesthesia, affecting about 20% of patients at the FDA-approved dose of 50 mg/m^2. Although topical emollients have been commonly used for symptom management, there are no good studies that demonstrate benefit; dose reduction is helpful to decrease risk in subsequent cycles.

KEY POINTS

- EGFR inhibitors commonly cause rashes.
  - Proposed treatments include the following:
    - Sunscreen
    - Skin moisturizers
    - Topical steroid creams
    - Topical clindamycin
    - Oral doxycycline
- Patients with rashes may be more likely to have EGFR inhibitor–induced tumor

regression or stability.

- Capecitabine-induced palmar–plantar erythrodysesthesia is best managed by dose attenuation.

CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

Chemotherapy-induced peripheral neuropathy (CIPN) is a common clinical problem, especially with platinum agents, taxanes, and vinca alkaloids. These agents can cause numbness, tingling, and pain, usually in a stocking–glove distribution. Additionally, data strongly support that the acute pain syndrome caused by paclitaxel, which has classically been identified as arthralgias and myalgias, is not from an injury to muscles or joints; rather, it appears to be a manifestation of an acute neuropathy.[199,200] ASCO chemotherapy-induced neuropathy guidelines, published in 2014, reviewed the value of strategies for preventing CIPN and for treating established CIPN.[201] Table 21-10, taken from this guideline, provides the results of this work. No agents were recommended for preventing CIPN and the only agent thought to be proven for treating established CIPN was duloxetine.[202] Subsequently published data further supported the value of duloxetine, noting that it decreases CIPN by a mild degree.[203]

Table 21-10 Summary Recommendations from ASCO Guideline on Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Guideline Question
What are the optimum prevention and treatment approaches in the management of chemotherapy-induced neuropathies in adult cancer survivors?
Target Population
▪ Adult cancer survivors with chemotherapy-induced neuropathies
Target Audience
▪ Health care practitioners who provide care to cancer survivors
Recommendations
▪ The following recommendations are evidence-based, informed by small randomized, controlled trials, and guided by clinical experience. The recommendations were developed by a multidisciplinary group of experts.
Prevention of CIPN
▪ There are no established agents recommended for the prevention of CIPN in patients with cancer undergoing treatment with neurotoxic agents. This is based on the paucity of high-quality, consistent evidence and a balance of benefits versus harms.
▪ Clinicians should not offer the following agents for the prevention of CIPN to patients with cancer undergoing treatment with neurotoxic agents:
• Acetyl-L-carnitine (ALC)
• Amifostine
• Amitriptyline
• Calcium/magnesium (CaMg) for patients receiving oxaliplatin-based chemotherapy
• Diethyldithiocarbamate (DDTC)
• Glutathione (GSH) for patients receiving paclitaxel/carboplatin chemotherapy
• Nimodipine
• ORG 2766
• All-trans retinoic acid
• RhuLIF (recombinant human leukemia inhibitory factor)
• Vitamin E
Venlafaxine is not recommended for routine use in clinical practice. While the venlafaxine data support its potential utility, the data were not strong enough to recommend its use in clinical practice until additional supporting data become available.
No recommendations can be made on the use of N-acetylcysteine, carbamazepine, glutamate, or glutathione for patients receiving cisplatin or oxaliplatin-based chemotherapy, goshajinkigan (GJG), omega-3 fatty acids, or oxcarbazepine for the prevention of CIPN at this time.
Treatment of CIPN
▪ For patients with cancer experiencing CIPN, clinicians may offer duloxetine.
No recommendations can be made on the use of:
• Acetyl-L-carnitine, noting that a positive phase III abstract supported its value, but this work has not yet been published in a peer-reviewed journal and a prevention trial suggested that this agent was associated with worse outcomes.
• Tricyclic antidepressants; however, based on the limited options that are available for this prominent clinical problem and the demonstrated efficacy of these drugs for other neuropathic pain conditions, it is reasonable to try a tricyclic antidepressant (e.g., nortriptyline or desipramine) in patients suffering from CIPN following a discussion with the patients about the limited scientific evidence for CIPN, potential harms, benefits, cost, and patient preferences.
• Gabapentin, noting that the available data were limited regarding its efficacy for treating CIPN. However, the panel felt that this agent is reasonable to try for selected patients with CIPN pain given that only a single negative randomized trial for this agent was completed, given the established efficacy of gabapentin and pregabalin for other forms of neuropathic pain, and given the limited CIPN treatment options. Patients should be informed about the limited scientific evidence for CIPN, potential harms, benefits, and costs.
• A topical gel treatment containing baclofen (10 mg), amitriptyline hydrochloride (40 mg), and ketamine (20 mg), noting that a single trial supported that this product did decrease CIPN symptoms. Given the available data, this agent is reasonable to try for selected patients with CIPN pain. Patients should be informed about the limited scientific evidence for the treatment of CIPN, potential harms, benefits, and costs.

Reprinted from Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2014;32:1941-1967. PMID: 24733808.

Additionally, pilot data support the value of topical cryotherapy for decreasing paclitaxel-caused CIPN.[204-206] Ongoing studies are further evaluating cryotherapy for this situation.

Substantial work has been done looking at genetic predispositions for chemotherapy-induced neuropathy. Although many reports have been published, no genetic tests have gotten to the point of being established and recommended for use in clinical practice to define patients who have a substantially high risk for chemotherapy-induced neuropathy. Having said this, patients who have family members with Charcot–Marie–Tooth–associated neuropathies may be predisposed to CIPN from neurotoxic chemotherapy. One report supports that genetic abnormalities associated with Charcot–Marie–Tooth–associated genes can increase the risk of chemotherapy-induced neuropathy.[207]

Relatively new data support that CIPN develops more often in overweight/obese patients and

in patients with diabetes, at least with some chemotherapy drugs, and that exercise might decrease this toxicity.[208-211]

KEY POINTS

- There are no established methods for preventing chemotherapy-induced neuropathy, other than limiting exposure to the offending drugs.
- The best-established drug for treating CIPN is duloxetine, but its efficacy is limited.

SEXUAL HEALTH

As highlighted in an article in the Art of Oncology section of the *Journal of Clinical Oncology,* "The Sounds of Silence: Sexuality Information for Cancer Patients,"[212] discussion of sexual health is something that rarely happens in oncologists' offices. There are at least two reasons this topic rarely is addressed. First, oncologists have limited experience and/or comfort with discussing this issue, and second, there are limited proven therapies available for patients with cancer who have sexuality concerns—at least with regard to therapies that an oncologist can administer. However, it is recommended that oncologists take a sexual history and refer patients to appropriate specialists if a problem is identified.[212]

A study examining sexuality issues among patients with cancer evaluated transdermal testosterone administration in women with symptoms of decreased libido. A number of prior trials with women who did not have cancer had evaluated testosterone in a similar dose and formulation. The results of these trials were positive, suggesting that testosterone improved libido, at least to some degree.[213,214] However, the results of a randomized, double-blind, placebo-controlled trial of transdermal testosterone in women with cancer were negative.[215] A potential explanation for the negative results for patients with cancer is that the women involved in this trial were postmenopausal and did not receive supplemental estrogen. In most of the previous trials in other patient groups, women had been premenopausal and/or had also been receiving estrogen-replacement therapy.

KEY POINTS

- Sexual health concerns are common in patients with cancer, but they are not commonly discussed by oncologists.
- Testosterone, without the addition of estrogen-replacement therapy, does not appear to help libido in postmenopausal women with cancer.

BONE HEALTH

Bone health issues in the general population are receiving more attention with the recognition of fracture problems associated with osteopenia/osteoporosis, the aging population, and the availability of treatment options for prevention and/or treatment of this situation. Women with breast cancer and men with prostate cancer have more bone-loss issues than patient

populations with most other cancers.

BREAST CANCER

Women with breast cancer are at an increased risk for complications from bone loss due to treatment-induced menopause. Treatment-induced menopause can occur as a result of chemotherapy or of oophorectomies performed for therapeutic or preventive reasons. In addition, aromatase inhibitors lower estrogen levels for postmenopausal women; by this means, this class of drugs increases the risk of osteoporosis and subsequent fractures. Given these heightened risks, ASCO guidelines recommend interval bone mineral density screening for women with breast cancer after they have undergone menopause.[216]

Current recommendations for women with osteopenia or osteoporosis include weight-bearing physical activity, a calcium intake of 1200 to 1500 mg per day (in diet and supplements), and vitamin D intake of 1000 international units (IU) per day. Smoking cessation and moderate or lessened alcohol intake is suggested. Bisphosphonates, available in intravenous or oral formulations, also are recommended for woman diagnosed with osteoporosis. Alternatively, denosumab can be used in this setting, although it is considerably more expensive.[217]

A number of clinical trials have been developed to examine bone loss issues among women with breast cancer. More than 200 premenopausal women receiving adjuvant chemotherapy for breast cancer were enrolled in a clinical trial in which they were randomly assigned to receive calcium and vitamin D or the same supplements plus oral weekly risedronate. This trial demonstrated that risedronate did not substantially attenuate the bone loss for these patients.[218] Another, similar trial, however, demonstrated that intravenous zoledronate decreased bone loss for these patients.[219] Nonetheless, there is no published evidence yet that these interventions decrease osteoporotic bone fractures in this setting. Thus, bisphosphonates have not been routinely recommended for preventing bone loss in premenopausal women receiving adjuvant chemotherapy for breast cancer.

Many trials also have examined the prevention of bone loss associated with aromatase inhibitor therapy. Large trials of women receiving aromatase inhibitors have been conducted in which patients were randomly assigned to receive a bisphosphonate (either intravenous zoledronic acid or oral risedronate) or no treatment. These trials demonstrated that bisphosphonate therapy attenuates the bone loss seen with use of an aromatase inhibitor.[220] Similar findings have been observed with patients randomly assigned to denosumab, an antibody targeted against receptor activator of nuclear factor kappa B (RANK) ligand and given by subcutaneous injections, compared with a placebo.[221] These trials did not report a substantial reduction in bone fractures; therefore, it has not been routinely recommended that such patients receive a bisphosphonate or denosumab as part of standard therapy, unless osteoporosis or marked osteopenia is present. Nonetheless, data from a meta-analysis of curatively treated patients with breast cancer randomly assigned to a bisphosphonate or a placebo support that, for postmenopausal women, those randomly assigned to receive bisphosphonates appeared to have improved survival.[222] This apparent antitumor effect has led to more recommendations for the use of these drugs in this population, although they are not routinely recommended by some breast cancer experts.

A randomized trial compared denosumab with zoledronic acid in 1026 patients with metastatic breast cancer.[223] This study supported that denosumab, compared with zoledronate, delayed skeletal-related events ($p = 0.01$), had better reductions in bone turnover markers, caused more hypocalcemia, had fewer renal toxicities and acute-phase reaction troubles, and

was associated with similar survival rates, time to disease progression, and incidences of osteonecrosis of the jaw. According to a 2011 updated ASCO guideline, there was not enough evidence to recommend either a bisphosphonate or denosumab over the other (Table 21-11).[216]

Table 21-11 Results of Phase III Randomized Trials Comparing Zoledronic Acid with Denosumab

Primary Cancer Site Evaluated by Trial	Time to First SRE				Overall Survival	Summary of AEs of Interest (trends and statistically significant; unadjusted)
	Median (months)*	HR	95% CI	p-value		
Solid tumors (not breast or prostate) and myeloma[177]	20.6 (Z) vs. 16.3 (D)	0.84	0.71, 0.98	< 0.001 (noninferiority)	No difference in overall population	Zoledronic acid: more acute phase reaction symptoms, renal AEs
				0.06 adjusted (superiority)	NSCLC: HR 0.79, 95% CI 0.66, 0.95	Denosumab: more hypocalcemia
					Myeloma: HR 2.26, 95% CI 1.13, 4.50	
Breast cancer[172]	NR (Z) vs. 26.4 (D)	0.82	0.71, 0.95	< 0.001 (noninferiority)	No difference	Zoledronic acid: more acute phase reaction symptoms, renal AEs
				0.01 (superiority)		Denosumab: more hypocalcemia, ONJ
Prostate cancer[173]	20.7 (Z) vs. 17.1 (D)	0.82	0.71, 0.95	< 0.001 (noninferiority)	No difference	Zoledronic acid: more acute phase reaction symptoms, renal AEs
				0.008 adjusted (superiority)		Denosumab: more hypocalcemia, ONJ

Abbreviations: AEs, adverse events; CI, confidence interval; D, denosumab; HR, hazard ratio; NR, not reached; NSCLC, non-small cell lung cancer; ONJ, osteonecrosis of the jaw; SREs, skeletal-related events; Z, zoledronic acid.

*The first number refers to denosumab and the second to zoledronic acid.

Reproduced with permission from West H. Denosumab for prevention of skeletal-related events in patients with bone metastases from solid tumors: incremental benefit, debatable value. J Clin Oncol. *2011;29:1095–1098. PMID: 21343550.*

PROSTATE CANCER

It has been well understood that men with prostate cancer receiving androgen ablation therapy have an increased risk of bone loss. Studies have randomly assigned men receiving androgen ablation therapy to a bisphosphonate or to no treatment. The results from these trials demonstrate an attenuation of bone loss with the use of a bisphosphonate. Similar data were seen in a trial, involving 1468 men, comparing denosumab with a placebo.[224] No clear evidence of decreased bone fractures, however, has been reported.[225] Thus, the recommendations for patients with nonmetastatic prostate cancer include bone density screening and treatment with a bone antiresorptive agent if marked osteopenia or osteoporosis develops.

Data support that bisphosphonates will decrease skeletal-related events for patients with metastatic prostate cancer. Denosumab is slightly better at decreasing skeletal-related events, and it decreases markers of bone turnover more than a bisphosphonate, although it is not related to improved survival rates and it comes at an increased economic cost.[226] Thus, as with

metastatic breast cancer, there is no clearly preferred agent (Table 21-11).[227]

MULTIPLE MYELOMA AND OTHER SOLID CANCERS

Similar data are available for bisphosphonates and denosumab in patients with myeloma and other solid cancers with bone metastases (Table 21-11). Notable differences are that patients with non-small cell lung cancer had a suggestion of improved survival rates with zoledronate over denosumab, while the opposite was seen for patients with multiple myeloma.[228]

OSTEONECROSIS OF THE JAW AND BRITTLE BONE FRACTURES

A serious side effect of intravenous bisphosphonate and denosumab therapy is osteonecrosis of the jaw.[229,230] This condition is relatively uncommon but can be clinically devastating when it occurs. It is particularly problematic for patients with poor dentition and/or for patients requiring dental work.

Somewhat like the problem of osteonecrosis of the jaw are reports of brittle bone fractures among patients who are on long-term bisphosphonate therapy. Although this phenomenon has not yet been established with the use of bisphosphonates to treat osteoporosis, there may be a higher risk for this problem among patients with cancer who are receiving higher-dose, longer-term bone antiresorptive therapy.

THERAPY FREQUENCY AND DURATION

There has been substantial interest in the frequency and duration of antiresorptive bone therapy for patients with cancer. Concerns about toxicity have led oncologists to question the routine use of long-term therapy for patients with cancer. The safest and most effective interval for treatment with these agents is yet to be defined. The 2011 updated ASCO guidelines stated that there is no proof that therapy longer than 1 year is more beneficial than 1 year of therapy.[216] A double-blind, placebo-controlled study by Hortobagyi et al.[231] looked at treatment intervals during the second year of zoledronate therapy in metastatic breast cancer. This trial randomly assigned 412 patients, who had previously received about a year of monthly zoledronate therapy, to receive 4 mg of zoledronate every 4 weeks or every 12 weeks. The results supported that there was no apparent advantage to the more frequent dosing. This trial replicated results from a previous similar trial (ZOOM TRIAL), noting that the prior trial was not double-blinded.[232] It should not be assumed that these data apply to denosumab dosing intervals, as bisphosphonates, but not denosumab, are present in bones for extended periods.

The CALGB (Alliance) 70604 study randomly assigned patients with bone metastases to receive a 2-year course of 4 mg of IV zoledronate every month compared with every 3 months, to evaluate the risks and benefits with each option. Data from this trial, supported that starting off with every-3-months treatment was equally as efficacious as monthly treatment.[233]

There has been much discussion about the use of vitamin D for patients with advanced cancer. At this time, it is clear that many patients have low vitamin D serum concentrations and that these low concentrations can be increased with oral vitamin D supplementation. It is not clear, however, whether vitamin D concentrations should be routinely measured for patients with advanced cancer and/or whether vitamin D supplementation increases quality or length of life. The 2011 version of the ASCO breast cancer metastatic bone disease guidelines recommends the use of calcium and vitamin D for patients receiving antiresorptive bone therapy, in doses that are common for patients who do not have cancer but who are receiving antiresorptive bone

therapy.[216]

KEY POINTS

- Bone loss is common with estrogen depletion in women and in men receiving androgen ablation therapy.
- Zoledronate, in patients with bone metastases, can be given every 3 months for 2 years, as opposed to monthly.
- Oral doses of calcium and vitamin D and weight-bearing exercise are recommended for patients at risk for bone loss.
- Bisphosphonates and denosumab can cause osteonecrosis of the jaw.
- Although both bisphosphonates and denosumab can decrease skeletal-related events in patients with bone metastases, and denosumab is slightly superior to zoledronate, available guidelines at this time do not recommend one over the other.

ANEMIA

Anemia is a common problem for patients with cancer. Multiple causes for anemia include myelophthisis, bleeding, hemolysis, deficiency of a micronutrient (e.g., iron, folate, or vitamin B_{12}), anemia of chronic disease, and other causes, including chemotherapy and radiation therapy.

Anemia can cause many symptoms, including fatigue, shortness of breath, and angina. Appropriate evaluation of patients with anemia is important and includes evaluation for sites of blood loss, hemolysis, and deficiencies of iron, folate, and/or vitamin B_{12}.

Erythropoietic agents, such as erythropoietin and darbepoetin, have been used to treat chemotherapy-induced anemia. Although they appear to be helpful for increasing hemoglobin concentrations for patients with cancer-associated (as opposed to chemotherapy-associated) anemia, there is evidence that these agents stimulate tumor growth and decrease survival for some patients; therefore, this indication is not approved by the FDA. For chemotherapy-associated anemia treatment, there is no convincing evidence that one agent is particularly better than the other—both erythropoietin and darbepoetin increase hemoglobin levels as well as decrease transfusion requirements. The compilation of available data does not suggest that these agents substantially improve quality of life, although there is a slight trend that they may do so.[234] Data support that intravenous iron can facilitate anemia correction when given with erythropoietic agents, especially for patients with low hepcidin concentrations.

Some data demonstrate that erythropoietic agents increase the risk of thromboembolic complications and that this might be a problem with higher hemoglobin levels.[234] For this reason, use of erythropoietic agents should be stopped when hemoglobin levels reach 12 mg/dL or higher. Rare cases of red cell aplasia have been reported in conjunction with the use of some erythropoietic agents. It is now well established that erythropoietic agents adversely affect survival, particularly for patients who are not receiving concomitant chemotherapy and have a baseline hemoglobin level of 12 or greater.[234]

There are risks and benefits for deciding to use erythropoietic agents rather than red blood

cell transfusions. The main disadvantage is that erythropoietic agents can increase the incidence of blood clots and may stimulate cancer growth and/or decrease survival, while the main advantage is that they decrease the need for red blood cell transfusions. On the other hand, transfusions cause transfusion reactions, viral infections, and alloantibodies and can increase the incidence of fluid and/or iron overload, while the advantage is that they cause a more rapid increase in hemoglobin and may improve symptoms faster.

Given the high profile of erythropoietic products in 2008, the FDA provided additional guidance regarding their use. These include the following recommendations:

- Use these agents only for patients receiving chemotherapy.
- Initiate use only when hemoglobin levels are 10.0 g/dL or lower.
- Administer the lowest possible doses that will gradually increase hemoglobin levels to a degree that will avoid transfusion requirements.
- Cease use when there is no longer a likelihood for needing transfusions.
- Avoid administering to patients for whom cure is the goal of therapy.

The Risk Evaluation and Mitigation Strategy (REMS) program, termed "APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe Use of ESAs [erythropoiesis-stimulating agents])" was approved by the FDA in February 2010. Per this communication, hospitals and physicians prescribing erythropoietic agents need to undergo training, maintain registration on a REMS program, and document in writing prior to an initiation of an erythropoietic agent to an individual patient that there was a discussion regarding the risks of blood clots, stroke, heart failure, heart attack, tumor progression, and/or death. This REMS program does not apply to patients receiving ESAs for myelodysplastic syndrome.

KEY POINTS

- Anemia is common in patients with cancer.
- Anemia is caused by multiple factors, including anticancer therapy with chemotherapy, radiation therapy, or surgery.
- Transfusions are recommended for patients with symptomatic anemia.
- For less severe anemia, erythropoietic agents decrease transfusion requirements and increase hemoglobin levels.
- Both darbepoetin and erythropoietin are relatively similar regarding efficacy and safety.
- Current recommendations are to cease use of erythropoietin products when the hemoglobin level is greater than or equal to 12 g/dL.

THROMBOEMBOLIC PREVENTION AND TREATMENT

ASCO guidelines regarding the use of anticoagulants for preventing and treating venous thromboembolic problems recommend that prophylaxis with anticoagulants should be

considered for patients with cancer who are hospitalized if they do not have evidence of bleeding or other contraindications.[235] The guidelines also recommend against the routine prophylaxis of patients with cancer who are ambulatory, with the exception of patients receiving thalidomide or lenalidomide. The guidelines state that patients undergoing major surgery for cancer should be considered for anticoagulation. With regard to choice of agent, they state that low-molecular-weight heparin is preferred over coumadin. These recommendations are summarized in Table 21-12.

Table 21-12 Summary Recommendations and Evidence Regarding ASCO Guidelines for Thromboembolic Treatment[211]

Patient Group	Role of VTE Prophylaxis	Evidence
Hospitalized patients with cancer	Patients with cancer should be considered candidates for VTE prophylaxis with anticoagulants (UFH, LMWH, or fondaparinux) in the absence of bleeding or other contraindications to anticoagulation.*	Multiple RCTs of hospitalized medical patients with subgroups of patients with cancer. The 2004 ACCP guidelines strongly recommend (1A) prophylaxis with either low-dose heparin or LMWH for bedridden patients with active cancer.
Ambulatory patients with cancer without VTE receiving systemic chemotherapy	Routine prophylaxis with an antithrombotic agent is not recommended except as noted below.	Routine prophylaxis in ambulatory patients receiving chemotherapy is not recommended because of conflicting trial results, potential bleeding, the need for laboratory monitoring and dose adjustment, and the relatively low incidence of VTE.
	LMWH or adjusted-dose warfarin (INR ~ 1.5) is recommended in patients with myeloma who are taking thalidomide or lenalidomide plus chemotherapy or dexamethasone.	This recommendation is based on nonrandomized trial data and extrapolation from studies of postoperative prophylaxis in orthopedic surgery and a trial of adjusted-dose warfarin in breast cancer.
Patients with cancer undergoing surgery	All patients undergoing major surgical intervention† for malignant disease should be considered for thromboprophylaxis with low-dose UFH, LMWH, or fondaparinux starting as early as possible, for at least 7 to 10 days unless contraindicated.*	RCTs of UFH and those comparing the effects of LMWH and UFH on DVT rates in patients with cancer indicate broadly similar prophylactic efficacies for these two agents.
	Mechanical methods may be added to anticoagulation in very-high-risk patients but should not be used alone unless anticoagulation is contraindicated.*	Based on a Cochrane review of 19 studies.
	LMWH for up to 4 weeks may be considered after major abdominal/pelvic surgery with residual malignant disease, obesity, and a previous history of VTE.	RCTs suggest that prolonging prophylaxis up to 4 weeks is more effective than short-course prophylaxis in reducing postoperative VTE.
Treatment of patients with established VTE to prevent recurrence	Treatment with LMWH is the preferred approach for the initial 5 to 10 days in a patient with cancer with established VTE.	Treatment with LMWH for 3 to 6 months is more effective than vitamin K antagonists given for a similar duration for preventing recurrent VTE.
	LMWH for at least 6 months is preferred for long-term anticoagulant therapy. Vitamin K antagonists with a targeted INR of 2 to 3 are acceptable when LMWH is not available.	The CLOT study demonstrated a relative risk reduction of 49% with LMWH versus a vitamin K antagonist. Dalteparin sodium was approved by the FDA in 2007 for extended treatment of symptomatic VTE to reduce the risk of recurrence of VTE in patients with cancer.
	Anticoagulation for an indefinite period should be considered for patients with active cancer (metastatic disease; continuing chemotherapy).	In the absence of clinical trials, benefits and risks of continuing LMWH beyond 6 months is a clinical judgment in the individual patient. Caution is urged in elderly patients and those with intracranial malignancy.
	Inferior vena cava filters are reserved for those with contraindications to anticoagulation or PE despite adequate long-term LMWH.	Consensus recommendation because of a lack of data in cancer-specific populations.
Anticoagulants in the absence of established VTE to improve survival	Anticoagulants are not currently recommended to improve survival in patients with cancer without VTE.	RCTs and meta-analyses of warfarin, UFH, and LMWH have reported encouraging but variable results, generally showing clinical benefit only in subgroup analyses.

*Relative contraindications to anticoagulation include, among other conditions, active, uncontrollable bleeding; active cerebrovascular hemorrhage; dissecting or cerebral aneurysm; bacterial endocarditis; pericarditis, active peptic or other gastrointestinal ulceration; severe, uncontrolled, or malignant hypertension; severe head trauma; pregnancy (warfarin); heparin-induced thrombocytopenia (heparin, LMWH); and epidural catheter placement.
†Laparotomy, laparoscopy, or thoracotomy lasting longer than 30 minutes.
Abbreviations: ACCP, American College of Chest Physicians; CLOT, Randomized Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer; DVT, deep venous thrombosis; FDA, U.S. Food and Drug Administration; INR, international normalized ratio; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; RCT, randomized controlled trial; UFH, unfractionated heparin; VTE, venous thromboembolism.
Reproduced with permission from Lyman GH, Khorana AA, Falanga A, et al. American Society of Clinical Oncology Guideline: Recommendations for Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer. J Clin Oncol. 2007;24:5490-5505. PMID: 17968019.

Newer agents, such as the oral direct factor Xa inhibitors apixaban and rivaroxaban, have been demonstrated to be noninferior to standard anticoagulant therapy for the treatment of established venous thromboembolic disease in studies that were conducted primarily with patients without cancer.[236-239] Although some clinicians are using these drugs for patients with

cancer, some investigators and clinicians feel that more specific studies should be completed with patients with cancer-related blood clots prior to more widespread use in patients with cancer. Efforts are ongoing to look at these agents, in controlled clinical trial settings, for both the treatment and the prevention of cancer-related blood clots.

KEY POINTS

- All patients with cancer should receive prophylactic anticoagulation when hospitalized (unless contraindicated).
- Ambulatory outpatients with cancer should not routinely receive anticoagulation (exception: those on thalidomide or lenolidamide).
- Low-molecular-weight heparin is preferred over warfarin in cancer patients.
- Factor Xa inhibitors are being studied for their role in anticoagulation in cancer patients.

ALOPECIA

Since the 1970s, scalp hypothermia (cryotherapy) has been reported to improve alopecia, a major untoward toxic effect of many chemotherapy regimens. The results from initial efforts with this therapy were less than ideal, and it largely went out of favor because of limited efficacy and concerns about patients potentially getting scalp metastases because of cryotherapy preventing chemotherapy from getting to the scalp.

Nonetheless, cryotherapy has had a resurgence of popularity in recent years. To date, there have been more than 50 published trials, many of them nonrandomized.[240,241] Scalp cryotherapy is relatively well tolerated and efficacy has improved since this treatment was first developed. Trials published since 1995 support that about three-quarters of patients are satisfied with the maintenance of their hair when they use the scalp cryotherapy. However, the therapy can be time-intensive and cumbersome. In some patients headaches can develop; also, patients can get too cold.

The incidence of scalp metastases among patients with cancer is quite low, although it may be higher for patients with hematologic malignancies.[242,243] In one retrospective trial, the incidence of scalp metastases in patients receiving scalp cryotherapy was 0.45% (2 of 442 patients).[244] In another retrospective cohort study, scalp metastases were seen in 1.1% and 1.2% of patients who did undergo scalp hypothermia as compared with those who did not.[245] A Dutch registry trial, involving 1411 patients, reported no observed scalp metastasis within this cohort.[246] Ongoing work is further evaluating cryotherapy methods, trying to increase efficacy and decrease the burden of this approach. Of note, fingertip cryotherapy has been shown to decrease docetaxel-induced nail toxicity.[240]

KEY POINTS

- Alopecia is a common side effect of cancer therapy.
- Scalp cryotherapy can be effective for selected patients.

- Fingertip cryotherapy can help reduce docetaxel-induced nail changes.

EARLY USE OF PALLIATIVE CARE

Palliative care is a rapidly growing subspecialty of medicine focused on the relief of symptoms and improvement in quality of life for patients with serious illness. Palliative care has often been confused with hospice and end-of-life care, but in reality, palliative care is appropriate throughout the entire spectrum of any cancer illness from initial diagnosis, through curative intent therapy, to early survivorship, subsequent relapse or recurrence, and through to advanced disease and end of life. The origin of palliative care is from the lessons learned from patients in hospice and end-of-life programs and extends those benefits to encompass the entire disease trajectory. The randomized study by Temel et al.[247] demonstrated that early palliative care improved symptom control and quality of life for patients newly diagnosed with stages 3 and 4 non-small cell lung cancer and also was associated with an overall survival advantage. Since this landmark publication, multiple other studies have shown improvement in patient well-being, symptomatic burden, decreased use of intensive care or hospital stay at the end of life, fewer doses of chemotherapy in the last 6 weeks of life, greater use of advanced directives, fewer complications for family and caregivers, and improved bereavement outcomes. Still being debated is whether these improvements also lead to a lower cost burden to the health care system or if similar survival improvements can be replicated. What is certain is that early use of palliative care does not shorten survival, but improves patient and family wellbeing.[248,249]

Acknowledging these important improvements in patient care, the 2016 ESMO/ASCO global curriculum for trainees in medical oncology have specific recommendations for training all oncologists in the general practice of palliative care, with an emphasis on recognizing when specialist palliative care consultation is warranted.[250,251] The well-trained oncology practitioner would be expected to demonstrate competence in evaluating and managing common symptoms such as pain, nausea, dyspnea. diarrhea, and other symptoms, as well as helping patients and their families elaborate specific goals of care and advanced care planning all under the umbrella of primary palliative care. It is well recognized that many patients with cancer present unique and highly challenging physical and psychosocial problems that would benefit from involvement of a multidisciplinary dedicated specialist palliative care program.

KEY POINTS

- Early use of palliative care consultations can improve patient symptom control and life quality.
- All oncologists should be trained in primary palliative care and should recognize when specialist palliative care referral is warranted.

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PALLIATIVE MEDICINE FOR CANCER

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Recent Updates

- ASCO guidelines recommend that patients with advanced cancer across all settings of care receive dedicated palliative care services early in the disease course and concurrent with active treatment. (Ferrell BR, *J Clin Oncol* 2017)
- The collective evidence via systematic review and meta-analysis of eight trials demonstrate consistent improvements in patient outcomes with the addition of palliative care to usual oncology care. (Kavalieratos D, *JAMA* 2016)
- Suggested triggers for patients with cancer who are hospitalized to receive inpatient specialty palliative care consultation include: advanced disease (any cancer stage IV plus stage III pancreas and lung cancer) with at least one unmet palliative care need (e.g., pain, advance care planning), and a previous hospitalization. (Adelson K, *J Oncol Pract* 2017)

OVERVIEW

In oncology, palliative care focuses on relief of suffering and improvement in quality of life for the patient with cancer and his or her caregivers, who may include family members and other loved ones. This involves viewing the patient and his or her loved ones as the unit of care, emphasizing a focus on understanding the stresses of the patient and the support system around them. As currently conceptualized, the suffering addressed by palliative care encompasses eight domains of quality care: structural aspects of care (e.g., the nature of supportive care services themselves), physical aspects of care (symptom assessment and management), psychologic (emotional) aspects of care, social (including both relational and logistical) aspects, spiritual/existential aspects, cultural aspects of care, legal and planning, and end-of-life needs. These areas of focus for patients enduring life-changing events, even in the case of curable disease, are the collective responsibility of the entire oncology team, and they are sometimes complex or time-intensive enough to warrant additional consultation.

Although palliative care is relevant across the cancer trajectory, and is not synonymous with end-of-life care, this chapter focuses on pain management, specialty palliative care services, and care near the end of life, including hospice. Here the goals of care shift from cure and disease-free survival to optimization of physical comfort, psychosocial well-being, and quality of life. A palliative care approach involves meticulous and regular assessments of distress across the full range of the patient's experiences—including physical symptoms, cognitive effects, and psychosocial concerns—that may diminish the patient's comfort and erode quality of life.

THE SCOPE OF PALLIATIVE CARE IN ONCOLOGY

It is important to provide a framework for delivery of palliative care to patients with cancer

through the lens of the workforce that provides the care. To many oncologists, the delivery of palliative care has a connotation of a specific service (e.g., delivered by fellowship-trained palliative care specialists) or a specific setting (e.g., patients near the end of life), which discounts the basic and fundamental delivery of supportive care services provided regularly by the oncologists themselves. This differentiation is explained by the framework initially proposed by Von Gunten,[1] which separates the basic skills and competencies of providing care supporting quality of life (termed "primary palliative care") from the complex services provided by specialists who have undergone additional training and offer consultative services (termed "secondary palliative care"). Further, the framework also includes tertiary palliative care services, such as inpatient palliative care units and centers of excellence, where research and education focus on the most complex of cases.

Remaining agnostic to the team providing the care, and acknowledging that most palliative care is delivered by the primary oncology team, it can be said that palliative care begins at the time of diagnosis and extends throughout the course of cancer care. This broader understanding of palliative care includes the care processes that oncologists provide in conjunction with treatment for the disease (e.g., nausea management during chemotherapy) but also extending beyond the conclusion of active treatment. Most simply stated, palliative care is about helping patients and their loved ones live life to the fullest when faced with the reality of life-threatening illness. The palliative focus requires specific considerations that must be part of an ongoing, carefully documented conversation about the individual's preferences (and values underpinning those preferences) for care in the context of his or her life.

A study by Bickel and colleagues aimed to identify the palliative care processes that fit within the usual scope of oncology practice versus those that may warrant consultation with a specialist.[2] Using a Delphi method of achieving consensus opinion, these investigators proposed 966 care processes to a multidisciplinary panel of 31 experts. Domains with the highest proportion of care processes endorsed by oncologists as fundamental to routine oncology practice included end-of-life care, communication and shared decision-making, and advance care planning. Domains that were least included by oncologists and thus have the most potential for referral to others included spiritual and cultural assessment and psychosocial assessment and management. Delineations between primary and secondary palliative care practices included care that involved pain not responsive to usual opioids, and depression and anxiety requiring more management than standard first-line therapy. Importantly, most of the care processes led the panel to conclude "unsure" regarding the role of oncologists versus other specialists, indicating that many decisions to refer outside the primary oncology team involve inherent capacity (e.g., part of usual care for a social worker, therapist, or chaplain), access to specialty palliative care services in the outpatient setting, and significant variations among oncologists in the time, comfort, and interest in addressing various quality-of-life needs.

EVIDENCE IN SUPPORT OF INTEGRATING ONCOLOGY AND PALLIATIVE CARE

There is increasing recognition that palliative care serves a vital role earlier in cancer management than originally conceived. Palliative care can—and should—be delivered simultaneously with antineoplastic treatment whenever the symptom burden is high or the aim of the therapy is not explicitly curative; ideally, oncologists and palliative care clinicians should work together on a day-to-day basis. This approach is supported by evidence that palliative care improves not only traditional symptom-focused and quality-of-life outcomes, but also survival. A randomized, controlled trial by Temel and colleagues suggested that early application

of palliative care improved life expectancy for patients with metastatic lung cancer by more than 2 months (a magnitude of benefit that has allowed many expensive targeted therapies to become licensed for use), improved quality of care, and reduced costs.[3] This high-profile study heightened awareness that the health care delivery system should make palliative care available to address the needs of patients who are suffering from advanced lung cancer before their last few days of life in order to improve overall survival and quality of life, as well as health care utilization. It is complemented by work demonstrating the health and survival benefits to caregivers long after they have relinquished their role.[2,3]

Since the publication of the Temel trial in 2010, further evidence from randomized, controlled trials have demonstrated the benefits of early integration of oncology and palliative care. For example, Bakitas et al.[2-4] randomly assigned patients with advanced cancer to early or delayed palliative care, starting the delayed group 90 days later than the early group. Remarkably, although there was no observed difference in patient-reported outcomes and resource use among the groups, 1-year survival rates were 63% in the early intervention group and 48% in the delayed group (a significant difference), highlighting the potential survival benefit of integrating the services of a palliative care specialist around the time of diagnosis of advanced disease. Additionally, in a trial of advanced lung cancer and gastrointestinal malignancies by Temel and colleagues, the investigators reported improvements in various outcomes across the two disease groups, though the effect in subgroup analysis remained significant only in the lung cancer cohort.[3] A systematic review and meta-analysis of 30 trials involving patients with cancer further concluded that there were consistent and significant improvements in symptoms and quality of life when palliative care is integrated with usual oncology care.[5] Most importantly, no study to date has shown any harm by integrating palliative care into oncology care.

Based on the rapidly expanding evidence base, a Provisional Clinical Opinion (PCO) was released in March 2012[6] and updated in 2016[7] by the American Society of Clinical Oncology (ASCO), which recommends that “inpatients and outpatients with advanced cancer should receive dedicated palliative care services, early in the disease course, concurrent with active treatment.” The authors cited the burgeoning collection of evidence demonstrating consistent patient and caregiver benefits of adding secondary palliative care services to usual oncology care, including nine randomized clinical trials (RCTs) and five secondary analyses from RCTs in the 2012 PCO.[6] Further, the rapid expansion of new therapeutics in oncology and our evolving understanding of their adverse effects, the psychosocial and financial implications to patients, and the prognostic uncertainty with great promise at the population level but no guarantees at the individual patient level, require even more integration between oncology and palliative care.

KEY POINTS

- Oncologists and their teams provide primary palliative care—the common and foundational services promoting quality of life—and refer the more complex needs to secondary palliative care services such as consultative teams.
- A growing body of evidence demonstrates the benefits of palliative care teams integrating into the usual care of patients with advanced cancer, especially early in the disease course.
- ASCO has released a formal guideline recommending integration of palliative care services concurrent with disease-directed treatment.

CONSULTING PALLIATIVE CARE

Palliative care consultation teams have expanded rapidly into cancer hospitals and clinics, with more than one-third of cancer centers reporting having access to a palliative care team.[8] Specialty palliative care teams often manage refractory pain or other physical symptoms and complex psychosocial symptoms (e.g., depression, anxiety, grief, and existential distress), assist with conflict resolution regarding goals or methods of treatment, and assist in addressing cases of nonbeneficial care. Palliative care consultation teams are intended to complement the role of the oncology team in providing primary palliative care, especially when needs or distress are complex. As mentioned, most patients with cancer do not require a palliative care consultation; rather, the needs of the patient and the capacity for the oncology team to provide those services should dictate when a consult is requested. Importantly, as the evidence base for palliative care grows, oncologists should incorporate those teams into the multidisciplinary approach, similar to how radiation oncology and surgical oncology are included for certain cancer types and stages.

Criteria or triggers for involving specialty palliative care services are evolving. Adelson et al.[9] have reported the results of a pilot program to automatically consult palliative care when patients with cancer are hospitalized.[9] Consultation criteria include any stage IV solid tumors or stage III lung or pancreas cancer, prior hospitalization within 30 days, length of stay longer than 7 days, and at least one uncontrolled symptom. The authors demonstrated high acceptance of the triggers, a decrease in the mortality index, and an almost 50% reduction in the 30-day hospital readmission rate. Triggers for when to include palliative care in the routine care of patients with cancer are still immature and in development. Clinicians should assess each patient and their caregivers for potential benefits from seeing a palliative care specialist and keep this option open at all times during the disease course.

CANCER-RELATED PAIN MANAGEMENT

For many patients with advanced cancer, pain is the most important primary palliative care symptom to assess and manage. It is distressful and common, with between 50% and 90% of patients with advanced cancer experiencing moderate to severe pain.[7-9] In the context of palliative and end-of-life care, where the focus of care is on relief of suffering, adequate pain management is imperative.

Of primary importance for the patient receiving palliative or end-of-life care is a basic pharmacotherapeutic approach that achieves the best possible pain relief through a combination of nonopioid and opioid analgesics, based on individual circumstances. The World Health Organization's (WHO's) three-step ladder for cancer pain relief remains the starting point for clinical management (Fig. 22-1). The WHO approach employs three categories of agents: opioid analgesics, nonopioid analgesics, and adjuvant therapies. An individualized combination of opioid and nonopioid drugs constitutes the foundation of pain management; to this foundation the clinician adds tailored care, selecting from a broad array of adjuvant interventions to achieve maximum comfort for the patient. Guidelines are available to assist the clinician in determining a foundation of treatment; for example, the National Comprehensive Cancer Network (NCCN) and American Pain Society both maintain publicly available guidelines that serve as excellent sources for cancer pain management.[10,11]

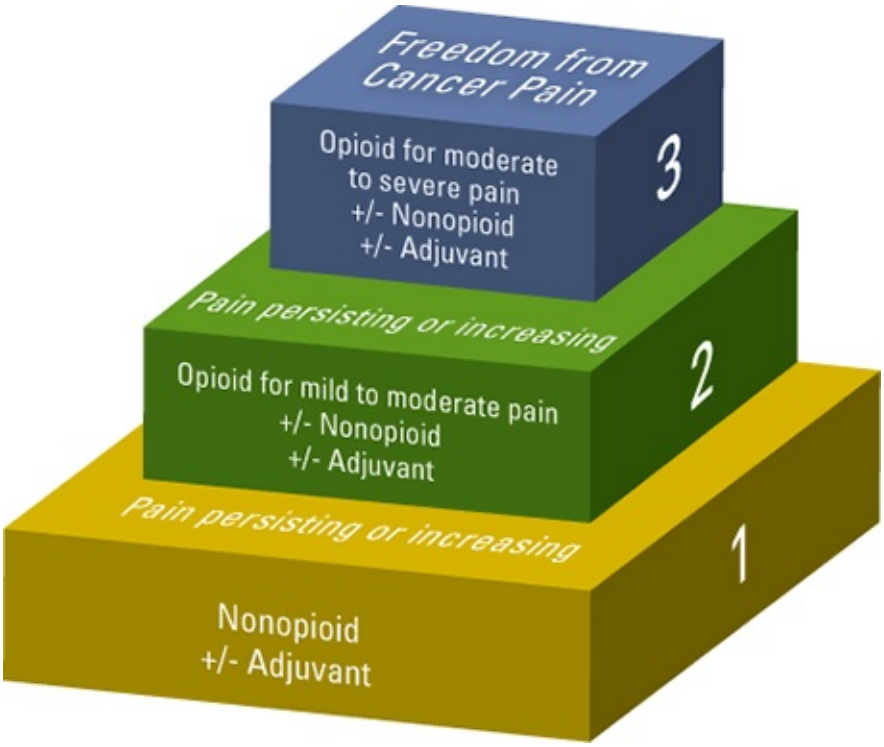

Fig. 22-1 World Health Organization Pain Relief Ladder.

Modified with permission from the World Health Organization. WHO's Pain Relief Ladder, www.who.int/cancer/palliative/painladder/en.

Pain management begins with a comprehensive diagnostic assessment that addresses the medical, psychological, and social components of pain.[7] The location and severity of the pain should be defined; common approaches use either a numeric rating scale (e.g., 0 to 10, with 0 representing no pain and 10 representing the worst possible pain) or a visual depiction such as the Wong-Baker Faces Pain Scale or the Iowa Pain Thermometer Scale.[12,13]

Pain should be classified as acute or chronic. *Acute pain* is characterized by a well-defined temporal pattern of onset, generally associated with subjective and objective physical signs and with hyperactivity of the autonomic nervous system. Usually self-limited, acute pain responds to treatment with analgesic drug therapy and to treatment of its precipitating cause. There are numerous specific acute cancer pain syndromes associated with diagnostic and therapeutic procedures or specific antitumor therapies (e.g., pain related to bone marrow biopsy). Acute pain can be further subdivided into subacute and episodic. *Subacute pain* occurs throughout several days, with a pattern of symptom progression. Episodic or intermittent pain occurs during confined periods of time, on a regular or irregular basis. Management of cancer-related acute pain syndromes is similar to that for any other acute pain management approach, following usual standards of care.

Table 22-1 **Non-opioid Analgesics for Mild to Moderate Pain**

Class	Generic Name	Half-Life (hours)	Dosing Schedule	Recommended Starting Dose (mg)	Maximum Daily Dose (mg)
Salicylates	Aspirin	3–12	q4–6h	2400*	6000
	Choline magnesium trisalicylate	9–17	q12h	200†	600
	Diflunisal	8–12	q12h	1500 for the first dose, then 1000 q12h	4000
p-Aminophenol derivative	Acetaminophen (paracetamol)	2–4	q4–6h	2600*	4000
Propionic acids	Ibuprofen	1.8–2	q4–8h	1200†	3200
	Fenoprofen	2–3	q4–6h	800*	3200
	Ketoprofen	2–3	q6–8h	150†	300
	Naproxen	13	q12h	550†	1100
	Naproxen sodium	13	q12h	550†	1100
Acetic acids	Etodolac	7	q6–8h	600†	1200
	Ketorolac	4–7	q6h	15–30 q6h IV, IM	120 IV, IM
				10 q6h PO	40 PO
Fenamates	Meclofenamic acid	1.3	q6–8h	150†	400
	Mefenamic acid	2	q6h	500 for the first dose, then 250 q6h	1000
COX2 inhibitor	Celecoxib	11	qd–q12h	100†	200

*Recommended daily starting dose.
†Recommended individual starting dose.
Abbreviations: h, hours; IM, intramuscularly; IV, intravenously; PO, orally; q, every; qd, every day.

Chronic pain persists for more than 3 months, with a less well-defined temporal onset and without the objective signs common to acute pain; most cancer-related pain treatment in the palliative care setting is for chronic pain. Treatment of chronic pain in the patient with cancer requires a careful assessment of not only the intensity of pain but also its broad multidimensional aspects. *Baseline pain* is the average pain intensity experienced for 12 or more hours during a 24-hour period. *Breakthrough pain* is a transient increase in pain to greater-than-moderate intensity, occurring on top of a baseline pain. Various epidemiologic studies have reported prevalence of breakthrough pain in 23 to 90% of patients with cancer.[14-17] The transitory increase in pain can mark the onset or worsening of pain at the end of a dosing interval or with a regularly scheduled analgesic. When caused by an action of the patient, it is termed “incident pain” (e.g., walking on a leg with a pathologic fracture).

According to the WHO ladder, pain treatment begins with nonopioid drugs alone or in combination (Table 22-1). The first options are acetaminophen and nonsteroidal anti-inflammatory agents. If these drugs are successful in achieving pain relief, no further therapy is necessary. However, if nonopioid drugs fail to provide adequate relief, the clinician can judiciously select from among multiple opioid options, including morphine, the WHO drug of choice, or derivatives of morphine, including hydromorphone, codeine, oxycodone, methadone, and fentanyl. The choice of agent depends upon the clinician’s comfort with using the drug, route of delivery, availability, cost, and patient factors such as age, renal function, comorbidities, and other concomitant drugs. Adjuvant, or coanalgesic, drugs are nonopioid medications that enhance the analgesia provided by opioids; their addition to an opioid regimen

can result in better pain control and/or fewer adverse effects (Table 22-2).[18]

Table 22-2 Co-analgesic Therapy for Common Cancer Pain Syndromes

Cancer Pain Syndrome	Coanalgesic Therapy
Bone metastases, soft-tissue infiltration, arthritis, serositis, and other inflammatory pain	Oral NSAIDs
	▪ Choline magnesium trisalicylate 1500 mg PO BID
	▪ Ibuprofen 800 mg PO TID
	▪ Naproxen 500 mg PO TID
Postoperative pain (plus arthritis, serositis, and other inflammatory pain syndromes in patients who cannot use oral NSAIDs)	Parenteral or enteral NSAIDs
	▪ Ketorolac 15–30 mg IV q6h (< 5 days)
	▪ Indomethacin 50 mg PR q6–8h
Acute nerve compression, visceral distention, increased intracranial pressure, soft-tissue infiltration	Corticosteroids
	▪ Dexamethasone 4–8 mg PO BID/TID
	▪ Methylprednisolone 16–32 mg PO BID/TID
Acute spinal cord compression, severe increased intracranial pressure	Corticosteroids
	▪ Dexamethasone 10–20 mg IV q6h
	▪ Methylprednisolone 40–80 mg IV q6h
Neuropathic pain	Tricyclic antidepressants*
	▪ Nortriptyline 100–150 mg PO at bedtime
	▪ Desipramine 100–300 mg PO at bedtime
	Anticonvulsants†
	▪ Gabapentin 300–900 mg PO at TID/QID
	▪ Carbamazepine 200 mg PO BID/QID
	▪ Clonazepam 0.25–0.5 mg PO TID
	Antispasticity drug
	▪ Baclofen 5–30 mg PO BID/TID
	Local anesthetic
	▪ Topical lidocaine 1–3 patches daily, 12 h on/12 h off
Bone pain from metastases	▪ Pamidronate 90 mg IV q3–4wk
	▪ Zoledronic acid 4 mg IV q4–6wk
	▪ Calcitonin 200 IU IV or intranasal BID
Bowel spasm from obstruction	▪ Scopolamine 0.4 mg IV or SC q4h
	▪ Octreotide 50–100 mcg SQ BID/TID

*Starting dose of nortriptyline and desipramine should be 25 mg PO at bedtime (10 mg if patient is frail or older) and increased by one tablet every 3 to 7 days, as tolerated, to attain the target dose. Serum drug levels should be checked at the target dose or at the maximum tolerated dose to assess patient adherence and prevent unexpected toxicity. The onset of pain relief should be expected at 1 to 2 weeks and mood elevation at 4 to 6 weeks at the maximum tolerated or target dose.
†Serum drug levels should be followed with carbamazepine to assess compliance and prevent unexpected toxicity. The multiple drug–drug interactions noted require review of all medications before initiation. Possible severe bone marrow suppression requires blood counts to be followed closely.
Abbreviations: BID, twice daily; h, hour(s); IV, intravenously; NSAID, nonsteroidal anti-inflammatory drug; PO, orally; PR, as needed; q, every; QID, four times daily; SC, subcutaneously; TID, three times daily, wk, week(s).

Because most pain managed in the cancer-related palliative care setting is chronic, the palliative approach should include an around-the-clock management strategy for continuous baseline pain, supplemented with additional medications for breakthrough or incident pain. Generally, long-acting sustained-release products and routine scheduled dosing are matched with short-acting rescue doses for breakthrough events. When opioids are prescribed, the breakthrough dose should usually be 10 to 20% of the total daily around-the-clock sustained-release dose (except in the case of methadone and short-acting fentanyl products, for which the short-acting dose is established by independent titration until analgesic efficacy is achieved). Further, because the maximal analgesic effect is reached at 1 hour, clinicians may

prescribe short-acting oral opioids to be taken as needed every 1 to 2 hours. The two scenarios in which this is especially helpful is when actively titrating oral opioids to better understand total opioid need and during the active dying phase, when opioid requirements are often dynamic.

Morphine continues to be the mainstay of opioid treatment, although its potential adverse effects can limit utility. Because many patients can tolerate morphine without adverse effects, morphine is the most cost-efficient and practical first-line opioid choice in most situations. Morphine-6-glucuronide, an active metabolite of morphine, contributes to analgesia and may worsen adverse effects as it accumulates in patients with renal dysfunction. Oxycodone is a practical alternative that does not have the same metabolite challenges as morphine and may, therefore, be a better choice for patients with poor hepatic or renal function. Long-acting and short-acting products are available for both morphine and oxycodone; typically, a sustained-release preparation is combined with as-needed doses of an immediate-release preparation, dosed at 10 to 20% of the total daily opioid dose. Coadministration of nonopioid and adjuvant drugs, as suggested by the WHO ladder, may help achieve optimal pain control with the least amount of constipation, sedation, and confusion.

If short-acting alternatives to morphine or oxycodone are needed, and for patients in whom morphine provides insufficient analgesia and/or causes intolerable adverse effects, hydromorphone may be a useful alternative. Because it has a short half-life, hydromorphone is commonly used in elderly patients. Hydromorphone's high solubility and availability in high-potency parenteral form (10 mg/mL) make it a practical choice for long-term parenteral administration. High doses may induce myoclonus, possibly as a result of accumulation of its metabolites.[19] A systematic review, originally published in 2002 and updated in 2009, reported little difference between morphine and hydromorphone in terms of analgesic efficacy, adverse effects, or patient preference, although evidence remains limited.[20] In prior studies, patients receiving hydromorphone exhibited less-favorable cognitive performance but reported better mood than did patients receiving morphine.[21,22]

Previously considered a late-line option for pain management, methadone is used with increasing frequency as the second- or even first-line drug for patients with cancer. Methadone is a unique opioid given that it is a μ-agonist and antagonist at the *N*-methyl-D-aspartate (NMDA) receptor, making it particularly useful for the treatment of neuropathic cancer pain. Unlike other opioids, one more advantage of using methadone is that there are no active metabolites, obviating dose adjustment in renal insufficiency.[23] However, there are a few unique characteristics of methadone that require expert oversight in its prescribing and monitoring. First, pharmacokinetic properties of methadone differ from those of morphine (Table 22-3); notably, it has a higher bioavailability and longer half-life.[24] The parenteral-to-oral ratio of methadone is 1:2, compared with 1:3 for morphine. Note that although the plasma half-life of methadone is long, with reports of as long as 50 hours in some patients with cancer, the duration of analgesia is 4 to 8 hours. By comparison, the half-lives of morphine, hydromorphone, and fentanyl are 2 to 4 hours, 2 to 3 hours, and 4 hours, respectively, and half-lives are more commensurate with analgesia.[25] The discrepancy between the analgesic duration and plasma half-life of methadone requires careful titration and monitoring and makes it a difficult drug to use in patients who are opioid-naive. Also, methadone interacts adversely with numerous other drugs and agents (e.g., selective serotonin reuptake inhibitors, antifungal agents, antibiotics, calcium-channel blockers, anticonvulsants, corticosteroids, grapefruit juice, and alcohol), given its metabolism primarily by CYP3A4 to inactive metabolites. Methadone's CYP3A4 interactions can limit its use when patients are participating in clinical trials. Third,

methadone requires QTc monitoring, and guidelines have been published in the chronic noncancer pain setting.[26] Of note, the degree of QTc monitoring should be balanced with prognosis and the patient's goals of care.

Conversion from other opioids to methadone is one of the most challenging aspects of methadone use. Studies of interindividual differences in response to opioid analgesics have demonstrated that greatly reduced dosages of methadone can affect analgesia for patients taking morphine or hydromorphone on a long-term basis. The most common conversion from morphine (compared with conversion from other opioids) is a 1:1 ratio, typically reported in single-dose studies, though this conversion ratio does not apply to continuous dosing. As a result of methadone's pharmacokinetic properties (i.e., extensive bioavailability, long half-life, lipophilicity, and incomplete cross-tolerance), higher dose ratios are usually necessary and close monitoring is warranted.[27] Consensus guidelines to assist clinicians with dose conversion from other opioids to methadone have been developed by a panel of experts in pain and palliative care, oncology, pharmacology, cardiology, and hospice (Table 22-4). These guidelines concur with specific dose ratios previously developed by Ripamonti et al through a prospective study.[28] From that study, the authors suggested that, for patients taking 30 to 90 mg of morphine, the dose ratio is 4:1 (4 mg morphine to 1 mg methadone); for those taking 90 to 300 mg daily, 6:1; and for 300 mg or more, 8:1. Based on survey data, Bruera et al.[29] developed a similar ratio for hydromorphone, advising a dose ratio of 1.6:1.0 for patients receiving more than 330 mg of hydromorphone and a dose ratio of 0.95:1.0 for patients receiving less than 300 mg. Current research is attempting to better elucidate the clinical pharmacology of methadone to facilitate its broader use.

Table 22-3 **General Comparison of Pharmacokinetic Properties of Methadone and Morphine**

Characteristic	Methadone	Morphine
Oral bioavailability	80%	35%
Protein binding	60–90%	35%
Elimination half-life	30 hours	3–4 hours
Active metabolites	No	Yes
Influenced by kidney disease	Slightly	Highly
Influenced by liver disease	Highly	Slightly
CYP3A4 interactions	Yes	No
QTc monitoring	Yes	No

Modified from Ripamonti C, Bianchi M. The use of methadone for cancer pain. Hematol Oncol Clin North Am. *2002;16:543–555.*

Meperidine is available in oral and intramuscular preparations, with a parenteral-to-oral ratio of 1:4, but it should not be used to manage chronic pain in the advanced cancer setting. Repetitive intramuscular administration (more than 250 mg/day) is associated with local tissue fibrosis and sterile abscess and can lead to accumulation of normeperidine, an active metabolite that can produce central nervous system (CNS) hyperexcitability.[30] This hyperirritability is characterized by subtle mood effects followed by tremors, multifocal

myoclonus, and occasional seizures. It occurs most commonly in patients with renal disease, but it can also occur after repeated administration in patients with normal renal function. Naloxone does not reverse meperidine-induced seizures, and its use in meperidine toxicity is controversial. Case reports have suggested that the use of naloxone in this setting has precipitated generalized seizures for some patients. In rare instances, CNS toxicity characterized by hyperpyrexia, muscle rigidity, and seizure has been reported after the administration of a single dose of meperidine to patients receiving treatment with monoamine oxidase inhibitors.

Table 22-4 **Conversion Table from Oral Morphine to Intravenous Methadone for Long-Term Administration**[31]

Total Daily Baseline Oral Morphine Dose (mg)	Conversion rate of morphine (mg) to methadone (mg)
<100	3:1
101–300	5:1
301–600	10:1
601–800	12:1
801–1000	15:1
>1000	20:1

Abbreviation: IV, intravenous.
The total daily methadone dose derived from the table may then be divided to reflect the intended dosing schedule (i.e., for administration every 8 hours, divide the daily methadone dose by 3).
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Transdermal patches offer a good option for pain control in the palliative or end-of-life setting when oral administration of drugs is difficult or undesirable; by maintaining constant plasma drug levels, transdermal systems may provide better sustained pain relief and reduce the incidence of adverse effects.[32] Fentanyl has been used effectively to manage both acute and chronic cancer-related pain. A multicenter, prospective, randomized, controlled study involving patients with advanced cancer who required opioids showed the transdermal fentanyl to be comparable with oral morphine and oral methadone in effectiveness and tolerability; patients randomly assigned to receive one of the three drugs also required similar quantities of symptomatic drugs and coanalgesics.[33,34] The half-life of fentanyl is 1 to 2 hours. Kornick et al.[34] have drafted guidelines for fentanyl use summarizing all current data. The uniqueness of the transdermal preparation facilitates management in patients who are unable to take drugs by mouth, allowing continuous opioid analgesia with minimal associated distress. Patches—available in doses of 12.5 to 100 µg/hour—are changed every 72 hours. When a patient begins using the fentanyl patch, there is as long as a 12- to 15-hour delay in the onset of analgesia, and alternative approaches must be used to maintain the patient's pain control during this period. Specific guidelines for switching to the fentanyl patch after an intravenous infusion of

fentanyl have been developed and are based on use of a 1:1 conversion ratio. Fentanyl also can be used as an anesthetic premedication, as well as intravenously and epidurally for pain control. Fentanyl, an opioid analgesic, is the drug most readily available in a transdermal patch form.

Breakthrough cancer pain, a condition that has only recently been described, involves the sudden onset of pain despite the use of usual long-acting medication. It may be associated with precipitating factors, can often manifest as end-of-dose pain when long-acting opioids are ready to be re-dosed, and can be related to the cancer itself or other associated factors.[35] Transmucosal immediate release fentanyl (TIRF) products have been developed specifically to address breakthrough cancer pain and come in many formulations, including oral, intranasal, and sublingual spray. Oral transmucosal fentanyl formulations have demonstrated effectiveness in treating breakthrough pain in 0.2- to 1.6-mg doses, providing onset of pain relief in as little as 5 minutes. Dose-titration trials have shown transmucosal, transbuccal, and intranasal fentanyl to be safe and effective, with the effective dose being a variable requiring titration in most patients (Table 22-5). This class of opioids is restricted to opioid-tolerant patients (at least 60 mg of morphine or its equivalent) with cancer. Prescribing transmucosal immediate-release fentanyl products requires registration through the Risk Evaluation and Mitigation Strategy (REMS) program.[36]

If severe pain persists or if the adverse effects of drugs are not tolerated, the oncologist should consider switching analgesics (e.g., from oral morphine to methadone), changing the route of administration (e.g., from oral to intravenous), or performing a procedural intervention (e.g., nerve block) for localized pain. A trial of an adjuvant drug together with an opioid and nonopioid drug may also be helpful. Adjuvants appropriate in this setting include anticonvulsants (gabapentin, pregabalin, carbamazepine, valproate) and antidepressants (amitriptyline, nortriptyline, imipramine, venlafaxine, duloxetine), especially when the patient is experiencing neuropathic pain.[37] Increasingly, adjuvant agents are being administered as the primary pain therapy, sometimes leading to complete response without requiring opioids (and thereby eliminating the problem of opioid adverse effects).

Table 22-5 **Opioid Analgesics Commonly Used in Cancer Pain Management**

Drug*	Half-Life (hr)	Duration of Action (hr)
Codeine	2–3	2–4
Oxycodone	2–3	2–4
Morphine	2–3	3–4
Hydromorphone	2–3	2–4
Methadone	15–190	4–8
Meperidine	2–3	2–4
Levorphanol	12–15	4–8
Fentanyl (parenteral)	1–2	1–3
Fentanyl (transdermal system)	—	48–72

*Oxycodone, hydromorphone, and morphine available in slow-release preparations.

Use of a neurostimulant or haloperidol may treat the side effect of excessive sedation or confusion while maintaining a patient's analgesia. Alternatively, excessive adverse effects resulting from systemic opioid delivery, such as confusion or sedation, may warrant a switch to epidural or intrathecal opioids. For localized pain, neurolytic blocks are indicated (e.g., celiac plexus block). For severe pain, unilateral and below-the-waist cordotomy may be appropriate, though the evidence base for the indications and efficacy of these newer procedures is still evolving.

For the patient receiving end-of-life care, pain must be both proactively and aggressively managed to ensure that the patient neither suffers nor dies with unrelieved pain. At this stage, it is especially important to educate family members and caregivers that addiction is not a concern and to reiterate the shared goal of maximizing the patient's comfort. For patients with a longer life expectancy or for those with a complex history with the use of opioids, best practices include the regular use of opioid agreements (sometimes referred to as "opioid/pain contracts"), baseline assessments of aberrant behaviors related to the use of opioids, careful consideration of urine screening to monitor compliance and illicit substance use, and identification of one clinician as the sole prescriber of opioid prescriptions. The best approach is to establish these processes as normative among all patients who are receiving regular opioid prescriptions so as to avoid issues of inequity in risk stratification and mitigation. Further, separating behaviors related to inadequate pain control (i.e., pseudoaddiction) from those related to addiction is paramount, as they may look similar. For example, patients may be constantly monitoring the time for when the next opioid dose is available ("clock watching"), which may appear to be a negative behavior but often reflects the need for long-acting medications or more frequent dosing of short-acting medications.

Behavioral approaches, such as guided imagery, may be integrated and used along with pharmacologic approaches. For example, cognitive behavioral therapy in the form of brief relaxation and distraction audiotapes have proven effective in relieving pain in the short term, although pain relief may not be sustained (e.g., for weeks postintervention).[38] Recent evidence

also highlights the utility of pain-coping skills approaches to building inherent emotional and cognitive resilience to the effects of somatic pain.[39,40]

KEY POINTS

- The best possible pain control in the patient receiving palliative and end-of-life care is of paramount importance.
- The WHO's three-step ladder provides the basis for good pain management.
- Morphine and oxycodone are the mainstays of opioid treatment, given the low cost and ready availability of oral long-acting preparations.
- Hydromorphone, with a short half-life but comparable analgesia with morphine, is useful in this population; fentanyl patches have the advantages of ease of application and long-lasting effect.
- Methadone may be a good choice for the home-based patient with advanced cancer but requires careful consideration of dose and monitoring for drug interactions.
- Transmucosal, transbuccal, and effervescent fentanyl products are useful alternatives for episodic breakthrough pain.

ISSUES RELEVANT TO PALLIATIVE CARE

COMMUNICATION

Communicating bad news to patients and families is a critical but challenging aspect of providing supportive care for patients who are terminally ill. The provision of accurate information to patients and caregivers can facilitate collaborative decision-making. Not only the content of the discussion but also the way the clinician delivers difficult news can have repercussions for the emotional health of both patients and their loved ones.[41]

Discussion of advance care planning is an important starting point for conversations at or near the end of life and, truly, for any patient with advanced and potentially life-limiting disease. It is important to understand the difference between advance care planning and advance directives. Advance care planning is a process whereby individuals consider their end-of-life treatment preferences and make them known to loved ones and health care professionals in the event of decisional incapacity. Components of advance care planning, which the patient may or may not have completed in written form, may include advance care directives, health care proxies or powers of attorney, living wills, and do-not-resuscitate orders. When a patient cannot communicate or loses decisional capacity, a selected health care proxy becomes the surrogate decision-maker. Individuals may formally designate a health care proxy and document end-of-life treatment preferences in an advance directive. An advance directive is a legal document representing a person's preferences regarding their medical care. It may be in the form of a living will, health care proxy, or physician note, which includes the name of the patient's health care proxy. However, the percentage of individuals with a documented advance directive remains low, even in the setting of serious illness such as advanced cancer, where documentation rates are 20%.[42] When these documents exist, they can be used as the basis of discussion about the patient's values and preferences for end-of-life care. When they have not

been completed, the oncologist can enlist the assistance of an appropriate individual (e.g., a social worker or member of the palliative care team) to help the family complete forms, after he/she has introduced the concept, explained the purpose, and discussed the benefits and process of advance care planning with the patient and any relevant family members or caregivers. In many cases, the patient with very advanced cancer may lose decisional capacity; here, an assessment should confirm this status, and, thereafter, a surrogate should be identified. Options for palliative care, including hospice, should be described at this time. Conversations should elicit the patient's and family's values, feelings, and preferences with respect to decision-making about end-of-life care.

Good communication in palliative and end-of-life care should begin with (1) assessment of the patient's and family's understanding of the likely course of the disease, the patient's capacity for decision-making or need for a surrogate, and the patient's and family's communication style; (2) clarification of how much information the patient would like and how much information should be given to the family; and (3) discussion of the patient's and family's preferences for care and quality of life. This approach, which emphasizes "asking permission" before embarking on a difficult discussion or addressing an important topic, is an important step to help in rapport-building and keeping communication lines open.[43] It should initiate an ongoing process of clear and consistent discussion with the patient and family regarding treatment, changes of status, prognosis, end of life, and patient and family needs. Timely advance-care planning discussions and readdressing of planning needs during disease transitions remain major predictors of aggressiveness of end-of-life care and hospice utilization, further reinforcing the role of these conversations in optimizing appropriate, patient-centered advanced cancer care.[44] When appropriate, the palliative care team and/or hospice clinicians can assist with these conversations.

Evidence demonstrates that many patients with metastatic cancer incorrectly perceive chemotherapy as being likely to cure them of disease, reflecting the gaps between clinicians' intentions and patients' perceptions. Underscoring this, a study from Weeks and colleagues demonstrated that more than 50% of patients with metastatic colon and lung cancer perceive their chemotherapy as being likely to cure their disease.[45] Discussing intent and potential benefits of cancer-directed therapies should be considered an integral component of the informed-consent process, alongside the usual conversations about risk and potential side effects of antineoplastic therapy.

Physicians sometimes unknowingly provide an overly optimistic evaluation of a patient's prognosis[46,47] or, alternatively, provide no prognostic information until the patient nears death.[48,49] Additionally, patients often interpret prognostic information in an optimistic way; many patients exhibit a tendency to believe that they will be an exception, the one to "beat the odds."[50] Patients' perceptions of prognosis and their choices regarding therapy are demonstrably influenced by the way in which they receive information from their physicians.[51,52] Information presented from a positive perspective (such as percentage of patients with a given condition who survive to the 5-year point) is perceived to be better than the same information delivered in negative terms (such as percentage of patients with this same condition who do not survive to 5 years). Patients who harbor falsely optimistic perceptions often opt for aggressive medical therapy, despite evidence that aggressive care—compared with palliative measures only—confers no survival benefit for terminally ill patients.[53]

Many physicians express concern that an accurate prognosis may undermine a patient's hope.[54,55] The value of hope is rated very highly by both patients and caregivers, who emphasize that they do not want doctors to lessen hope, even at the end of life.[56,57] In terminal

illness, however, physicians can redefine hope—without implying a cure—by helping patients come to a realistic understanding of their prognosis and by setting realistic goals, such as reduction of pain, alleviation of distress, and achievement of closure with family members.[41] Similarly, many people worry that an accurate prognosis will diminish the patient's "fighting spirit," especially when there is coexisting depression. Although it is essential to address any presenting psychiatric illness, little evidence exists to suggest that a "fighting spirit" improves morbidity or mortality.[58] In reality, many patients struggle to cope with news of a poor prognosis; this struggle is often apparent in seemingly contradictory expressions of unrealistic hope for longevity alongside awareness of prognosis (e.g., by discussing funeral plans).[59]

Although most guidelines for delivering bad news to patients and families do not have empirical evidence to support their use, they are based on viable communication principles and consensus expert opinion, and, therefore, have good face validity.[60,61] A formal discussion of bad news might best be preceded by thorough preparation. Clinicians should discuss how patients would like to receive prognostic information (and whether they actually desire it) before starting any conversation involving bad news. The physician should consider that patients and families hold different views about who should participate in such discussions, what information should be included, the appropriate setting, and who should convey the information. Clinicians should ideally endeavor to be prepared with accurate, up-to-date information and to deliver the news themselves. Communication techniques that convey compassion and alignment with the patient's feelings of disappointment with bad news should be used. Phrases such as "I wish things were different" and "We are in a different place" are useful ways to express alliance with the patient and a potential need for transition in the goals of care.[62] If possible, the setting should be private and free from distractions, and the oncologist should be seated.[60]

To evaluate the patient's and family's levels of understanding and to anticipate their reactions, the clinician should initiate any discussion of bad news by inquiring about what they already know and what they want to know. This enables the patient and family to determine the level of information they seek and how to best convey that information. The physician can then deliver the information but should pause frequently to verify understanding and to allow for questions; a reasonable approach is to provide no more than three items of information before pausing to ensure that the patient and his or her family understand and do not have questions. At the end of the discussion, the clinician should confirm that the patient and family have a sound understanding—for example, by asking them to summarize the information in their own words. Finally, a clear agenda should be established, covering what the patient and family will do, what the physician will do, and when the next contact will occur.

Cross-cultural reviews have helped expand the literature related to communication in palliative and end-of-life care; these perspectives are particularly relevant to clinicians treating increasingly heterogeneous populations. An Indian review reported on collusion in palliative care communications resulting in, for example, nearly half of patients with cancer in India being unaware of their diagnosis and treatment.[63] Similar cultural norms with respect to truth-telling and withholding of information have been reported in Chinese culture.[64] In both instances, strong family values include a central role for family members in managing the patient's disease, communication, and health care at or near the end of life. Of relevance to the U.S. oncologist, these studies suggest the importance of (a) being aware that patients with a background in other cultures may have different expectations for communication, and (b) explaining and discussing the communication plan with the patient and family members to establish common expectations. Be sure not to make any assumptions about how much or how little a patient wants to know based on his or her cultural background. Inquiry is key. Where

available, an interpreter or other cultural liaison may be of help in facilitating effective communications.

PSYCHOLOGIC DISTRESS

Patient

Death is a process fraught with emotion for patients as well as for family members, other informal caregivers, and health care providers, all of whom have a unique relationship to the dying patient. Although psychosocial concerns frequently occur at the end of life, they can be difficult to detect or diagnose. Certain psychological states that may resemble depression are, in fact, normal at the end of life; physical symptoms normally experienced by the patient at the end of life may otherwise constitute somatic diagnostic criteria for psychiatric illnesses. Nevertheless, health care clinicians must remain vigilant for signs and symptoms of distress, which include concerns about illness, sadness, anger, feelings of loss of control, poor sleep, poor appetite, poor concentration, and preoccupation with thoughts of illness and death. Awareness of psychological concerns takes on greater importance for clinicians treating patients who are terminally ill, for whom psychological distress may increase as death approaches.[65]

It is estimated that as many as 82% of patients who are terminally ill experience some form of psychiatric illness,[66,67] including adjustment disorder (10 to 16%),[68,69] depressive disorders (3 to 82%),[68,69] and anxiety disorders (7 to 79%).[66,69] Risk factors for distress in patients with cancer include cognitive impairment, communication barriers (e.g., language, literacy), history of psychiatric disorder, history of substance abuse, history of depression or suicidality, psychosocial issues (e.g., family conflict, young/dependent children, limited social support, living alone), financial concerns, and uncontrolled symptoms.

Although the end of life is frequently marked by psychiatric symptoms, physicians often struggle to address emotional concerns during the medical interview. Many physicians report feeling uncertain about their ability to effectively discuss emotional topics, especially those that accompany bad news.[60,70] Reimbursement restrictions and the typical structure of the medical interview further discourage some clinicians from freely discussing psychosocial issues.[71] Physicians often fear that discussions that address emotional content will take too much time or elicit powerful feelings that the patient will be unable to manage. The evidence, however, should dispel this concern: research demonstrates that medical encounters are shorter when the physician openly acknowledges the patient's emotional concerns.[72]

Distress in patients with advanced cancer can be identified using a simple screening tool such as the NCCN Distress Thermometer (Fig. 22-2), which asks the patient to rate his or her distress on a 0 to 10 visual scale from "no distress" (0) to "extreme distress" (10). Many other distress assessment instruments exist; one systematic review identified 33 instruments of varying lengths examined in 106 validation studies. In patients receiving palliative care, the Combined Depression Questions performed best of the ultrashort measures (1 to 4 items). Among the short instruments (5 to 20 items), the Hospital Anxiety and Depression Scale (HADS) and the Center for Epidemiologic Studies—Depression Scale demonstrated adequate psychometric properties. Long instruments (21 to 50 items) are also available but are often less clinically feasible in the palliative care setting; ones exhibiting robust psychometrics are the Beck Depression Inventory (BDI), General Health Questionnaire—28, Psychosocial Screen for Cancer, Questionnaire on Stress in Cancer Patients—Revised, and Rotterdam Symptom Checklist.[73]

For patients who report significant distress, appropriate referral to psychiatric care, psychotherapy, counseling or social work services, and/or chaplaincy is warranted.

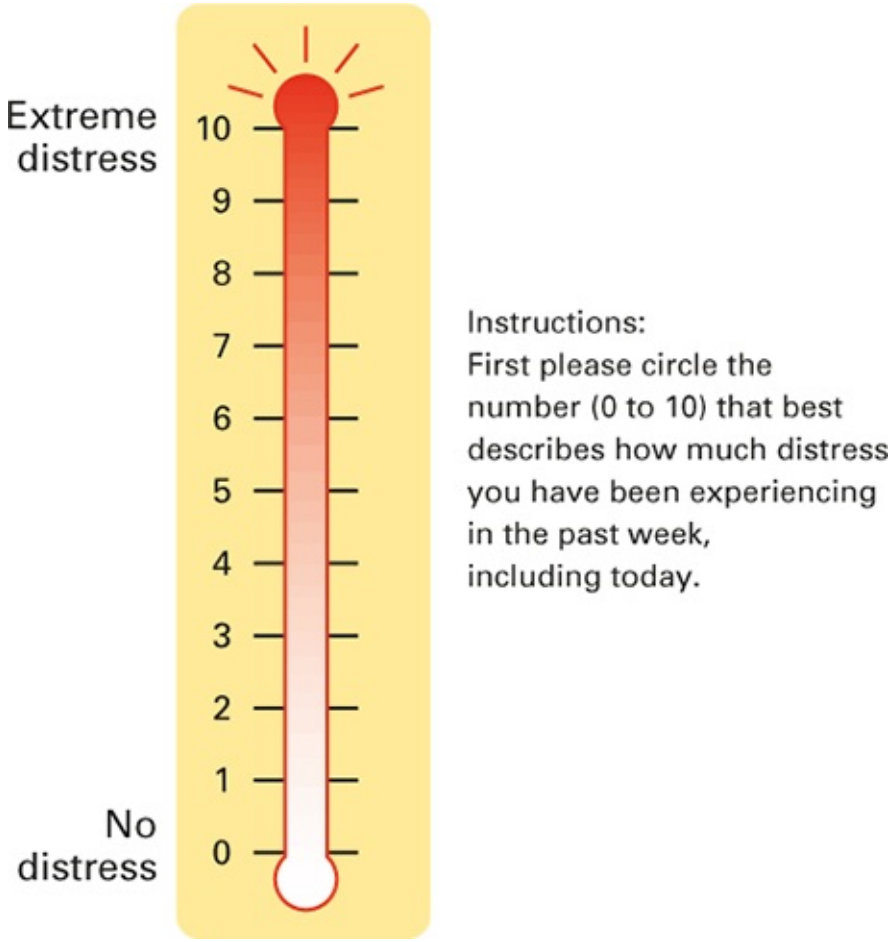

Fig. 22-2 National Comprehensive Cancer Network Distress Thermometer.

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Caregiver/Family

Psychosocial problems are not limited to the patient with a terminal illness. Studies have found that 32 to 70% of caregivers (primarily family members, but also including other informal caregivers) of patients with advanced cancer experience a level of distress or depressive symptoms high enough to suggest clinical depression.[74-76] Caregivers often are unprepared for the various commitments—financial, emotional, and physical—that are involved in caring for a dying loved one.[77] Furthermore, many caregivers lack the medical knowledge and skills necessary to anticipate the needs of the patient. Because of the multiple demands of caregiving, family members often are forced to leave their jobs or to work part-time, which adds financial stress at a time that is already emotionally challenging. Moreover, by attending to the needs of their dying loved one, caregivers often neglect their own health and emotional needs.[78]

Certain characteristics of caregivers are associated with negative effects of caregiving. These include age of the caregiver, ethnicity, sex, socioeconomic status, and caregiver health and functional status. Younger, nonwhite, female, and less affluent individuals tend to experience greater negative effects such as distress or depressive symptoms. Other factors associated with negative effects include the duration and intensity of caregiving, mood and

physical health of the caregiver, a recurrence of the patient's illness, and the caregiver's subjective sense of burden.[79]

Providing effective symptom relief is a primary way in which physicians can help both caregivers and patients who are terminally ill.[80] Just as treating depression can improve pain control, control of both pain and nonpain symptoms has been shown to help alleviate or prevent depression.[81,82] Patients who have higher levels of symptom distress or depression are more likely to have caregivers with greater depressive symptoms and negative perceptions of their own health.[83-85] When a patient who is terminally ill experiences a reduction in distress, it also can help decrease the caregiving burden and the psychological effects of terminal illness on caregivers.

Support of caregivers has become an important topic within oncology. The latest data report that as many as 40% of all U.S. adults are now caring for a sick or elderly family member.[86] These caregivers are having important effects on the treatment and outcomes of the patients they care for. For example, one retrospective cohort study of a large cancer registry by Aizer et al.[87] showed that patients with spouses were less likely to present with metastatic disease, more likely to receive curative therapy, and less likely to die from cancer after adjusting for demographics, stage, and treatment. Another study demonstrated that the quality and frequency of interactions between patients and caregivers predicts hospital readmission—an important measure of care quality.[88] Further, Dionne-Odom et al.[89] demonstrated the benefits of caregiver support through palliative care, noting improvements in depression and stress burden when clinicians focus on the caregiver's needs early in the care of patients with advanced cancer. Because many patients with advanced cancer experience an unplanned hospital admission in the last months of life, caregiver support is increasingly recognized as a way oncology teams can further patient-centered, resource-efficient care.

In offering supportive care at the end of life, the clinician exerts a powerful therapeutic effect simply by being present. By being available, by communicating openly about difficult topics, and by addressing symptoms that are causing distress, the physician can provide significant support. Caregivers particularly value the support and respect of their health care providers; those who report that physicians listen to their opinions and concerns are less likely to report depressive symptoms.[90,91] Good communication, which includes anticipatory guidance and clear explanations of what to expect, is an essential therapeutic tool. By providing appropriate referrals to assistance agencies, such as hospice, physicians can greatly support family members.[92] In all cases, effective communication, listening, and availability contribute substantially to alleviating suffering at the end of life.

SPIRITUAL/EXISTENTIAL SUFFERING

As the patient nears the end of life, the spiritual needs of the patient, family members, and other caregivers typically become heightened. Good care of the spirit is essential to high-quality end-of-life care. Care of the spirit involves helping the patient and loved ones address existential issues that may occur, such as "Why me?", "What is the meaning of life?", "Why am I here?", "What have I achieved in my life?", "How do I fit into the universe?", and "What will happen to 'me' after my death?" The clinician should recognize that the spiritual belief systems of all parties concerned, as well as their personal belief systems regarding our spiritual nature, will influence how they react to these broad spiritual questions.

Although physicians typically are not trained to provide spiritual care, patients and families often assume that their health care professionals will be able to adequately introduce and

discuss issues surrounding care of the spirit. Many people consider an expected death to be a valuable opportunity to address any outstanding spiritual issues, and they expect that this work will take place in the context of their loved one's medical care. Yet, for many clinicians, the prospect of providing spiritual care to someone at the end of life presents a formidable challenge.

Oncologists may tend to refer to a patient's, family's, or caregiver's belief system (e.g., religious affiliation) to evaluate their orientation toward spirituality, life, dying, and death. However, although patients may name a particular belief system, one cannot assume that particular interpretations or beliefs apply, even if they are commonly associated with the declared religion or belief system. Although a religion may provide a broad frame of reference for a person's beliefs, it cannot supply the detail required to understand the ways in which a patient may respond to arising spiritual concerns or to determine how to best support him or her with spiritual care. Belief systems may help structure broad conversations that occur around life and death; however, clinicians should remember that spirituality and religion are different. A patient need not adhere to any system of belief to successfully resolve existential or spiritual issues. One also must recognize that belief systems may either relieve or worsen anxiety and fear as death approaches. Both fear induced by a lack of faith and fear of losing faith in the face of the unknown can exacerbate anxiety. At times, a patient's belief system is tested at the end of life either by the disease (e.g., "Only bad people get this disease, and I have been good") or by the mode of death (e.g., "No one should suffer like this").

Cancer care at the end of life, perhaps more than in any other phase of the illness, involves multidisciplinary efforts. Each member of the end-of-life care team must possess the key competency of being comfortable with exploring and discussing spiritual issues. Because spiritual concerns may be broached by patients and their families at any time, each care team member should be ready and able to discuss spiritual care, both in a manner appropriate for the specific context and professionally. Although certain issues may need to be referred to an appropriate person in the pastoral care team, many spiritual issues can be explored safely by the team member with whom they are first raised. To be able to converse meaningfully with patients about their beliefs and concerns, clinicians must themselves have contemplated the important spiritual and existential questions. During spiritual conversations with patients, however, clinicians should not attempt to share their own perspectives; rather, the clinician's attention should be on trying to understand the depths and nuances of the patient's orientation toward this potentially complex area of life. This understanding will assist clinicians in identifying needs that other professionals (e.g., chaplains, psychotherapists) should address; the oncologist's responsibility is to guide the delivery of compassionate care and to incorporate insights about the patient's spiritual/existential status into clinical decisions so as to best treat the patient as a whole person.

Many people, especially in developed nations, encounter death infrequently; they may even be well into adulthood before they are first confronted by death. As a person observes the death of a loved one, especially when it is the first time they have witnessed this process, his or her reckoning with mortality can be profound. This personal experience can manifest in a variety of emotions such as anger, fear, or powerlessness. At times, these feelings can be directed toward clinical staff as well as toward family members, the dying person, a deity, or some other construct. As death nears, many patients are forced to confront questions that they might otherwise prefer to ignore. Chief among these are questions concerning the nature and purpose of suffering and the injustice of a painful or premature death.

As patients articulate their beliefs and interpretations about spiritual issues with family

members, the emotional rawness of dying and death can become magnified. A family's long-ignored or contentious issues often emerge at this time. When these situations arise, clinicians can help by refocusing family members on the real purpose of spiritual care: to support patients as they explore and express their spirituality at the end of life, to the extent that they wish and in the manner most meaningful and comfortable for them. Avoid focusing on answers and simply listen and validate. Containing or managing family conflict is crucial to ensuring that patients can approach death with calm and in a context of full support for their medical, psychosocial, and spiritual needs.

Many people value the opportunity to make peace with God, the universe, a deity, or a belief system as death approaches. Those who are dying, their families, and caregivers will appreciate the clinician's efforts to ensure that they have the space, quiet, encouragement, and support to explore spiritual issues that are important to them.

DEPRESSION

Identifying and differentiating between preparatory grief and depression in patients who are dying can be quite difficult, even for seasoned clinicians. In general, depressed patients tend to remain in a persistent state of sadness, to have a poor view of themselves, to sustain a sense of hopelessness, and to derive little pleasure from new situations or from memories of past events.[93,94] By contrast, patients with normal grief reactions typically experience a progression of feelings, are able to maintain a realistic view of themselves, and can modify their health care goals to maintain hope. Diagnosing depression at the end of life is of paramount importance; studies have demonstrated that untreated depression results in an increase in morbidity and sequelae, including suicide. Depression, as well as hopelessness, loss of meaning in life, and loss of interest in activities, ranks among the risk factors for the desire to hasten death.[41,95] Patients whose psychosocial needs are acknowledged are less likely to persist in their desire for death.[96] When a patient expresses a desire to hasten death, requests should be addressed explicitly and should prompt a reassessment of symptom control, psychosocial issues such as relationship strain or fear of caregiver burden, spiritual/existential suffering, and psychological issues such as depression. The care plan should be clarified with renewed attention to how best to relieve physical, psychological, interpersonal, and spiritual suffering.[10]

Studies in patients with cancer at the end of life report prevalence rates of general depression and depressive mood ranging from 21 to 37%.[67,97] The median prevalence of major depressive disorder in patients with advanced cancer has been reported to be 15%.[98] Several instruments have been created or adapted to help identify depression in the terminally ill. Well-recognized and validated instruments include the BDI-Short Form (BDI-SF),[99] HADS,[100] Edmonton Symptom Assessment Scale (ESAS),[101] Edinburgh Depression Scale, and Brief Edinburgh Depression Scale (BEDS).[102] Considerable efforts have been devoted to developing simple one- and two-item verbal screens for depression, but a Bayesian meta-analysis has found that, although these brief methods perform well at excluding depression in the nondepressed person, they perform poorly at identifying depression; two-item measures are superior to single-item screens, but neither is sufficient for depression assessment.[103] Oncologists may elect to use these brief assessments for convenience and as an initial screen but should not rely exclusively on them. Assessment for symptoms of depression in patients who are terminally ill is a critical component of care and warrants a more thorough assessment using a well-validated instrument.

Guidelines established for the general care of psychiatric illness may be applied to the

treatment of depression for patients who are terminally ill, but with certain adjustments. Referral should be made to an appropriate clinician, ideally a palliative care expert, psychiatrist, or psychologist with expertise in management of psychological disorders who can tailor care to this stage of illness. Treatments, particularly pharmacologic therapies, must take into account the patient's prognosis. For example, when the patient has a limited life expectancy, selective serotonin reuptake inhibitors may not exert an effect quickly enough; psychostimulants may offer a more realistic treatment strategy.

DELIRIUM

Characterized by disturbance of consciousness, cognition, and perception, delirium occurs in 28 to 83% of patients as death approaches; it often provokes considerable distress among patients, families, caregivers, and medical providers who are witnessing the patient's transition toward death.[104,105] Delirium is generally an indirect result of various factors associated with the patient's underlying cancer, such as adverse treatment effects, metabolic disorder, nutritional deficiency, or infection; adverse effects of medications seem to be the most common cause of delirium for patients near the end of life.[106]

Three types of delirium are observed in the palliative care population: agitated/hyperactive delirium, hypoactive delirium, and terminal delirium (also referred to as "terminal agitation"; see the section on "Management of the Last Days of Life"). In contrast to hyperactive delirium, hypoactive delirium is underrecognized, as patients may experience auditory or visual hallucinations, but may remain quiet about them. In each case, onset is signaled by an acute change in the patient's level of arousal, which can manifest as disorientation, visual or auditory hallucinations, a change in speech patterns, memory or language alteration, or upset of the sleep/wake cycle. Symptoms typically wax and wane over time.[107]

For clinical diagnosis, delirium is assessed at the bedside using instruments such as the Delirium Rating Scale,[108] Confusion Assessment Method,[109] Delirium Symptom Interview,[110] Memorial Delirium Assessment Scale,[111] or the more general and widely recognized Mini–Mental State Examination.[112]

To manage delirium, the first step is to screen for and treat any underlying reversible causes; these may include CNS events, bladder outlet or bowel obstruction, hypoxia, metabolic disorder, and medication/substance effects or withdrawal. If these potential causes are ruled out, the clinician typically discontinues all medications (especially psychoactive ones) that are not necessary and not associated with an acute withdrawal syndrome. Reorienting the patient to time and place, ensuring that family and other familiar individuals are available, and restoring normal surroundings and routine can be very helpful. Thereafter, the goal of treating delirium is to restore patients to a condition that more closely reflects their baseline mental state, rather than to suppress agitation or to sedate them.[113] For patients receiving palliative care, intravenous or oral haloperidol is the drug of choice and is titrated upward, as necessary, from a starting dose of 0.5 mg twice daily; haloperidol's antiemetic effect can have supplemental benefits. For more severe delirium or persistent symptoms despite haloperidol, alternative agents include olanzapine (2.5 to 7.5 mg/day every 2 to 4 hours as needed or 5 to 20 mg/day PO/SL) or chlorpromazine (25 mg to 100 mg/day PO/PR/IV every 4 hours as needed); for mild to moderate delirium, alternative agents include risperidone (0.5 to 1.0 mg PO twice daily), and quetiapine fumarate (25 to 200 mg PO/SL twice daily).[10] However, data do not suggest that these medications are more effective or safer than haloperidol, and they are generally more expensive. Though they may help calm the delirious patient, benzodiazepines (e.g., lorazepam,

midazolam) are generally avoided because they can worsen delirium by further sedating and disinhibiting the patient or by causing agitation.

The effectiveness of medical approaches may be enhanced by the presence of family and friends, familiar surroundings, consistent care staff, and a tranquil setting. Satisfactory management of delirium results in adequate control of delirium symptoms, reduction in patient and family distress, regaining a sense of control, relief of caregiver burden, and improved quality of life. Reassessment should be iteratively conducted to ensure ongoing and adequate management of this troubling symptom.

KEY POINTS

- Although psychologic distress is normal among patients who are terminally ill, clinicians should remain alert for signals of true psychiatric illness.
- A majority of patients who are dying experience psychologic distress. Physicians must be prepared to address related issues using both medical and psychosocial means and to make appropriate referrals.
- Clinicians should be adequately conversant in spiritual matters but should primarily adopt a stance of listening, understanding, and supporting spiritual exploration. Appropriate referrals can be made when the patient is receptive.
- Depression is characterized by a persistent set of emotional symptoms, negative self-analysis, and a lack of pleasure and hope. Identifying and treating depression and its sequelae are important for reducing end-of-life morbidity as well as the desire for hastened death.
- Delirium is frequently a source of great distress for the patient, his or her loved ones, and the care team. The clinician should screen for and treat any underlying reversible causes.

MANAGEMENT OF THE LAST DAYS OF LIFE

Clinicians should actively recognize the process of dying as a result of cancer. The diagnosis is supported by a continued deterioration of a person's overall condition, with increasing lethargy, decreasing levels of consciousness, and at times, increasing confusion, increasing time asleep, less spontaneous movement, decreased urinary output, inability to regulate body temperature, and changes in patterns of respiratory effort (e.g., Cheyne–Stokes breathing). For many people, systemic signs can include progressive hypotension, diminishing oxygenation, and progressive loss of peripheral perfusion causing mottling of the skin. Researchers have identified a "top eight" list of signs of impending death—nonreactive pupils, decreased response to verbal stimuli, decreased response to visual stimuli, inability to close eyelids, drooping of the nasolabial fold, hyperextension of the neck, grunting of vocal cords, and upper gastrointestinal bleeding.[114] Given the unfamiliarity of caregivers with the signs and symptoms of the dying process, it is critical to share information and educate them so as to minimize fear and anxiety. Frequently, hospice programs will have an informational brochure or handout that can be shared with loved ones who are interested. Alternatively, the terminal phase of cancer may be signaled by a sudden change in condition: an intracerebral bleed, a pulmonary embolus, a perforated viscous, or overwhelming sepsis. When this change is superimposed on an already moribund

condition, continued symptom control becomes the primary goal. Understanding patients' wishes—often through conversations they have had with their families both throughout the course of their illness and during the course of life—will help determine the best course of action. Many people, in the event of a catastrophic change in their condition, may wish to focus on comfort; others may wish to try to achieve functional improvement, however limited at this phase of life.

Whether the end of life approaches as an expected deterioration or as an unexpected catastrophic decline, the issue of comfort is paramount. Clinicians should ensure that all clinical actions contribute to the comfort of the person who is dying.

NURSING CARE

Attention to the nursing care of the dying patient is crucial. Regular check of vital signs should be replaced, at this stage, with regular (e.g., every 4 hours) check of symptoms. Mouth care, to ensure that the dying person's mouth is clean and moist, will aid comfort. Eyes can also can become dry and painful and may require additional supportive measures such as eye lubricants and/or drops. Proper skin care includes regular repositioning of the patient to relieve musculoskeletal pain from inertia and to avoid the excruciating (and difficult to control) pain of skin tears and pressure sores. Use of a pressure-relieving mattress is advised. An air mattress will facilitate shifting of the person's weight. The head of the bed can be elevated to help reduce noisy upper respiratory tract secretions. Urinary retention and fecal impaction should be evaluated, and treated if present.

TERMINAL SECRETIONS

Noisy ventilation ("death rattle" or "terminal secretions"), caused by oscillatory movements of accumulated bronchial mucosa and salivary secretions, is common among patients who are dying and are unable to clear secretions by coughing or swallowing.[115] The symptom usually occurs after patients are unconscious, although it may nonetheless cause considerable distress to families and caregivers. Previous observational studies have estimated that death rattle occurs in as many as 92% of patients who are unconscious and dying.[116]

Intervention to reduce secretions is often instituted to alleviate the distress of attendant family members, even when the patient seems settled. Standard nonpharmacologic practices for alleviating death rattle include suctioning, positioning (reverse Trendelenburg), reducing parenteral and enteral fluids, and explaining to the patient's family or other caregiver(s).

The mainstay of the pharmacologic management of death rattle are anticholinergic agents, also known as muscarinic receptor blockers.[115,117] These drugs include scopolamine, hyoscyamine, glycopyrrolate, and atropine. The primary difference in these drugs is whether they are tertiary amines that cross the blood–brain barrier (scopolamine, atropine) or quaternary amines, which are less likely to do so (e.g., hyoscyamine, glycopyrrolate). However, all these drugs have the potential for central and peripheral anticholinergic side effects, including, but not limited to, delirium and urinary retention, which need to be monitored closely. Atropine, a widely available drug, is frequently used in home care for the treatment of death rattle; a common approach is 1% atropine ophthalmic solution, 1 to 2 drops SL every 4 hours as needed.[10] Scopolamine (hyoscyamine hydrobromide), a muscarinic receptor antagonist, has been reported to more potently inhibit production of bronchial secretions and cause less tachycardia.[118] Scopolamine and atropine can cause central effects such as sedation, confusion, or paradoxical excitation, especially in elderly patients. Hyoscine butylbromide, a

semisynthetic derivative of scopolamine, is effective in treating respiratory tract secretions, has peripheral effects similar to scopolamine, and has no central adverse effects.[119]

Some research has been conducted regarding the relative effectiveness and frequency of adverse effects of atropine, scopolamine, and hyoscine butylbromide for treating death rattle in patients who are terminally ill. In an open-label, multisite, prospective, randomized, phase III trial, 333 patients who were terminally ill and had death rattle were randomly assigned to receive 0.5 mg of atropine, 20 mg of hyoscine butylbromide, or 0.25 mg of scopolamine, initiated in subcutaneous bolus followed by continuous administration. In patients across all three study arms, death rattle decreased to a nondisturbing intensity or disappeared after 1 hour in 42%, 42%, and 37% of cases, respectively ($p = 0.72$); effectiveness improved over time without significant differences among the treatment groups.[120] Although to date this is the largest randomized, controlled trial of anticholinergics for death rattle, it has numerous limitations, including its unblinded design, failure to standardize across sites, and lack of a placebo control.[121] Indeed, although other randomized, controlled trials have been few and have had small sample sizes, they have failed to establish the superiority of one drug (including placebo) compared with another.[122] One might conclude, then, that the anticholinergics are equally ineffective in alleviating death rattle. Given the scant and inconclusive evidence, a 2008 Cochrane review, updated in 2010 to include the previous study, advised that clinicians have an ethical obligation to closely monitor patients for lack of therapeutic benefit and adverse effects and to discontinue ineffective or detrimental treatments. More important than treatment with anticholinergics may be discussing death rattle with family members, so as to reduce their distress; these conversations should address cause, implications, and caregivers' fears and concerns.[123]

MEDICATIONS

As the patient nears the end of life, the clinician should review all medications and continue only those that contribute to increased comfort. Similarly, implanted defibrillators, and possibly pacemakers as well, can be deactivated. Diagnostic tests and functions (e.g., transfusions, needle sticks, intake and output, blood glucose monitoring, oxygen saturation monitoring, suctioning) can be discontinued if deemed unnecessary for symptom control and comfort.[10] In deciding which medications to discontinue, all medications should be reconsidered for their benefit to the patient, not only those that were introduced for symptom control in the palliative phase of the illness. For example, for type 1 diabetes, insulin may be necessary to prevent hyperglycemia to spare the patient unquenchable thirst. Essential medications should be obtained in a form that can be administered to someone who may not predictably be swallowing. Alternative formulations include sublingual, subcutaneous, intravenous, transdermal, intranasal, and rectal. Doses of medications retained for symptom management should be increased as necessary to optimize comfort. In general, rather than discontinuing medications, tests, or monitoring devices all at once, consider a stepwise approach, which may feel less shocking and give loved ones more time to process.

OTHER INTERVENTIONS

Nutrition and Hydration

As patients are actively dying, any nutritional supplements and any parenteral hydration should be reviewed. Almost always, parenteral hydration should be stopped, with appropriate advice to the family, because overhydration will worsen respiratory symptoms and enteral fluids will

potentially cause secretions in the gut that may cause vomiting. This requires in-depth conversations with and education of the family and caregivers. Recognize that stopping nutrition and/or hydration can be an emotionally charged issue for loved ones, which may require time to process and extra support from nonmedical colleagues, such as those in social work and chaplaincy, to address emotional and existential-related issues.

Management of Terminal Delirium

Physical agitation can occur in the patient's final days. The clinician should first ensure that this agitation is not a result of pain, urinary retention, or constipation. Terminal delirium (also known as "terminal agitation")—delirium that occurs in the setting of the active dying process—requires a different approach from hyperactive and hypoactive delirium. In this case, benzodiazepines are the drug class of choice to palliate symptoms. When symptoms are severe, sedation may be required through the use of continuous infusion of a benzodiazepine or barbiturate (midazolam or pentobarbital are most commonly used).[124,125] Palliative sedation can be considered if other causes of agitation are ruled out or if agitation persists despite appropriate treatment. Imminently dying patients have a prognosis of hours to days. If palliative sedation is being considered, prognosis should be confirmed by two physicians. First, informed consent should be obtained from the patient or his or her family or another surrogate; this process should involve discussion of goals of treatment, the patient's status, prognosis, and expected outcomes. Family members or surrogates should fully understand that palliative sedation will render the patient unconscious; they should be allowed to voice feelings and concerns related to this scenario. However, palliative sedation should be reserved for the most extreme cases, when the patient and/or family exhibit considerable distress, and implemented in monitored surroundings. As terminal sedation frequently involves the use of medications like midazolam and propofol, palliative care specialists and/or specialists from anesthesia/pain or critical care should be involved if terminal sedation is considered.

Communication with the Family and/or Caregivers

Communication with the family or other loved ones involved in the last stages of caregiving should be a key focus for health professionals as a patient nears death. What does the family expect? How well do they understand the patient's condition and the dying process? A trusted clinician should clearly—but compassionately—describe the process of dying. Patients should be reassured that, in most cases, the person dying gently slips into a coma and life ebbs away with no dramatic manifestations.[126] The clinician should emphasize that, at this important phase, the sole focus of care is the dying person's comfort—and that current medical practice has multiple strategies to optimize comfort.

Management of Care for the Unconscious Patient

Even when a patient is unconscious, clinical staff should carefully assess him or her to ensure comfort. Available tools to assess nonverbal signs of pain include the Assessment of Discomfort and Dementia,[127] Checklist of Nonverbal Pain Indicators,[128] Pain Assessment in Advanced Dementia, Behavioral Pain Scale, and Critical Care Pain Observation Tool.[129] Evaluation cannot be done from the door of the patient's room. An examination is required, with special attention to the face (Is it relaxed?), respiration (Is it regular, not labored?), and positioning (Is the patient positioned comfortably?). The clinician should continue to explain to

the patient what is happening in the clinical examination, as if he or she were conscious; it is important for family members to understand that people, even when unconscious, may still recognize their voices and their touch. The clinician should also reassure the family that symptom-control medications will be continued to ensure the patient's comfort even though consciousness has been lost. There is no concern that these medications will hasten death, especially if continued at the same dose.

Many family members have a strong desire to be present at the time of death. This specific time point can be difficult to predict, even as the patient's body shuts down. The need to be present varies from family to family, and within families, from one individual to another. If family members have a particular wish to be present at the patient's time of death, the clinician may want to set up a vigil roster to ensure that one member of the family is always present during the patient's last days.

HOSPICE AND END-OF-LIFE CARE

Hospice is one of the most effective, yet underutilized resources for patients, families, and oncologists as patients approach the end of life with advanced cancer. Regarding efficacy, consistent data demonstrate the benefits of hospice for patients and caregivers regarding quality of life, symptoms, and depression.[5] Also, hospice increases quality of care near the end of life and reduces overall health care costs.[130] Further data highlight a potential survival advantage, with specific cancers like pancreas and lung cancers demonstrating a survival advantage of weeks to months with even 1 day of hospice, versus none.[131] Some data highlight that despite its existence and availability across most counties in the United States for almost 35 years, referrals to hospice continue to be underutilized for patients near the end of life; when referrals are made they are often late. For example, data from the National Hospice and Palliative Care Organization (NHPCO) reveals that up to 50% of patients have an average length of stay of 3 days or less. When looking at average length of stay, which is affected by outliers, the Centers for Medicare and Medicaid Service hospice data from 2009 show numbers in the range of 37 to 59 days. Further research in this area demonstrates medians near the 3-week mark.[132]

Late referrals to hospice stem from both patient and oncologist factors. A study of patients with advanced lung cancer revealed that only 53% of patients had discussed hospice with their oncologists 4 to 7 months after diagnosis; predictors of not having the discussion involved patients having overly optimistic assessments of prognosis and lacking moderate to severe pain or dyspnea. In other words, patients with a poor understanding of prognosis who feel well often do not bring up hospice to their oncologists, and likewise the topic is not approached by their care team, ultimately leading to delayed referrals.

Hospice Eligibility

Quite simply, cancer patients are eligible for the Medicare Hospice Benefit if two physicians determine that a terminal diagnosis exists and that the average life expectancy of the patient is 6 months or less if the disease runs its usual course. The latter part of this statement is very important, as the "usual course" for any disease is variable. Many times patients are admitted to hospice for a total of more than 6 months; errors in prognostication are not red flags to Medicare, nor do they highlight any errors on the part of the admitting physicians as long as proper documentation regarding the expected course is in place.

Up to 90% of hospice participants elect to use the Medicare Hospice Benefit, an earned

benefit as part of Medicare Part A, to pay for hospice. Patients who use their Part A Benefit for other purposes, such as an acute hospitalization or active rehabilitation within a skilled nursing facility cannot simultaneously be enrolled in hospice. This leads to quandaries when patients are seeking an approach focused on care near the end of life, but are reliant on the 24-hour caregiving services or are interested in the intensive physical rehabilitation provided in skilled nursing facilities.

Lastly, there remains a common misperception regarding the need for patients to have a "Do Not Attempt Resuscitation" order in place prior to referral to hospice. In fact, there is no stipulation of this to participate in residential hospice under Medicare, and further the coercion of patients into a particular resuscitation status can lead to immense penalties for individual clinicians and their organizations. It remains extraordinarily important to speak with patients and their families about decisions for care during times of crisis or near the end of life, but oncology teams must remain agnostic as to the outcome while using a truly shared decision-making approach.

Hospice Care Provision

There are approximately 6100 hospices in operation in the United States, covering all 50 states and most territories. Most are independent and free-standing agencies not restricted to serving patients of any particular nursing home, hospital, or home health agency. Hospices are required to provide six foundational services in participating in the Medicare Hospice Benefit, including physician medical director, nursing services, social work services, spiritual support, bereavement support, and volunteers. These services are provided along the spectrum of hospice care, often beginning with a comprehensive assessment of needs during the admission process, with frequent reevaluations of needs along the trajectory of care. Integral to this care is the role of the oncology team, who are considered partners in the patient's care. As an example of this, with the right billing and coding approach, oncology practices can be paid for seeing patients who are receiving hospice care, truly reflecting a concurrent care approach.

Many patients with cancer hold an incorrect understanding of hospice as a "place to go," instead of a type of care optimized to patient and family needs near the end of life. The most recent data from the NHPCO highlight that up to 60% of patients die in their own residence, including home or long-term care facility.

Course of Care

Hospice is generally provided within one of four levels of care: Routine Home Care, Continuous Home Care, General Inpatient Care, and Inpatient Respite Care. The majority of patients (>90%) receive Routine Home Care, residing in their usual place of residence with a focus on preventing crises and being in familiar surroundings. Within Continuous Home Care, the hospice team comes to the residence to provide brief and continuous crisis-directed care, to make the patient comfortable and avoid visits to the emergency department or hospital. General Inpatient Care is used when acute crises, often in the last few weeks of life, cannot be managed at home and require admission to a special hospice facility or through contracted beds in an acute care hospital. Lastly, Inpatient Respite Care is a time-limited admission to an approved facility to allow caregivers some time away and respite.

CARE AFTER DEATH

The clinician's role does not end immediately upon the death of the patient. Follow-through with the patient's body, logistical considerations, and family members and other caregivers are crucial last steps in end-of-life care. The clinicians and medical staff involved in the patient's end-of-life care should reflect upon the quality of the patient's death, with a "good death" defined as one that minimized distress and suffering for the patient, family members, and other caregivers; honored the patient's and family's desires; and upheld standards of care clinically, ethically, and culturally.[10]

Immediately after the patient's death, the clinician should allow the family time with the body, if they so desire. Treatment of the body should be respectful and culturally sensitive. If not addressed previously, plans for eye donation (allowable in many cancers except some leukemias and eye malignancies) and autopsy are discussed, addressing any family member or caregiver concerns. The clinician files a death certificate, completes any other required forms, and conveys information to the funeral director as needed. Additionally, he or she should inform the patient's other health care providers of the death.

Attention should be directed to family members and other caregivers. The normal bereavement process should be described to them; information regarding available bereavement support should be provided, and referral can be made to appropriate services. Palliative care providers can help the oncologist identify family members who may be at risk for complicated bereavement, and they can follow through with requisite care. Formal expressions of condolences on the patient's death, such as with a card, phone call, or brief letter, can be immensely meaningful and supportive to family members and caregivers.

KEY POINTS

- At the very end of life, the patient's comfort should be the primary focus. Unconscious patients should be treated with the same degree of care, concern, and communication as conscious patients.
- Physical care should address mouth care and musculoskeletal positioning, with attention given to maintaining skin integrity and comfort.
- Terminal secretions can be addressed with the careful administration of anticholinergic agents, as well as with attentive nursing care, positioning, and suctioning.
- All medications, medical interventions, nutritional supplements, and hydration efforts should be reviewed in order to continue only those that directly contribute to comfort.
- If agitation occurs, clinicians should determine the source, if possible, and address appropriately.
- The wishes of family members with regard to being present at the time of death should be respected and facilitated to the greatest degree possible.

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127. Kovach CR, Noonan PE, Griffie J, et al. The assessment of discomfort in dementia protocol. *Pain Manag Nurs.* 2002;3:16–27. PMID: 11893998.
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SELF-EVALUATION

1 EPIDEMIOLOGY AND PREVENTION

SELF-EVALUATION

1. EPIDEMIOLOGY AND PREVENTION QUESTIONS

1-1 A study in the *Journal of Clinical Oncology* focused on patients with stage III colon cancer who were randomly assigned to two different adjuvant chemotherapy regimens and followed for disease recurrence and death. The study queried 1038 patients in the trial regarding the use of multivitamins and found that 49.9% reported taking multivitamins during adjuvant chemotherapy treatment. The use of multivitamins, compared to non-use, was not associated with disease-free survival or overall survival.

What kind of study is this?

A. Case–control study
B. Cohort study
C. Cross-sectional study
D. Randomized trial

1-2 A study is conducted to determine the effect of emotional stress on the risk of breast cancer. Interviews are sought with 208 patients with breast cancer and also with 208 controls. All participants are asked to complete well-validated questionnaires to measure emotional stress. Of the 208 patients with breast cancer, 181 (87%) complete the questionnaires and 39% of them are found to have significant stress. Among the controls, 124 (60%) complete the questionnaires and 29% of them are found to have significant stress. The researchers conclude that emotional stress is associated with breast cancer risk.

Of what type of bias may this be an example?

A. Lead-time bias
B. Recall bias
C. Protopathic bias
D. Selection bias
E. Healthy worker bias

1-3 We have made significant progress in reducing the incidence rates of a number of cancers. However, for which of the following cancers are the incidence rates continuing to rise in the United States?

A. Lung cancer
B. Colon cancer
C. Gastric cancer
D. Esophageal adenocarcinoma

1-4 Racial disparities or differences in incidence and/or mortality for specific cancers

between different racial groups are a focus of concern and epidemiologic research. In particular, blacks in the United States frequently have worse mortality outcomes for many cancers as compared to whites for a variety of reasons.

For which of the following do blacks have worse outcomes than whites?

A. Prostate cancer
B. Breast cancer
C. Multiple myeloma
D. All of the above

1-5 A total of 100 patients are screened for cancer using a newly developed test with the following results:

- 8 results are true positives
- 1 result is a false positive
- 1 result is a false negative
- 90 results are true negatives

Which of the following formulas gives you the specificity of the test?

A. 90 divided by (1 + 90)
B. 8 divided by (1 + 90)
C. 90 divided by (90 + 8)
D. 8 divided by (8 + 1)

1-6 When a heavy smoker discontinues smoking, it can take 10 or more years before his or her risk of lung cancer begins to fall significantly.

What is the most likely explanation for this?

A. Cigarette smoke contains tumor initiators.
B. Cigarette smoke contains tumor promoters.
C. Cigarette smoke contains nicotine.
D. Cigarette smoke contains acetone and benzene.

1-7 It is estimated that infectious agents have currently been identified as the etiologic factors for about 20% of cancers worldwide. As a result, vaccinations, as have been introduced for human papillomavirus, will prevent certain cancers in the future.

Which of the following cancers will remain stable in incidence in the future?

A. Cervical cancer
B. Anal cancer
C. Rectal cancer
D. Oral cancer

1-8 Racial disparities in outcomes between blacks and whites have been of significant concern for a large number of malignancies for the past two decades. These differences may, of course, reflect a variety of etiologies, but the one that seems most important across the spectrum of cancer types is:

A. Genetic polymorphisms associated with African descent
B. Differences in access to care
C. Tolerability of chemotherapy related to ethnic neutropenia
D. Cultural differences in acceptance of offers to enter clinical trials, when available

1. EPIDEMIOLOGY AND PREVENTION RATIONALES

1-1 B

A cohort study is a study in which two groups are compared on the basis of an exposure of interest to determine whether there is an association between the exposure and the outcome of interest. In this example, the exposure is multivitamin use, and the outcome is survival. The randomization to the chemotherapy regimens was just the backdrop to the multivitamin exposure and was not directly related to the cohort study.

Suggested Reading

Ng K, Meyerhardt JA, Chan JA, et al. Multivitamin use is not associated with cancer recurrence or survival in patients with stage III colon cancer: findings from CALGB 89802. *J Clin Oncol*. 2010;28:4354–4363. PMID: 20805450.

1-2 D

Studies are subject to a number of biases. This is an example of selection or volunteer bias—not everyone who was eligible for the study participated, and participation was significantly different between the cases and the controls in ways that could certainly have affected the results. Lead-time bias is usually important in screening studies and reflects earlier detection because of screening, something not relevant in this context. Recall bias would be differential response to a questionnaire by someone with the disease as compared to a control and might be relevant in a study like this, but the question does not provide any evidence for this type of bias. Protopathic bias is a bias that results from the effect of the disease on the exposure rather than the other way around, as for, example, if having breast cancer led to having increased stress (the direction of the causal arrow is reversed). While that may be present here, we are not given any evidence to support that. There is no relevance to the healthy worker effect in this scenario.

Suggested Reading

Colditz GA. Overview of the epidemiology methods and applications: strengths and limitations of observational study designs. *Crit Rev Food Sci Nutr*. 2010;50 Suppl 1:10–12. PMID: 21132580.

1-3 D

Esophageal adenocarcinoma has been increasing because of a combination of factors, including increasing obesity and gastroesophageal reflux disease. There has been a concomitant increase in mortality from this disease. Squamous cell carcinoma of the esophagus has been declining because of the decline in the prevalence of tobacco use. Lung cancer rates are falling because of the decreased prevalence of tobacco smoking, while colon cancer rates are decreasing because of the increased use of colon cancer screening and the removal of adenomatous polyps. Gastric cancer has been on a steady decline for decades, presumably reflecting changes in dietary patterns as well as a decrease in peptic ulcer disease.

Suggested Reading

Abrams JA, Sharaiha RZ, Gonsalves L, Lightdale CJ, Neugut AI. Dating the rise of esophageal adenocarcinoma: analysis of Connecticut Tumor Registry data, 1940-2007. *Cancer Epidemiol Biomarkers Prev.* 2011;20:183–186. PMID: 21127287.

1-4 D

Prostate cancer is generally twice as frequent among blacks as among whites, with a concomitantly higher mortality rate. Breast cancer has a lower incidence rate among blacks but the mortality rate is nonetheless higher. Multiple myeloma is also higher in incidence and mortality among blacks.

Suggested Reading

Lux MP, Fasching PA, Beckmann MW. Hereditary breast and ovarian cancer: review and future perspectives. *J Mol Med*. 2006;84:16–28. PMID: 16283147.

1-5 A

When screening for a disease with a test, the following outcomes are possible:

	Disease Present	Disease Absent
Positive Result	True Positive (A)	False Positive (B)
Negative Result	False Negative (C)	True Negative (D)

The specificity is the proportion of people without the disease who have a negative test result: D divided by (B + D) (answer A). Answers B and C are not really meaningful statistics. Sensitivity is the proportion of people with the disease who have a positive test result: A divided by (A + C) (answer D). In this example, the specificity is 90 divided by 91 (98.9%).

Suggested Reading

Reintgen DS, Clark RA (eds.). *Cancer Screening.* St. Louis, MO: Mosby; 1996.

1-6 A

The long delay in the decline of risk for lung cancer stems from the fact that cigarette smoke is an initiator. Initiators are carcinogens that affect the early stages of the carcinogenic process and therefore have their effect years before the malignancy actually appears. Hence, the decline in risk upon cessation of smoking follows a reverse pattern, requiring years before their initiating effect has dissipated. Cigarette smoke does contain promoters as well, but they are not responsible for this long delay.

Suggested Reading

Hazelton WD, Clements MS, Moolgavkar, SH. Multistage carcinogenesis and lung cancer mortality in three cohorts. *Cancer Epidemiol Biomarkers Prev*. 2005;14:1171–1181. PMID: 15894668.

Meza R, Hazelton WD, Colditz, GA, et al. Analysis of lung cancer incidence in the Nurses' Health and the Health Professionals' Follow-Up Studies using a multi-stage carcinogenesis model. *Cancer Causes Control*. 2008;19:317–328. PMID: 18058248.

1-7 C

All the other cancers are associated with human papillomaviruses of one type or another and can be prevented by vaccination. Rectal cancer has no known association with infectious agents.

Suggested Reading

McNamara M, Batur P, Walsh JM, Johnson KM. HPV update: vaccination, screening, and associated disease. *J Gen Intern Med.* 2016;31:1360–1366. PMID: 27184752.

1-8 B

While genetic or biologic differences between races or ethnic groups may play a role in differences in outcomes, the primary difference across cancer types in the consistently worse outcomes for blacks versus whites stems from differences in access to care. As a consequence, blacks have less cancer prevention and staging up front and thus present with later stage disease, on average, and then tend to be treated at lesser-quality hospitals and by poorer-quality physicians, and to thereby get worse and later treatment.

Suggested Reading

Shavers VL, Brown ML. Racial and ethnic disparities in the receipt of cancer treatment. *J Natl Cancer Inst.* 2002;94:334–357. PMID: 11880473.

SELF-EVALUATION

2. MOLECULAR BIOLOGY QUESTIONS

2-1 A 35-year-old woman with breast cancer presents to your clinic for evaluation. Her family history is positive for breast cancer in her mother (diagnosed at age 45) and in her sister (diagnosed at age 37). Her maternal uncle developed prostate cancer at age 63.

Which of the following is true?

A. Immunohistochemistry of her tumor is likely to show overexpression of mismatch repair proteins.
B. Genetic analysis is likely to show germline defects in genes involved in the DNA repair pathway.
C. Her history suggests that her tumor is resistant to DNA damaging agents.
D. Cytogenetic analysis is likely to show translocations involving the *HER2* gene.

2-2 A 69-year-old man presents with weight loss and vague abdominal pain. A CT scan shows innumerable lesions in the liver and a biopsy shows poorly differentiated carcinoma. An extensive workup shows no apparent primary tumor, and he is diagnosed with cancer of unknown primary site. He submits his tumor biopsy sample for a study aimed at defining the genetic landscape of unknown primary tumors.

Which of the following genetic changes is likely to be found in his tumor tissue?

A. Amplification of *TP53*
B. Deletion or inactivating mutation of *MYC*
C. Silencing of *KRAS*
D. Deletion or inactivating mutation of *PTEN*

2-3 A 58-year-old man presents with metastatic esophageal cancer. His tumor is sent for molecular testing and is found to overexpress HER2. Trastuzumab is administered.

Which of the following is a possible mechanism of resistance to this agent?

A. Activation of the PI3K/AKT pathway
B. Mutation in the tyrosine kinase domain of the HER2 receptor
C. Increased cellular activity of the drug efflux protein MDR1
D. Epigenetic silencing of cyclin-dependent kinases 4 and 6 (*CDK4/CDK6)*

2-4 A 35-year-old man with a family history of colon cancer is diagnosed with Lynch syndrome. A screening colonoscopy demonstrates a tumor in the ascending colon, and surgery is performed. Final staging shows a pT3N0 (stage II) adenocarcinoma. Analysis of his tumor shows it to be microsatellite-unstable/MSI-high.

Which of the following is characteristic of this disease?

A. An increased risk of tumors in the pituitary, parathyroid, and pancreas
B. Inferior survival compared to patients with sporadic colon cancers
C. Loss of expression of mismatch repair proteins by immunohistochemistry
D. Tumors show extensive gain and loss of chromosomal material

2-5 A 65-year-old man from Southern China presents with a left neck mass, sinus fullness, and frequent epistaxis. Fine-needle aspiration of the left neck mass shows squamous cell carcinoma. Otolaryngology evaluation shows an extensive mass in the left nasopharynx and biopsy confirms squamous cell carcinoma. Molecular analysis with in situ hybridization is positive for Epstein–Barr encoded RNA, indicating Epstein-Barr virus (EBV)—associated nasopharyngeal carcinoma.

Pathogenic viruses can promote cancer through which of the following mechanisms?

A. Inhibition of cyclin/CDK complexes
B. Increased degradation of antiproliferative proteins
C. Decreased expression of angiogenic growth factors
D. Inhibition of antiapoptotic pathways

2-6 A 45-year-old female nonsmoker presents with hemoptysis, headache, and weight loss. CT of the chest shows a left-sided lung mass with associated ipsilateral lymphadenopathy and evidence of liver metastasis in the dome of the liver. MRI of the brain shows multiple lesions that are worrisome for metastasis. A CT-guided biopsy of the lung lesions shows adenocarcinoma.

Which of the following chromosomal translocations is most likely to be present in her tumor sample?

A. *TMPRSS2/ERG*
B. *EML4/ALK*
C. *BCR/ABL1*
D. *SS18/SSX2*

2-7 A 38-year-old man is diagnosed with a glioma and is treated with tumor resection. The tumor is further evaluated with exome sequencing to subclassify his disease and to identify genetic events that may guide therapy.

Which of the following changes is likely to be detected by exome sequencing?

A. Mutations in isocitrate dehydrogenase 1 (*IDH1)*
B. Deletion of epidermal growth factor receptor (*EGFR)*
C. Amplification of the short arm of chromosome 1 and the long arm of chromosome 19 (1p/19q)
D. Extensive methylation of CpG islands

2-8 A 45-year-old man is diagnosed with acute lymphocytic leukemia. Intensive chemotherapy results in cancer remission, and stem cell transplantation is considered.

Which of the following molecular techniques is used to identify a suitable human leukocyte antigen (HLA)-matched donor?

A. Cytogenetic analysis for chromosomal translocations involving HLA gene loci
B. Methylation analysis to identify HLA gene-silencing events
C. Gene expression assays to profile HLA antigens present on the cell surface
D. DNA sequencing of HLA genetic loci

2-9 A 65-year-old man presents with generalized lymphadenopathy and weight loss. Physical exam shows bilateral cervical adenopathy. Lab tests are performed and show a lactate dehydrogenase twice the upper limit of normal, a hematocrit of 28, a platelet count of 124, and a white blood cell count of 2.4. A CT scan shows cervical, mediastinal, and abdominal adenopathy, as well as mild splenomegaly. An excisional biopsy and bone marrow evaluation are performed. Pathologic analysis confirms lymphoma.

Which of the following describes a molecular feature of human lymphoma?

A. Double-hit lymphomas show dual loss of Myc and Bcl2 and/or Bcl6.
B. The t(11;14) translocation found in the majority of mantle cell lymphomas leads to aberrant expression of cyclin D1.
C. CD30 is a nuclear kinase that drives cell-cycle progression in the majority of Hodgkin lymphomas.
D. Human papillomavirus promotes Burkitt lymphoma by producing proteins that directly interfere with p53 and Rb.

2. MOLECULAR BIOLOGY RATIONALES

2-1 B

Germline defects in genes involved in the DNA repair pathway, including *ATM, BRCA1, BRCA2,* and *CHEK2,* are commonly found in patients with a family history of breast cancer. These mutations also predispose to other cancers, including prostate cancer in males. A is incorrect, as loss of expression, not overexpression, of mismatch repair proteins would be found in familial cancer syndromes. C is incorrect, as defects in DNA repair typically increase sensitivity to DNA damaging agents and PARP inhibitors. D is incorrect, as *HER2* gene translocations are not typically found in breast cancer. Overexpression of *HER2* can be found in breast cancer, but the majority of familial breast cancers are negative for *HER2* overexpression.

Suggested Reading

Kleibl Z, Kristensen VN. Women at high risk of breast cancer: molecular characteristics, clinical presentation and management. *Breast.* 2016;28:136–144. PMID: 27318168.

Lee J, Ledermann JA, Kohn EC. PARP inhibitors for BRCA1/2 mutation-associated and BRCA-like malignancies. *Ann Oncol*. 2014;25:32–40. PMID: 24225019.

Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med*. 2016;375:443–453. PMID: 27433846.

2-2 D

The listed genes are either tumor suppressor genes (*TP53* and *PTEN)* or oncogenes (*KRAS* and *MYC*). Tumor suppressor genes are frequently inactivated through gene silencing, deletion, or mutation. Oncogenes are frequently activated by gene amplification. D is the correct answer,

as deletion or mutation of the tumor suppressor gene *PTEN* is frequently seen in human cancers. The *TP53* tumor suppressor gene is frequently mutated or deleted in human cancers, not amplified. The *MYC* oncogene is overexpressed in human cancers via amplification or chromosomal translocation; it is not deleted or inactivated. The *KRAS* oncogene is overactive in human cancers because of activating mutations, most commonly in codons 12 and 13, but also in codons 59, 61, 117, and 146. The highly related *NRAS* gene can also be mutated in analogous sites. *KRAS* and *NRAS* mutations are clinically relevant, as they are biomarkers of colorectal cancers that are insensitive to the anti-EGFR monoclonal antibody cetuximab.

Suggested Reading

Beroukhim R, Mermel CH, Porter D, et al. The landscape of somatic copy-number alteration across human cancers. *Nature*. 2010;463:899–905. PMID: 20164920.

Chalhoub N, Baker SJ. PTEN and the PI3-kinase pathway in cancer. *Annu Rev Pathol*. 2009;4:127–150.PMID: 18767981.

Kandoth C, McLellan MD, Vandin F, et al. Mutational landscape and significance across 12 major cancer types. *Nature*. 2013;502:333–339. PMID: 24132290.

Meyer N, Penn LZ. Reflecting on 25 years with MYC. *Nat Rev Cancer.* 2008;8:976–990. PMID: 19029958.

Pylayeva-Gupta Y, Grabocka E, Bar-Sagi D. RAS oncogenes: weaving a tumorigenic web. *Nat Rev Cancer*. 2011;11:761–774. PMID: 21993244.

Vousden KH, Prives C. Blinded by the light: the growing complexity of p53. *Cell.* 2009;137:413–431. PMID: 19410540.

2-3 A

Trastuzumab is a monoclonal antibody that recognizes the extracellular domain of the HER2 receptor. It is effective in the therapy of HER2 overexpressing cancers, including breast cancers and gastroesophageal cancers. The intracellular PI3K/AKT signaling network is downstream of the HER2 receptor, and overactivity of PI3K or AKT is implicated in resistance to trastuzumab. Mutation of the HER2 tyrosine kinase domain may cause resistance to small-molecule tyrosine kinase inhibitors but is not thought to play a major role in resistance to anti-HER2 antibodies; thus, answer B is incorrect. The drug efflux protein MDR1 can decrease intracellular levels of anticancer compounds. Since trastuzumab functions outside the cell, MDR1 is not relevant to trastuzumab resistance and answer C is incorrect. Cyclin-dependent kinases (CDKs) are nuclear proteins that promote cell-cycle progression; while overactivity of these kinases via amplification or constitutive activation could mediate resistance to targeted therapies, silencing would be expected to cause growth arrest; therefore, answer D is incorrect. In fact, CDK4/6 inhibitors are active therapies for some cancers.

Suggested Reading

Arteaga CL, Engelman JA. ERBB receptors: from oncogene discovery to basic science to mechanism-based cancer therapeutics. *Cancer Cell*. 2014;25:282–303. PMID: 24651011.

Chen KG, Sikic BI. Molecular pathways: regulation and therapeutic implications of multidrug resistance. *Clin Cancer Res*. 2012;18:1863–1869. PMID: 22344233.

Rugo HS, Vidula N, Ma C. Improving response to hormone therapy in breast cancer: new targets, new therapeutic options. *Am Soc Clin Oncol Educ Book*. 2016;35:e40–54. PMID: 27249746.

2-4 C

The patient is a young man with Lynch syndrome and colon cancer. Lynch syndrome is caused by inactivating mutations in any of the mismatch repair genes *MSH2, MLH1, PMS2,* and *MSH6*. Loss of mismatch repair leads to characteristic mutations in repeated DNA sequences throughout the genome, known as “microsatellite instability.” Patients with Lynch syndrome are at very high risk for colon cancer and uterine cancer, but they are also at risk for other cancers, including at alternative gastrointestinal sites (stomach, bile duct, small bowel, and pancreas),

ovary, urinary tract, brain, and skin. Immunohistochemistry to assess for loss of mismatch repair protein expression is recommended for all colorectal cancer samples to identify Lynch-associated cancers. Therefore, answer C is correct. Loss of mismatch repair leads to very high levels of mutation across the genome, and this feature predicts response to immune checkpoint inhibitors. Tumors of the pituitary, parathyroid, and pancreas are not typical of Lynch syndrome but instead suggest multiple endocrine neoplasia type 1 (MEN1), which is due to mutation of the *MEN1* gene. Microsatellite-unstable tumors have improved prognosis compared to microsatellite stable tumors, so answer B is incorrect. In fact, emerging data show that microsatellite instability predicts response to immune checkpoint inhibitors. Extensive gain and loss of chromosomal material (also known as "chromosomal instability," or "CIN+") is a common feature of human cancers. However, large-scale genomic analyses by The Cancer Genome Atlas show that microsatellite-unstable tumors associated with Lynch syndrome are mutually exclusive from those that have CIN, so answer D is incorrect.

Suggested Reading

Lynch HT, Snyder CL, Shaw TG, et al. Milestones of Lynch syndrome: 1895-2015. *Nat Rev Cancer.* 2015;15:181–194. PMID: 25673086.

The Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. *Nature*. 2012;487:330–337. PMID: 22810696.

Vasen HFA, Tomlinson I, Castells A. Clinical management of hereditary colorectal cancer syndromes. *Nat Rev Gastroenterol Hepatol.* 2015;12:88–97. PMID: 25582351.

2-5 B

Endemic nasopharyngeal cancer is frequently associated with EBV infection. EBV and other cancer-associated viruses produce proteins that promote cancer through interference with normal cellular pathways and activation of the "hallmarks of cancer." These hallmarks include increased proliferation, increased angiogenesis, and decreased apoptosis. Answers A, C, and D each describe phenotypes opposite to the hallmarks of cancer and thus are incorrect. B is the correct answer. Viral proteins can promote proliferation through destruction of antiproliferative proteins. For example, the human papillomavirus (HPV) protein E6 targets the tumor suppressor p53 for proteasomal degradation and the HPV protein E7 targets the retinoblastoma (Rb) tumor suppressor protein for proteasomal degradation. How EBV contributes to nasopharyngeal cancer is less clear, but there is growing evidence that EBV gene products lead to activation of the proproliferative protein kinase B pathway.

Suggested Reading

Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell.* 2000;100:57–70. PMID: 10647931.

Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011;144:646–674. PMID: 21376230.

Mesri EA, Feitelson M, Munger K. Human viral oncogenesis: a cancer hallmarks analysis. *Cell Host Microbe*. 2014;15:266–282. PMID: 24629334.

2-6 B

The patient has metastatic non–small cell lung cancer. The clinical history (young age, female sex, no smoking history, adenocarcinoma) suggests the presence of a molecular driver mutation. Answer B is correct. This translocation is present in 2 to 7% of unselected patients with lung cancer. It is important to identify these patients, as they have very high response rates to tyrosine kinase inhibitors including crizotinib. The other answers are incorrect. The *TMPRSS2/ERG* translocation is associated with prostate cancer and is present in approximately half of patients. The *BCR/ABL1* translocation is a near-universal feature of

chronic myeloid leukemia and is the basis for the treatment of these patients with tyrosine kinase inhibitors. The *SS18/SSX2* translocation is characteristic of synovial sarcoma.

Suggested Reading

Mughal TI, Radich JP, Deininger MW, et al. Chronic myeloid leukemia: reminiscences and dreams. *Haematologica*. 2016;101:541–558. PMID: 27132280.

Nielsen TO, Poulin NM, Ladanyi M. Synovial sarcoma: recent discoveries as a roadmap to new avenues for therapy. *Cancer Discov*. 2015;5:124–134. PMID: 25614489.

Shaw AT, Solomon B. Targeting anaplastic lymphoma kinase in lung cancer. *Clin Cancer Res.* 2011;17:2081–2086. PMID: 21288922.

The Cancer Genome Atlas Research Network. The molecular taxonomy of primary prostate cancer. *Cell*. 2015;163:1011–1025. PMID: 26544944.

2-7 A

Various technologies are used to assess the genetics of human cancers. Exome sequencing, as the name implies, gives information on mutations in expressed genes. Exome sequencing is not ideal for detection of gene amplifications or deletions and cannot give information on DNA methylation. Gene amplifications and deletions are usually identified using karyotyping, fluorescence in situ hybridization, or array-based comparative genomic hybridization. The methylation of gene promoters is an important epigenetic regulator of gene expression. DNA methylation is detected using bisulfite sequencing or related array-based techniques. Recent studies of glioma show discrete genetic subtypes of this disease, and these subtypes can influence both therapy and prognosis. Mutations in *IDH1* will be readily detected with exome sequencing. Gliomas show amplifications of *EGFR*, not deletions, so B is incorrect. Likewise, they show deletion of 1p/19q, not amplification, so C is incorrect. Methylation also defines glioma subtypes, with glioma CpG island methylator phenotype (G-CIMP)–positive subtypes having a favorable prognosis.

Suggested Reading

Ceccarelli M, Barthel FP, Malta TM, et al. Molecular profiling reveals biologically discrete subsets and pathways of progression in diffuse glioma. *Cell*. 2016;164:550–563. PMID: 26824661.

Noushmehr H, Weisenberger DJ, Diefes K, et al. Identification of a CpG Island methylator phenotype that defines a distinct subgroup of glioma. *Cancer Cell*. 2010;17:510–522. PMID: 20399149.

2-8 D

This question assesses the understanding of specific molecular techniques in general as well as in the specific context of HLA typing. Cytogenetic analysis uses chromosomal spreads or array-based technologies to look for gain or loss of chromosomal material. DNA methylation analysis uses specialized PCR techniques to identify methylation of gene promoters. This methylation can significantly alter gene expression, generally via gene silencing. Comprehensive and global assessment of gene expression can be performed using array-based or nucleic acid sequencing–based techniques. Flow cytometry is a protein-based method that uses tagged antibodies that recognize specific cell-surface or intracellular proteins to discriminate cell populations based on protein expression. DNA sequencing uses a variety of techniques to achieve sequence-level characterization of precise areas of the genome. This can be limited to polymorphisms within genes but is also readily expanded to include whole genes, whole exomes (constituting all expressed genes), or whole genomes. Only some of the techniques listed in the question are relevant to the dual HLA typing of cancer patients and their potential stem cell donors. The HLA genes encode cell-surface protein receptors involved in antigen

presentation and other immune functions. These proteins are nearly ubiquitous in their expression and are the major determinants of suitability of stem cell donors. HLA matching is known to have a major impact on patient outcomes, and it is important to understand the HLA system and the various techniques used to ascertain HLA type. Given that HLA molecules are cell-surface receptors, serologic techniques, including enzyme-linked immunosorbent assay (ELISA) and flow cytometry, can be used as an initial assay of HLA type. Most HLA-specific antisera cannot adequately discriminate minor differences in HLA molecules, rendering serologic typing "low resolution." With this in mind, serologic techniques have largely been replaced by DNA-based, "high resolution" or "allele level" DNA-sequencing technologies. These techniques can pick up sequence-level differences between very closely related sequences. They are very useful for detecting small polymorphisms within the HLA system and therefore provide the highest level of HLA matching between stem cell donor and recipient. Returning to the answers listed, the techniques of cytogenetic analysis (answer A) and methylation analysis (answer B) are accurately described, but have no role in HLA typing; thus, these answers are incorrect. Answer C is incorrect because it mismatches the technology (gene expression analysis) with the data obtained (cell-surface protein expression). As previously noted, antibody/serologic methods can be used to characterize cell-surface expression of HLA proteins, but these protein-based techniques are largely obsolete. Answer D is correct; most HLA typing is now performed using DNA-sequencing technologies.

Suggested Reading

Latham K, Little A-M, Madrigal JA. An overview of HLA typing for hematopoietic stem cell transplantation. In Beksaç M (ed.), *Bone Marrow and Stem Cell Transplantation*. New York, NY: Springer; 2014:73–85. PMID: 24473779.

2-9 B

Lymphoma encompasses a broad range of disease entities with different clinical features, molecular features, and prognoses. Diffuse large B-cell lymphoma is a curable disease that can be risk-stratified clinically, using the International Prognostic Index, or pathologically, using gene expression profiling or other molecular analyses. Double-hit lymphoma is a recently described entity with combined overexpression of both c-Myc and either Bcl-2 or Bcl-6. This combined activation of a strong driver of proliferation (c-Myc) with an inhibitor of apoptosis (Bcl-2 or -6) portends a poor prognosis. Answer A is incorrect, as dual deletion of these proteins would be expected to suppress, not promote, lymphomagenesis. Mantle cell lymphoma is another aggressive subtype of non-Hodgkin lymphoma that is characterized by the t(11;14) translocation. This translocation involves the immunoglobulin heavy chain locus on chromosome 14 and the cyclin D locus on chromosome 11. This results in the overexpression of the cyclin D1 oncogene in MCL cells. Answer B is correct. Hodgkin lymphoma is a highly curable lymphoma characterized by nearly universal CD30 expression. CD30 is a cell-surface protein that is targeted by the antibody-drug conjugate brentuximab vedotin. CD30 is not located in the nucleus. Thus, answer C is incorrect. Burkitt lymphoma is an aggressive lymphoma associated with EBV infection. It is not clear how EBV contributes to Burkitt lymphoma, but it is likely that EBV proteins inhibit apoptosis. HPV is not associated with Burkitt lymphoma, but is associated with squamous cell carcinomas of multiple sites, including the oropharynx and the cervix. The HPV proteins E6 and E7 appear to contribute to cancer in part by promoting the destruction of the p53 and Rb proteins.

Suggested Reading

Deutsch YE, Tadmor T, Podack ER, et al. CD30: an important new target in hematologic malignancies. *Leuk Lymphoma.* 2011;52:1641–1654. PMID: 21619423.
Mesri EA, Feitelson M, Munger K. Human viral oncogenesis: a cancer hallmarks analysis. *Cell Host Microbe*. 2014;15:266–282. PMID: 24629334.
Pérez-Galán P, Dreyling M, Wiestner A. Mantle cell lymphoma: biology, pathogenesis, and the molecular basis of treatment in the genomic era. *Blood*. 2011;117:26–38. PMID: 20940415.
Sesques P, Johnson NA. Approach to the diagnosis and treatment of high-grade B-cell lymphomas with *MYC* and *BCL2* and/or *BCL6* rearrangements. *Blood.* 2017;129:280–288. PMID: 27821509.

3 CLINICAL PHARMACOLOGY
SELF-EVALUATION

3. CLINICAL PHARMACOLOGY QUESTIONS

3-1 A 65-year-old woman with metastatic renal cell carcinoma is receiving treatment with sunitinib. The drug was well-tolerated with no significant toxicities in the first cycle. She presents in cycle 4 with fatigue, mild nausea, and anorexia, with the significant problem being that of fatigue. She denies any headache, diarrhea, or pain. The drug is withheld, and nausea and anorexia improve but not the fatigue.

What is the most likely reason for the observed toxicity?

A. Electrolyte abnormalities
B. Concurrent infection
C. Hypothyroidism
D. Disease progression

3-2 A 58-year-old woman with a diagnosis of metastatic squamous cell lung cancer is referred to you. She was started on paclitaxel/carboplatin. She had a CT scan of the chest prior to cycle 2 to rule out a pulmonary embolism, which demonstrated a significant shrinkage of the tumor. A severe hypersensitivity reaction develops within 5 minutes after the start of the paclitaxel infusion on cycle 2 day 1, with hives, shortness of breath, pruritus, and chest discomfort.

What is the most appropriate course of action?

A. Stop paclitaxel/carboplatin and start her on gemcitabine/carboplatin
B. Stop paclitaxel/carboplatin and start her on nivolumab
C. Desensitize and rechallenge with paclitaxel
D. Substitute nab-paclitaxel (paclitaxel protein-bound) for paclitaxel

3-3 All of the following anticancer agents require dose adjustments for hepatic dysfunction, except:

A. Carboplatin
B. Irinotecan
C. Docetaxel
D. Cyclophosphamide

3-4 A 55-year-old woman is diagnosed with metastatic colorectal cancer and referred to you. She is started on 5-fluorouracil–leucovorin–oxaliplatin (FOLFOX) combined with bevacizumab. A severe hypersensitivity reaction to oxaliplatin develops during the first cycle of therapy. For cycle 2, she is treated with infusional 5-fluorouracil–leucovorin–irinotecan (FOLFIRI) in combination with bevacizumab. She presents to your clinic after 10 days with fatigue, anorexia, nausea with no vomiting, and diarrhea controlled by

loperamide. She's febrile with a temperature of 38.8°C. Her complete blood count demonstrates a total white cell count of 950 cells/μL with an absolute neutrophil count of 100 cells/μL, a platelet count of 100,000/μL, and a hematocrit of 36 g/dL. The liver- and renal-function tests are normal except for a total bilirubin of 2.4 mg/dL (at baseline, bilirubin was 2.1 mg/dL). She uses lisinopril for hypertension and loratadine for seasonal allergies. You admit her to the inpatient unit for management of febrile neutropenia. For her next cycle of therapy, you will:

A. Stop FOLFIRI and start on a checkpoint inhibitor (pembrolizumab)
B. Test for *KRAS* mutation and if present, give cetuximab–irinotecan
C. Administer FOLFIRI without the bevacizumab
D. Reduce the dose of irinotecan in subsequent cycles

3-5 A 45-year-old physician is referred to you because of an accelerated phase of Philadelphia chromosome–positive chronic myelogenous leukemia. You start her on imatinib, 600 mg daily. She presents to the emergency department 3 weeks later with tinea pedis and is started on ketoconazole. She follows up with you a week later for her first evaluation. She has abdominal pain and cramps, diarrhea, diffuse maculopapular rash, peripheral edema, and nausea. Her platelet count is low and liver enzymes are all elevated.

What is the most appropriate next step?

A. Perform bone marrow aspiration and biopsy to rule out progressive disease
B. Perform pancultures to rule out infection
C. Discontinue imatinib until she improves with supportive care and then start nilotinib
D. Discontinue ketoconazole

3-6 Immune-related adverse events of immune checkpoint inhibitors include all of the following except:

A. Fatigue
B. Bloody diarrhea resulting from colitis
C. Shortness of breath and pulmonary infiltrates on CT scan
D. Hepatitis
E. Uveitis

3-7 Which of the following agents is not a prodrug?

A. Temsirolimus
B. Codeine
C. Morphine
D. Cyclophosphamide
E. Temozolomide

3-8 A 60-year-old never-smoker is diagnosed with stage IV adenocarcinoma of the left upper lobe of the lung with bone metastases. Mutational analysis reveals a deletion 19 mutation in the kinase domain of the EGFR gene. She is started on erlotinib, 150 mg daily, with a dramatic response within 2 months. After 18 months, she presents with increasing cough, shortness of breath, and fatigue. CT scan of the chest reveals multiple bilateral

pulmonary nodules with evidence of pleural studding. There is no hilar or mediastinal adenopathy.

What is the most appropriate next step in this patient's management?

A. Stop erlotinib and start her on afatinib
B. Start her on pemetrexed and carboplatin
C. Start her on pembrolizumab
D. Obtain a pleural biopsy and analyze the tumor for the presence of a T790M mutation

3. CLINICAL PHARMACOLOGY RATIONALES

3-1 C

The toxicities described are more consistent with sunitinib-induced hypothyroidism. This side effect is common with a number of kinase inhibitors and should be suspected in all cases of severe fatigue.

Suggested Reading

Dy GK, Adjei AA. Understanding, recognizing, and managing toxicities of targeted anticancer therapies. *CA Cancer J Clin*. 2013;63:249–2793. PMID: 23716430.

3-2 D

Paclitaxel hypersensitivity is due to Cremophor-L, the solvent in which it is diluted. Abraxane is nanoparticle albumin-bound paclitaxel, which is not dissolved in Cremophor and thus causes no hypersensitivity. With the availability of nab-paclitaxel (paclitaxel protein-bound), desensitizing patients with severe hypersensitivity as seen here is not necessary.

Suggested Reading

de Leon MC, Bolla S, Greene B, Hutchinson L, Del Priore G.Successful treatment with nab-paclitaxel after hypersensitivity reaction to paclitaxel and docetaxel. *Gynecol Oncol Case Rep*. 2013;5:70–71. PMID: 24371703.

3-3 A

Carboplatin is not metabolized in the liver, and liver dysfunction has no effect on its disposition. Dose adjustments are, however, made for renal impairment. All the other agents are metabolized by the liver, and dose adjustments are necessary in cases of hepatic dysfunction.

Suggested Reading

Go RS, Adjei AA. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. *J Clin Oncol*. 1999;17:409–422. PMID: 10458260.

3-4 D

The toxicity described is consistent with irinotecan. The isolated elevation in bilirubin represents Gilbert's syndrome, in which a polymorphism in the promoter of the UGT1A1*28 reduces SN-38 glucuronidation and excretion causing toxicity at standard doses of irinotecan.

Suggested Reading

Innocenti F, Undevia SD, Iyer L, et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe

neutropenia of irinotecan. *J Clin Oncol.* 2004;22:1382–1388. PMID: 15007088.
Pizzolato JF, Saltz LB. The camptothecins. *Lancet.* 2003;361:2235–2242. PMID: 12842380.

3-5 D

Imatinib is a substrate for CYP3A4/5, for which ketoconazole is a strong inhibitor. Concomitant administration of the two drugs can lead to inhibition of imatinib metabolism, increased plasma levels, and subsequent toxicity. Discontinuation of ketoconazole should resolve the toxicity. Nilotinib is effective in Philadelphia chromosome–positive CML. However, it is also a substrate for CYP3A4/5 and cannot be used in this situation.

Suggested Reading

Niwa T, Imagawa Y, Yamazaki H. Drug interactions between nine antifungal agents and drugs metabolized by human cytochromes P450. *Curr Drug Metab.* 2014;15:651–679. PMID: 25429674.
Drugs.com [Internet]. Imatinib Information from Drugs.com; c1996-2012 [Updated: 2017 December 3; Cited: 2017 December 5]. Available from: https://www.drugs.com/mtm/imatinib.html.

3-6 A

Checkpoint inhibitors can cause general nonspecific side effects such as fatigue, nausea, and vomiting. These are not typical immune-mediated toxicities. All the others are immune-mediated. Shortness of breath and pulmonary infiltrates are consistent with immune pneumonitis.

Suggested Reading

Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur J Cancer*. 2016;54:139–148. PMID: 26765102.

3-7 C

All these agents are inactive until metabolized to their active moieties, which are rapamycin (temsirolimus), morphine (codeine, which is 3-methylmorphine), MTIC (temozolomide), and phosphoramide mustard (cyclophosphamide). Morphine is not a prodrug.

Suggested Reading

Knox RJ, Connors TA. Prodrugs in cancer chemotherapy. *Pathol Oncol Res.* 1997;3:309–324. PMID: 11173653.

3-8 D

Resistance to EGFR tyrosine kinase inhibitors is common. In cases of an initial dramatic response followed by progression, the presence of the T790M resistant mutation is seen in about 60% of patients. The third-generation inhibitor, osimertinib, has significant activity, which is superior to chemotherapy in this group. Afatinib has limited efficacy in T790M mutant lung cancer. Anecdotal evidence suggests that the immune checkpoint inhibitors have limited efficacy in *EGFR* mutant lung cancer.

Suggested Reading

Wang S, Cang S, Liu D. Third-generation inhibitors targeting *EGFR* T790M mutation in advanced non-small cell lung cancer. *J Hematol Oncol.* 2016;9:34. PMID: 27071706.

4 PRINCIPLES OF IMMUNO-ONCOLOGY AND BIOLOGIC THERAPY

SELF-EVALUATION

4. PRINCIPLES OF IMMUNO-ONCOLOGY AND BIOLOGIC THERAPY
QUESTIONS

4-1 The interaction between tumor cells and immune cells comprises a complex cycle of events that involve components of both the innate and the adaptive immune system. This interaction has been explored therapeutically, leading to major advances in the treatment of solid and hematologic malignancies.

Which of the following best describes aspects of the cancer–immune interaction?

A. During the antigen presentation process, class I MHC molecules interact predominantly with CD4+ T cells through the T-cell receptor.
B. CTLA-4 and PD-1 are positive costimulatory cell surface molecules induced upon activation of T cells.
C. Additional modulators of the immune response include the costimulatory receptors CD137, CD27, OX40, and ICOS, and the coinhibitory molecules BTLA, LAG3, TIM3, and PD-1H.
D. Regulatory T cells that express FOXP3 are associated with the production of interferon-gamma and interleukin-2, involved in apoptosis through granule exocytosis and the release of perforin and granzymes.

4-2 The development of monoclonal antibodies has revolutionized the treatment of both solid and hematologic malignancies. Therapeutic monoclonal antibody constructs can be chimeric (i.e., mouse variable chain fused to a human constant chain), humanized (i.e., mouse hypervariable/complementarity-determining regions grafted to human Ig), or fully human (termed “umab”). Many of these antibodies have been effective as monotherapy for cancer.

Which of the following applies to the mechanism of action of therapeutic monoclonal antibodies in oncology?

A. Monoclonal antibodies can elicit both immune-mediated and nonimmune antitumor responses. Among the immune effector pathways, complement-mediated cytotoxicity (CMC) and antibody-dependent cellular cytotoxicity (ADCC) can result in antitumor effect.
B. Because of the short half-life (days), antiangiogenic monoclonal antibodies require frequent (i.e., weekly) intravenous administration.
C. The antitumor effect from trastuzumab, an anti-HER2 monoclonal antibody, results from on-target nonimmune effects, through the induction of cell cycle arrest and the inhibition of transcription factors.
D. The development of infusion reaction and cutaneous toxicity (rash) has been

associated with clinical benefit from monoclonal antibodies targeting EGFR and PDGFR.

4-3 A 54-year-old woman with a history of well-controlled hypertension and diabetes who is currently receiving treatment for relapsed chronic lymphocytic leukemia presents for the second infusion of fludarabine, cyclophosphamide, and ofatumumab. During the infusion, agitation and dyspnea develop and she describes a sensation of chest oppression.

What is the most likely explanation for the patient's symptoms?

A. Because of the risk of severe neutropenia associated with the use of this treatment regimen, sepsis is the most likely explanation for this case; intravenous fluids and broad-spectrum antibiotics should be initiated immediately.
B. Infusion reactions may occur during the treatment with ofatumumab, a human IgG1 monoclonal antibody, even when premedication with antihistamines and acetaminophen has been administered.
C. Acute coronary syndrome must be investigated, as has been associated with the use of fludarabine in patients with preexisting conditions.
D. Neurotoxicity of acute onset attributed to cyclophosphamide is the most likely diagnosis; treatment should be discontinued and treatment with methylene blue should be initiated.

4-4 A 55-year-old man with *BRAF* wild-type melanoma presents for reassessment and continued treatment with nivolumab. He reports progressive fatigue and intermittent headaches, more pronounced following the second infusion of the anti-PD-1 agent. His physical exam and vital signs are unremarkable.

What is the most likely explanation for the patient's symptoms?

A. Immune-mediated hepatitis is frequently associated with the use of anti-PD-1 agents. In randomized trials, grade 3 or 4 treatment-related hepatitis developed in approximately 8 to 10% of the patients receiving treatment for melanoma.
B. Fatigue is a common adverse event associated with the use of both nivolumab and pembrolizumab. In the setting of a normal physical exam and vital signs, continued treatment is appropriate.
C. Thyroiditis or hypothyroidism is not a possibility at this point because of the short treatment duration. This endocrine immune-mediated adverse event is usually of late onset (beyond week 16 to 20).
D. Although an uncommon event, the clinical presentation of treatment-related hypophysitis can be vague, and a thorough hormonal evaluation and MRI are recommended in this case.

4-5 A 71-year-old man with metastatic, PD-L1–positive, non-small cell lung cancer being treated with pembrolizumab is admitted to the hospital following the fourth infusion because of cough, low-grade fever, and dyspnea. Oxygen saturation on room air was 86% upon admission. Chest x-ray revealed new, randomly distributed nodular opacities measuring up to 3 cm.

Which of the following is the most appropriate approach?

A. Perform CT of the chest and bronchoscopy. Start oral prednisone 1 mg/kg/day or equivalent, followed by a slow steroid taper over 4 to 6 weeks.
B. Perform CT of the chest and bronchoscopy. Start intravenous methylprednisolone and broad-spectrum antibiotics, followed by frequent reassessments.
C. Perform CT of the chest. Continue treatment with pembrolizumab, as radiologic findings suggest pseudoprogression.
D. Perform CT of the chest and bronchoscopy. Start infliximab, followed by steroid taper over 1 to 2 weeks in order to minimize the risk of opportunistic infections.

4-6 Adoptive cell therapies represent a particular form of immunotherapy that involves the use of cells expanded, engineered, or generated ex vivo.

Which of the following concepts are applicable to adoptive cell therapies?

A. Recombinant chimeric antigen receptors (CARs) are composed of an extracellular antigen-recognition domain, a transmembrane domain, and an intracellular signaling domain and can redirect antigen-specific T-cell responses.
B. Because of the high specificity of antigen-directed responses, toxicities associated with T cells harboring CARs are uncommon.
C. Reprogrammed T-cell receptors (TCRs) can result in antitumor effect through the recognition of antigens, irrespectively of their expression through the MHC.
D. Although costimulatory signals can be coupled to the extracellular and transmembrane domains or CARs, a major limitation of the use of this form of adoptive cell therapy is associated with the inability to enhance cellular responses stimulated by the intracellular domain.

4-7 A 36-year-old woman who is currently receiving treatment for *BRAF V600E* mutant metastatic melanoma with the combination of ipilimumab and nivolumab is admitted to the hospital because of grade 2 persistent elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and fatigue, refractory to oral prednisone. Screening for viral hepatitis is negative and CT of the abdomen reveals no signs of disease metastatic to the liver or biliary obstruction. IV methylprednisolone is started. Nevertheless, following 3 days of treatment, AST and ALT levels continue to increase to grade 3.

What would be the most appropriate next step?

A. Administer infliximab; currently available evidence suggests that treatment with steroids and/or immunosuppressive agents in this setting is associated with reduced efficacy of immune checkpoint blockade.
B. Administer mycophenolate mofetil; currently available evidence suggests that treatment with steroids and/or immunosuppressive agents in this setting is associated with reduced efficacy of immune checkpoint blockade.
C. Administer infliximab; currently available evidence suggests that treatment with steroids and/or immunosuppressive agents in this setting does not limit the efficacy of immune checkpoint blockade.
D. Administer mycophenolate mofetil; currently available evidence suggests that

treatment with steroids and/or immunosuppressive agents in this setting does not limit the efficacy of immune checkpoint blockade.

4-8 A 24-year-old man recently diagnosed with localized, high-grade, synovial sarcoma of the left arm measuring 14 cm presents for treatment initiation with neoadjuvant epirubicin and ifosfamide.

Regarding the use of hematopoietic growth factor/colony-stimulating factor (CSF) in clinical practice, which of the following recommendations is in line with currently available guidelines?

A. In patients presenting with febrile neutropenia, CSF should be routinely used as adjunctive treatment with antibiotic therapy.
B. Secondary prophylaxis with CSF is recommended for patients who experienced a complication from a prior cycle of chemotherapy, despite dose reduction or treatment delay.
C. Pegylated forms of recombinant CSF should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy.
D. Primary prophylaxis with a CSF should be added to the first cycle and continued through subsequent cycles for patients who have an approximately 10% or higher risk of febrile neutropenia (based on patient-, disease-, and treatment-related factors) or for those receiving dose-dense chemotherapy.

4. PRINCIPLES OF IMMUNO-ONCOLOGY AND BIOLOGIC THERAPY RATIONALES

4-1 C

In addition to the interaction between MHC molecules and the T-cell receptor, T-cell activation requires signaling of the CD3 transduction module and additional modulatory coreceptors, either costimulatory (CD137, CD27, OX40, ICOS) or coinhibitory (CTLA-4, PD-1, BTLA, LAG3, TIM3, PD-1H) (answer C correct). Class I MHC molecules are involved in antigen presentation to CD8+ T cells (answer A incorrect). As mentioned above, CTLA-4 and PD-1 are negative cell-surface coreceptors (answer B incorrect). Regulatory T cells maintain tolerance by suppressing the expansion of effector cells through the production of the production of IL-10 and TGF-β (answer D incorrect).

Suggested Reading

Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity.* 2013;39:1–10. PMID: 23890059.
Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature*. 2011;480:480–489. PMID: 22193102.

4-2 A

Monoclonal antibodies usually exhibit long half-lives and are usually administered every 14 to 21 days (answer B incorrect). The mechanisms of action of trastuzumab are not completely described, and involve both complement-mediated cytotoxicity (CMC) and antibody-dependent cellular cytotoxicity (ADCC) (answer C incorrect). The development of rash (and not infusion reactions) has been associated with clinical benefit from anti-EGFR monoclonal antibodies

(cetuximab, panitumumab) (answer D incorrect).

Suggested Reading

Scott AM, Allison JP, Wolchok JD. Monoclonal antibodies in cancer therapy. *Cancer Immun.* 2012;12:14. PMID: 22896759.
Gharvan H, Groninger H. Kinase inhibitors and monoclonal antibodies in oncology: clinical implications. *Nat Rev Clin Oncol*. 2016;13:209–227. PMID: 26718105.

4-3 B

Although this regimen is associated with an elevated risk of myelotoxicity, febrile neutropenia and sepsis usually occur during the nadir (answer A incorrect). Infusion reactions associated with ofatumumab occurred in approximately 60% of the patients treated with this regimen in a phase III trial; premedication with acetaminophen and antihistamines is advised (answer B correct). Alternatives C and D describe unusual treatment complications. Of note, neurotoxicity is more frequently associated with the use of ifosfamide.

Suggested Reading

Robak T, Warzocha K, Govind Babu K, et al. Ofatumumab plus fludarabine and cyclophosphamide in relapsed chronic lymphocytic leukemia: results from the COMPLEMENT 2 trial. *Leuk Lymphoma.* 2016;12:1–10. Epub 2016 Oct 12. PMID: 27731748.
van Oers MHJ, Kuliczkowski K, Smolej L, et al. Ofatumumab maintenance versus observation in relapsed chronic lymphocytic leukaemia (PROLONG): an open-label, multicentre, randomised phase 3 study. *Lancet Oncol.* 2015;16:1370–1379. PMID: 26377300.

4-4 D

Although grade 3 or higher treatment-related hepatitis may occur with PD-1 blockade, the incidence is usually less than 1 to 2% (answer A incorrect). Thyroiditis and hypothyroidism are frequent complications associated with the use of nivolumab and pembrolizumab. Although it is more frequently diagnosed around weeks 8 to 12, thyroid dysfunction may occur early during treatment and should be considered in the differential diagnosis in this case (answer C incorrect). Answer D is correct and self-explanatory.

Suggested Reading

Weber JS, Yang JC, Atkins MB, et al. Toxicities of Immunotherapy for the Practitioner. *J Clin Oncol.* 2015;33:2092–2099. PMID: 25918278.
Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. *JAMA Oncol*. 2016;2:1346–1353. PMID: 27367787.

4-5 B

Although oral steroids can be used in the setting of pneumonitis associated with PD-1 blockade, the patient presented with hypoxia and symptoms that suggest a life-threatening complication; intravenous steroids, broad-spectrum antibiotics, and potentially, immunosuppressive agents are the standard approach (answer A incorrect/answer B correct). Radiologic findings can be misleading, and pseudoprogresson is an infrequent pattern of response to PD-1 therapy; therefore, other diagnoses should be considered in this situation (answer C incorrect). Once the diagnosis of treatment-related pneumonitis is established, a prolonged steroid taper during the course of 4 to 6 weeks is advised (answer D incorrect).

Suggested Reading

Naidoo J, Wang X, Woo KM, et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1

therapy. *J Clin Oncol.* 2017;35:709–717. Epub 2016 Sep 30. PMID: 27646942.
Nishino M, Giobbie-Hurder A, Hatabu H, et al. Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. *JAMA Oncol.* 2016;2:1607–1616. PMID: 27540850.

4-6 A

Toxicities from adoptive cell therapies can be limiting; they include cytokine release syndrome, hypotension, pyrexia, and neurologic adverse events (answer B incorrect). The use of adoptive cell therapy with reprogrammed TCRs are limited to specific HLA subtypes, involved in antigen presentation (answer C incorrect). Second- and third-generation CAR T-cells constructs include intracellular costimulatory signaling moieties, resulting in enhanced antitumor effect in preclinical models (answer D incorrect).

Suggested Reading

Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. *Science.* 2015;348:62–68. PMID: 25838374.
Jackson HJ, Rafiq S, Brentjens RJ. Driving CAR T-cells forward. *Nat Rev Clin Oncol.* 2016;13:370–383. PMID: 27000958.

4-7 D

The use of infliximab is associated with a risk of intrinsic hepatotoxicity and should be avoided in patients with immune-mediated hepatitis or AST or ALT elevation in the setting of immune checkpoint blockade. Analyses of patients treated with ipilimumab, nivolumab, or the combination of the two suggest that treatment efficacy is maintained in patients treated with corticosteroids and/or immunosuppressive agents for the management of immune-related adverse events, and should be administered following currently available guidelines.

Suggested Reading

Horvat TZ, Adel NG, Dang TO, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. *J Clin Oncol.* 2015;33:3193–3198. PMID: 26282644.
Champiat S, Lambotte O, Barreau E, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. *Ann Oncol.* 2016;27:559–574. PMID: 26715621.
Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and PD-L1 immune checkpoint antibodies. *Ann Oncol*. 2015;26:2375–2391. PMID: 26371282.

4-8 C

Currently available guidelines recommend against the routine use of CSF as adjunctive treatment with antibiotic therapy in patients presenting with febrile neutropenia. CSF should be considered for patients with high-risk factors (expected prolonged and profound neutropenia, age > 65 years, uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction or sepsis, invasive fungal infection, hospitalization at the time of fever development) (answer A incorrect). Dose reduction or treatment delay may be a reasonable alternative to the use of CSF in select situations (answer B incorrect). Alternative C is correct: Pegfilgrastim should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy because it stimulates myeloid cells to divide and because dividing cells are sensitive to cytotoxic chemotherapy, posing the risk of aggravating leukopenia.
Primary prophylaxis with a CSF should be added for patients who have an approximately 20% or higher risk of febrile neutropenia (based on patient-, disease-, and treatment-related factors) and for patients receiving dose-dense chemotherapy when considered appropriate (answer D incorrect)

Suggested Reading

Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2015;33:3199–3212. PMID: 26169616.

Timmer-Bonte JN, Adang EM, Smith HJ, et al. Cost-effectiveness of adding granulocyte colony-stimulating factor to primary prophylaxis with antibiotics in small-cell lung cancer. *J Clin Oncol*. 2006;24:2991–2997. PMID: 16682725.

Vogel CL, Wojtukiewicz MZ, Carroll RR, et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. *J Clin Oncol*. 2005;23:1178–1184. PMID: 15718314.

5 CLINICAL TRIALS AND BIOSTATISTICS

SELF-EVALUATION

5. CLINICAL TRIALS AND BIOSTATISTICS QUESTIONS

5-1 A randomized clinical trial was conducted to compare overall survival between two treatments for patients with colorectal cancer. The median survival was 8.8 months in arm A and 8.1 months in arm B, with a hazard ratio of 0.88 and a p value of 0.12.

Which of the following is the most appropriate conclusion from this information?

A. There is a 12% chance that the two treatments have the same overall survival.
B. The two treatments are equivalent to one another.
C. A confidence interval is needed to properly interpret the results of this study.
D. There is a statistically significant difference in the survival of the two treatments.

5-2 A study was conducted to examine the association between EGFR status and treatment response. A chi-square test was conducted to test this association, and the chi-square statistic was 2.53, with a p value of 0.112.

Which of the following statements is correct?

A. The researcher should conclude that there is a significant association between EGFR status and treatment response at the 5% level.
B. If there was no association between EGFR status and treatment response, the chance of obtaining a chi-square statistic of 2.53 or larger in this study would be 11.2%.
C. There is an 11.2% chance that there is no association between EGFR status and treatment response.
D. There is an 11.2% chance that there is an association between EGFR status and treatment response.

5-3 A researcher is designing a controlled clinical trial to detect an improvement in the response rate of a drug from 50% for the control drug to 70% for the new drug. The researcher determines that the sample size, which yields 80% power to detect this improvement, is 93 per group, using a type I error rate of 5%.

Which of the following statements is correct?

A. The given sample size of 93 per group would have more than 80% power to detect an improvement in the response rate from 50% to 80%.
B. A sample size of 150 per group would have less than 80% power to detect this same improvement.
C. The given sample size of 93 per group would have more than 80% power to detect an improvement in the response rate from 50% to 60%.
D. The confidence interval for the difference in response rates would get wider if a

sample size of 150 per group were used, instead of 93 per group.

5-4 A study was conducted to evaluate association between various single-nucleotide polymorphisms (SNPs) and complete remission (CR) status posttreatment among patients with acute myelogenous leukemia. The abstract reported that a particular SNP was associated with a higher CR rate ($p = 0.041$).

What additional information would be most helpful in interpreting this finding?

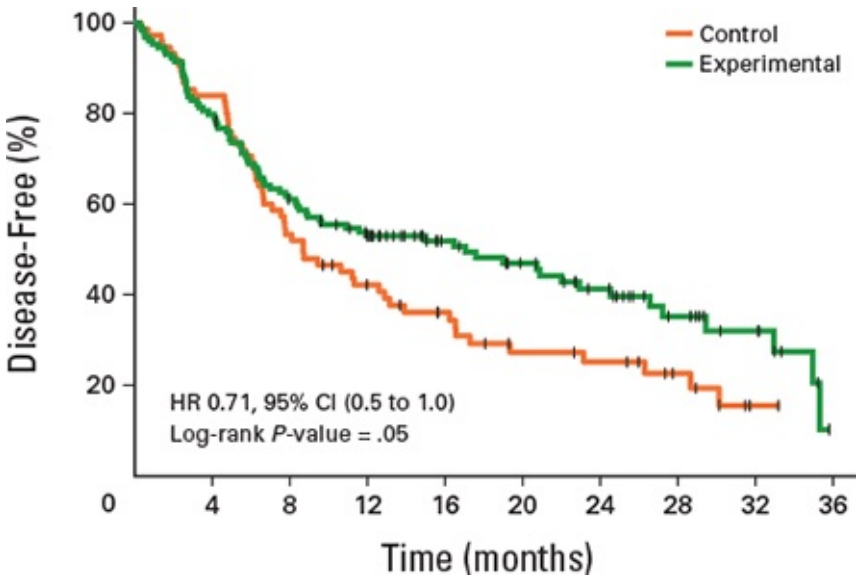
A. The proportions of patients in complete remission in each group
B. The number of SNPs that were evaluated and examined for association with CR status
C. The number of patients who were SNP-negative and those who were SNP-positive
D. A confidence interval for the difference in CR rates

5-5 A study was conducted to assess the association between a particular gene expression level and serum LDH levels. The study found a correlation of $r = 0.15$ and $p < 0.0001$.

Which of the following is the most appropriate conclusion from this information?

A. 15% of the variation in serum LDH is attributed to variation in the gene expression level.
B. The small p value indicates a very strong linear relationship.
C. There is a positive association between the gene expression level and serum LDH.
D. Based on the small p value, it is valid to conclude that a causal link exists between gene expression level and serum LDH.

5-6 A randomized clinical trial was conducted to compare overall survival between two treatments for patients with colorectal cancer. The median survival was 8.8 months in arm A and 8.1 months in arm B, with a hazard ratio of 0.88 and a p value of 0.12.



Which of the following is the most appropriate conclusion from this information?

A. The hazard ratio (HR) indicates that the experimental treatment is 0.71 times as likely to experience death or disease relapse as the control group at any time.

B. The observed median time to death or relapse was less than 6 months in the control group.
C. The disease-free survival probability at 2 years for the experimental arm is approximately 60%.
D. Only patients who have had at least 2 years of follow-up are used to estimate 2-year survival.

5-7 A randomized phase II clinical trial demonstrated promising results on a biomarker target of angiogenesis inhibition in patients with high-grade serous ovarian cancer ($p < 0.001$). A randomized phase III trial was conducted that had 90% power to detect a 15% difference in survival at 3 years. The results were disappointing and showed virtually no differences in overall survival.

Which of the following is the most appropriate conclusion from this information?
A. The phase II trial was subject to bias.
B. The good results of the phase II trial were an anomaly due to chance.
C. The results of the phase III trial were worse than they should have been due to chance.
D. There is not a good correlation between angiogenesis inhibition biomarker and long-term survival.

5. CLINICAL TRIALS AND BIOSTATISTICS RATIONALES

5-1 C

The p value of 0.12 indicates that there is a 12% chance of getting a more extreme hazard ratio if there was really no treatment effect, not that there is a 12% chance the two treatments have the same survival. Since $p > 0.05$, there is not a statistically significant difference. A nonsignificant p value does not mean the two treatments are equivalent to one another. A confidence interval provides information on how close the survival of the two groups could be and helps one understand the study results.

Suggested Reading

Guyatt G, Jaeschke R, Heddle N, et al. Basic statistics for clinicians: 1. Hypothesis testing. *Can Med Assoc J.* 1995;152:27–32. PMID: 7804919.

Guyatt G, Jaeschke R, Heddle N, et al. Basic statistics for clinicians: 2. Interpreting study results: confidence intervals. *Can Med Assoc J.* 1995;152:169–173. PMID: 7820798.

Motulsky H. *Intuitive Biostatistics: A Nonmathematical Guide to Statistical Thinking, 3rd ed.* New York, NY: Oxford University Press, 2014; 233–250.

5-2 B

The p value is the likelihood of obtaining a result at least as extreme as what was observed in the study, if there was really no effect.

Suggested Reading

Guyatt G, Jaeschke R, Heddle N, et al. Basic statistics for clinicians: 1. Hypothesis testing. *Can Med Assoc J.* 1995;152:27–32. PMID: 7804919.

Motulsky H. *Intuitive Biostatistics: A Nonmathematical Guide to Statistical Thinking, 3rd ed.* New York, NY: Oxford University Press; 2014:233–250.

5-3 A

Power increases with sample size and magnitude of treatment effect. Confidence interval width decreases with sample size.

Suggested Reading

Guyatt G, Jaeschke R, Heddle N, et al. Basic statistics for clinicians: 1. Hypothesis testing. *Can Med Assoc J.* 1995;152:27–32. PMID: 7804919.

Guyatt G, Jaeschke R, Heddle N, et al. Basic statistics for clinicians: 2. Interpreting study results: confidence intervals. *Can Med Assoc J.* 1995;152:169–173. PMID: 7820798.

Motulsky H. *Intuitive Biostatistics: A Nonmathematical Guide to Statistical Thinking, 3rd ed.* New York, NY: Oxford University Press; 2014:233–250.

5-4 B

While the sample size, the proportions of patients in CR, and a confidence interval for the difference in CR rates are all useful information, the number of SNPs examined can have a major impact on how the p value should be interpreted. The reported result is only marginally statistically significant, and could well be produced by chance by screening a large number of SNPs. Even if only a small number of SNPs were analyzed, it would weaken the significance of these findings. For example, a Bonferroni correction applied to the testing of five SNPs would require a significance level of 0.01 for each endpoint in order to achieve an overall significance level of 0.05. It is not necessary to actually make an explicit adjustment, but knowing the number of comparisons is critical for placing the results in context.

Suggested Reading

Waalen J, Beutler E. Beware of multiple comparisons: a study of symptoms associated with mutations of the HFE hemochromatosis gene. *Clin Chim Acta.* 2005;361:128–134. PMID: 15993396.

5-5 C

The p value does not provide any information on the magnitude of the effect, in this case the linear relationship, or provide any evidence about a causal effect versus simply an association. The variation attributable to gene expression is the square of the correlation, $r^2 = 0.15^2$, rather than 15%. The direction of the correlation of 0.15 indicates a positive association.

Suggested Reading

Guyatt G, Walter S, Shannon H, et al. Basic statistics for clinicians: 4. Correlation and regression. *Can Med Assoc J.* 1995;152:497–504. PMID: 7859197.

5-6 A

The median time to death or relapse is approximately 8 months in the control group. The disease-free survival probability at 2 years in the experimental arm is approximately 40%. Patients with less than 2 years of follow-up contribute information about 2-year survival until they are censored. The hazard ratio of 0.71 indicates that patients receiving the experimental treatment are 0.71 times as likely to die or relapse as the control group at any time.

Suggested Reading

Green S, Benedetti J, Smith A, et al. *Clinical Trials in Oncology, 3rd ed.* Boca Raton, FL: Chapman & Hall/CRC Taylor & Francis Group; 2012:23–30.

Guyatt G, Jaeschke R, Heddle N, et al. Basic statistics for clinicians: 1. Hypothesis testing. *Can Med Assoc J.* 1995;152:27–32. PMID: 7804919.

Guyatt G, Jaeschke R, Heddle N, et al. Basic statistics for clinicians: 2. Interpreting study results: confidence intervals. *Can Med Assoc J.* 1995;152:169–173. PMID: 7820798.

5-7 D

The researchers used a randomized phase II trial, so there should be no issue with bias, and the small p value indicates that the phase II results were not a chance anomaly. Since the phase III trial was powered adequately, those results should not have been worse than expected just by chance. The main issue is that the angiogenesis inhibition biomarker may not correlate well with long-term survival.

Suggested Reading

Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med.* 1996;125:605–613. PMID: 8815760.
Friedman LM, Furberg CD, DeMets DL. *Fundamentals of Clinical Trials, 2nd ed.* New York, NY: Springer-Verlag; 1998.
Piantadosi S. *Clinical Trials: A Methodologic Perspective, 2nd ed.* Hoboken, NJ: Wiley; 2005:211–221.

6 GENETIC TESTING FOR HEREDITARY CANCER SYNDROMES

SELF-EVALUATION

6. GENETIC TESTING FOR HEREDITARY CANCER SYNDROMES QUESTIONS

6-1 A 33-year-old woman has a significant family history of breast cancer, including her mother with breast cancer at age 42 (deceased at age 45), a maternal aunt with breast cancer at age 64, and a maternal grandmother with breast cancer at age 51 (deceased at age 72). The patient's affected maternal aunt recently underwent genetic testing and was found to have a pathogenic variant (mutation) in the *ATM* gene. Based on this family history, you recommended that your patient undergo genetic testing for the familial *ATM* pathogenic mutation. When you receive the results, you find that your patient has tested negative for the familial *ATM* mutation.

Based on your patient's negative/normal genetic test result, which of the following is the most appropriate statement regarding your patient's future risk?

A. Since she tested negative for the familial mutation, her risk for breast cancer is equivalent to the general population risk.
B. The patient and her husband are at increased risk to have a child with ataxia telangiectasia (AT).
C. Given the familial *ATM* mutation, she is at increased risk for breast cancer compared to the general population.
D. The patient's mother and maternal grandmother's genetic status are unknown, and thus there could be additional factors in this family that could lead the patient to still have an elevated risk for breast cancer.

6-2 A 29-year-old man with colorectal cancer was found to have a germline *MSH6* mutation. The patient reports to you that his fiancée's mother has a history of endometrial cancer, initially diagnosed at age 48. The patient asks you if his future offspring could be at greater risk for cancer given both his personal diagnosis and his fiancée's maternal family history of cancer.

Which of the following conditions could most likely pose a risk to the patient's future offspring?

A. Fanconi anemia
B. Ataxia telangiectasia
C. Constitutional mismatch repair deficiency syndrome
D. Nijmegen breakage syndrome

6-3 A 29-year-old woman of Ashkenazi Jewish ancestry, who has no personal cancer

history, elects to undergo genetic testing for the three common *BRCA1* and *BRCA2* Ashkenazi founder mutations, since her mother recently died of ovarian cancer at age 64. The mother did not undergo genetic testing prior to her passing. The patient also reported having a maternal uncle who was diagnosed with prostate cancer (high Gleason score). Your patient's results return with negative/normal findings.

Which of the following would be an appropriate next step?

A. Inform the patient that she is still at high risk for ovarian cancer based on her mother's history of cancer and a risk-reducing bilateral salpingo-oophorectomy (BSO) should be planned immediately.
B. Inform the patient that she is at high risk for breast cancer given her Ashkenazi Jewish ancestry and that risk-reducing bilateral mastectomy should be planned immediately.
C. Inform the patient that her risk for ovarian cancer cannot be determined at this time, as the negative test results are not informative; and inform the patient that the maternal uncle affected with prostate cancer should pursue individualized genetic risk assessment.
D. Inform the patient that her risk for ovarian cancer is equivalent to that of the general population.

6-4 A 54-year-old man with a stage II poorly differentiated gastric adenocarcinoma underwent genetic testing and was found to have a genetic variant of uncertain significance in the *CDH1* gene.

What is the most appropriate recommendation for the patient's unaffected family members (i.e., children and siblings)?

A. The patient's family should undergo genetic testing for the *CDH1* variant to determine if they must approach family planning via in vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD).
B. The patient's family should not pursue genetic testing for the *CDH1* variant, since its significance is undetermined.
C. The patient's family should undergo genetic testing for the *CDH1* variant to determine whether upper endoscopy screening for diffuse gastric cancer is warranted.
D. The patient's family should undergo genetic testing for the *CDH1* variant to determine whether prophylactic total gastrectomy is warranted.

6. GENETIC TESTING FOR HEREDITARY CANCER SYNDROMES RATIONALES

6-1 D

Germline mutations in moderate-penetrance genes may not be the sole explanation for a family history of cancer. In this family, genetic testing has not been performed on all cancer-affected individuals. Option A is not correct, as the "true negative" result does not apply to a moderate-penetrance gene in this situation. The patient in question may have inherited other risk alleles from her grandmother and mother that may lead to her still having an increased risk for cancer.

Option B is not correct; since the patient is not a carrier for an *ATM* mutation, she is not at risk for passing it on to her offspring. Even if the patient's partner were an *ATM* mutation carrier, a child would not have AT unless it had biallelic germline mutations. Option C is not correct because although the patient may still be at increased risk for breast cancer, it is not because of the presence of the *ATM* mutation in the family. Option D is correct because a provider needs to recognize that the possibility of unidentified risk alleles from the mother and grandmother may still pose risks for the patient.

Suggested Reading

Domchek SM, Bradbury A, Garber JE, et al. Multiplex genetic testing for cancer susceptibility: out on the high wire without a net? *J Clin Oncol*. 2013;31:1267–1270. PMID: 23460708.

Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol.* 2016;13:581–588. PMID: 27296296.

6-2 C

All of the options are severe childhood-onset syndromes that are associated with cancer risks. Adult heterozygous carriers of mutations in genes associated with these syndromes may also have cancer risks. Option A is not correct in this situation, as Fanconi anemia is caused by biallelic mutations in genes such as *BRCA2, BRIP1, PALB2, RAD51, RAD51C, BRCA1,* and *XRCC2*. Option B is not correct in this situation, as ataxia telangiectasia is caused by biallelic mutations in *ATM.* Option D is not correct in this situation, as Nijmegen breakage syndrome is caused by biallelic mutations in *NBN.* Option C is correct, as the patient is known to have a mutation in the *MSH6* gene, which is a mismatch repair Lynch syndrome–associated gene. A history of early-onset endometrial cancer in the patient's fiancée's mother should raise suspicion for Lynch syndrome. *MSH6* gene mutations are associated with a high risk for endometrial cancer. Biallelic mutations in the Lynch syndrome genes, including *MSH6,* can lead to constitutional mismatch repair deficiency syndrome.

Suggested Reading

Bakry D, Aronson M, Durno C, et al. Genetic and clinical determinants of constitutional mismatch repair deficiency syndrome: report from the constitutional mismatch repair deficiency consortium. *Eur J Cancer.* 2014;50:987–996. PMID: 24440087.

Chrzanowska KH, Gregorek H, Dembowska-Bagińska B, Kalina MA, Digweed M. Nijmegen breakage syndrome (NBS). *Orphanet J Rare Dis.* 2012;7(1):13. PMID: 22373003.

Meyer S, Tischkowitz M, Chandler K, et al. Fanconi anaemia, BRCA2 mutations and childhood cancer: a developmental perspective from clinical and epidemiological observations with implications for genetic counselling. *J Med Genet.* 2014;51:71–75. PMID: 24259538.

Suarez F, Mahlaoui N, Canioni D, et al. Incidence, presentation, and prognosis of malignancies in ataxia-telangiectasia: a report from the French National Registry of Primary Immune Deficiencies. *J Clin Oncol*. 2015;33:202–208. PMID: 25488969.

6-3 C

A mutation has not been previously documented in this family. In families in which no genetic mutation has been identified, an unaffected individual is not an ideal genetic testing candidate. The patient's "negative" result is considered to be an "uninformative negative" result, as there are several possible explanations for this situation: (1) the mother did harbor a *BRCA1* or *BRCA2* pathogenic mutation, but just by 50/50 chance, the daughter/patient did not inherit the mutation; (2) the mother carried a different mutation in the *BRCA1* or *BRCA2* gene that could not be detected by the testing method used in the daughter/patient's testing and the patient does or does not also carry this undetected mutation; (3) the mother carried a pathogenic mutation in a different ovarian cancer predisposition gene that again the daughter/patient may

or may not also carry; (4) the mother's cancer was due to sporadic, nonhereditary factors. Therefore, the patient's risk for ovarian cancer cannot be determined at this time. The patient's negative results are not informative for family members, because if the mother did indeed carry one of the three common Ashkenazi Jewish *BRCA1* or *BRCA2* founder mutations, other family members could have inherited the familial mutation.

Option A is not correct because although the patient might be at a high risk for ovarian cancer, a BSO at age 29 would not be medically sound. Option B is not correct, as Ashkenazi Jewish ancestry does not automatically predispose one to a risk for breast cancer high enough to warrant bilateral mastectomies. Option D is not correct, as the patient may have inherited other risk alleles that were not tested for and that still predispose her to an increased risk for ovarian cancer.

Suggested Reading

Berliner JL, Fay AM, Cummings SA, Burnett B, Tillmanns T. NSGC practice guideline: risk assessment and genetic counseling for hereditary breast and ovarian cancer. *J Genet Couns*. 2013;22:155–163. PMID: 23188549.

Riley BD, Culver JO, Skrzynia C, et al. Essential elements of genetic cancer risk assessment, counseling, and testing: updated recommendations of the National Society of Genetic Counselors. *J Genet Couns*. 2012;21:151–161. PMID: 22134580.

6-4 B

Since the patient's identified *CDH1* genetic variant is of uncertain significance, testing his family members for this genetic variant is not recommended, as it will not clarify their personal cancer risk or their personal medical management recommendations. In fact, genetic testing of family members for uncertain genetic variants may lead to harm, as a family member may misinterpret risks and management options. For example, if a family member tests positive for the uncertain genetic variant, he or she may pursue unnecessary medical procedures that carry risks (such as prophylactic total gastrectomy, upper endoscopy, and IVF with PGD). Alternatively, if a family member tests negative for the uncertain genetic variant, they may inappropriately believe that they do not have a risk for cancer and may disregard symptoms or recommended general population screening exams.

Option A is incorrect for the reasons discussed above, but also because even in situations of a truly pathogenic germline mutation, IVF with PGD is not mandatory. Option C is incorrect for the reasons discussed above, but also because even in situations of a truly pathogenic *CDH1* germline mutation, upper endoscopy has not proved to be an effective method of screening for and detecting diffuse gastric cancer. Option D is incorrect, for the reasons already discussed.

Suggested Reading

Riley BD, Culver JO, Skrzynia C, et al. Essential elements of genetic cancer risk assessment, counseling, and testing: updated recommendations of the National Society of Genetic Counselors. *J Genet Couns*. 2012;21:151–161. PMID: 22134580.

Rubin LR, Werner-Lin A, Sagi M, et al. 'The BRCA clock is ticking!': negotiating medical concerns and reproductive goals in preimplantation genetic diagnosis. *Hum Fertil*. 2014;17:159–164. PMID: 25105219.

van der Post RS, Vogelaar IP, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers *J Med Genet.* 2015;52:361–374. PMID: 25979631.

7 BREAST CANCER
SELF-EVALUATION

7. BREAST CANCER QUESTIONS

7-1 A postmenopausal woman with newly diagnosed, metastatic, estrogen receptor–positive, breast cancer asks about the benefit of palbociclib in her situation.

Which of the following do you tell her?

A. In the first-line metastatic setting, when added to an aromatase inhibitor (AI), palbociclib increases progression-free survival by about 10 months, as compared with an AI alone.
B. When combined with an AI, palbociclib increases overall survival in the first-line setting, compared with an AI alone.
C. Palbociclib is associated with a substantial rate of febrile neutropenia.
D. The main toxic effect of palbociclib is mucositis.

7-2 A 40-year-old woman with a strong family history of breast and ovarian cancers, but no personal history of breast cancer, has been diagnosed as having a deleterious *BRCA2* gene mutation. She is adamantly opposed to mastectomy at this time. She does not want any more children and asks about removal of her ovaries.

Which of the following is true about risk-reducing bilateral salpingo-oophorectomies?

A. This will reduce her risk of ovarian cancer but will not reduce her risk of breast cancer.
B. This will reduce her risk of ovarian cancer and breast cancer by about 50% each.
C. This will reduce her risk of ovarian-type cancer by about 85% and reduce her risk of breast cancer by about 50%.
D. This will reduce her risk of ovarian-type cancer by about 85% but will not reduce her risk of breast cancer.

7-3 A patient with resected breast cancer presents to her medical oncologist and asks about the potential value of obtaining the 21-gene expression assay (Oncotype DX).

Which the following is most accurate?

A. The 21-gene assay provides prognostic information in patients with estrogen receptor–positive breast cancer treated with hormone therapy alone and also provides predictive information regarding the additional value of chemotherapy for improving outcome.
B. The prognostic and predictive information provided by the 21-gene assay is supported by prospective evidence in node-positive patients.
C. The 21-gene assay provides only prognostic, not predictive, information.
D. There are no data about the utility of the 21-gene assay in patients with involved

axillary lymph nodes.

7-4 A 45-year-old patient with a resected HER2-positive breast cancer is concerned about receiving doxorubicin, which another physician recommended to her. She has a 2-cm, clinically node-negative cancer and asks whether she can be treated without an anthracycline.

Which of the following can you tell her?

A. It is reasonable for her to receive, in a postoperative adjuvant setting, weekly paclitaxel and trastuzumab for 12 weeks, followed by completion of a year of adjuvant trastuzumab.
B. Adjuvant doxorubicin therapy is still standard in this situation.
C. It is reasonable for her to receive, in a preoperative adjuvant setting, weekly paclitaxel and trastuzumab for 12 weeks, followed by completion of a year of adjuvant trastuzumab.
D. It is reasonable for her to be treated with postoperative adjuvant trastuzumab and pertuzumab, without any cytotoxic chemotherapy.

7-5 A 45-year-old woman with history of a 3-cm, node-positive, triple-negative breast cancer (TNBC) diagnosed 3 years ago comes to see you. She had a wide local excision and adjuvant chemotherapy with weekly paclitaxel for 12 weeks and then four cycles of dose-dense doxorubicin/cyclophosphamide. This was followed by whole-breast radiation. Nine months later, she had a 4-cm local recurrence, with similar receptor characteristics, that led to a mastectomy. All known disease was resected and a metastatic workup was negative. She asks you whether additional systemic therapy is recommended.

Which of the following is the most appropriate next step for this patient?

A. Observation with no additional chemotherapy, given that she has already received such
B. Weekly paclitaxel and then doxorubicin/cyclophosphamide should be repeated
C. Palbociclib is recommended, since she has already had chemotherapy
D. It is reasonable to give a platinum-based chemotherapy regimen in an adjuvant fashion

7-6 A 55-year-old postmenopausal woman presents to your clinic with a clinical 4-cm, node-positive, grade 3 breast cancer that is estrogen receptor–negative, progesterone receptor–negative, and HER2-negative. Her surgeon recommended neoadjuvant therapy and she inquires as to the benefit of carboplatin when combined with standard anthracycline- and taxane-based chemotherapy.

With regard to the CALGB 40603 and GeparSixto studies, which evaluated neoadjuvant administration of carboplatin with standard anthracycline and taxane-based chemotherapy for triple-negative breast cancer, which of the following is the most appropriate counseling to provide for this patient?

A. Adding carboplatin will not significantly increase her odds of achieving a complete pathologic response.

B. Adding carboplatin will significantly increase her odds of achieving a complete pathologic response; however, there is conflicting data about whether it will improve her 3-year disease-free survival rate.
C. Adding carboplatin has consistently been shown to significantly improve 3-year disease-free survival; thus, it has become the new standard neoadjuvant therapy approach for stages II and III triple-negative breast cancer.
D. The addition of carboplatin did not significantly increase treatment-related toxicity beyond that of standard taxane-based chemotherapy.

7-7 A patient with metastatic hormone receptor–negative, HER2-positive breast cancer has progressive disease in her liver and lungs after undergoing concomitant treatment with first-line taxane, trastuzumab, and pertuzumab. She is asymptomatic for her disease, and her performance status and organ function are good.

Which of the following would you recommend?
A. Lapatinib and capecitabine
B. Trastuzumab emtansine (T-DM1)
C. Trastuzumab and vinorelbine
D. Trastuzumab and lapatinib

7-8 A patient with hormone receptor–positive breast cancer and bone metastases tells you that she has heard about targeted therapy options whereby hormonal treatment was administered with palbociclib or with everolimus. She wants to know how they compare and contrast.

Which of the following do you tell the patient regarding these two treatment approaches?
A. Palbociclib causes substantial mucositis.
B. Everolimus is recommended in combination with endocrine therapy as first-line treatment for hormone receptor–positive, HER2-negative metastatic breast cancer.
C. Everolimus causes substantial mucositis, which may be largely prevented by a steroid, prescribed as a 2-minute swish-and-spit process four times a day (QID).
D. Both drugs are generally given orally for 3 weeks followed by a week of rest.

7-9 A 46-year-old premenopausal woman had a resected, grade 1, 2-cm, node-negative breast cancer that was strongly hormone receptor–positive, HER2-negative. No adjuvant chemotherapy was recommended. Adjuvant tamoxifen was recommended by the patient's primary oncologist. She presents to you asking for a second opinion with regard to the role of ovarian function suppression in her situation.

Which of the following is true?
A. There are no clinical trial data to provide information regarding the pros and cons of ovarian function suppression in this situation.
B. The SOFT clinical trial demonstrated that the addition of ovarian function suppression to tamoxifen improved disease-free survival in the overall group of study patients evaluated.
C. The SOFT clinical trial demonstrated that the addition of ovarian function

suppression to tamoxifen improved both disease-free survival and overall survival in the overall group of study patients evaluated.

D. In the SOFT clinical trial, the benefit of the addition of ovarian function suppression to endocrine therapy appeared to be confined to patients who received adjuvant chemotherapy, probably because of their younger age and higher-risk disease.

7-10 A 40-year-old, premenopausal woman was diagnosed with a strongly hormone receptor–positive, HER2-negative breast cancer. One axillary lymph node was positive. She received appropriate local regional therapy. It was decided that adjuvant chemotherapy was not to be administered. She was prescribed tamoxifen. The patient asked about the role of bone-modifying agents in her situation.

Which of the following is true?

A. Adjuvant zoledronic acid is helpful for preventing bony metastases in premenopausal women receiving tamoxifen.

B. Adjuvant denosumab has been shown to be superior to zoledronic acid for preventing bony metastases in premenopausal women receiving tamoxifen.

C. A meta-analysis of randomized, placebo-controlled, bisphosphonate trials supports the use of adjuvant bisphosphonates, as they are associated with a reduction in the risk of recurrence, distant recurrence, bone recurrence, and breast cancer mortality for premenopausal women receiving tamoxifen.

D. A meta-analysis of randomized, placebo-controlled, bisphosphonate trials supports the use of adjuvant bisphosphonates, as they are associated with a reduction in the risk of recurrence, distant recurrence, bone recurrence, and breast cancer mortality for postmenopausal women, including premenopausal women receiving ovarian function suppression or who undergo ovarian ablation or therapeutic bilateral salpingo-oophorectomy.

7-11 A 35-year-old woman presents with a family history that includes a 32-year-old sister who was diagnosed with breast cancer and was found to have a *BRCA1* mutation. The patient was tested and has the same *BRCA1* mutation. She has a paternal aunt who was diagnosed with ovarian cancer at age 50. She asks you what it means for her to have this *BRCA1* mutation.

Which of the following is true?

A. Her lifetime risk for the development of breast cancer is in the 50 to 75% range, with an ovarian cancer risk of more than 25%.

B. A risk-reducing bilateral mastectomy would decrease her breast cancer risk by about 50%.

C. A risk-reducing bilateral salpingo-oophorectomy will reduce the risk of ovarian cancer developing by about 50%.

D. If a unilateral breast cancer develops, her risk of a contralateral breast cancer is not any higher than a patient without a *BRCA* mutation.

7-12 A 40-year-old patient comes to you for a second opinion. She was diagnosed with a 2.7-cm, clinically node-negative, hormone receptor–negative, HER2-negative breast cancer

and received neoadjuvant chemotherapy with doxorubicin/cyclophosphamide, followed by weekly paclitaxel. She had a complete clinical response to therapy and then underwent definitive breast surgery. There was a pathologic complete response (pCR) in the breast and axillary lymph nodes. The patient is concerned about her prognosis, given what she has heard about triple-negative breast cancer.

What can you tell her?

A. Her prognosis is poor, as she suspected, given that she had the TNBC, despite the fact she achieved a pCR.
B. Her prognosis is better than that for patients who have significant residual cancer (no pCR) surgically resected.
C. Her prognosis will be improved should she receive platinum-based chemotherapy postoperatively.
D. Her prognosis will be improved should she receive capecitabine for eight cycles postoperatively.

7-13 A patient presents with metastatic breast cancer associated with relatively prominent bony metastases that had both lytic and blastic components. To date, she has not had any substantial pain or other problems related to them. The patient asks about the use of a bone-modifying agent to try to decrease bone-related problems.

Which of the following bone-modifying regimens would you recommend for this patient and why?

A. Zoledronic acid may be preferable because denosumab is associated with higher rates of osteonecrosis of the jaw.
B. Denosumab may be preferable because zoledronic acid causes more hypocalcemia than does denosumab.
C. Zoledronic acid may be preferable, given that randomized data support its administration at 3-month intervals for 2 years, as opposed to 1-month intervals, with similar efficacy.
D. Denosumab may be preferable, as randomized data support its administration at 3-month intervals, as opposed to 1-month intervals, with similar efficacy.

7-14 A patient with HER2-positive breast cancer asks about the utility of pertuzumab for HER2-positive breast cancer.

Which of the following can you tell her?

A. Pertuzumab, when administered with trastuzumab- and taxane-based chemotherapy in the neoadjuvant setting, was associated with a significantly increased pCR rate compared with trastuzumab- and taxane-based chemotherapy alone, thus leading to its accelerated U.S. Food and Drug Administration (FDA) approval in the neoadjuvant setting for management of stages II and III HER2-positive breast cancer.
B. In 2016, pertuzumab was approved by the FDA for the treatment of HER2-positive breast cancer in the adjuvant setting.
C. In HER2-positive metastatic disease, the addition of pertuzumab to

trastuzumab/taxane increases disease-free, but not overall, survival.

D. Pertuzumab does not cause any more toxicity than that commonly seen with trastuzumab.

7. BREAST CANCER RATIONALES

7-1 A

In the first-line setting, palbociclib improved progression-free survival from about 10 months to 20 months (PALOMA-1 phase II randomized trial) and 15 months to 25 months (phase III PALOMA-2 trial). In PALOMA-2, the combination therapy was not associated with an improvement in overall survival. Palbociclib causes neutropenia, its most prominent toxic effect; however, febrile neutropenia is uncommon.

Suggested Reading

Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol.* 2015;16:25–35. doi: 10.1016/S1470-2045(14)71159-3. Epub 2014 Dec 16. PMID: 25524798.

Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375:1925–1936. doi: 10.1056/NEJMoa1607303. PMID: 27959613.

7-2 C

Removal of the ovaries will reduce breast cancer incidence by about 50% and ovarian-type cancer (including primary peritoneal and fallopian tube cancers) incidence by about 85%. Newer information suggests that ovarian-type cancers can arise in fallopian tubes, and thus they are commonly removed when ovaries are removed.

Suggested Reading

Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA*. 2010;304:967–975. PMID: 20810374.

Kauff ND, Domchek SM, Friebel TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. *J Clin Oncol*. 2008;26:1331–1337. PMID: 18268356.

Metcalfe K, Lynch HT, Foulkes WD. Effect of oophorectomy on survival after breast cancer in BRCA1 and BRCA2 mutation carriers. *JAMA Oncol.* 2015;1:306–313. PMID: 26181175.

7-3 A

The 21-gene assay (Oncotype DX) does provide both prognostic and predictive information. Prospective-retrospective data from a single study demonstrate that the 21-gene assay may have utility in patients with positive lymph nodes.

Suggested Reading

Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol.* 2010;11:55–65. PMID: 20005174.

Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med*. 2004;351:2817–2826. PMID: 15591335.

Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol*. 2006;24:3726–3734. PMID: 16720680.

7-4 B

A recent trial involved patients with resected HER2 positive breast cancers that were ≤ 3 cm and node negative. Weekly paclitaxel and trastuzumab was prescribed for 12 weeks followed by trastuzumab monotherapy to complete a full year course. The 3-year progression-free survival in this trial was more than 98%. It is not reasonable to treat her in the neoadjuvant setting, as her lymph node status has not been definitively determined. At this time, pertuzumab and trastuzumab, without cytotoxic chemotherapy, has not been evaluated in this situation.

Suggested Reading

Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med.* 2015;372:134–141. doi: 10.1056/NEJMoa1406281. PMID: 25564897.

7-5 D

Systemic therapy is often administered following completion of local treatment for a locoregional recurrence, based on data supporting its efficacy. An international trial, CALOR (Chemotherapy as Adjuvant for Locally Recurrent Breast Cancer; BIG 1-02/IBCSG 27-02/NSABP B-37), enrolled 162 of a planned 977 patients with invasive breast cancer in whom an isolated local and/or regional ipsilateral recurrence developed following mastectomy or breast-conserving therapy. Patients received radiation therapy, endocrine therapy, or trastuzumab as appropriate, and were also randomly assigned to receive chemotherapy or not. The chemotherapy regimen selection and duration of treatment was per physician choice. The 5-year disease-free survival was improved with chemotherapy (69%) compared with no chemotherapy (57%). The benefit was primarily seen in triple-negative breast cancer (67% vs. 35%, chemotherapy vs. no chemotherapy). The 5-year overall survival was comparable between the two groups; numerically, but not statistically, higher in the chemotherapy group (88% vs. 76%, chemotherapy vs. no chemotherapy). Although this is a highly underpowered study, it does support the use of chemotherapy following local or regional disease recurrence in select circumstances. It is quite reasonable to give platinum-based chemotherapy to this patient with a recurrent triple-negative breast cancer.

Suggested Reading

Aebi S, Gelber S, Anderson SJ, et al. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial. *Lancet Oncol*. 2014;15:156–163. PMID: 24439313.

7-6 B

Given the relationship between pathologic complete response (pCR) and disease-free survival, several neoadjuvant clinical trials have been designed to evaluate novel chemotherapy regimens with an overarching goal of improving on existing pCR rates associated with standard therapy. In CALGB 40603, the addition of neoadjuvant carboplatin to anthracycline- and taxane-based chemotherapy was evaluated in patients with clinical stages II and III triple-negative breast cancer (TNBC). Rates of pCR in the breast and axilla were 41% for standard chemotherapy and 54% when carboplatin was added to the regimen ($p = 0.0029$). This significant improvement in pCR was also achieved when carboplatin was added to a more complex neoadjuvant anthracycline- and taxane-based regimen that included bevacizumab in patients with TNBC (absolute increase of 16.3%) participating in the GeparSixto trial. Despite encouraging results in a population in need of better therapies, the 3-year event-free survival (EFS) results for these trials yielded different conclusions. In CALGB 40603, there was an

absolute gain in EFS of 4.9%; however, this was not statistically significant. In GeparSixto, there was an absolute gain in EFS of 9.7%, that was statistically significant. Notably, patients in GeparSixto had a better overall prognosis (more T1 and N0 disease), a larger incremental benefit from carboplatin, as well as a larger cumulative dose and longer overall duration of anthracycline and taxane chemotherapy, as compared with patients in CALGB 40603. Thus, recognizing that the platinum agents can be toxic and that these trials lack long-term safety data, as well as the discrepant EFS outcomes between these trials, many experts still consider the use of carboplatin in TNBC to be investigational. Biomarkers predictive of carboplatin benefit are needed to help guide patient selection. Optimal dosing and schedule for carboplatin, which also varied in these two trials, remain to be determined. The addition of carboplatin to standard chemotherapy did result in a few notable increased hematologic toxicities (neutropenia and thrombocytopenia).

Suggested Reading

Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). *J Clin Oncol.* 2015;33:13–21. PMID: 25092775.

Sikov WM, Berry DA, Perou CM, et al. Event-free and overall survival following neoadjuvant weekly paclitaxel and dose-dense AC +/– carboplatin and/or bevacizumab in triple-negative breast cancer: outcomes from CALGB 40603 (Alliance). Paper presented at 38th Annual San Antonio Breast Cancer Symposium, December 2015. Abstract S2-05.

von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol.* 2014;15: 747–756. PMID: 24794243.

von Minckwitz G, Loibl S, Schneeweiss A, et al. Early survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto). Paper presented at: 38th Annual San Antonio Breast Cancer Symposium, December 2015. Abstract S2-04.

7-7 B

The EMILIA study evaluated the impact of T-DM1 on progression-free survival (PFS) and overall survival (OS) compared with combination lapatinib and capecitabine among 991 patients with HER2-positive metastatic breast cancer whose disease had progressed following treatment. Treatment with T-DM1 resulted in a 12.8% improvement in overall response rate, a 3-month improvement in PFS, and a 32% reduction in the risk of death, compared with lapatinib and capecitabine; as a result, the FDA approved T-DM1 in 2013. The differences in PFS and OS in favor of T-DM1 were both highly statistically significant. T-DM1 was also less toxic than capecitabine/lapatinib. A second trial, the TH3RESA study, involved 602 patients with recurrent HER2-positive breast cancer randomly assigned to T-DM1 or the treatment of physician's choice. Approximately 30% of the patients enrolled had received more than five prior regimens for recurrent disease. The primary endpoint was PFS and was in favor of T-DM1 (HR, 0.53; $p < 0.0001$). The superiority of T-DM1 was also seen among patients who had received prior trastuzumab. Based on the consistent results from EMILIA and TH3RESA studies, T-DM1 offers an effective and tolerable option for treating HER2-positive disease that has progressed following trastuzumab and taxane chemotherapy.

Suggested Reading

Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 2012;367:1783–1791. PMID: 23020162.

Wildiers H, Kim SB, Gonzalez-Martin A, et al. T-DM1 for HER2-positive MBC: primary results for TH3RESA, a phase 3 study of T-DM1 vs treatment of physicians choice. Paper presented at: European Cancer Congress, Amsterdam, the Netherlands, 2013.

7-8 C

Palbociclib is a CDK4/6 inhibitor that causes neutropenia as its major toxic effect, usually not associated with serious neutropenic infections. It is generally given orally for 3 weeks followed by a week of rest. It does not usually cause substantial mucositis.

Everolimus, which is generally given continuously, can cause substantial mucositis that, per one phase II trial, appears to be largely prevented by dexamethasone, prescribed as a 2-minute swish-and-spit process four times a day (QID). Additionally, at the San Antonio Breast Cancer Symposium in 2016, a prospective phase II randomized trial of two steroid-based mouth rinses as oral prophylaxis for patients receiving 10 mg of everolimus was presented. These two rinses included the following: (1) 320 ml diphenhydramine, 2 g tetracycline, 80 mg hydrocortisone, 40 mg nystatin, and water; or (2) prednisolone 15 mg/ml and 1.8% alcohol. Participants were instructed to swish and spit one of these two solutions four times a day. The incidence of stomatitis and related adverse events appeared to be relatively low in both arms of the study (29% and 27.5% in arms 1 and 2, respectively over 12 weeks). The incidence of grade 2 adverse events was 12% and 8% in arms 1 and 2, respectively.

Everolimus is generally given to patients who have progressed on a first-generation aromatase inhibitor, and it is prescribed with exemestane. It is generally given continuously, as opposed to having rest weeks.

Suggested Reading

Jones VL, Jensen LL, McIntyre KJ, et al. Evaluation of miracle mouthwash (MMW) plus hydrocortisone versus prednisolone mouth rinses as prophylaxis for everolimus-associated stomatitis: preliminary results of a randomized phase II study. *Cancer Res*. 2016;76:abstract P1-15-06.

Rugo HS, Seneviratne L, Beck JT, et al. Prevention of everolimus/exemestane (EVE/EXE) stomatitis in postmenopausal (PM) women with hormone receptor-positive (HR+) metastatic breast cancer (MBC) using a dexamethasone-based mouthwash (MW): Results of the SWISH trial. *J Clin Oncol*. 2016;34(15_suppl):525–525.

7-9 D

The SOFT clinical trial evaluated the role of ovarian function suppression in adjuvant endocrine therapy for premenopausal women with operable breast cancer. In the primary analysis of all patients participating in SOFT, the addition of ovarian function suppression to tamoxifen did not significantly improve disease-free survival (DFS), as compared with tamoxifen alone. However, those who received exemestane with concurrent ovarian function suppression, as compared with tamoxifen alone, did achieve significant gains in DFS and reductions in any breast cancer recurrence and also distant recurrence. This benefit was confined to those who received adjuvant chemotherapy, probably because of their younger age and higher-risk disease.

Suggested Reading

Francis PA, Regan MM, Fleming GF, et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2015;372:436–446. PMID: 25495490.

Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med.* 2014;371:107–118. PMID: 24881463.

7-10 D

Several trials have evaluated the role of bisphosphonates in the adjuvant care of women with early-stage breast cancer. Not only do these agents improve bone health, but some studies have also suggested improvement in breast cancer outcomes. A meta-analysis of 26 trials and data from more than 18,000 individual patients (over 11,000 being postmenopausal) revealed a reduction of recurrence, distant recurrence, bone recurrence, and breast cancer mortality

among postmenopausal women receiving an adjuvant bisphosphonate. Current ASCO/CCO guidelines recommend that, if available, zoledronic acid (4 mg intravenously every 6 months) or clodronate (1600 mg/d orally) be considered as adjuvant therapy for postmenopausal patients with breast cancer who are deemed candidates for adjuvant systemic therapy. Postmenopausal patients include those with natural menopause or ovarian suppression induced by medical therapy or ablation (e.g., surgery or radiation).

Suggested Reading

Coleman R, Powles T, Paterson A, et al. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet.* 2015;386:1353–1361. PMID: 26211824.

Dhesy-Thind S, Fletcher GG, Blanchette PS, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2017;35:2062–2081. doi: 10.1200/JCO.2016.70.7257. PMID: 28618241.

7-11 A

Mutations in *BRCA1* appear to be associated primarily with breast and ovarian cancer risk; this contrasts with *BRCA2* mutations, which can be associated with other malignancies, such as prostate cancer (relative risk [RR] with age younger than 65, 7.33), pancreatic cancer (RR, 3.51), malignant melanoma (RR, 2.58), gallbladder and bile duct cancer (RR, 4.97), and stomach cancer (RR, 2.59). The risk of developing male breast cancer before age 80 is approximately 7% among *BRCA2* mutation carriers. Among women with *BRCA1* or *BRCA2* mutations, the risk of breast cancer over a lifetime is an estimated 50% to 75%. The risk of developing ovarian cancer is higher with a *BRCA1* mutation (30 to 40%) than with a *BRCA2* mutation (10 to 20%). The development of contralateral breast cancer is also increased (RR for *BRCA2,* 3.4; RR for *BRCA1,* 4.5), although this risk is less pronounced among women older than age 50 (10.8%) compared with patients who were diagnosed at younger than age 30 (28.2%).

Suggested Reading

Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. *J Natl Cancer Inst*. 1999;91:1310–1316. PMID: 10433620.

Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol*. 2007;25:1329–1333. PMID: 17416853.

Thompson D, Easton DF. Cancer incidence in BRCA1 mutation carriers. *J Natl Cancer Inst* 2002;94:1358–1365. PMID: 12237281.

7-12 B

Although, in general, TNBC is associated with a less favorable overall prognosis, this subtype of breast cancer is more chemosensitive and has a greater propensity of achieving a pCR with neoadjuvant chemotherapy, compared with hormone receptor–positive disease. Patients with TNBC who achieve a pCR have a favorable OS. While there is information to support that platinum-based chemotherapy is more effective in patients with TNBCs, as opposed to other molecular types of breast cancer, there is no established role for using such therapy in the adjuvant setting. Similarly, the CREATE-X trial suggests that patients with residual HER2-negative breast cancer following neoadjuvant chemotherapy do benefit from adjuvant capecitabine, there is no role for it in patients who achieve a pCR.

Suggested Reading

Haddad TC, Goetz MP. Landscape of neoadjuvant therapy for breast cancer. *Ann Surg Oncol*. 2015;22:1408–1415. PMID:

25727557.
Kaufmann M, Hortobagyi GN, Goldhirsch A, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. *J Clin Oncol*. 2006;24:1940–1949. PMID: 16622270.
Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med. 2017;376:2147–2159. doi: 10.1056/NEJMoa1612645. PMID: 28564564.
von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol*. 2012;30:1796–1804. PMID: 22508812.

7-13 C

Metastatic breast cancer to bone can produce osteoblastic and/or osteolytic bone lesions, both of which are associated with activation of osteoclasts. Breast cancer cells involving the bone can also secrete cytokines that stimulate the receptor activator of nuclear factor kappa B ligand (RANKL) secretion by osteoblasts, which mediates osteoclast survival. Bisphosphonates are pyrophosphate analogs that are internalized by osteoclasts, disrupting function and resulting in apoptosis. Approved bisphosphonates (pamidronate, zoledronic acid) have been shown to reduce the incidence of skeletal-related events (SREs), the time to the occurrence of SREs, and pain. Denosumab, a humanized monoclonal antibody to RANKL, also has been shown to decrease SREs, and in one head-to-head comparison with zoledronic acid, denosumab was found to be more effective in preventing SREs. Zoledronic acid use is associated with renal compromise and requires renal dosing; whereas hypocalcemia is more common with denosumab. Both drugs are associated with about a 2% incidence of osteonecrosis of the jaw.
According to 2011 updated ASCO guidelines, there was not enough evidence to recommend a bisphosphonate over denosumab or vice versa. While past recommendations had been to use either of these drugs monthly, in a presentation at the 2014 annual ASCO meeting, a randomized trial evaluated the use of the second year of zoledronate following a year of monthly dosing. This trial randomly assigned patients to receive zoledronate at monthly versus 3-monthly intervals, with equivalent results. In early 2017, published results from a randomized trial comparing upfront zoledronate at monthly versus 3-monthly intervals for 2 years revealed equivalence. Similar data are not available for denosumab, and the different mechanisms of action for denosumab and zoledronate does not allow for one to assume that the data would be similar for these two drugs.

Suggested Reading

Himelstein AL, Foster JC, Khatcheressian JL, et al. Effect of longer-interval vs standard dosing of zoledronic acid on skeletal events in patients with bone metastases: a randomized clinical trial. *JAMA.* 2017;317:48–58. PMID: 28030702.
Hortobagyi GN, Lipton A, Chew HK, et al. Efficacy and safety of continued zoledronic acid every 4 weeks versus every 12 weeks in women with bone metastases from breast cancer: results of the OPTIMIZE-2 trial. *J Clin Oncol*. 2014;32:abstr LBA9500.
Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol.* 2010;28:5132–5139. doi: 10.1200/JCO.2010.29.7101. Epub 2010 Nov 8. PMID: 21060033.
Van Poznak CH, Temin S, Yee GC, et al. American Society of Clinical Oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. *J Clin Oncol.* 2011;29:1221–1227. PMID: 21343561.

7-14 A

Pertuzumab does improve the pathologic complete response rate in patients with HER2-positive breast cancer who are treated with it in a neoadjuvant setting. The NeoSphere trial was an open-label, phase II study that randomly assigned 417 patients to four cycles of docetaxel combined with either trastuzumab alone, pertuzumab alone, or both agents, versus combination

pertuzumab and trastuzumab without docetaxel (the nonchemotherapy arm). The combination pertuzumab and trastuzumab with docetaxel achieved the highest pCR rate, 39.3%, compared with the other groups. As of 2016, results from a completed adjuvant chemotherapy trial with this drug had not yet been reported. Nonetheless, National Comprehensive Cancer Network (NCCN) guidelines do support that it is reasonable to use pertuzumab in an adjuvant therapy setting, when it might have been used in a neoadjuvant setting, had not the patient was received breast cancer surgery. In the metastatic disease setting, pertuzumab added to trastuzumab/taxane substantially improved disease-free and overall survival (from a median of 40 months to 56 months). Pertuzumab can cause bothersome diarrhea in a substantial proportion of patients, something that is not commonly seen with trastuzumab.

Suggested Reading

Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13:25–32. PMID: 22153890.

Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med.* 2015;372:724–734. PMID: 25693012.

8 LUNG CANCER
SELF-EVALUATION

8. LUNG CANCER QUESTIONS

8-1 A 72-year-old man with a 30-pack-year smoking history is diagnosed with stage IV lung adenocarcinoma metastatic to bone and liver. He has an excellent performance status. Laboratory results are within normal limits. Molecular testing is negative for an *EGFR* mutation, *ALK* translocation, and *ROS1* rearrangement. Tumor programmed death ligand 1 (PD-L1) expression by the Dako 22C3 antibody is high, at 75%.

What is the most appropriate treatment for this patient?

A. Carboplatin/paclitaxel with bevacizumab
B. Cisplatin/pemetrexed
C. Cisplatin/gemcitabine
D. Pembrolizumab

8-2 A 34-year-old female never-smoker presents with cough and shortness of breath. She is diagnosed with stage IV lung adenocarcinoma metastatic to liver, bone, and pleura. Molecular testing shows an *EGFR* exon 19 deletion. The patient is treated with erlotinib and her disease has excellent clinical and radiographic response. One year later she has increasing liver metastases and increased pleural effusion with shortness of breath. The effusion is drained and tumor cells are noted. The cell block is sent for molecular testing and shows a new *EGFR T790M* mutation.

What is the most appropriate treatment for this patient?

A. Cisplatin/pemetrexed
B. Osimertinib
C. Afatinib
D. Cisplatin/gemcitabine

8-3 A 42-year-old woman is diagnosed with stage IV non-small cell lung carcinoma (NSCLC)–adenocarcinoma subtype metastatic to pleura, liver, bone, and adrenal gland. Molecular testing is positive for an *ALK* translocation by fluorescence in situ hybridization (FISH). She is started on crizotinib with an excellent disease response. Ten months later progressive disease develops in her liver, adrenal gland, and lung.

What is the most appropriate next treatment for this patient?

A. Cisplatin/pemetrexed
B. Docetaxel
C. Alectinib
D. Osimertinib

8-4 A 66-year-old man with a 70-pack-year smoking history has a right upper lobectomy for a 5-cm, right-upper-lobe NSCLC with squamous histology. Two hilar lymph nodes are also positive for squamous cell lung carcinoma. Another 10 lymph nodes, including those in the mediastinum, are sampled and negative for cancer. The patient comes to see you in clinic. He recovered well from surgery and has excellent performance status. All laboratory values are within normal limits.

What is the most appropriate next management step for his stage II NSCLC squamous histology?

A. Adjuvant chemotherapy with cisplatin/pemetrexed
B. Adjuvant chemotherapy with carboplatin/paclitaxel paired with bevacizumab
C. Adjuvant nivolumab
D. Adjuvant chemotherapy with cisplatin/docetaxel

8-5 A 54-year-old man presents with right-sided chest wall pain. Chest x-ray reveals a pleural effusion and mass. Positron-emission tomography–computed tomography (PET/CT) demonstrates pleural masses and effusion with fluorodeoxyglucose (FDG)-avid hilar and mediastinal lymph nodes. Pleural biopsy and mediastinoscopy demonstrate mesothelioma epithelioid subtype in both the pleural and the mediastinal lymph nodes. The patient's disease is deemed surgically unresectable. Other than his chest wall pain he has no other symptoms and is active.

What is the most appropriate systemic treatment for this patient's unresectable pleural mesothelioma epithelioid subtype?

A. Cisplatin/pemetrexed
B. Cisplatin/pemetrexed with bevacizumab
C. Cisplatin/gemcitabine
D. Cisplatin/navelbine

8-6 A 68-year-old woman with a 40-pack-year smoking history is diagnosed with stage IV lung adenocarcinoma metastatic to bone and liver. She has an excellent performance status. Laboratory results are within normal limits. Molecular testing is negative for an *EGFR* mutation, *ALK* translocation, and *ROS1* rearrangement. Tumor PD-L1 expression by the Dako 22C3 antibody is low, at 5%.

Which of the following is the most appropriate systemic treatment for this patient's stage IV lung adenocarcinoma?

A. Cisplatin/pemetrexed
B. Erlotinib
C. Cisplatin/gemcitabine
D. Pembrolizumab

8-7 A 64-year-old man with a 60-pack-year smoking history is diagnosed with a 2-cm, right-upper-lobe lung mass on a screening chest CT. Biopsy shows lung adenocarcinoma. PET/CT and magnetic resonance imaging (MRI) of the brain reveal no sites of metastatic disease. He has a video-assisted thoracoscopic surgery (VATS) right upper lobectomy

with a 2-cm right-upper-lobe lung adenocarcinoma. Surgical margins are all negative, and none of the 11 lymph nodes sampled, including 6 mediastinal lymph nodes, show any cancer. He has an excellent performance status. Laboratory results are within normal limits.

What is the most appropriate next step for this patient's lung adenocarcinoma?

A. Adjuvant cisplatin/pemetrexed
B. Observation with follow-up appointments and chest CT
C. Adjuvant cisplatin/vinorelbine
D. Adjuvant pembrolizumab

8-8 A 76-year-old man with a 60-pack-year smoking history is diagnosed with stage IV squamous lung cancer metastatic to bone, pleura, and liver. The patient receives carboplatin and paclitaxel with progressive disease after four cycles of treatment. He still has excellent performance status. Laboratory results are within normal limits.

What the most appropriate next systemic treatment for this patient's stage IV squamous lung carcinoma?

A. Nivolumab
B. Docetaxel
C. Pemetrexed
D. Erlotinib

8-9 A 62-year-old man with a 70-pack-year smoking history presents with right-upper-body chest wall pain, ptosis, miosis, and anhidrosis. He is diagnosed with a 6-cm mass at the right lung apex invading the adjacent rib. Biopsy shows squamous cell lung cancer. PET/CT shows the FDG-avid right apex mass and rib invasion. No other sites of disease are noted. He has excellent performance status. Laboratory and pulmonary-function test results are within normal limits.

What is the most appropriate treatment plan for this patient?

A. Combined chemoradiation
B. Combined chemoradiation followed by surgical resection
C. Surgical resection followed by adjuvant chemotherapy
D. Surgical resection alone

8-10 What is the most common resistance mechanism to first- and second-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs)?

A. *MET* amplification
B. *PIK3CA* mutation
C. *ALK* translocation
D. *EGFR T790M* mutation

8-11 A 63-year-old woman presents with cough. Chest x-ray shows a left-upper-lobe lung mass. PET/CT shows FDG avidity of the lung mass, mediastinal lymph nodes, and bilateral supraclavicular nodes. Biopsy of the right supraclavicular node shows lung

adenocarcinoma. Brain MRI is negative for intracranial metastatic disease. She has an excellent performance status.

What is the most appropriate treatment for this patient?

A. Platinum-based chemotherapy followed by surgical resection
B. Surgical resection followed by platinum-based chemotherapy
C. Platinum-based chemotherapy followed by observation
D. Platinum-based chemotherapy with concurrent radiation
E. Platinum-based chemotherapy with concurrent radiation followed by surgical resection

8-12 A 56-year-old man with a 50-pack-year smoking history is diagnosed with stage IV NSCLC-squamous histology metastatic to bone and liver. He has an excellent performance status. Laboratory results are within normal limits. Tumor PD-L1 expression by the Dako 22C3 antibody is low, at 5%.

What is the most appropriate treatment for this patient?

A. Cisplatin/pemetrexed
B. Carboplatin/paclitaxel with bevacizumab
C. Pembrolizumab
D. Cisplatin/gemcitabine (with or without necitumumab)

8-13 A 65-year-old man with a 70-pack-year smoking history is diagnosed with a left hilar mass. Biopsy reveals small cell lung cancer. PET/CT shows an FDG-avid aortopulmonary window and other ipsilateral mediastinal nodes. MRI of the brain is negative for metastatic disease. His performance status is excellent.

What is the most appropriate initial treatment for this patient?

A. Chemoradiation concurrent with cisplatin/etoposide
B. Chemotherapy with cisplatin/etoposide
C. Chemoradiation concurrent with cisplatin/etoposide followed by surgical resection
D. Chemotherapy with cisplatin/irinotecan

8-14 A 42-year-old male never-smoker presents with cough. Chest x-ray shows a left-lower-lobe lung mass. PET/CT shows that the mass is FDG-avid and that there are FDG-avid metastases to liver, bone, and contralateral lung. MRI of the brain is negative for intracranial metastatic disease. Fine-needle aspiration of a liver metastasis reveals lung adenocarcinoma. There is not enough tissue for molecular testing and determination of PD-L1 expression. The patient has excellent performance status and is minimally symptomatic.

What is the most appropriate next step?

A. Core biopsy of tumor for molecular testing of *EGFR* mutation, *ALK* translocation, and *ROS1* translocation and determination of PD-L1 expression
B. Initiate chemotherapy with cisplatin and pemetrexed.
C. Initiate EGFR-TKI therapy with erlotinib.

D. Initiate chemotherapy with cisplatin/gemcitabine.

8-15 A 47-year-old man with stage IV NSCLC-adenocarcinoma histology on chemotherapy has a worsening cough with shortness of breath. PET/CT shows progression of disease with worsening bilateral lung masses, mediastinal adenopathy, and liver metastases. MRI of the brain is negative for intracranial metastatic disease. Molecular testing demonstrates a *ROS1* translocation.

What is the most appropriate treatment for this patient?

A. Docetaxel
B. Alectinib
C. Osimertinib
D. Crizotinib
E. Erlotinib

8. LUNG CANCER RATIONALES

8-1 D

In the KEYNOTE-024 trial, 305 patients with PD-L1 expression on at least 50% of tumor cells and no *EGFR* mutation or *ALK* translocation were randomly assigned to receive either pembrolizumab or the investigator's choice of platinum-based chemotherapy. The primary endpoint of progression-free survival (PFS) was superior in the pembrolizumab arm compared to chemotherapy arm (median PFS, 10.3 months; 95% CI; 6.7, not reached; vs. median PFS, 6.0 months; 95% CI; 4.2, 6.2; HR, 0.50; 95% CI; 0.37, 0.68; $p < 0.001$). Overall survival (OS) was also significantly and substantially improved in the pembrolizumab arm (HR, 0.60; 95% CI; 0.41, 0.89; $p = 0.005$). The response rate was higher with pembrolizumab (44.8% vs. 27.8%), and treatment-related adverse events of any grade were less frequent (occurring in 73.4% vs. 90.0% of patients), as were serious treatment-related adverse events (26.6% vs. 53.3%). Based on these data, pembrolizumab is now FDA-approved as first-line treatment for stage IV NSCLC with PD-L1 expression on at least 50% of tumor cells using the companion diagnostic Dako 22C3 antibody.

Suggested Reading

Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. *N Engl J Med.* 2016;375(19):1823–1833. PMID: 27718847.

8-2 B

The third-generation EGFR tyrosine kinase inhibitor (TKI) osimertinib binds potently to mutant *EGFR* harboring the *T790M* gatekeeper resistance mutation. It has been approved for use in advanced *EGFR*-mutant non-small cell lung carcinoma (NSCLC) with the *T790M* mutation after progression on prior EGFR-TKI. For these patients, median progression-free survival (PFS) was 9.6 months and objective response rate (RR) was 61%. PFS and objective RR with osimertinib were substantially lower in treated patients with *EGFR-T790M*–negative tumors (PFS, 2.8 months; overall response rate , 21%).

Suggested Reading

Jänne PA, Yang JC, Kim DW, et al., AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med*. 2015;372:1689–9169. PMID: 25923549.

8-3 C

Alectinib and ceritinib are next-generation ALK inhibitors that are active in *ALK*-rearranged NSCLC that has progressed on crizotinib. The FDA approved alectinib in 2015 for the treatment of *ALK*-rearranged NSCLC after progression of disease on crizotinib. This approval was based on clinical trials in metastatic *ALK*-rearranged NSCLC showing a response rate of 50% in patients with progressive disease on crizotinib with median duration of response of 11.2 months. It is also highly active in the central nervous system (CNS) with CNS response rates of 64.0% (95% CI; 49.2, 77.1), CNS disease control rate of 90.0% (95% CI; 78.2, 96.7), and median CNS duration of response of 10.8 months in a pooled analysis.

Suggested Reading

Gadgeel SM, Gandhi L, Riely GJ, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. *Lancet Oncol.* 2014;15:1119–1128. Epub 2014 Aug 18. PMID: 25153538.

8-4 D

The patient has stage II NSCLC-squamous histology based on hilar lymph nodes positive for squamous cell lung cancer. Multiple clinical trials and meta-analyses have shown the benefit of adjuvant cisplatin-based chemotherapy in this setting. The benefit of carboplatin-based therapy is less well-proved. Pemetrexed is not approved or as effective in squamous cell histology NSCLC. Adjuvant programmed death 1 inhibitors are currently being studied in clinical trials, but their efficacy in the adjuvant setting is not yet proven. The ECOG 1505 clinical trial showed no benefit to adjuvant bevacizumab in NSCLC and carboplatin. In this study, all cisplatin-based regimens tested were comparable as adjuvant-based therapy.

Suggested Reading

Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med.* 2004;350:351–360. PMID: 14736927.

Douillard JY, Rosell R, De Leana M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol.* 2006;7:719–727. PMID: 16945766.

Pignon, JP, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol.* 2008 Jul 20;26(21):3552–3559. PMID: 18506026.

Wakelee HA, et al. E1505: Adjuvant chemotherapy +/- bevacizumab for early stage NSCLC—Outcomes based on chemotherapy subsets. *J Clin Oncol.* 2016;34 (suppl; abstr 8507).

8-5 B

A phase III study in which cisplatin was compared with cisplatin/pemetrexed demonstrated a 9-month median survival for patients treated with cisplatin alone and a 12-month survival for patients treated with the combination ($p = 0.02$), making this regimen, until recently, the standard of care for patients with advanced mesothelioma. Response rates were 41.3 and 16.7% in the pemetrexed/cisplatin arm and control arm, respectively. In a more recent randomized, phase III trial, bevacizumab added to cisplatin/pemetrexed improved OS (median, 18.8 months; 95% CI; 15.9, 22.6, vs. 16.1 months; 95% CI; 14.0, 17.9; HR, 0.77; 95% CI; 0.62, 0.95]; $p = 0.0167$). More grade 3 or higher hypertension (23% vs. 0%) and thrombotic events (6% vs. 1%) were noted with bevacizumab. Thus, cisplatin/pemetrexed with bevacizumab should be considered the new standard of care in patients with unresectable

malignant pleural mesothelioma who are bevacizumab-eligible.

Suggested Reading

Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol.* 2003;21:2636–2644. PMID: 12860938.

Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet.* 2016;387:1405–1414. PMID: 26719230.

8-6 A

Pembrolizumab is approved as first-line treatment for PD-L1 expression of at least 50% of tumor cells. Erlotinib is inferior to platinum-based chemotherapy in EGFR wild-type stage IV non-small cell lung carcinoma (NSCLC). Overall survival and progression-free survival is superior with cisplatin/pemetrexed compared to cisplatin/gemcitabine in stage IV nonsquamous NSCLC.

Suggested Reading

Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med.* 2009;361:947–957. PMID: 19692680.

Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823–1833. PMID: 27718847.

Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol.* 2008;26:3543–3551. PMID: 18506025.

8-7 B

The patient has a stage IA NSCLC. No benefit has been shown for adjuvant chemotherapy in stage IA NSCLC. In the LACE meta-analysis there was even a trend toward harm when stage IA patients were treated with adjuvant chemotherapy.

Suggested Reading

Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol.* 2008;26:3552–3559. PMID: 18506026.

8-8 A

In the phase III CHECKMATE-017 trial that randomly assigned 272 patients with stage IV squamous cell lung cancer with progression on or after platinum-based chemotherapy to nivolumab or docetaxel, OS was substantially improved (median, 9.2 months vs. 6.0 months, $p < 0.001$; HR, 0.59; 1-year OS, 42% vs. 24%). Unlike nonsquamous NSCLC, clinical outcome to nivolumab was not associated with PD-L1 expression in squamous NSCLC.

Suggested Reading

Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373:123–135. PMID: 26028407.

8-9 B

Pancoast, or superior sulcus tumors, in the upper lobe adjoining the brachial plexus are frequently associated with Horner syndrome (ptosis, miosis, and anhidrosis) or shoulder and arm pain; the latter is caused by rib destruction, involvement of the seventh cervical vertebra or

T1 nerve roots, or both. The Southwest Oncology Group (SWOG) intergroup phase II trial involving patients with T3/4N0/1M0 superior sulcus NSCLC established the current standard of care, which consists of cisplatin/etoposide and concomitant radiation therapy 45 Gy followed by attempted surgical resection. Among patients with available surgical specimens, 54 (65%) showed either a complete pathologic response or minimal microscopic disease on pathologic evaluation. The 2-year survival rate was 55% for all eligible patients and 70% for patients who had a complete resection.

Suggested Reading

Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Clin Oncol.* 2007;25:313–318. PMID: 17235046.

8-10 D

EGFR T790M prevents first- and second-generation EGFR-TKIs such as erlotinib, gefitinib, and afatinib from fastening to the ATP-binding domain of EGFR. It occurs in 50 to 60% of tumors resistant to these earlier EGFR-TKIs. Osimertinib has activity against *EGFR T790M* and is approved for patients whose tumors harbor this mechanism of resistance.

Suggested Reading

Jänne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med.,* 2015;372:1689–1699. PMID: 25923549.

Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med.* 2011;3:75ra26. PMID: 21430269.

8-11 D

The patient has stage IIIB NSCLC, for which surgery is not indicated. Concurrent chemotherapy and radiation has a small but not insignificant 5-year survival of approximately 15% in stage IIIB NSCLC.

Suggested Reading

Albain KS, Crowley JJ, Turris AT 3rd, et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. *J Clin Oncol.* 2002;20:3454–3460. PMID: 12177106.

Gandara DR, Chansky K, Albain KS, et al. Long-term survival with concurrent chemoradiation therapy followed by consolidation docetaxel in stage IIIB non-small-cell lung cancer: a phase II Southwest Oncology Group Study (S9504). *Clin Lung Cancer.* 2006;8:116–121. PMID: 17026812.

8-12 D

A phase III trial of more than 1700 patients with chemotherapy-naive disease has been reported, comparing pemetrexed/cisplatin with gemcitabine/cisplatin. OS was the same between the two arms, with an improved toxicity profile in the pemetrexed arm. However, in a prespecified subset analysis, OS was statistically superior for cisplatin/pemetrexed compared with cisplatin/gemcitabine for patients with adenocarcinoma (12.6 months vs. 10.9 months) and large cell carcinoma histology (10.4 months vs. 6.7 months). Conversely, patients with squamous cell histology experienced a significant improvement in survival with cisplatin/gemcitabine compared with cisplatin/pemetrexed (10.8 months vs. 9.4 months). Necitumumab modestly improved OS when added to cisplatin and gemcitabine in squamous NSCLC. In the SQUIRE trial, 1093 patients were randomly assigned to receive either

cisplatin/gemcitabine or cisplatin/gemcitabine plus necitumumab. The addition of necitumumab modestly improved OS (median, 11.5 months vs. 9.9 months; HR, 0.84; p = 0.012) and progression-free survival (PFS) (HR, 0.85; p = 0.020), though no difference in overall response rate (ORR) was noted (31% vs. 29%; p = 0.400).

Suggested Reading

Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol.* 2008;26:3543–3551. PMID: 18506025.

Thatcher N, Hirsch FR, Luft AV, et al. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. *Lancet Oncol.* 2015;16:763–774. PMID: 26045340.

8-13 A

The patient has limited-stage small cell lung cancer. Adding radiation therapy to the thorax in addition to chemotherapy with cisplatin/etoposide is associated with a small but significant improvement in long-term survival for patients with limited-stage disease, providing an additional 5% improvement in 3-year survival compared with chemotherapy alone. Chemotherapy given concurrently with thoracic radiation is superior to sequential chemoradiation.

Suggested Reading

Murray N, Coy P, Pater JL, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. *J Clin Oncol.* 1993;11:336–344. PMID: 8381164.

Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet.* 2015;385:36–42. PMID: 25230595.

Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med.* 1999;340:265–271. PMID: 9920950.

Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. *J Clin Oncol.* 1992;10:890–895. PMID: 1316951.

8-14 A

All patients with stage IV nonsquamous NSCLC should have molecular testing for *EGFR* mutation, *ALK* translocation, and *ROS1* translocation as well as patients with a squamous histology and a light smoking history or scant tissue specimen. Broad genomic profiling for additional potentially actionable molecular alterations is also recommended. All patients should also have quantification of PD-L1 expression for eligibility for first-line pembrolizumab based on improvement of PFS and OS compared to platinum-based chemotherapy when expression is at least 50%. The patient is minimally symptomatic from his disease, so a repeat biopsy is feasible.

Suggested Reading

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer Version 1.2018 – November 17, 2017. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

8-15 D

ROS1 gene rearrangements are oncogenic drivers present in about 2% of NSCLC tumors. *ROS1* is an orphan tyrosine kinase of the insulin receptor family located on chromosome 6 and with sequence homology to ALK. Gene rearrangements of *ROS1* lead to constitutive activation of this tyrosine kinase. Like many oncogene-addicted lung cancers, *ROS1*-rearranged tumors commonly arise in young nonsmokers with lung adenocarcinoma histology. In addition to being

an *ALK* and *MET* inhibitor, crizotinib is a potent inhibitor of *ROS1* and has impressive activity in lung cancers with *ROS1* gene rearrangements, as evident from an exceptionally high ORR (~72%) and median PFS (19.2 months).

Suggested Reading

Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Eng J Med.* 2014;371:1963–1971. PMID: 25264305.

9 HEAD AND NECK CANCERS
SELF-EVALUATION

9. HEAD AND NECK CANCERS QUESTIONS

9-1 A 72-year-old man with a history of a thyroid goiter presents to an emergency department with a rapidly enlarging mass in his lower right neck and difficulty breathing. He is found to have stridor on physical exam, and an emergent tracheostomy is placed. During this procedure, a biopsy of the thyroid mass is also completed, which reveals an undifferentiated malignancy replacing normal thyroid gland and composed of undifferentiated epithelial cells with significant atypia and high mitotic activity. Tumor necrosis and vascular invasion are seen, and the tumor does not stain positive for thyroid transcription factor 1 (TTF-1). Computed tomography with contrast of the neck confirms a 4.5-cm mass arising from the left lobe of the thyroid gland with extension into adjacent structures, including the trachea. Further staging identifies multiple nodules in both lungs suspicious for metastatic disease. The family asks you to be honest about diagnosis and prognosis of this cancer.

Which of the following statements would be true about his diagnosis?

A. The brain is an uncommon site of metastasis.
B. Surgical resection would be recommended at this time.
C. Palliative radiation can be used to control disease in the neck and provide relief for breathing symptoms.
D. The prognosis is good, with a median survival of more than 6 years.

9-2 A 45-year-old man was incidentally found by his primary care physician to have a nontender, mobile lymph node in his right neck on physical exam. When the mass persisted after a course of antibiotics, he was referred to an ear, nose, and throat doctor, who confirmed a single lymph node in the right neck but did not find any other abnormalities on physical exam. He performed an excisional biopsy of the lymph node 1 week later and confirmed a basaloid poorly differentiated squamous cell carcinoma, positive for p16 by immunohistochemistry. The results of FDG-PET are worrisome for two additional malignant lymph nodes in the right neck and some mild, asymmetric uptake in the right base of the tongue but no evidence of distant metastatic disease.

What is the next step in management?

A. Radiation therapy alone to the right base of tongue and right neck
B. Exam under anesthesia and biopsies to identify a potential primary site
C. Induction chemotherapy therapy followed by chemotherapy and radiation
D. Concurrent chemotherapy and radiation therapy followed by three cycles of adjuvant chemotherapy

9-3 A 60-year-old man was treated 4 months ago for a locally advanced laryngeal cancer

with concurrent cisplatin and radiation therapy. He has finally recovered from the toxic effects of treatment and completes a routine posttreatment PET/CT scan. Although he is asymptomatic, the PET/CT reveals bilateral lung nodules and multiple liver lesions consistent with metastatic disease. Biopsy of one of the liver lesions confirms a moderately differentiated squamous cell carcinoma histologically consistent with the primary laryngeal cancer.

Which of the following is an FDA-approved treatment for this patient?

A. Hepatic artery embolization for the liver lesions
B. Nivolumab, 3 mg/kg every 2 weeks
C. A regimen of gemcitabine 1000 mg/m^2 (days 1 and 8) and cisplatin 80 mg/m^2 (day 1) every 3 weeks
D. Carboplatin at a dose of area under the curve (AUC) 5 and paclitaxel at a dose of 175 mg/m^2 every 3 weeks

9-4 A 60-year-old man with a lifelong history of chewing tobacco is diagnosed with a T4bN2b cancer of the tongue. The patient is considered a candidate for concurrent cisplatin and radiation therapy but asks if getting chemotherapy first (or induction) chemotherapy could help him at all.

Which of the following statements about induction chemotherapy is most accurate?

A. The combination of docetaxel/cisplatin/5-fluorouracil (5-FU) resulted in better response rates and overall survival compared to cisplatin/5-FU when used as induction chemotherapy.
B. Induction chemotherapy followed by chemoradiation led to an improved overall survival compared to chemoradiation alone.
C. Induction chemotherapy with cisplatin/5-FU followed by radiation alone leads to improved tumor control compared to concurrent cisplatin and radiation.
D. A common toxicity of induction therapy with docetaxel/cisplatin/5-FU is cardiac dysfunction presenting as heart failure or arrhythmia.

9-5 A 62-year-old man who had never smoked noted a new hoarseness that he initially thought was laryngitis. When it persisted, he was seen by an ear, nose, and throat doctor, who performed a diagnostic laryngoscopy in the office identifying a small ulcerated mass arising from the left vocal cord without significant extension and measuring about 1.5 cm in greatest diameter. The vocal cords were mobile bilaterally. The patient reported no difficulty with swallowing or pain. A biopsy confirmed a squamous cell carcinoma. He was diagnosed with a stage I glottic cancer and radiation therapy was recommended.

Which of the following statements is most appropriate about this case?

A. This tumor will stain positive for human papillomavirus.
B. Chemotherapy should be administered concurrently with the radiation.
C. The patient should undergo surgical resection before radiation therapy.
D. Gastroesophageal reflux disease is a known risk factor for laryngeal cancer.

9-6 A 65-year-old woman with a long history of metastatic papillary thyroid cancer with known pulmonary nodules that had been relatively stable over the prior 3 years presented for evaluation. She had undergone a thyroidectomy and neck node dissection 7 years ago and received radioactive iodine ablative treatment on three separate occasions. Her most recent radioactive iodine scan performed a month ago was negative for uptake. FDG-PET with cross-sectional imaging revealed a dramatic increase in the activity, number, and size of innumerable pulmonary metastases.

Which of the following is an FDA-approved medication for metastatic papillary thyroid cancer?

A. Lapatinib
B. Gemcitabine
C. Lenvatinib
D. Pembrolizumab

9-7 A 48-year-old woman with a history of metastatic medullary carcinoma of the thyroid presented for routine follow-up. She was originally diagnosed with medullary thyroid cancer about 8 years ago and was originally treated with thyroidectomy. Soon after diagnosis, she was found to have asymptomatic nodules that remained relatively stable and asymptomatic, so she was on active surveillance. Recently she received external-beam radiation therapy to palliate pain related to a new bone lesion and was also found at that time to have enlargement of bilateral pulmonary nodules. Tumor markers, including calcitonin and carcinoembryonic antigen, have also doubled in the past 6 months. She was started on vandetanib 300 mg daily.

Which of the following is a commonly reported toxicity associated with vandetanib therapy?

A. Cardiomyopathy
B. Diarrhea
C. Leukopenia
D. Neuropathy

9-8 A 42-year-old man from mainland China was originally diagnosed with a locally advanced Epstein Barr virus (EBV)–related nasopharyngeal cancer to the cervical lymph nodes. He was treated with concurrent cisplatin and radiation but elected not to pursue adjuvant chemotherapy at that time. It had been 2 years since his initial treatment when a cough developed that prompted a chest x-ray, which revealed a potential nodule in the right lung. A subsequent CT scan of the chest, abdomen, and pelvis confirmed multiple suspicious lesions in the mediastinal lymph nodes, lung, and liver. A biopsy of one of the lung nodules confirmed metastatic EBV-related nasopharyngeal cancer. He has no other medical problems and is relatively asymptomatic from his tumor except for the cough.

Which of the following combinations has level I evidence for the first-line treatment of recurrent or metastatic nasopharyngeal carcinoma?

A. The combination of docetaxel/cisplatin/5-fluorouracil
B. The combination of cetuximab and paclitaxel

C. The combination of cisplatin and gemcitabine
D. The combination of carboplatin and paclitaxel

9. HEAD AND NECK CANCERS RATIONALES

9-1 C

This presentation is consistent with an anaplastic thyroid cancer (ATC). While ATC makes up about 5% of all thyroid cancers, it is responsible for about 50% of deaths attributed to a thyroid cancer. It presents as metastatic disease in most cases, including to the brain. The 5-year survival is estimated at 5%, and the median survival at presentation is generally less than 6 months. Surgical resection is not recommended, given the inability to complete adequate oncologic resection and the aggressive nature of the metastatic lesions. Palliative radiation to the neck is considered to improve quality of life.

Suggested Reading

Akaishi J, Sugino K, Kitagawa W, et al. Prognostic factors and treatment outcomes of 100 cases of anaplastic thyroid carcinoma. *Thyroid.* 2011; 21:1183–1189. PMID: 21936674.

9-2 B

This patient has a p16-positive squamous cell carcinoma of unknown primary site at the moment, with suggestion of the right base of the tongue as the primary site. Given the importance in confirming a primary site to limit the potential radiation field, it is important to consider further workup with an exam under anesthesia and biopsies before proceeding with further treatment.

Suggested Reading

Mendenhall WM, Mancuso AA, Amdur RJ, et al. Squamous cell carcinoma metastatic to the neck from an unknown head and neck primary site. *American Journal of Otolaryngology*. 2001;22(4):261–267. PMID: 11464323.

9-3 B

The patient now has a platinum-refractory head and neck squamous cell carcinoma (HNSCC), defined as progression of disease within 6 months of platinum therapy. Based on the results of Checkmate-141, a randomized phase III study of nivolumab or standard-care chemotherapy (docetaxel, cetuximab, or methotrexate) in patients whose disease progressed after platinum therapy, patients treated with nivolumab were more likely to be alive at 1 year. Although carboplatin and paclitaxel are often used in routine care, nivolumab is the agent that has FDA approval. The combination of gemcitabine and cisplatin is used in the management of recurrent or metastatic nasopharyngeal cancer.

Suggested Reading

Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2007;357:1695–1704. PMID: 17960012.

9-4 A

In this T4b tumor, which is by definition unresectable, both concurrent systemic chemotherapy with cisplatin plus radiation therapy or induction therapy followed by concomitant chemotherapy with radiation could be considered. However, two randomized, phase III trials have shown that

the use of induction chemotherapy yielded superior results with a three-drug regimen of taxanes, cisplatin, and 5-FU when compared with the two-drug regimen of cisplatin and 5-FU. There were increased rates of neutropenia in the three-drug arm compared to cisplatin/5-FU alone. Multiple studies have failed to show a survival benefit of induction therapy followed by concurrent chemoradiation in an unselected cohort of patients with head and neck cancer who had locally advanced disease.

Suggested Reading

Cohen EEW, Karrison TG, Kocherginsky M, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. *J Clin Oncol.* 2014; 32: 2735–2743. PMID: 25049329.

Hitt R, Grau JJ, López-Pousa A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. *Ann Oncol.* 2014;25:216–225.PMID: 24256848.

Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med.* 2007;357:1705–1715. PMID: 17960013.

Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med.* 2007;357:1695–1704. PMID: 17960012.

9-5 D

Most HPV-related tumors arise in the oropharynx. Radiation therapy alone is a reasonable approach to patients with early-stage laryngeal cancer, and surgery is required only if there is evidence of persistent or recurrent disease. Chemotherapy is recommended only for advanced tumors. Risk factors for the development of laryngeal tumors include smoking cigarettes and chronic reflux disease.

Suggested Reading

Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. *Lancet.* 2008;371:1695–1709. PMID: 18486742.

Chung CH, Zhang Q, Kong CS, et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. *J Clin Oncol.* 2014;32:3930–3938. PMID: 25267748.

9-6 C

The FDA first approved doxorubicin for the management of differentiated thyroid cancer based on a nonrandomized study demonstrating a response rate of 20%. Sorafenib was approved by the FDA following positive results from the randomized DECISION trial. Lenvatinib is the drug most recently approved for the treatment of locally recurrent or progressively metastatic differentiated thyroid cancer that is refractory to radioactive iodine treatment. The remainder of agents are not currently approved for the management of differentiated thyroid cancer.

Suggested Reading

Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in locally advanced or metastatic, radioactive iodine-refractory, differentiated thyroid cancer: a randomized, double-blind, phase 3 trial. *Lancet.* 2014;384:319–328. PMID: 24768112.

Gottlieb J, Hill S. Chemotherapy of thyroid cancer with Adriamycin — experience with 30 patients. *N Engl J Med.* 1974; 290:193–197. PMID: 4808917.

Schlumberger M, Tahara M, Wirth L, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med*. 2015;372:621–630. PMID: 25671254.

9-7 B

Medullary thyroid cancer arises from the parafollicular, or C, cells and therefore is not sensitive to radioactive iodine therapy. Vandetanib is an oral tyrosine kinase inhibitor that targets RET and is FDA-approved for the treatment of progressive metastatic medullary thyroid cancer. In a

pivotal study, patients treated with vandetanib experienced a substantial improvement in progression-free survival, which was not reached but was estimated to be 30.5 months, compared to 19.3 months in the placebo arm. Side effects commonly seen with vandetanib therapy include diarrhea, fatigue, rash, mucositis, liver-function test elevation, anemia, and thrombocytopenia. Neuropathy, leukopenia, and cardiomyopathy are not normally associated with vandetanib therapy.

Suggested Reading

Haddad R. How to incorporate new tyrosine kinase inhibitors in the treatment of patients with medullary thyroid cancer. *J Clin Oncol.* 2013;31:3618–3620. PMID: 24002516.

Wells SA, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol.* 2012;30:134–141. PMID: 22025146.

9-8 C

There are multiple active agents for the management of recurrent or metastatic nasopharyngeal cancer, but results of a phase III trial of gemcitabine 1000 mg/m^2 (days 1 and 8) and cisplatin 80 mg/m^2 showed an improved progression-free survival compared to cisplatin 80 mg/m^2 and 5-fluoruracil 4000 mg/m^2 in a 96-hour continuous infusion of 7.0 months (range, 4.4–10.9) versus 5.6 months (3.0–7.0) (hazard ratio, 0.55; 95% CI; 0.44, 0.68]; $p < 0.0001$). The combination of docetaxel, cisplatin, and 5-fluoruracil is a standard induction regimen not generally combined for nasopharyngeal cancer. Cetuximab is not routinely used for EBV-related nasopharyngeal cancer.

Suggested Reading

Zhang L, Huang Y, Hong S, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomized open-label, phase 3 trial. *Lancet.* 2016;388:1883–1892. PMID 27567279.

10 GASTROINTESTINAL CANCERS
SELF-EVALUATION

10. GASTROINTESTINAL CANCERS QUESTIONS

10-1 A 50-year-old man presents to his primary care physician for an annual evaluation. He is an obese white male, with a body mass index of 32 and has a stressful job working in finance. He has chronic heartburn and does not exercise regularly. He had an endoscopy several years ago that revealed reflux esophagitis. He undergoes another endoscopy, which reveals a distal esophageal adenocarcinoma.

What is the most likely risk factor for this patient's malignancy?

A. Esophageal achalasia
B. Barrett's esophagus
C. Reflux gastritis
D. Plummer–Vinson syndrome

10-2 A 62-year-old woman presents with a 3-month history of progressive dysphagia. She has lost 10 lb. She is referred for an upper endoscopy, which reveals a distal esophageal mass; biopsy confirms adenocarcinoma. The patient has a CT scan of the chest, abdomen, and pelvis, which identifies a mass at the gastroesophageal junction, with slightly enlarged lymph nodes, measuring 1.5 to 2 cm, located at the gastroesophageal junction. There is no evidence of distant metastatic disease.

Which of the following is the most appropriate next test or management recommendation?

A. Systemic chemotherapy for metastatic esophageal cancer to lymph nodes
B. Endoscopic ultrasound to complete staging
C. PET scan to complete staging
D. Referral for resection

10-3 A 44-year-old man presents to his internist with dysphagia and a 10-lb weight loss. He has been fatigued for the past 6 months, and despite eating less, finds his stomach to be distended. He is found to have a distal gastric cancer on upper endoscopy, and biopsy reveals a poorly differentiated adenocarcinoma. CT scan of chest, abdomen, and pelvis reveal bilobar liver metastases, confirmed to be adenocarcinoma on CT-guided fine-needle aspiration. He presents to you for consideration of treatment. You order a molecular profile of his tissue biopsy, which reveals the following: mutations in *TP53, SMAD4,* and *RUNX1,* no mutations in *KRAS* or *NRAS*, and *ERBB2* amplification (FISH 2.4).

What is the most appropriate treatment for this patient?

A. Epirubicin/cisplatin/5-fluorouracil + trastuzumab

B. Cisplatin/capecitabine + cetuximab
C. Cisplatin/capecitabine
D. Cisplatin/capecitabine + trastuzumab

10-4 A patient with metastatic gastric cancer presents to your office for a second opinion. His tumor is HER2-negative. He had been treated with FOLFOX chemotherapy for 6 months before discontinuing oxaliplatin because of progressive neuropathy, but he continued leucovorin/5-fluorouracil. His disease progressed after 8 months of systemic therapy (e.g., 6 months of FOLFOX plus 2 months of LV/5-FU), and a CT scan shows new bilateral pulmonary metastases. You discuss treatment options with him. He has grade I neuropathy but remains functional and active. His laboratory evaluation includes hemoglobin 11.5 g/dL, platelets 172,000/mm, and adequate kidney and liver function.

Which of the following is the most appropriate management recommendation?
A. Paclitaxel + ramucirumab
B. Resume oxaliplatin (e.g., FOLFOX)
C. Best supportive care
D. Paclitaxel + trastuzumab

10-5 You meet a patient with newly diagnosed diffuse gastric cancer in consultation. The patient is a 38-year-old man who presented with early satiety and a 15-lb weight loss. He has a family history of gastric cancer in his mother and maternal aunt (both diagnosed in their 50s), and a cousin on his mother's side has lobular breast cancer.

What is the most likely genetic defect that is responsible for this patient's family history?
A. Mutation in *MLH1*
B. Mutation in *TP53*
C. Mutation in *CDH1*
D. Mutation in *CTNNB1*

10-6 A 68-year-old woman with no significant comorbidities presents to you for consultation following abdominal surgery for a pancreatic mass. The patient was found to have a 4.2 cm × 3.6 cm pancreatic head mass with invasion of the duodenum. No adenopathy was identified, and it was a well-differentiated adenocarcinoma. The patient underwent a pancreaticoduodenectomy 4 weeks ago and has recovered remarkably well. She is maintaining her weight, and on examination, she is generally well, with a mild superficial seroma at the site of her midline abdominal wound. After searching the internet, she is anxious about her risk of recurrence and wants her treatment to be the most aggressive it can be.

What would be the most appropriate management once her abdominal wound heals?
A. FOLFIRINOX
B. Gemcitabine, docetaxel, and capecitabine
C. Radiation to the pancreatic bed
D. Gemcitabine/capecitabine

10-7 A 56-year-old woman presents with bandlike abdominal pain that has been progressive over the past several months and recently has woken her at night. A CT scan reveals a mass in the proximal duodenum, adjacent to the pancreatic head. There is biliary ductal and pancreatic ductal dilatation. No evidence of metastases are identified. On endoscopic ultrasonography, an ampullary mass is identified without extension into the pancreas and no involvement of the celiac or superior mesenteric arteries. Biopsy reveals an adenocarcinoma with hepatobiliary-type histology. The patient is referred for a Whipple procedure. He asks about his prognosis.

Assuming a complete resection, relative to pancreatic cancer, what is this patient's most likely prognosis?

A. Same as a pancreatic head cancer
B. Same as a pancreatic tail cancer
C. Generally worse than pancreatic head cancer
D. Generally better than pancreatic head cancer

10-8 A 44-year-old, non-obese woman presents to her primary care office with abdominal pain. A CT scan reveals a 1.8-cm lesion in the right hepatic lobe (segment 7). A workup is negative for hepatitis B and C, and there is no evidence of cirrhosis or nonalcoholic steatohepatitis (NASH). Her AFP was 10.5 ng/ml (normal is < 8.5 ng/ml). The patient has no family history of malignancy. She is referred to a hepatobiliary surgeon for resection.

What is the most likely diagnosis of malignancy in this patient?

A. Fibrolamellar cancer
B. Hepatocellular cancer
C. Focal nodular hyperplasia
D. Cholangiocarcinoma

10-9 A 68-year-old man was found to have multifocal hepatocellular cancer with metastases to the lungs. The patient has a history of hepatitis C, previously treated and cured, though not before the development of cirrhosis. The patient received sorafenib therapy, which he tolerated well. He recently discontinued sorafenib treatment after 10 months, with disease progression in his liver. He presents to you for consultation regarding further therapy. His liver-function tests remain within normal limits, with a platelet count of 105,000/mm^3, hemoglobin of 10.5 g/dL, and a prothrombin time international normalized ratio (PT INR) of 1.6.

Which of the following is the most appropriate next step?

A. Referral to interventional radiology for liver-directed therapy
B. Therapy change to regorafenib or nivolumab
C. Referral to radiation oncology for external beam radiotherapy
D. Addition of doxorubicin to sorafenib

10-10 A 56-year-old accountant was recently diagnosed with sigmoid colon cancer. She undergoes a left hemicolectomy, and the pathology report states poorly differentiated adenocarcinoma with mucinous nests, with extension beyond the pericolic adipose tissue,

pT4N2, with 3 of 18 lymph nodes identified in the surgical specimen containing malignancy. The patient is very anxious.

Would oxaliplatin-based adjuvant therapy be considered, and if so, for how long?

A. Oxaliplatin-based adjuvant therapy is indicated for 6 months
B. Oxaliplatin-based adjuvant therapy is indicated for 3 months
C. Oxaliplatin-based adjuvant therapy is indicated for 12 months
D. Oxaliplatin-based adjuvant therapy is not indicated

10-11 A 54-year-old man has metastatic *KRAS*-mutant colorectal cancer of the descending colon, with metastases to the liver and lungs. He has received multiple lines of therapy over 2.5 years and his disease is refractory to oxaliplatin, fluoropyrimidines, and irinotecan. He is considering either regorafenib or TAS-102 treatment, and he comes to you for an opinion. He wants to know which treatment will give him the best chance of response.

Which of the following is the most appropriate advice you can give this patient?

A. TAS-102 has a higher response rate than regorafenib.
B. Regorafenib has a higher response rate than TAS-102.
C. Both drugs have a response rate of around 10%.
D. The two drugs are similar, with very few patients who achieve a partial response to therapy.

10-12 A 48-year-old man presents with rectal bleeding. He was found to have a fungating mass about 6 cm from the anal verge, with biopsy confirming adenocarcinoma. Preoperative staging, including endorectal ultrasonography and pelvic MRI reveals a clinical stage T3N1 locally advanced rectal cancer. The patient is wondering about the value of preoperative fluorouracil-sensitized radiotherapy.

Preoperative chemoradiotherapy is most likely to benefit which of the following?

A. Overall survival in patients with locally advanced rectal cancer
B. Improved rate of local recurrence and overall survival for locally advanced rectal cancer
C. Improved rate of local recurrence but no improvement in overall survival for locally advanced rectal cancer
D. Reduced toxicity and rate of local recurrence, but no impact on overall survival for locally advanced rectal cancer

10. GASTROINTESTINAL CANCERS RATIONALES

10-1 B

Barrett's esophagus is the primary risk factor for esophageal adenocarcinoma. It is associated with obesity and commonly observed in white men working in high-stress positions. Achalasia and Plummer–Vinson syndrome are risk factors for squamous cell carcinoma.

Suggested Reading

Crew KD, Neugut AI. Epidemiology of upper gastrointestinal malignancies. *Semin Oncol*. 2004;31:450–464. PMID: 15297938.
Shaheen N, Ransohoff DF. Gastroesophageal reflux, Barrett esophagus, and esophageal cancer: scientific review. *JAMA.* 2002;287:1972–1981. PMID: 11960540.

10-2 C

The patient has a locally advanced distal esophageal adenocarcinoma, with evidence of wall thickening and regional lymph node metastases. A PET scan is indicated to identify occult metastatic disease, as its identification would change the treatment approach. An endoscopic ultrasound will not add to the staging information.

Suggested Reading:

Ajani JA, D'Amico TA, Almhanna K, et al. Esophageal and esophagogastric junction cancers, version 1.2015. *J Natl Compr Canc Netw.* 2015;13:194–227. PMID: 25691612.
Findlay JM, Bradley KM, Malle EJ, et al. Pragmatic staging of oesophageal cancer using decision theory involving selective endoscopic ultrasonography, PET and laparoscopy. *Br J Surg.* 2015;102:1488–1499. PMID: 26458070.

10-3 D

Based on the ToGA study, patients with HER2-positive gastric and gastroesophageal junction adenocarcinoma experience a significant survival advantage with the addition of trastuzumab to cisplatin and fluoropyrimidine. Trastuzumab would not be given with epirubicin, as they are both cardiotoxic. Because of the low prevalence of mutations in *KRAS* or *NRAS*, epidermal growth factor receptor (EGFR) antibody receptor inhibitors have been examined in gastric and esophageal cancers. Both cetuximab and panitumumab have been evaluated in combination with chemotherapy, both with negative phase III results.

Suggested Reading

Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010;376:687–697. PMID: 20728210.
Lordick F, Kang YK, Chung HC, et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomized, open-label phase 3 trial. *Lancet Oncol.* 2013;14:490–499. PMID: 23594786.
Waddell T, Chau I, Cunningham D, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomized, open-label phase 3 trial. *Lancet Oncol* 14(6): 481–489. PMID: 23594787.

10-4 A

This patient remains functional and active. He would benefit from second-line chemotherapy. Resuming FOLFOX would not be indicated given the short time (< 6 months) from discontinuing oxaliplatin and disease progression. The patient is HER2-negative, so trastuzumab is not indicated. Paclitaxel + ramucirumab would be the best option.

Suggested Reading

Ford HE, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophageal adenocarcinoma (COUGAR-02): an open-label, phase 3, randomised controlled trial. *Lancet Oncol*. 2014;15:78–86. PMID: 24332238.
Wilke H, Muro K, Van Cutsem E, et al. Ramicirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-esophageal junction adenocarcinoma (RAINBOW): a double-blind randomised phase 3 trial. *Lancet Oncol.* 15:1224–1235. PMID: 25240821.

10-5 C

Hereditary diffuse gastric cancer is a genetic predisposition syndrome characterized by early onset (age < 40) diffuse gastric cancer, family history of diffuse gastric cancer, and lobular breast cancer and signet ring cell colon cancer. It is caused by a germline mutation in *CDH1*. In a patient with a known *CDH1* mutation, prophylactic gastrectomy is recommended.

Suggested Reading

Fitzgerald RC, Hardwick R, Huntsman D, et al. Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. *J Med Genet.* 2010;47:436–444. PMID: 20591882.

Huntsman DG, Carneiro F, Lewis FR, et al. Early gastric cancer in young, asymptomatic carriers of germ-line E-cadherin mutations. *N Engl J Med*. 2001;344:1904–1909. PMID: 11419427.

10-6 D

There are now several studies that demonstrate a proven benefit of adjuvant therapy in resected pancreas cancer. Standard adjuvant options include gemcitabine monotherapy, gemcitabine with capecitabine, or adjuvant 5-fluorouracil. Though there is controversy regarding the role of adjuvant radiation, it is not indicated as monotherapy. When given, it should be given with chemotherapy sensitization.

Suggested Reading

Neoptolemos JP, Moore MJ, Cox TF, et al. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. *JAMA.* 2012;308:147–156. PMID: 22782416.

Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet* 2017;389:1011–1024. PMID: 28129987.

Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs. observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA.* 2007;297:267–277. PMID: 17227978.

10-7 D

Historically, ampullary carcinomas are felt to carry a favorable prognosis. These tumors are known for their high rates of resectability and good prognosis following pancreaticoduodenectomy. In one series of 152 consecutive patients, the 5-year disease-free survival rate was 47.1%, highlighting the better survival than with true pancreatic cancers.

Suggested Reading

Colussi O, Voron T, Pozet A, et al. Prognostic score for recurrence after Whipple's pancreaticoduodenectomy for ampullary carcinomas: results of an AGEO retrospective multicenter cohort. *Eur J Surg Oncol*. 2015;41:520–526. PMID: 25680954.

10-8 A

The most likely cancer diagnosis is fibrolamellar cancer. Fibrolamellar cancer is generally seen in younger patients, is much more likely to be resectable, and is less commonly associated with infection or cirrhosis. In contrast, hepatocellular cancer is more typical in patients older than age 65. The alpha-fetoprotein (AFP) tumor marker is not always helpful in distinguishing between the two diseases.

Suggested Reading

Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet.* 2003;362:1907–1917. PMID: 14667750.

Torbenson M. Review of the clinicopathologic features of fibrolamellar carcinoma. *Adv Anat Pathol*. 2007;14:217–223. PMID: 17452818.

10-9 B

Regorafenib was examined against best supportive care in the second-line setting for patients with advanced hepatocellular carcinoma that progressed or was intolerant to sorafenib in a phase III random assignment study. In this study, 573 patients were randomly assigned 2:1 to receive regorafenib 160 mg or placebo daily. Patients who received regorafenib experienced an improvement in survival (median survival, 10.6 months, vs. 7.8 months with placebo, HR, 0.63; 95% CI; 0.5, 0.79; $p < 0.0001$). Additionally, nivolumab was recently approved for advanced hepatocellular cancer that has progressed on first line therapy. Local–regional treatment options would be less preferred than systemic therapy because the patient has extrahepatic disease. The combination of doxorubicin with sorafenib was shown to not be better than sorafenib alone.

Suggested Reading

Abou-Alfa G, et al. (2016). Phase III study of sorafenib plus doxorubicin versus sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol.* 2016;34 (suppl 4S; abstr 192).

Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;389:56–66. PMID: 27932229.

El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017;389(10088):2492–2502. PMID: 28434648.

10-10 A

Patients with pT4N2 colon cancers have a moderate-high risk of recurrence. This patient would be considered to have high-risk stage III colorectal cancer, for which 6 months of adjuvant oxaliplatin-based chemotherapy (FOLFOX, leucovorin, 5-fluorouracil, oxaliplatin or XELOX capecitabine, oxaliplatin) would be indicated.

Suggested Reading

Benson AB, Venook AP, Cederquist L, et al. Colon cancer, version 1.2017, NCCN Clinical practice guidelines. *J Natl Compr Canc Netw.* 2017;15:370–398. PMID: 28275037.

Gunderson LL, Jessup JM, Sargent DJ, et al. Revised TN categorization for colon cancer based on national survival outcomes data. *J Clin Oncol.* 2010;28:264–271. PMID: 19949014.

Shi Q, Sobrero AF, Shields AF, et al. Prospective pooled analysis of six phase III trials investigating duration of adjuvant oxaliplatin-based therapy (3 vs 6 months) for patients with stage III colon cancer: the IDEA (International Duration Evaluation of Adjuvant chemotherapy) collaboration. *J Clin Oncol.* 2017;35 (suppl; abstr LBA1).

10-11 D

Both TAS-102 and regorafenib are approved for salvage treatment for advanced colorectal cancer. Studies compared the two drugs with best supportive care and significantly improved overall survival compared with placebo. However, neither drug is associated with having a meaningful response rate to treatment.

Suggested Reading

Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicenter, randomized, placebo-controlled, phase 3 trial. *Lancet.* 2013;381:303–312. PMID: 23177514.

Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015;372:1909–1919. PMID: 25970050.

10-12 D

The long-standing question about whether preoperative or postoperative chemoradiation results

in improved outcomes was definitively answered by the results of a large German randomized trial that compared standard continuously infused fluorouracil plus radiation either before or after quality-controlled total mesorectal excision (TME) surgery. Patients undergoing preoperative combined-modality therapy had a lower rate of local recurrence (6% vs. 13% at 5 years), a lower rate of acute and chronic toxicities, and a significantly higher rate of sphincter preservation compared with postoperative chemoradiation ($p = 0.006$).

Suggested Reading

Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004;351:1731–1740. PMID: 15496622.

11 GENITOURINARY CANCERS
SELF-EVALUATION

11. GENITOURINARY CANCERS QUESTIONS

11-1 A 76-year-old man with chemotherapy-naive castration-resistant metastatic prostate cancer (CRPC) has recently progressed on abiraterone acetate with symptomatic bone metastases and pelvic lymph node enlargement. His medical oncologist has discussed changing his treatment plan to chemotherapy.

Which of the following is the most appropriate chemotherapy plan?

A. Cabazitaxel 20 mg/m^2 every 3 weeks
B. Docetaxel 75 mg/m^2 every 3 weeks
C. Cabazitaxel 25 mg/m^2 every 3 weeks
D. Paclitaxel 175 mg/m^2 every 3 weeks

11-2 A 73-year-old woman with muscle-invasive urothelial carcinoma of the bladder receives neoadjuvant chemotherapy with gemcitabine and cisplatin and undergoes a radical cystectomy and pelvic lymph node dissection with pathology revealing pT3-N1 disease. Three months after surgery, she develops lower back pain and CT reveals retroperitoneal and pelvic adenopathy.

Which of the following is the most appropriate treatment?

A. Docetaxel
B. Atezolizumab
C. Pemetrexed
D. Bevacizumab

11-3 A 28-year-old man with an advanced good-risk nonseminomatous germ cell tumor reports increasing back pain after two cycles of chemotherapy with bleomycin, etoposide, and cisplatin (BEP). Serum tumor markers are declining; however, a CT scan reveals an enlarging partially cystic-appearing retroperitoneal mass.

Which of the following is the most appropriate next step in management?

A. Continue BEP.
B. Change to paclitaxel, ifosfamide, and cisplatin (TIP).
C. Stop chemotherapy and administer radiation therapy.
D. Proceed to surgery.

11-4 Inactivation of the tumor suppressor gene *SMARCB1* is associated with a type of kidney cancer seen in patients with which of the following conditions?

A. Hereditary leiomyomatosis renal cell carcinoma
B. Birt-Hogg-Dubé syndrome
C. Sickle cell trait
D. von Hippel-Lindau syndrome

11-5 A 71-year-old man with castration-resistant metastatic prostate cancer receiving degarelix has multiple new osseous metastases seen on bone scan. His medical oncologist recommends initiation of abiraterone acetate with prednisone. The patient is concerned about potential side effects.

Which of the following is a potential side effect that will require specific monitoring?
A. Pancreatitis
B. Hepatic dysfunction
C. Neutropenia
D. Hyperlipidemia

11-6 A 72-year-old woman with a 40-pack-year smoking history, coronary artery disease, and diabetes mellitus develops gross hematuria. A cystoscopy and complete transurethral resection of a small bladder tumor is performed with pathology revealing urothelial carcinoma with invasion of the muscularis propria. A CT scan reveals no evidence of metastatic disease. She declines a radical cystectomy.

Which of the following is the most appropriate next step in management?
A. Surveillance with cystoscopy and urine cytology every 3 months
B. Radiation therapy
C. Neoadjuvant chemotherapy followed by radiation therapy
D. Radiation therapy and concomitant chemotherapy

11-7 After a long bicycle race, a 25-year-old otherwise healthy man develops pain in the right testicle. He eventually seeks the attention of his primary care physician whose exam reveals a tender, firm right testis. An ultrasound reveals a solid 1.5-cm right testicular mass. Serum tumor markers are normal. He undergoes a right radical inguinal orchiectomy with pathology revealing a pT1 seminoma. A CT scan of the abdomen and pelvis and chest x-ray are normal.

Which of the following is the most appropriate next step in management?
A. Surveillance
B. Three cycles of carboplatin
C. One cycle of etoposide and cisplatin
D. Primary retroperitoneal lymph node dissection

11-8 A 57-year-old woman with metastatic clear cell renal cell carcinoma treated with pazopanib has developed progression in lung and lymph node metastases. After a thorough discussion of potential second-line treatment options, a therapy proven to offer a survival benefit is chosen.

Which of the following therapies is associated with a survival benefit in the second-line setting?

A. Axitinib
B. Everolimus
C. Cabozantinib
D. Temsirolimus

11-9 A 76-year-old man with a prostate-specific antigen (PSA) recurrence after radical prostatectomy and no definitive evidence of metastatic disease is initiating androgen deprivation therapy. He is concerned about bone loss having already experienced a vertebral fracture 3 years earlier.

Which of the following therapies is associated with a proven bone protective effect in this setting?

A. Denosumab
B. Bicalutamide
C. Zoledronic acid
D. Abiraterone acetate

11-10 A 63-year-old woman with metastatic clear cell renal cell carcinoma has been receiving nivolumab with excellent tolerability. A CT scan at 8 weeks reveals stable lung nodules and mediastinal adenopathy; however, there is one new right hilar node.

Which of the following is the next best step in management?

A. Continue nivolumab at higher dose level.
B. Switch to axitinib.
C. Continue nivolumab at the same dose.
D. Switch to everolimus.

11-11 A 48-year-old man with no prior medical history develops gross hematuria and CT imaging reveals a left renal pelvis mass with associated retroperitoneal adenopathy. A biopsy of the mass reveals urothelial carcinoma. The patient's mother was treated for endometrial cancer, and his maternal uncle died of metastatic colon cancer at the age of 53. The patient has two sons and is concerned about a possible hereditary syndrome.

Which of the following genes is most likely involved if a hereditary syndrome is present?

A. *APC*
B. *FH*
C. *MSH2*
D. *BRCA2*

11-12 A 21-year-old man has recently undergone a primary retroperitoneal lymph node dissection for a stage IIA nonseminomatous germ cell tumor without complication. The pathology reveals embryonal carcinoma involving a 2-cm node with evidence of extranodal extension. Serum tumor markers are normal.

What is the next most appropriate step in management?

A. Surveillance with serial visits including tumor markers and imaging studies
B. Adjuvant chemotherapy
C. Radiation therapy
D. Re-exploration to complete node dissection

11. GENITOURINARY CANCERS RATIONALES

11-1 B

Two randomized trials compared docetaxel-based therapy to mitoxantrone and prednisone in patients with metastatic CRPC. A significant improvement in overall survival (OS) was demonstrated for patients who received docetaxel leading to the FDA approval for docetaxel with prednisone for men with metastatic CRPC. Cabazitaxel is approved as second-line chemotherapy after docetaxel, based on the results of the TROPIC trial demonstrating an OS benefit for cabazitaxel as compared to mitoxantrone (both administered with prednisone). Two recent phase III studies have clarified the role for cabazitaxel in metastatic CRPC. The PROSELICA trial established the noninferiority and improved tolerability of cabazitaxel at 20 mg/m^2 as compared to 25 mg/m^2, and the FIRSTANA trial comparing docetaxel to cabazitaxel in the first-line setting did not demonstrate superiority in OS for cabazataxel as compared to docetaxel in chemotherapy-naïve patients.

Suggested Reading

de Bono JS, Hardy-Bessard AC, Kim CS, et al. Phase III non-inferiority study of cabazitaxel (C) 20 mg/m^2 (C20) versus 25 mg/m^2 (C25) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel (D). *J Clin Oncol*. 34, 2016 (suppl; abstr 5008).

de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet.* 2010;376:1147–1154. PMID: 20888992.

Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med.* 2004;351:1513–1520. PMID: 15470214.

Sartor, AO, Oudard S, Sengelov L, et al. Cabazitaxel vs docetaxel in chemotherapy-naive (CN) patients with metastatic castration-resistant prostate cancer (mCRPC): a three-arm phase III study (FIRSTANA). *J Clin Oncol*. 34, 2016 (suppl; abstr 5006).

Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med.* 2004;351:1502–1512. PMID: 15470213.

11-2 B

The IMvigor 210 study of the immune checkpoint inhibitor atezolizumab in patients with locally advanced or metastatic urothelial carcinoma whose disease progressed after prior platinum-based chemotherapy for metastatic disease or within 12 months of perioperative platinum-based chemotherapy resulted in a significantly improved response rate (compared to historical control). With a median follow-up of 11.7 months, ongoing responses were recorded in 38 (84%) of 45 responders. The median overall survival was 11.4 months (95% CI; 9.0, not estimable) in patients with increased PD-L1 expression in immune cells (IC2/3 group). Atezolizumab demonstrated good tolerability with grade 3-4 immune-mediated adverse events occurring in 15 (5%) of 310 treated patients. Based on this study, atezolizumab was approved by the FDA for patients with locally advanced or metastatic disease who progress during or following platinum-containing chemotherapy.

Suggested Reading

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet*. 2016;387:1909–20. PMID: 26952546.

11-3 D

The patient has growing teratoma syndrome and the management is surgery. A plan to proceed with chemotherapy alone will not result in treatment of the growing teratoma and will put the patient at risk for further progression and associated complications.

Suggested Reading

Jeffery GM, Theaker JM, Lee AH, et al. The growing teratoma syndrome. *Br JUrol.* 1991;67:195–202. PMID: 2004236.
Tongaonkar HB, Deshmane VH, Dalal AV, et al. Growing teratoma syndrome. *J Surg Oncol.* 1994;55:56–60. PMID: 8289455.

11-4 C

Renal medullary carcinoma, a rare and aggressive neoplasm that most often occurs in the setting of sickle cell trait or sickle cell disease, has the tumor suppressor gene *SMARCB1* inactivation in all cases, mostly due to balanced translocations, which makes it share oncogenic pathways with pediatric malignant rhabdoid tumors.

Suggested Reading

Calderaro J, Masliah-Planchon J, Richer W, et al. Balanced translocations disrupting SMARCB1 are hallmark recurrent genetic alterations in renal medullary carcinomas. *Eur Urol*. 2016;69:1055–61. PMID: 26433572.

11-5 B

Toxicities associated with abiraterone acetate include hypertension, edema, hypokalemia, adrenal insufficiency, congestive heart failure, elevated aspartate aminotransferase (AST), and alanine aminotransferase (ALT) as well as others. Hepatotoxicity is rare but can be severe and fatal with a specific recommendation to monitor liver function during treatment.

Suggested Reading

de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med.* 2011;364:1995–2005. PMID: 21612468.
Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med.* 2013;368:138–148. PMID: 23228172.

11-6 D

Trimodality bladder preservation including a transurethral resection that is as complete as is safely possible followed by combined modality therapy with radiation and chemotherapy is an alternative to radical cystectomy in appropriately selected patients with muscle-invasive bladder cancer. Combined modality therapy is superior to radiation therapy alone, and there is no clear role for neoadjuvant chemotherapy in bladder preservation protocols. Muscle-invasive bladder cancer is a potentially lethal phenotype, and surveillance is not recommended.

Suggested Reading

Efstathiou JA, Spiegel DY, Shipley WU, et al. Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: the MGH experience. *Eur Urol.* 2012;61:705–711. PMID: 22101114.
James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med.* 2012;366:1477–1488. PMID: 22512481.

11-7 A

After a radical inguinal orchiectomy, standard treatment options for stage I seminoma include surveillance, adjuvant radiotherapy, and one or two cycles of single-agent carboplatin, recognizing that approximately 80% of these patients will not have required treatment, and the long-term survival is nearly 100% regardless of the initial option chosen. Based on the excellent outcome for patients with stage I seminoma and the potential for long-term radiation-related toxicity, including secondary malignancies, surveillance represents a preferred strategy for the treatment of patients with clinical stage I disease. Both primary retroperitoneal lymph node dissection and one cycle of etoposide and cisplatin represent options for the treatment of clinical stage I nonseminomatous germ cell tumors.

Suggested Reading

Hanna NH, Einhorn LH. Testicular cancer–discoveries and updates. *N Engl J Med.* 2014;371:2005–2016. PMID: 25409373.
Nichols CR, Roth B, Albers P, et al. Active surveillance is the preferred approach to clinical stage I testicular cancer. *J Clin Oncol*. 2013;31:3490–3493. PMID: 24002502.

11-8 C

A phase III trial (METEOR) compared cabozantinib, an oral, small molecule tyrosine kinase inhibitor that targets VEGFR as well as MET and AXL, with everolimus in patients with advanced renal cell carcinoma that had progressed after VEGFR-targeted therapy and demonstrated an improvement in response, progression-free survival and overall survival (median survival of 21.4 months (95% CI; 18.7, not estimable) with cabozantinib and 16.5 months (95% CI; 14.7, 18.8) with everolimus (HR, 0.66; 95% CI; 0.53, 0.83; p = 0.00026). The other agent associated with a survival benefit in the second-line setting is the anti-PD-1 antibody, nivolumab. No survival benefit has been seen with axitinib or everolmus, and temsirolimus is associated with a survival benefit in the first-line setting in patients with poor-risk disease.

Suggested Reading

Choueiri TK, Escudier B, Powles T, et al. Cabozantanib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2016;17:917–927. PMID: 27279544.

11-9 A

The HALT study examined the role of denosumab at 60 mg subcutaneously every 6 months in men receiving androgen deprivation therapy (ADT) for nonmetastatic prostate cancer. The 1568 participants were randomly assigned to either denosumab or placebo. Bone mineral density of the lumbar spine increased by 5.6% in the denosumab group compared with a loss of 1.0% in the placebo group ($p < 0.001$) at 24 months, and there was also a decreased incidence of new vertebral fractures at 36 months (1.5% vs. 3.9% with placebo; relative risk, 0.38; 95% CI; 0.19, 0.78; $p = 0.006$). In 2011, the FDA approved denosumab (60 mg every 6 months) to increase bone mass in men at high risk for fracture who are receiving ADT for nonmetastatic prostate cancer.

Suggested Reading

Smith MR, Egerdie B, Hernandez Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med.* 2009;361:745–755. PMID: 19671656.

11-10 C

Nivolumab was approved by the FDA for the treatment of advanced renal cell carcinoma (RCC) in patients who have received prior anti-angiogenic therapy based on the results of a randomized, open-label, phase III study that compared nivolumab with everolimus in previously treated patients with RCC and demonstrated a significant overall survival (OS) benefit for nivolumab (HR, 0.73; p = 0.002). The median OS was 25.0 months (95% CI; 21.8, not estimable) with nivolumab and 19.6 months (95% CI; 17.6, 23.1) with everolimus. Response assessment was performed at 8-week intervals during the first year and the median time to response was 3.5 months (range, 1.4 to 24.8) among patients with a response. If using immune-related response criteria, the presence of a new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements. There is no dose modification when using nivolumab.

Suggested Reading

Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med.* 2015;373:1803–1813. PMID: 26406148.

Nishino M, Giobbie-Hurder A, Gargano M, et al. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. *Clin Cancer Res*. 2013;19:3936–3943. PMID: 23743568.

11-11 C

Hereditary nonpolyposis colon cancer (HNPCC) syndrome, also known as Lynch syndrome, is an autosomal dominant condition associated with a high risk of colon cancer and additional malignancies including endometrial, ovarian, stomach, small intestine, upper urinary tract as well as others. The hallmark of HNPCC is defects in DNA mismatch repair genes including *MSH2*, *MLH1*, *MSH6*, *PMS2*, and *PMS1.*

Suggested Reading

Engel C, Loeffler M, Steinke V, et al. Risks of less common cancers in proven mutation carriers with Lynch syndrome. *J Clin Oncol.* 2012;30:4409–4415. PMID: 23091106.

11-12 B

The likelihood of micrometastatic disease is 50% or more for patients with an involved node diameter of more than 2 cm, more than five involved nodes, or any extranodal extension (pathologic N2). Assuming that serum tumor marker levels return to normal after surgery, these patients should receive two cycles of adjuvant chemotherapy which results in a 98 to 99% likelihood of cure.

Suggested Reading

Kondagunta GV, Motzer RJ. Adjuvant chemotherapy for stage II nonseminomatous germ-cell tumors. *Semin Urol Oncol.* 2002;20:239–243. PMID: 12489056.

Motzer RJ, Sheinfeld J, Mazumdar M, et al. Etoposide and cisplatin adjuvant therapy for patients with pathologic stage II germ cell tumors. *J Clin Oncol.* 1995;13:2700–2704. PMID: 7595727.

12 GYNECOLOGIC CANCERS
SELF-EVALUATION

12. GYNECOLOGIC CANCERS QUESTIONS

12-1 A 49-year-old woman seeks your advice regarding her genetic testing results. Her mother had ovarian cancer at age 55. The patient underwent genetic testing and was found to carry a *BRIP1* mutation.

Which management strategy do you recommend to her in terms of her ovarian cancer risk?

A. Screening for ovarian cancer with transvaginal sonograms and CA125 testing
B. Bilateral salpingo-oophorectomy
C. Annual pelvic examination with no specific ovarian cancer screening
D. Treatment with raloxifene

12-2 A 65-year-old woman was treated with cisplatin plus radiation for stage III squamous cell carcinoma of the cervix 2 years ago. A cough and mild dyspnea on exertion has developed. A chest x-ray showed multiple bilateral lung lesions. A biopsy of one lung lesion showed squamous cell carcinoma consistent with metastatic disease from the cervix cancer. CT imaging confirmed the multiple lung metastases as well as liver metastases.

What is your management recommendation?

A. Treatment with weekly paclitaxel
B. Treatment with intraperitoneal cisplatin plus intravenous and intraperitoneal paclitaxel
C. Treatment with paclitaxel, cisplatin, and bevacizumab
D. Treatment with nivolumab

12-3 A 48-year-old presents with menometrorrhagia, pelvic pain, and a uterine mass. She underwent hysterectomy and bilateral salpingo-oophorectomy. Pathology was read as low-grade endometrial stromal sarcoma, confined to the uterus. There is no evidence of metastatic disease on postresection imaging. She seeks your advice on management.

You recommend:

A. Surgical staging with lymph node dissection and omentectomy to confirm stage I disease
B. Estrogen-replacement therapy until the age of natural menopause
C. Adjuvant pelvic radiation
D. Observation

12-4 Which of the following is associated with an increased risk for epithelial ovarian cancer?

A. Germline *p53* mutation
B. Use of oral contraceptives for more than 10 years
C. Cigarette smoking
D. Nulliparity

12-5 A 58-year-old woman presented with postmenopausal bleeding. She underwent hysterectomy, bilateral salpingo-oophorectomy (BSO), lymph node evaluation, and washings. Pathology from the surgical staging showed FIGO grade 2 endometrioid endometrial carcinoma, 2 mm out of 16-mm myometrial invasion, no lymphovascular invasion, negative cytology from the washings, and no tumor in the BSO or lymph nodes. She is referred to you for advice regarding adjuvant therapy.

You recommend:
A. Intravaginal radiation therapy (vaginal brachytherapy) (IVRT)
B. Whole pelvic radiation
C. Paclitaxel plus carboplatin and IVRT
D. Tamoxifen for 5 years

12-6 A 62-year-old woman with stage III endometrioid endometrial carcinoma seeks your advice regarding adjuvant treatment. She reports no family history of breast, colon, or ovarian cancer. The pathology report notes that the tumor shows microsatellite instability, and immunohistochemical staining for MSH6 is absent.

In addition to providing a recommendation for adjuvant treatment, you recommend:
A. Tumor genomic profiling to identify a possible *KRAS* mutation
B. Genetic counseling and testing for Lynch syndrome–related germline mutations
C. Genetic counseling and testing for *BRCA1* or *BRCA2* mutations
D. Immunohistochemistry for estrogen receptors and progesterone receptors on the tumor tissue

12-7 A 75-year-old woman was treated for stage III ovarian cancer with intraperitoneal cisplatin plus intravenous and intraperitoneal paclitaxel. She entered a first complete clinical remission but still suffers from peripheral neuropathy that makes it difficult for her to button her clothes or wear shoes other than sneakers. She returned to you in follow-up reporting bloating and discomfort. CT imaging shows peritoneal carcinomatosis and a small right pleural effusion. She completed first-line chemotherapy 5 months ago.

The patient has no other comorbidities and normal organ function. You recommend:
A. Surgical debulking followed by platinum-combination chemotherapy
B. Weekly paclitaxel plus bevacizumab
C. Liposomal doxorubicin plus bevacizumab
D. Liposomal doxorubicin plus carboplatin

12-8 A 62-year-old was treated with weekly paclitaxel plus every-3-week carboplatin for stage III ovarian cancer following optimal surgical debulking and was in complete clinical remission. Her last chemotherapy was 18 months ago. Your referral for genetic

counseling and testing showed that she carries no germline *BRCA1* or *BRCA2* mutation. She had a rising CA125 and imaging showed multisite recurrent disease, including retroperitoneal and mediastinal lymphadenopathy. She says her treatment goal is to prolong her time to disease progression as long as possible.

You recommend:

A. Surgical debulking followed by intraperitoneal cisplatin plus intravenous and intraperitoneal paclitaxel
B. Carboplatin plus gemcitabine plus bevacizumab followed by bevacizumab maintenance
C. Liposomal doxorubicin plus carboplatin followed by bevacizumab maintenance
D. Carboplatin plus gemcitabine plus rucaparib followed by rucaparib maintenance

12-9 Your patient with recurrent ovarian cancer was treated with paclitaxel plus carboplatin as first-line therapy and entered a first complete clinical remission. At the time of recurrence, 8 months later, she was treated with liposomal doxorubicin plus carboplatin with initial response followed by progression of disease after cycle 5. She has a germline deleterious *BRCA1* mutation. She is started on oral rucaparib.

Which of the following is a potential toxicity of this agent?

A. Myelodysplastic syndrome
B. Hand–foot syndrome
C. Reversible posterior leukoencephalopathy syndrome
D. Gastrointestinal fistula

12. GYNECOLOGIC CANCERS RATIONALES

12-1 B

Although the lifetime risk for ovarian cancer is not as great as with germline *BRCA* mutations, germline *BRIP1* mutations confer an increased risk for ovarian cancer of sufficient magnitude to merit recommendation for RRSO. Although the ideal age for RRSO in *BRIP1* mutation carriers has not been established, recommendations are that this discussion should take place when the woman is age 45 to 50. The FDA specifically recommends against screening for ovarian cancer in women at general risk and in women at increased genetic risk for ovarian cancer. Pelvic examination has not been shown to reduce ovarian cancer risk or to detect ovarian cancer at an early stage. Raloxifene treatment has been shown to decrease the risk of breast cancer, but is not known to decrease the risk of ovarian cancer.

Suggested Reading

Daly MB, Pilarski R, Berry M, et al. Genetic/familial high-risk assessment: breast and ovarian, version 2.2017. *J Natl Compr Canc Netw.* 2017;15:9–20. PMID: 26850485.

12-2 C

A phase III trial demonstrated improved overall survival with the addition of bevacizumab to paclitaxel plus cisplatin in patients with metastatic cervix cancer. Intraperitoneal cisplatin plus intravenous and intraperitoneal paclitaxel are first-line treatment options for optimally debulked

ovarian cancer. Nivolumab is a treatment for lung cancer, but is investigational as a treatment for metastatic cervix cancer.

Suggested Reading

Tewari KS, Sill MW, Long HJ 3rd, et al. Incorporation of bevacizumab in the treatment of recurrent and metastatic cervical cancer: a phase III randomized trial of the Gynecologic Oncology Group. *N Engl J Med.* 2014;370:734–743. PMID: 24552320.

12-3 D

Although surgical assessment of lymph nodes is part of staging for endometrial carcinoma and carcinosarcoma, resection of normal-appearing lymph nodes is not mandated for low-grade endometrial stromal sarcomas (ESSs). Low-grade ESS tumors nearly always express estrogen receptors and progesterone receptors. The risk for recurrence is increased in the setting of continued estrogen stimulation such that estrogen-replacement therapy would not be recommended. Adjuvant pelvic radiation has not been shown to improve survival outcomes. Low-grade ESS generally has a good prognosis, and for disease limited to the uterus, observation is appropriate.

Suggested Reading

Amant F, Floquet A, Friedlander M, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for endometrial stromal sarcoma. *Int J Gynecol Cancer*. 2014;24:S67–S72. PMID: 25033257.

12-4 D

Germline *p53* mutations in Li–Fraumeni syndrome have not been shown to increase the risk for epithelial ovarian cancer. Oral-contraceptive use is associated with a decreased risk of ovarian cancer. Smoking has not been associated with increased risk. Older age and family history are risk factors for ovarian cancer, as are nulliparity, infertility, early menarche, and late menopause.

12-5 A

This patient has a stage IB endometrial cancer. She is younger than age 60, and the tumor is not deeply invasive and does not show lymphovascular invasion, and the cytology is negative. Clinical trials for these intermediate-risk cancers have shown that survival outcomes are not superior for whole-pelvis radiation compared to intravaginal brachytherapy. Intravaginal brachytherapy has fewer short- and long-term side effects. Long-term follow-up (median follow-up, 20.5 years) of 568 patients with early-stage endometrial cancer treated with either whole-pelvis radiation plus vaginal brachytherapy or with vaginal brachytherapy alone showed no survival benefit to whole-pelvis radiation, and among women younger than age 60, pelvic radiation was associated with decreased survival and increased risk for second malignancies. A phase III trial in high-to-intermediate-risk endometrial cancer did not show benefit to adjuvant chemotherapy compared to pelvic radiation. Tamoxifen is associated with an increased risk of endometrial cancer and has not been studied as adjuvant treatment for endometrial cancer.

Suggested Reading

Onsrud M, Cvancarova M, Hellebust TP, et al. Long-term outcomes after pelvic radiation for early-stage endometrial cancer. *J Clin Oncol.* 2013;31:3951–3956. PMID: 24019546.

12-6 B

Endometrial carcinoma is one of the most common Lynch syndrome–associated cancers and is often the first cancer diagnosed in women with Lynch syndrome. The microsatellite instability, and the absence of staining for a mismatch repair enzyme both indicate the possibility that this patient has Lynch syndrome, thus genetic counseling and testing is indicated. Genomic profiling may be expected to find numerous somatic tumor mutations but is not standard in endometrial cancer, and the results would not affect adjuvant treatment recommendations. Endometrioid endometrial carcinoma is not considered a *BRCA* mutation–related cancer. Many endometrial carcinomas, especially those of lower FIGO grade, express estrogen receptor and/or progesterone receptor by immunohistochemistry; immunohistochemistry for estrogen receptor and progesterone receptor is not standard for all endometrial carcinomas, and the results would not affect the adjuvant treatment recommendations for a patient with stage III disease.

Suggested Reading

Goodfellow PJ, Billingsley CC, Lankes HA, et al. Combined microsatellite instability, MLH1 methylation analysis, and immunohistochemistry for Lynch syndrome screening in endometrial cancer from GOG210: an NRG Oncology and Gynecologic Oncology Group study. *J Clin Oncol*. 2015;33:4301–4308. PMID: 26552419.

12-7 C

This patient has platinum-resistant recurrent ovarian cancer, since her platinum-free interval is less than 6 months. Patients with platinum-resistant disease should be treated with systemic nonplatinum therapy. Bevacizumab is FDA-approved for treatment of platinum-resistant ovarian cancer in combination with weekly paclitaxel or liposomal doxorubicin or topotecan for patients who have had two or fewer lines of treatment. For this patient, re-treatment with paclitaxel is not recommended because she has persistent neuropathy that interferes with activities of daily living. Surgical debulking is not recommended for patients with platinum-resistant carcinomatosis. Platinum-combination chemotherapy is appropriate for patients with platinum-sensitive recurrent disease (platinum-free interval of more than 6 months).

Suggested Reading

Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrence ovarian cancer: the AURELIA open-label phase III trial. *J Clin Oncol.* 2014;32:1302–1308. PMID: 24637997.

12-8 B

This patient has platinum-sensitive, recurrent ovarian cancer since her platinum-free interval is greater than 6 months. GOG 213 is studying whether surgery followed by chemotherapy is superior to chemotherapy in patients who are surgical candidates and have platinum-sensitive recurrence. However, for this patient with metastatic disease in lymph nodes above the diaphragm, surgery would not be the optimal choice, and, similarly, treatment with intraperitoneal chemotherapy would not likely be best for a patient with retroperitoneal and mediastinal lymph node disease. Carboplatin plus gemcitabine plus bevacizumab followed by bevacizumab prolongs PFS compared to carboplatin plus gemcitabine in patients with platinum-sensitive recurrent disease. Bevacizumab is FDA-approved for use in this setting. Liposomal doxorubicin plus carboplatin is a reasonable treatment for platinum-sensitive recurrent ovarian cancer, but adding maintenance bevacizumab has not been studied following this combination. The PARP inhibitor rucaparib is FDA-approved as single-agent treatment for patients with recurrent ovarian cancer who have had two or more lines of therapy and who have a germline

or somatic *BRCA* mutation. Rucaparib is not approved as combination treatment followed by maintenance therapy for platinum-sensitive disease. Single-agent PARP inhibition maintenance treatment for patients who have responded to platinum-based treatment of platinum-sensitive disease is a treatment option (based on three separate studies in slightly different patient populations using olaparib or rucaparib or niraparib).

Suggested Reading

Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol.* 2012;30:2039–2045. PMID: 22529265.

12-9 A

As of May 2017, there are three PARP inhibitors approved by the FDA for treatment of ovarian cancer. Olaparib and rucaparib are approved as monotherapy for recurrent disease; niraparib is approved as maintenance therapy following response to platinum-based treatment of recurrent disease. Olaparib is approved for single-agent therapy following at least four prior lines of treatment in patients with deleterious *BRCA1* or *BRCA2* mutations. Rucaparib is approved as single-agent therapy for patients who have had at least two prior lines of therapy and have a germline or somatic mutation in *BRCA1* or *BRCA2*. All three PARP inhibitor agents are oral. Common side effects are nausea, fatigue, and decreased appetite. Niraparib is associated with more myelosuppression; rucaparib is associated with more liver-function abnormalities. Myelodysplasia and acute leukemia are rare but serious potential toxicities of all three PARP inhibitors. Bevacizumab toxicities include hypertension, gastrointestinal fistula, and reversible posterior leukoencephalopathy syndrome.

The safety of rucaparib was evaluated in 377 patients with advanced ovarian cancer. The most common adverse reactions (greater than or equal to 20%) experienced by patients were nausea, fatigue (including asthenia), vomiting, anemia, abdominal pain, dysgeusia, constipation, decreased appetite, diarrhea, thrombocytopenia, and dyspnea. Adverse reactions led to dose discontinuation in 10% of patients, most frequently from fatigue/asthenia (2%).

Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) was reported in 2 of 377 (0.5%) patients with ovarian cancer. In addition, AML was reported in 2 (< 1%) patients with ovarian cancer enrolled in a blinded, randomized trial evaluating rucaparib compared with placebo. Patients should be monitored for hematologic toxicity at baseline and monthly thereafter, and use of rucaparib should be discontinued if MDS/AML is confirmed.

Suggested Reading

U.S. Food and Drug Administration. Rucaparib. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm533891.htm. Accessed October 26, 2017.

13 MELANOMA
SELF-EVALUATION

13. MELANOMA QUESTIONS

13-1 A 29-year-old woman was recently diagnosed with a 0.6-mm-thick left shoulder melanoma. There was no ulceration. She has no significant medical history. A review of systems and physical exam, includng lymph node exam, were normal.

Which of the following imaging studies is indicated for this patient?

A. CT scan of the chest/abdomen/pelvis
B. CT scan of the chest/abdomen/pelvis and brain MRI
C. PET/CT scan
D. Ultrasonography of the axillary lymph nodes
E. No imaging studies

13-2 A 57-year-old man presents with a changing pigmented skin lesion on his scalp. An excisional biopsy confirms a 1.3-mm superficial spreading melanoma with no ulceration. The surgeon recommends a wide excision and sentinel lymph node biopsy (SLNB).

Which of the following statements regarding sentinel lymph node mapping and biopsy is correct?

A. Sentinel lymph node biopsy is not indicated, given the thickness of this melanoma.
B. Sentinel lymph node biopsy in addition to wide excision improves survival compared to wide excision alone.
C. Sentinel lymph node biopsy is an important surgical staging procedure but is not associated with an improvement in overall survival.
D. Given the location of the melanoma on the scalp, a sentinel lymph node biopsy is not indicated.

13-3 A 45-year-old man undergoes a wide local excision and sentinel lymph node biopsy for a T4bN3b (stage IIIC) scalp melanoma.

Which of the following statements regarding adjuvant therapy for this patient is correct?

A. Adjuvant ipilimumab at 3 mg/kg has demonstrated a survival advantage compared to placebo in randomized trials.
B. Adjuvant pembrolizumab has demonstrated an overall survival advantage compared to placebo in randomized trials.
C. Adjuvant ipilimumab at 3 mg/kg has demonstrated a recurrence-free survival (RFS) advantage compared to placebo in randomized trials.
D. Adjuvant nivolumab has demonstrated an overall survival advantage compared to placebo in randomized trials.

13-4 A 55-year-old woman undergoes a wide local excision and sentinel lymph node biopsy for a T4bN3b (stage IIIC) scalp melanoma. She begins adjuvant therapy with ipilimumab 10 mg/kg. After the second infusion, severe treatment-related diarrhea with no evidence of perforation develops, and the patient is started on high-dose prednisone. After 4 weeks, she has been unable to taper off steroids and has been hospitalized twice for treatment-related diarrhea.

Which of the following interventions are indicated?

A. Infliximab, continuation of ipilimumab after resolution of diarrhea
B. Infliximab, permanent discontinuation of ipilimumab
C. Permanent discontinuation of ipilimumab
D. Mycophenolate mofetil, continuation of ipilimumab after resolution of diarrhea
E. Mycophenolate mofetil, permanent discontinuation of ipilimumab

13-5 A 48-year-old woman has a history of stage III melanoma. She completed surgical resection with no adjuvant treatment 1 year earlier. She now presents with radiographic evidence of stage IV disease, with lung nodules seen on CT scan. A lung biopsy confirms metastatic melanoma. Her oncologist has suggested treatment with nivolumab.

Which of the following statements best describes the mechanism of action of nivolumab?

A. Cytotoxic T-lymphocyte antigen 4 (CTLA-4) blockade
B. CD40 agonist
C. CD20 antagonist
D. Oncolytic virus
E. Programmed death receptor 1 (PD-1) blockade

13-6 A 58-year-old woman with melanoma metastatic to lungs, liver, bone, and lymph nodes presents for her third cycle of ipilimumab and nivolumab. She reports a new severe central headache that has not responded to nonsteroidal anti-inflammatory drugs (NSAIDs). On physical exam, she has no abnormal findings.

What is the most appropriate management?

A. Order a brain MRI with thin cuts through the pituitary gland.
B. Do not order imaging, start corticosteroids.
C. Do not order imaging, check labs for endocrinopathies.
D. Permanently discontinue ipilimumab.

13-7 A 64-year-old man presents with newly diagnosed stage IV melanoma. Imaging identifies several liver, lung, and bone metastases. He remains asymptomatic, with an excellent performance status. Mutation testing confirms *BRAF* V600E mutation.

What treatment is indicated?

A. Vemurafenib
B. High-dose IL-2
C. Dacarbazine
D. Ipilimumab

E. Either targeted therapy with BRAF/MEK inhibition or immunotherapy with single-agent PD-1 blockade or dual PD-1/CTLA-4 blockade or a clinical trial are reasonable treatment options.

13-8 A 35-year-old woman presents to your office with a new diagnosis of biopsy-confirmed metastatic melanoma. You request molecular testing of her tumor.

Which of the following mutations is most common in melanoma and most likely to respond to molecularly targeted therapies?

A. *BRAF* V600R
B. *KIT* K642E
C. *NRAS* Q61R
D. *BRAF* V600E
E. *BRAF* V600K

13-9 A 67-year-old man with stage IV melanoma has been receiving treatment with pembrolizumab for metastatic melanoma. His sites of metastatic disease include liver and subcutaneous nodules. He is seen in the office for his fourth dose of treatment. He reports new dyspnea and is found to have hypoxia.

Which of the following pembrolizumab-related adverse events should be considered in the differential diagnosis?

A. Pulmonary embolus
B. Myocardial infarction
C. Pneumonitis
D. Fungal pneumonia
E. Pleural effusion

13-10 A 63-year-old patient with metastatic melanoma with a *BRAF* V600E mutation is currently receiving combination therapy with dabrafenib and trametinib. Three weeks after starting treatment a fever (temperature, 102°F) develops. He also reports chills. He has no other symptoms at this time.

What is the most appropriate next step in the management of this patient?

A. Send patient to the emergency department for evaluation for neutropenic fever.
B. Hold dabrafenib and trametinib and start nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen.
C. Hold dabrafenib and trametinib and start oral steroids.
D. Continue dabrafenib and discontinue trametinib.

13-11 A 67-year-old patient with stage IV melanoma has been receiving treatment with pembrolizumab. He is seen in the office for his sixth dose of treatment. His laboratory studies show evidence of hypothyroidism and the patient reports mild fatigue.

What do you recommend at this time?

A. Discontinue pembrolizumab.

B. Continue pembrolizumab and start thyroid hormone-replacement therapy.
C. Hold pembrolizumab and start steroids and thyroid hormone-replacement therapy.
D. Switch treatment to ipilimumab.
E. Hold therapy until thyroid abnormalities resolve.

13. MELANOMA RATIONALES

13-1 E

The staging evaluation of a patient with stage I melanoma should include a physical examination together with a skin and lymph node exam. Blood work and imaging is not routinely recommended in the absence of any clinical signs or symptoms of metastatic disease. The majority of patients who present with melanoma do not have distant metastatic disease at presentation; therefore, extensive evaluation with imaging to assess for distant metastases have a low yield and are not indicated in asymptomatic patients. Staging evaluation with CT scans of the chest/abdomen/pelvis can be considered in patients with high-risk disease (stage IIB or III) in whom the risk of metastatic disease is higher.

Suggested Reading

National Comprehensive Cancer Network (NCCN) guidelines. https://www.nccn.org.

13-2 C

Sentinel lymph node mapping provides important prognostic information for patients with melanoma. It should be performed in all patients with melanomas ≥ 1 mm. The Multicenter Selective Lymphadenectomy Trial 1 (MLST-1) randomly assigned 2001 patients undergoing wide excision to SLNB or observation. There was no difference in overall survival in patients randomly assigned to SLNB compared to those undergoing observation only. The presence of involved lymph node metastasis on SLNB was prognostic of a worse survival than those who had no involved lymph nodes on the SLNB.

Suggested Reading

Morton DL, Thompson JF, Cochrane AJ, et al. Final trial report of sentinel lymph node biopsy versus nodal observation in melanoma. *N Eng J Med.* 2014; 370:599–609. PMID: 24521106.

13-3 B

The EORTC trial compared adjuvant ipilimumab 10 mg/kg with placebo in patients with resected stage III melanoma. The primary endpoint was RFS, with improved RFS in patients who received ipilimumab. Five-year overall survival (OS) was improved with adjuvant ipilimumab. There was also, however, a significant risk of severe toxicity with ipilimumab, with death in 1% of patients treated with this drug. Either close observation alone or clinical trials remain reasonable options after resection of stage III disease, in addition to adjuvant ipilimumab. PD-1–blocking agents are being studied in adjuvant therapy trials currently, with no survival data reported to date.

Suggested Reading

Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2015;16:522–530. PMID: 25840693.
Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. *N*

Engl J Med. 2016;374:1845–1855. PMID: 27717298.

13-4 B

In severe immune-mediated colitis related to ipilimumab that does not improve within 1 to 2 days after starting oral prednisone 1 mg/kg daily, patients should be admitted for intravenous high-dose steroids. Patients with immune-mediated small bowel enteritis may not be able to absorb oral steroids. Patients who do not improve with intravenous steroids can be increased to an intravenous equivalent of 2 mg/kg daily of prednisone. Patients who do not respond to higher-dose steroids, are unable to transition to oral steroids, or are unable to taper the steroid dose should be treated with infliximab. Any patient with severe treatment-related enteritis or colitis requiring high-dose steroids requires permanent discontinuation of ipilimumab. Mycophenolate mofetil can be used in cases of immune-mediated hepatitis related to ipilimumab that is not responsive to high-dose steroids.

Suggested Reading

Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. *JAMA Oncol.* 2016;2:1346–1353. PMID: 27367787.

13-5 E

Pembrolizumab and nivolumab are human PD-1 blocking antibodies that are FDA-approved for the treatment of metastatic melanoma and other cancers. The PD-1/programmed death ligand 1 (PD-L1) pathway limits T-cell responsiveness and cytotoxic T-cell activity. Blocking PD-1 augments T-cell activity and has resulted in durable responses and improved survival in patients with advanced melanoma. CTLA-4 blockade is the mechanism of action of ipilimumab. Rituximab is a chimeric monoclonal antibody directed against CD20 that is used in the treatment of hematologic malignancies. CD40 agonists are in development as another means of T-cell activation to effect antitumor immunity. Oncolytic viral therapies, including talimogene laherparepvec, use the viral replication machinery of attenuated viruses to effect tumor cell death.

Suggested Reading

Ott PA, Hodi FS, Kaufman HL, et al. Combination immunotherapy: a road map. *J Immunother Cancer.* 2017;5:16. PMID: 28239469.

13-6 A

Ipilimumab is associated with significant toxic effects that are immune-related adverse events. These immune-mediated reactions may involve any organ system; however, the most common immune-related adverse events are enterocolitis (diarrhea), dermatitis (rash), and endocrinopathies (including thyroiditis resulting in hypo- or less commonly hyperthyroidism and hypophysitis, which can result in endocrinopathies, including adrenal insufficiency). In this patient, the presentation is consistent with immune-mediated hypophysitis without the development of symptomatic adrenal insufficiency or crisis (nausea, vomiting, fever, extreme fatigue, low blood pressure). An MRI is indicated primarily to confirm that the new severe headache is not in fact due to new metastatic disease or a new bleed in the central nervous system. In some cases. MRI does identify an enlarged pituitary gland due to lymphocytic infiltration. Treatment of immune-mediated endocrinopathies does not require interruption of ipilimumab or high-dose steroids, as these toxic effects are usually permanent and can be

managed with treatment of the endocrinopathies, with hormone replacement as appropriate. In a patient presenting with signs and symptoms of adrenal insufficiency or crisis with no headache, an MRI is not required. A low cortisol level in the setting of symptoms of adrenal insufficiency or crisis is diagnostic and the patient should be started on replacement physiologic-dose steroid (hydrocortisone 20 mg daily) with consideration of higher dose and observation until clinically stable. Patients usually have resolution of all symptoms within 1 to 2 days of receiving physiologic-dose steroid replacement.

Suggested Reading

Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. *JAMA Oncol.* 2016;2:1346–1353. PMID: 27367787.

13-7 E

Either BRAF-targeted therapy or a PD-1 blockade–containing immunotherapy are reasonable first-line treatment options for patients with *BRAF* V600E mutant melanoma. Both approaches have demonstrated survival benefit in randomized phase III trials. Ipilimumab is not an appropriate first-line therapy option for metastatic melanoma, as pembrolizumab, nivolvumab, and the combination of ipilimumab/nivolumab have all demonstrated improved survival compared to ipilimumab in patients with previously untreated metastatic melanoma. Ipilimumab remains an active therapy option with durable responses that can be considered as a second-line treatment option in patients with disease progression on single-agent PD-1 blockade.

Suggested Reading

Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *The Lancet Oncology.* 17(9):1248–1260. PMID: 27480103.

Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in previously untreated melanoma. *The New England journal of medicine*. 2015;373(1):23–34. PMID: 26027431.

Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *New England Journal of Medicine.* 2015;372(26):2521–2532. PMID: 25891173.

13-8 D

BRAF V600E is the most commonly associated somatic mutation in melanoma. Approximately 50% of patients with cutaneous melanoma have somatic mutant *BRAF* in the tumor. *BRAF* V600K and *BRAF* V600R mutations are identified less frequently, with responses to BRAF and MEK inhibition also observed for patients with *BRAF* V600K mutations, although with a lower response rate and lower duration of response. *KIT* mutations are also observed in melanoma, more often in acral and mucosal melanomas. *NRAS* and *NF1* mutations are observed in melanoma as well.

Suggested Reading

Curtin JA, Busam K, Pinkel D, et al. Somatic activation of KIT in distinct subtypes of melanoma. *J Clin Oncol.* 2006;24:4340–4346. PMID: 16908931.

Krauthammer M, Kong Y, Bacchiocchi A, et al. Exome sequencing identifies recurrent mutations in NF1 and RASopathy genes in sun-exposed melanomas. *Nat Genet*. 2015;47:996–1002. PMID: 26214590.

Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med.* 2015;372:30–39. PMID: 25399551.

13-9 C

PD-1–blocking drugs can cause pneumonitis, which in rare cases can be severe or life-

threatening. It is important to recognize this adverse event early, hold therapy, and initiate treatment with high-dose steroids. Pulmonary embolism and myocardial infarction have not been observed as common side effects of immunotherapy; however, immune-mediated myocarditis has been rarely observed and can result in death. Early intervention with cardiology evaluation and high-dose steroids should be initiated in a patient in whom treatment-related myocarditis is suspected.

Suggested Reading

Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. *JAMA Oncol.* 2016;2:1346–1353. PMID: 27367787.

13-10 B

The combination of dabrafenib and trametinib has a greater incidence of pyrexia compared with single agent BRAF or MEK inhibitors and is an important side effect about which to educate patients. In general, holding treatment and providing supportive care and NSAID usually results in control of fever. These targeted agents are unlikely to cause neutropenia. Fever is most likely related to treatment. In this patient, with no other localizing symptoms for infections, infection is unlikely. Steroids are treatment for the immune-related toxicities of the immunotherapy agents.

Suggested Reading

Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med.* 2015;372:30–39. PMID: 25399551.

13-11 B

Immunotherapy-related endocrinopathies are usually irreversible and require treatment with permanent hormone-replacement therapy, in this case, levothyroxine. Unlike other severe immune-related adverse events, which require permanent discontinuation and high-dose steroids, immunotherapy treatment can be continued in the presence of endocrinopathies. High-dose steroids are not required because the toxicity is not considered reversible. Ipilimumab has a higher incidence of endocrinopathies than the PD-1–blocking drugs.

Suggested Reading

Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. *JAMA Oncol.* 2016;2:1346–1353. PMID: 27367787.

14 SARCOMA
SELF-EVALUATION

14. SARCOMA QUESTIONS

14-1 A 20-year-old college student presents with an enlarging, painless mass in the right proximal anterior thigh. Magnetic resonance imaging (MRI) with contrast identifies an 11-cm, heterogeneously enhancing mass in the adductor magnus. Core needle biopsy reveals alveolar soft part sarcoma (ASPS). Polymerase chain reaction detects ASPSCR1-TFE3 fusion transcript confirming the diagnosis. Computed tomography (CT) of the chest, abdomen, and pelvis is normal.

Which of the following is the most appropriate addition to complete resection of the sarcoma?

A. No adjuvant therapy
B. Radiation
C. Radiation and doxorubicin/ifosfamide
D. Radiation and sunitinib

14-2 A 64-year-old man with metastatic leiomyosarcoma involving liver and lung received primary treatment of sarcoma with doxorubicin. After the sixth cycle, CT of the chest, abdomen, and pelvis demonstrated disease progression in lung and liver. His Eastern Cooperative Oncology Group (ECOG) performance score is 0. Liver-function tests and cardiac ejection fraction are within the normal ranges. He is considering treatment with trabectedin.

Which of the following is more likely to occur with treatment using trabectedin compared to dacarbazine?

A. Lower risk of treatment-related death
B. Objective tumor response
C. Longer time to sarcoma progression
D. Longer survival duration

14-3 A 25-year-old man presents with localized high-grade osteosarcoma in the left proximal humerus. There is no evidence of metastasis on MRI of the arm, CT of the chest, or technetium bone scan. He receives two cycles of doxorubicin, cisplatin, and methotrexate and undergoes resection of the proximal humerus with endoprosthetic reconstruction. Pathology reports a 9 × 6 × 4 cm high-grade osteoblastic osteosarcoma with less than 1% residual viable tumor resected with negative surgical margins. There are no postoperative complications.

Which of the following is the most appropriate next step?

A. No adjuvant therapy

B. Continue with doxorubicin, cisplatin, and methotrexate chemotherapy
C. Start interferon alpha-2b
D. Adjuvant radiation therapy

14-4 A 64-year-old woman presents with worsening fatigue and pallor. Physical exam is notable for pale mucous membranes and skin tone and mild tachycardia. Complete blood count reveals a microcytic anemia. Colonoscopy and upper endoscopy reveal a submucosal lesion in the gastric fundus with ulcerated overlying mucosa and stigmata of bleeding. CT with oral and intravenous contrast of the chest, abdomen, and pelvis show an enhancing mass in the stomach but no other abnormality. The mass is resected, and pathology describes a 7-cm spindle cell tumor with 15 mitoses per 5 mm^2 (50 high-power fields of view) and negative surgical margins. Immunohistochemistry demonstrates tumor expression of CD117 and DOG-1. Polymerase chain reaction detects a mutation in exon 11 of *KIT.*

Which of the following is the most appropriate next step?
A. Begin imatinib 400 mg twice daily with a planned duration of therapy of 1 year
B. Begin imatinib 400 mg per day with a planned duration of therapy of 3 years
C. Refer to gastroenterology for yearly endoscopy
D. Evaluate in 6 months with CT of the abdomen/pelvis

14-5 A 46-year-old woman with pelvic pain and vaginal bleeding is diagnosed with high-grade leiomyosarcoma in her uterus. A total abdominal hysterectomy is performed. The sarcoma is 8 cm in largest dimension and is confined to the myometrium and endometrium. There is no evidence of metastasis on CT of the chest, abdomen, and pelvis. She enrolls in a randomized clinical trial of adjuvant chemotherapy and receives four cycles of treatment with gemcitabine and docetaxel followed by four cycles of doxorubicin. Sixteen months after enrolling in the study, multiple lung nodules measuring up to 2 cm are seen on CT, and imaged-guided percutaneous biopsy demonstrates high-grade leiomyosarcoma on pathology. Her ECOG performance score is 0, and she desires treatment for the sarcoma.

Which of the following chemotherapies is most likely to delay progression of the sarcoma?
A. Dacarbazine
B. Eribulin
C. Olaratumab
D. Trabectedin

14-6 A 56-year-old man with metastatic gastrointestinal stromal tumor (GIST) involving the peritoneum and liver has evidence of tumor progression in multiple masses after 3 years of therapy with imatinib 400 mg daily. Two months after increasing imatinib to 400 mg twice daily, further tumor progression is noted on CT. Treatment is changed to sunitinib 37.5 mg daily. After 12 months of therapy, CT of the abdomen and pelvis demonstrates significant enlargement in multiple enhancing masses in the peritoneum. His ECOG performance score is 1.

Which of the following is the most appropriate next drug therapy?

A. Dasatinib 100 mg once daily
B. Palbociclib 125 mg once daily for 21 consecutive days every 28 days
C. Pazopanib 400 mg twice daily
D. Regorafenib 160 mg once daily for 21 consecutive days every 28 days

14-7 A 78-year-old man presents with slowly enlarging red-purple macular lesions coalescing in plaques on the dorsum of the right foot and ankle over an 8-cm area. The lesions are not ulcerated or painful. Biopsy reveals a bland spindle cell process admixed with proliferation of vascular channels. Immunohistochemistry of the tissue detects human herpesvirus 8 (HHV-8). There is no evidence of skin involvement in other parts of the body, lymphadenopathy, or immunodeficiency, and the HIV test is seronegative.

Which of the following is the most appropriate next management of the disease?

A. Combined antiretroviral therapy
B. Topical alitretinoin
C. Intralesional vincristine
D. Intravenous liposomal doxorubicin

14-8 A 24-year-old man presents with pain in the right hip that has been present for more than 9 months and was initially attributed to his job working in a factory. CT demonstrates an enhancing destructive soft-tissue mass involving the right ilium and sacrum. A core needle biopsy is performed; it demonstrates a small, round, blue cell tumor with expression of CD99 in a membranous pattern on immunohistochemistry. A provisional diagnosis of Ewing sarcoma is made. Molecular diagnostics is requested to confirm the diagnosis.

Which of the following genetic abnormalities is commonly seen in Ewing sarcoma?

A. Amplification of MDM2
B. Translocation between *CIC* and *DUX4*
C. Translocation between *EWSR1* and *FLI1*
D. Translocation between *SYT* and *SSX1*

14-9 A 58-year-old man presents with cough and chest pain. He has a painless mass in the distal left thigh that has been enlarging for about 12 months. CT of the chest demonstrates more than 20 nodules in the lung ranging between 5 mm and 5 cm. MRI of the thigh shows a heterogeneously enhancing 8-cm mass. Percutaneous biopsy of a lung nodule shows high-grade, undifferentiated pleomorphic sarcoma. Cardiac, liver, and renal functions are normal. The ECOG performance score is 1.

Which of the following would be an expected benefit of the addition of olaratumab to doxorubicin therapy compared with doxorubicin therapy alone?

A. Greater likelihood of objective tumor response
B. Improvement in tumor progression-free survival but not overall survival
C. Improvement in overall survival
D. Reduction in risk of mucositis

14. SARCOMA RATIONALES

14-1 B

Alveolar soft part sarcoma (ASPS) is an aggressive soft-tissue sarcoma with high risk of local recurrence after resection and metastasis to lung and brain, but it is resistant to cytotoxic chemotherapy, including doxorubicin and ifosfamide. Radiation significantly reduces the risk of sarcoma recurrence after resection and is recommended treatment for soft-tissue sarcoma arising in an extremity. Exceptions to treatment with adjuvant radiation include atypical lipomatous tumors, and small (< 5 cm) sarcomas superficial to muscle and fascia resected with wide negative margins. Preoperative radiation carries an increased risk of postoperative complications, including infection and wound dehiscence but a lower risk of long-term fibrosis and lymphedema as compared with postoperative radiation. Sunitinib has activity in locally advanced/metastatic ASPS, but sunitinib has not been formally evaluated as adjuvant therapy.

Suggested Reading

Davis AM, O'Sullivan B, Turcotte R, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. *Radiother Oncol*. 2005;75:48–53. PMID: 15948265.

O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomized trial. *Lancet*. 2002;359:2235–2241. PMID: 12103287.

Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol*. 1998;16:197–203. PMID: 9440743.

14-2 C

Treatment with trabectedin was compared to that with dacarbazine in patients with locally advanced or metastatic leiomyosarcoma or liposarcoma who had previously received an anthracycline and at least one other cytotoxic chemotherapy in an open-label, randomized, phase III trial. There was a significant improvement in sarcoma progression-free survival (PFS) in the group receiving trabectedin (hazard ratio, 0.55, 95% confidence interval 0.44, 0.70). The median PFS was 4.2 months and the 6-month PFS rate was 37% for trabectedin compared to 1.5 months and 15% for dacarbazine. However, there was no statistically significant difference in objective tumor response rate or overall survival between the treatments. Treatment-related toxicity led to death in 2% of patients treated with trabectedin and no deaths in patients treated with dacarbazine. Trabectedin is indicated for the treatment of patients with unresectable or metastatic leiomyosarcoma or liposarcoma who previously received an anthracycline regimen.

Suggested Reading

Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional therapy: results of a phase III randomized multicenter clinical trial. *J Clin Oncol*. 2016;34:786–793. PMID: 26371143.

14-3 B

Patients should continue with the same chemotherapy in the adjuvant setting to reduce the risk of metastases. Early randomized trials of chemotherapy compared with no chemotherapy in patients with operable high-grade osteosarcoma demonstrated a lower relapse rate and improved overall survival rate in patients who received chemotherapy. The EURAMOS-1 international study examined, in a randomized trial, the effect of adding pegylated interferon alpha-2b after standard doxorubicin, cisplatin, and methotrexate in the postoperative treatment of patients younger than age 40 with a good histologic tumor response (< 10% residual viable

tumor) to preoperative doxorubicin, cisplatin and methotrexate. The addition of interferon alpha-2b was associated with grade 3 or 4 toxicity, primarily hematologic, in 50% of the patients but did not improve the event-free or overall survival rates in an intention-to-treat analysis. However, one-quarter of the patients randomly assigned to interferon did not start the treatment. The primary risk to patients with completely resected osteosarcoma is development of metastasis (which develops in more than 80% of patients who experience relapse of osteosarcoma), and adjuvant radiation would not have a significant impact on relapse-free or overall survival.

Suggested Reading

Bernthal NM, Federman N, Eilber FR, et al. Long-term results of a randomized, prospective clinical trial evaluating chemotherapy in patients with high-grade, operable osteosarcoma. *Cancer*. 2012;118:5888–5893. PMID: 22648705.

Bielack SS, Smeland S, Whelan JS, et al. Methotrexate, doxorubicin, and cisplatin (MAP) plus maintenance pegylated interferon alfa-2b versus MAP alone in patients with resectable high-grade osteosarcoma and good histologic response to preoperative MAP: first results of the EURAMOS-1 good response randomized controlled trial. *J Clin Oncol*. 2015;33:2279–2287. PMID: 26033801.

14-4 B

This patient has a gastric gastrointestinal stromal tumor (GIST) that was localized at diagnosis and has had complete resection of the cancer. Pathology describes a tumor with a high mitotic rate, and based on the tumor size, location, and mitotic rate, the estimated risk of GIST recurrence without adjuvant therapy is approximately 50% (American Joint Committee on Cancer [AJCC] stage 3A GIST). Treatment of patients with a high-risk (≥ 50%) of GIST recurrence after complete resection using imatinib 400 mg/day demonstrated improved relapse-free, and preplanned subgroup analysis detected the largest improvement in recurrence-free survival in patients with a mutation in exon 11 of *KIT* assigned to 3 years compared to 1 year of adjuvant imatinib (hazard ratio, 0.35). Because there is risk of relapse in the liver or peritoneum, surveillance using CT or MRI of the abdomen and pelvis is appropriate and should be performed every 3 to 6 months for at least the first 5 years and subsequently less frequently after resection of GIST with risk of recurrence. Recurrence outside the stomach mucosal or muscular layers is more likely to occur than relapse within the stomach after complete oncologic resection of a gastric GIST. Endoscopic ultrasound may be useful for serial observation of an incidentally discovered GIST less than 1 cm in which the biologic behavior is uncertain or when tumors are resected with a positive surgical margin.

Suggested Reading

Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA*. 2012;307:1265–1272. PMID: 22453568.

Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol*. 2005;29:52–68. PMID: 15613856.

14-5 D

Radiologic evidence of metastases developed in the lung about 8 months after the completion of adjuvant chemotherapy with gemcitabine/docetaxel and doxorubicin. A randomized, open-label, phase III study of trabectedin compared with dacarbazine demonstrated significant improvement in sarcoma progression-free survival (PFS) in the group of patients with locally advanced or metastatic leiomyosarcoma or liposarcoma who received trabectedin compared to the group who received dacarbazine. The median PFS was more than twice as long and the 6-month PFS rate was more than twice as high in the group receiving trabectedin compared to

participants receiving dacarbazine. A randomized, open-label, phase III trial of eribulin compared with dacarbazine in patients with locally advanced or metastatic leiomyosarcoma or liposarcoma resulted in a 2-month improvement in median overall survival (OS) for patients who received eribulin compared to dacarbazine, but there was no difference in PFS. In a preplanned subgroup analysis, there was no difference in OS in patients with leiomyosarcoma; the overall survival improvement with eribulin treatment was seen only in patients with liposarcoma. In the United States and Europe, eribulin is approved as treatment for patients with liposarcoma after treatment with an anthracycline.

Suggested Reading

Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional therapy: results of a phase III randomized multicenter clinical trial. *J Clin Oncol*. 2016;34:786–793. PMID: 26371143.

Schoffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicenter, phase 3 trial. *Lancet*. 2016;387:1629–1637. PMID: 26874885.

14-6 D

Regorafenib is the only drug approved by the U.S. Food and Drug Administration (FDA) for treatment of advanced or metastatic GIST after treatment with imatinib and sunitinib. Treatment of patients with advanced GIST refractory to imatinib and sunitinib using regorafenib resulted in a median progression-free survival (PFS) of 5 months compared to 1 month in patients receiving placebo. The 6-month PFS rate was 38% in patients receiving regorafenib and 0% in patients receiving placebo. There was no difference in overall survival, most likely because 85% of patients receiving placebo crossed over to regorafenib treatment upon GIST progression. Dasatinib and pazopanib inhibit KIT and PDGFR kinase activity, and they have been evaluated in phase 2 studies in patients with advanced/metastatic GIST, but treatment of GIST with dasatinib or pazopanib has not been shown to produce a better outcome than treatment with regorafenib. Palbociclib inhibits cyclin-dependent kinase 4 and has activity in well-differentiated/dedifferentiated liposarcoma.

Suggested Reading

Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381:295–302. PMID: 23177515.

14-7 B

The patient has cutaneous classic Kaposi sarcoma (KS) in the foot and ankle. Observation of the lesions without treatment is a good option for patients in whom the lesions are not progressing or symptomatic. In patients with cutaneous KS that is progressing and confined to a relatively limited geographic area, topical treatment with alitretinoin, an endogenous retinoid, may result in control of the disease in about one-third of cases. The principle side effects are skin irritation, pain, itching, and dry desquamation. For small lesions (< 1 to 2 cm), intralesional injection with vincristine or vinblastine has been associated with high rates of tumor regression, but in this patient with a relatively wide area of involvement, intralesional therapy is not practical. Cryotherapy is effective in controlling small KS lesions. Radiation is effective in controlling cutaneous KS and is useful when there is a larger area of skin involvement or KS fails to respond to topical therapy. Combined antiretroviral therapy may induce regression of KS in patients with HIV following reconstitution of the immune system. Because of side effects

associated with intravenous chemotherapy, treatment with liposomal doxorubicin is usually reserved for extensive skin, lymph node, or visceral involvement by KS.

Suggested Reading

Brambilla L, Bellinvia M, Tourlaki A, et al. Intralesional vincristine as first-line therapy for nodular lesions in classic Kaposi sarcoma: a prospective study in 151 patients. *Br J Dermatol*. 2010;162:854–859. PMID: 19995366.

Morganroth GS. Topical 0.1% alitretinoin gel for classic Kaposi sarcoma. *Arch Dermatol*. 2002;138:542–543. PMID: 11939830.

Walmsley S, Northfelt DW, Melosky B, et al. Treatment of AIDS-related cutaneous Kaposi's sarcoma with topical alitretinoin (9-cis-retinoic acid) gel. P*J Acquir Immune Defic Syndr*. 1999;22:235–246. PMID: 10770343.

14-8 C

The most common translocation in Ewing sarcoma involves *EWSR1* on chromosome 22 and *FLI1* on chromosome 11, which occurs in about 85% of cases. Translocation between *EWSR1* and *ERG* on chromosome 21 is less common, occurring in about 5% to 10% of cases. Translocation involving *BCOR* and *CCNB3* on chromosome X is seen in a small percentage of Ewing-like sarcomas that lack *EWSR1* rearrangement, and it may be responsive to chemotherapy. Rearrangement between *CIC* on chromosome 19 and *DUX4* on chromosome 4 are seen in a small percentage of Ewing-like tumors but are less sensitive to chemotherapy than Ewing sarcoma. Translocation between *SYT* and *SSX1* occurs in synovial sarcoma.

Suggested Reading

Cohen-Gogo S, Cellier C, Coindre JM, et al. Ewing-like sarcomas with BCOR-CCNB3 fusion transcript: a clinical, radiological and pathological retrospective study from the Societé Francaise des Cancers de L'Enfant. *Pediatr Blood Cancer.* 2014;61:2191– 2198. PMID: 25176412.

Choi EY, Thomas DG, McHugh JB, et al. Undifferentiated small round cell sarcoma with t(4;19)(q35;q13.1) CIC-DUX4 fusion: a novel highly aggressive soft tissue tumor with distinctive histopathology. *Am J Surg Pathol.* 2013;37:1379–1386. PMID: 23887164.

Desmaze C, Brizard F, Turc-Carel C, et al. Multiple chromosomal mechanisms generate an EWS/FLI1 or an EWS/ERG fusion gene in Ewing tumors. *Cancer Genet Cytogenet*. 1997;97:12–19. PMID: 9242212.

14-9 C

The combination of olaratumab, a recombinant human monoclonal blocking antibody to platelet-derived growth factor receptor alpha was compared to doxorubicin alone in patients with locally advanced or metastatic soft-tissue sarcoma in an open-label, phase Ib and randomized phase II trial. The objective response rate was not significantly different between the groups (18% for the combination and 12% for doxorubicin). Median overall survival was longer with the combination, 26.5 months, compared with 14.7 months with doxorubicin. Median progression-free survival was in favor of the combination arm (6.6 vs. 4.1 months), but the difference was not statistically significant. Adverse events that were more frequent in the combination arm compared to the doxorubicin arm included mucositis, neutropenia, nausea, vomiting, and diarrhea, but the rates of febrile neutropenia were similar. Olaratumab is approved for treatment of locally advanced or metastatic soft-tissue sarcoma in combination with doxorubicin in patients for which an anthracycline chemotherapy is appropriate.

Suggested Reading

Tap WD, Jones RL, Van Tine BA, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet. 2016;388:488–497. PMID: 27291997.

15 CENTRAL NEVOUS SYSTEM TUMORS
SELF-EVALUATION

15. CENTRAL NERVOUS SYSTEM TUMORS QUESTIONS

15-1 A 46-year-old woman presents with new headaches and expressive speech difficulty. Magnetic resonance imaging (MRI) of the brain identified a left frontal infiltrating, heterogeneously enhancing mass. This was resected, and the pathology was reported as World Health Organization (WHO) Grade IV glioblastoma (isocitrate dehydrogenase [*IDH*] wild-type).

What is the most appropriate next step in treatment after she recovers from surgery?

A. Involved-field radiation therapy (RT)
B. Involved-field RT with concurrent temozolomide 75 mg/m^2 daily
C. Involved-field RT followed by procarbazine–lomustine–vincristine (PCV) chemotherapy
D. Involved-field RT with concurrent bevacizumab 10 mg/kg every 2 weeks

15-2 A 35-year-old man presents after a generalized seizure and was found to have an enhancing right frontal mass on MRI. This was resected, and the pathology indicated WHO Grade III anaplastic oligodendroglioma (*IDH*-mutant, 1p/19q codeleted).

Which treatment plan is indicated?

A. RT followed by PCV chemotherapy
B. RT with concurrent and adjuvant temozolomide
C. RT with concurrent temozolomide and bevacizumab followed by adjuvant temozolomide
D. RT monotherapy

15-3 A 52-year-old man presents with a 1-month history of progressive memory loss and executive dysfunction. MRI of the head showed bilateral periventricular enhancing lesions in the brain. Biopsy revealed primary CNS large B-cell lymphoma. Body PET/CT and bone marrow biopsy were negative.

What is the most appropriate initial treatment?

A. Whole-brain RT
B. Rituximab, cyclophosphamide, doxorubicin, Oncovin (vincristine), and prednisone (R-CHOP)
C. High-dose methotrexate
D. Involved-field RT with concurrent temozolomide

15-4 A 16-year-old boy presents with a 2-month history of headaches and difficulty balancing. Imaging demonstrates an enhancing cerebellar mass that obstructs the fourth ventricle.

He undergoes resection, and pathology reveals medulloblastoma (WNT-activated).

What type of radiation therapy is indicated?

A. Whole-brain RT
B. Whole ventricular RT
C. Craniospinal irradiation
D. Craniospinal irradiation with posterior fossa boost

15-5 A 26-year-old man presents after two partial seizures comprised of left arm shaking. MRI demonstrates a nonenhancing mass in the right parietal lobe without significant associated edema. Resection is completed and pathology is reported as a low-grade glioma (WHO Grade II).

Which molecular characteristics predict the best prognosis in low-grade glioma?

A. *IDH* mutant, 1p19q noncodeleted (intact)
B. *IDH* mutant, *ATRX* mutant
C. *IDH* wild-type, *MGMT* hypermethylated
D. *IDH* mutant, 1p19q codeletion

15-6 A 64-year-old woman with no history of cancer presents after a generalized seizure and is found to have several enhancing lesions throughout the brain.

Which systemic malignancy has the highest propensity to metastasize to the central nervous system?

A. Melanoma
B. Non–small cell lung cancer (NSCLC)
C. Breast cancer
D. Colon cancer

15-7 A 37-year-old man presents with a 1-year history of progressive headaches. MRI of the head demonstrates a large, 4-cm, uniformly enhancing mass in the brain that is separated from the brain parenchyma and associated with an enhancing "tail."

Based on the imaging, what is the most likely diagnosis?

A. Glioblastoma
B. Primary CNS lymphoma
C. Meningioma
D. Ependymoma

15. CENTRAL NERVOUS SYSTEM TUMORS RATIONALES

15-1 **B**

Initial postoperative management of glioblastoma includes involved-field RT for 6 weeks with concurrent daily temozolomide. Studies support the use of RT followed by PCV chemotherapy only in *IDH*-mutant, 1p19q codeleted gliomas. Up-front bevacizumab monotherapy has not been shown to improve survival.

Suggested Reading

Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 2009;10:459–466. PMID: 19269895.

Thomas AA, Brennan CW, DeAngelis LM, Omuro AM, et al. Emerging therapies for glioblastoma. *JAMA Neurol.* 2014;71:1437–1444. PMID: 25244650.

15-2 A

PCV chemotherapy after radiation has been shown to significantly improve survival in patients with oligodendrogliomas that harbor both *IDH* mutation and 1p/19q codeletion. These genetic changes are more important than WHO grade in determining treatment. There are as yet no data to support the use of temozolomide over PCV chemotherapy in patients with 1p/19q codeleted gliomas.

Suggested Reading

Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. *N Engl J Med.* 2016;374:1344–1355. PMID: 27050206.

van den Bent MJ. Practice changing mature results of RTOG study 9802: another positive PCV trial makes adjuvant chemotherapy part of standard of care in low-grade glioma. *Neuro Oncol.* 2014;16:1570–1574. PMID: 25355680.

van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol.* 2013;31:344–350. PMID: 23071237.

15-3 C

Periventricular homogenously enhancing lesions are classic for primary CNS lymphoma. High-dose methotrexate remains the initial treatment of choice. Radiation, additional chemotherapy, and autologous stem cell transplantation are possible options for consolidation treatment. Primary CNS lymphoma is generally not responsive to R-CHOP.

Suggested Reading

Korfel A, Schlegel U. Diagnosis and treatment of primary CNS lymphoma. *Nat Rev Neurol*. 2013;9:317–327. PMID: 23670107.

Rubenstein JL, Gupta NK, Mannis GM, et al. How I treat CNS lymphomas. *Blood.* 2013;122:2318–2330. PMID: 23963042.

15-4 D

Medulloblastoma typically occurs in the posterior fossa and can contribute to hydrocephalus. This tumor carries a high risk of leptomeningeal seeding. Initial management includes craniospinal irradiation with a boost to the primary tumor site (usually the posterior fossa). The WNT molecular subgroup of medulloblastoma has the best prognosis, with long-term survival in more than 90% of patients (5-year survival rate over 95%).

Suggested Reading

Massimino M, Biassoni V, Gandola L, et al. Childhood medulloblastoma. *Crit Rev Oncol Hematol.* 2016;105:35–51. PMID: 27375228.

Taylor MD, Northcott PA, Korshunov A, et al. Molecular subgroups of medulloblastoma: the current consensus. *Acta Neuropathol.* 2012;123:465–472. PMID: 22134537.

15-5 D

Gliomas arising from mutations in *IDH* with 1p/19q codeletion are associated with the best prognosis. The 5-year survival typically ranges from 50 to 80%, and the addition of PCV chemotherapy has been shown to greatly improve outcomes. Tumors with *IDH* mutation and

ATRX mutation (mutually exclusive from 1p/19q codeletion), as often seen with anaplastic astrocytoma, have an intermediate prognosis. *IDH* wild-type tumors have the worst prognosis, regardless of histologic diagnosis. *MGMT* hypermethylation indicates better prognosis and response to chemotherapy in WHO Grade IV glioblastoma.

Suggested Reading

Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. *N Engl J Med.* 2016;374:1344–1355. PMID: 27050206.

Eckel-Passow JE, Lachance DH, Molinaro AM, et al. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. *N Engl J Med*. 2015;372:2499–2508. PMID: 26061753.

The Cancer Genome Atlas Research Network. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. *N Engl J Med*. 2015;372:2481–2498. PMID: 26061751.

15-6 A

Although brain metastases from NSCLC and breast cancer are most frequently seen because of their increased incidence, melanoma has a higher propensity to metastasize to the brain or CNS. Other systemic malignancies with high neurotropism include small cell lung cancer and choriocarcinoma.

Suggested Reading

Arvold ND, Lee EQ, Mehta MP, et al. Updates in the management of brain metastases. *Neuro Oncol.* 2016;18:1043–1065. PMID: 27382120.

Eichler AF, Loeffler JS. Multidisciplinary management of brain metastases. *Oncologist*. 2007;12:884–898. PMID: 17673619.

15-7 C

Classic imaging characteristics of meningiomas include an extraaxial location (separated from the brain parenchyma), uniform enhancement, and a frequently seen dural “tail” (contrast-enhanced thickening of the adjacent meninges). Most meningiomas are benign (WHO Grade I), and maximal safe resection is indicated if there are symptoms and/or significant mass effect.

Suggested Reading

Baig M, Klein JP, Mechtler LL. Imaging of brain tumors. *Continuum (Minneap Minn).* 2016;22:1529–1552. PMID: 27740987.

Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. *J Neurooncol*. 2010;99:307–314. PMID: 20821343.

16 LEUKEMIAS
SELF-EVALUATION

16. LEUKEMIAS QUESTIONS

16-1 A 59-year-old woman presents with pancytopenia and is found to have acute myeloid leukemia (AML) with 25% myeloid blasts and complex cytogenetic abnormalities in the bone marrow. Her medical history is notable only for diagnosis of breast cancer 5 years ago, for which she underwent partial mastectomy, radiation, and anthracycline-containing adjuvant chemotherapy. Her ECOG performance status is 1, and echocardiography shows a left ventricular ejection fraction of 56%. She has eight younger siblings with no known medical problems.

What is the most appropriate initial treatment strategy?

A. Best supportive care (i.e., antibiotics, and red blood cell and platelet transfusions)
B. Chemotherapy with conventional daunorubicin and cytarabine (3+7) followed by three to four cycles of cytarabine-based postremission chemotherapy if remission is achieved
C. Chemotherapy with conventional daunorubicin and cytarabine (3+7) followed by allogeneic transplantation once an HLA-matched–related or unrelated donor is found if remission is achieved
D. Immediate allogeneic transplantation once an HLA–matched–related or unrelated donor is identified without prior chemotherapy

16-2 A 36-year-old man presents with cervical lymphadenopathy, fever, and weight loss. His blood counts are notable for an elevated white blood cell count (19,000/µL) with 44% circulating blasts, anemia, and thrombocytopenia. A bone marrow examination reveals an abnormal lymphoid cell population that expresses CD10, CD19, CD20, CD22, and CD45. Cytogenetic studies show a normal male karyotype, and PCR studies fail to detect a *BCR-ABL1* translocation. A lumbar puncture shows no evidence of CNS leukemia.

In addition to a pediatric-inspired multiagent chemotherapy, what other agent is appropriate to use for initial treatment?

A. No additional agent indicated
B. Blinatumomab
C. Rituximab
D. Inotuzumab ozogamicin

16-3 A 24-year-old man presents with fever, night sweats, and shortness of breath. Laboratory studies are notable for significant leukocytosis (74,000/µL) with 68% circulating blasts, a hematocrit of 29%, and a platelet count of 28,000/µL. Multiparameter flow cytometry identifies the blasts to express CD13, CD15, CD33, CD34 (dim), and CD38. Cytogenetic analyses show a normal male karyotype, and molecular studies

detect a mutation in *NPM1* but not in *FLT3* or *CEBPA.* The patient is otherwise healthy, and his ECOG performance status is 1. He has three siblings who range in age from 26 to 31.

What is the most appropriate treatment strategy?

A. Daunorubicin (90 mg/m^2) and cytarabine (3+7); plan on allogeneic transplantation (e.g., from HLA-matched sibling) during first complete remission
B. Daunorubicin (90 mg/m^2) and cytarabine (3+7); plan on cytarabine-based postremission chemotherapy and use allogeneic transplantation only if response to chemotherapy is inadequate
C. Daunorubicin (60 mg/m^2) and cytarabine (3+7); plan on allogeneic transplantation (e.g., from HLA-matched sibling) during first complete remission
D. Chemotherapy with daunorubicin (60 mg/m^2) and cytarabine (3+7); plan on cytarabine-based postremission chemotherapy and use allogeneic transplantation only if response to chemotherapy is inadequate

16-4 A 48-year-old woman was diagnosed with T-cell acute lymphoblastic leukemia (T-ALL) 8 months ago and achieved a complete remission with multiagent chemotherapy. She declined allogeneic transplantation at that time and received further postremission chemotherapy. She now experiences fevers and bone pain, symptoms similar to those she had when her disease was initially diagnosed. Further assessment with peripheral-blood and bone marrow examinations indeed confirm recurrent T-ALL. Her ECOG performance status is 1, and echocardiography shows a left ventricular ejection fraction of 55%.

Besides referral for consideration of allogeneic hematopoietic stem cell transplantation, what is the most appropriate next step in her treatment?

A. Nelarabine
B. Immunotherapy with inotuzumab ozogamicin
C. Immunotherapy with blinatumomab
D. Referral to a clinical trial for immunotherapy with CD19-directed chimeric antigen receptor (CAR) T cells

16-5 A 45-year-old man presents with growing masses around his neck, early satiety, night sweats, and weight loss. On physical examination, he has bulky supraclavicular and axillary lymphadenopathy, and you can feel the tip of his spleen 8 cm below the left costal margin. His peripheral-blood counts are notable for an elevated white blood cell count of 135,000/µL with a large predominance of mature-looking lymphocytes, anemia (hemoglobin 10 g/dL), and thrombocytopenia (88,000/µL). Immunophenotyping studies of the peripheral blood show the presence of a clonal B-cell population expressing CD19, CD20, and CD23. A 17p13 deletion is found by fluorescence in situ hybridization (FISH).

Which treatment do you recommend as next step?

A. Bendamustine in combination with rituximab
B. Single-agent treatment with ibrutinib
C. Rituximab in combination with idelalisib

D. Symptomatic treatment only

16-6 A 70-year-old man presents with weakness, fatigue, left upper quadrant pain, and early satiety. His spleen is palpable 10 cm below the left costal margin. Laboratory studies reveal pancytopenia; on review of his peripheral-blood smear, abnormal cells with an eccentric, spongiform kidney-shaped nucleus and some filamentous cytoplasmic projections are seen. Bone marrow is inaspirable, but a biopsy reveals the presence of clonal B cells that express CD19, CD20, CD25, CD103, and CD123 infiltrating more than 50% of the marrow space.

Which molecular abnormality would be strongly supportive of your suspected diagnosis and involved in the pathogenesis of this disease?

A. Mutation in either *IDH1* or *IDH2*
B. Mutation in *RUNX1*
C. Overexpression of *BCL-2*
D. Mutation in *BRAF*

16-7 A slender 66-year-old woman presents with a 15-lb weight loss with extensive sweats over the past 2 to 3 months and abdominal discomfort. She is found to have mild leukocytosis (12,000/µL), anemia (hemoglobin 9.8 g/dL), and thrombocytopenia (63,000/µL); occasional (<0.5%) circulating blasts are seen. You can feel the tip of her spleen 7 cm below the left costal margin. A bone marrow biopsy shows grade 2 reticulin and collagen fibrosis as well as megakaryocytic proliferation and atypia; CD34+ cells are estimated at 2 to 3%. Molecular studies for the *JAK V617F* mutation are negative, but a mutation in *CALR* is detected. Calculation of her Dynamic International Prognostic Scoring System (DIPSS)–plus score indicates her disease to be intermediate 2 risk. Her medical history is otherwise notable only for osteoarthrosis, and her ECOG performance status is 1.

What is the most appropriate initial treatment strategy?

A. Observation and use of hydroxyurea as needed for constitutional symptoms
B. Splenectomy
C. Chemotherapy with azacitidine or decitabine
D. Treatment with ruxolitinib

16-8 A 65-year-old woman is referred to you after she was found to have an elevated hematocrit (46.5%) and mild thrombocytosis (497,000/µL) when she was evaluated by her primary care physician for chronic headaches (which developed over the past 1 to 2 years), hypertension, and night sweats. Further laboratory testing shows an erythropoietin level in the high-normal range but no *JAK2 V617F* mutation. Other than being a smoker (1 to 2 packs a day for the past 20 years) and being obese (body mass index, 32), her medical history is unremarkable.

What is the most appropriate next step?

A. Assess for mutations in *CALR* or *MPL*
B. Assess for secondary causes of an elevated hematocrit

C. Start low-dose aspirin and use intermittent phlebotomies to keep hematocrit < 42%
D. Start low-dose aspirin and hydroxyurea and use intermittent phlebotomies to keep hematocrit < 42%

16-9 A 48-year-old man presents with worsening fatigue and is found to have pancytopenia. Bone marrow examination reveals a diagnosis of acute myeloid leukemia (AML) with 54% myeloid blasts. Cytogenetic studies demonstrate the presence of a t(9;11)(p21.3;q23.3) abnormality, and fluorescence in situ hybridization studies confirm *KMT2A* (*MLL*) rearrangement. Molecular studies do not detect any mutations in *FLT3, NPM1,* or *CEBPA.* His medical history is notable for a diagnosis of testicular cancer 5 years ago, for which he underwent curative-intent chemotherapy. His ECOG performance status is 1, and a multigated acquisition (MUGA) scan shows a normal left ventricular ejection fraction. He is treated with daunorubicin and cytarabine (3+7) and achieves a complete remission after the first cycle of chemotherapy. Neither of his two brothers is HLA-identical, but a fully HLA-matched unrelated donor has been identified.

What is the most appropriate curative-intent postremission treatment strategy?

A. Maintenance therapy with azacitidine for 24 months
B. Chemotherapy with three to four cycles of a cytarabine-based regimen only. Because of the favorable-risk cytogenetic risk and the optimal response to initial chemotherapy, allogeneic transplantation during first complete remission is not indicated
C. Referral for HLA-matched unrelated donor allogeneic transplantation with reduced-intensity conditioning
D. Referral for HLA-matched unrelated donor allogeneic transplantation with myeloablative conditioning

16-10 A 26-year-old woman presents with easy bruising, bleeding gums, recurrent prolonged nose bleeds, and worsening fatigue. Peripheral-blood studies show pancytopenia with a white blood cell count of 3100/µL, a hematocrit of 22%, and a platelet count of 8000/µL. Fibrinogen is reduced, at 75 mg/dL. You provide transfusion support and clotting factor replacement and initiate treatment with all-trans retinoic acid (ATRA) for suspected acute promyelocytic leukemia (APL). This diagnosis is confirmed via bone marrow examination on the next day.

Besides transfusion support and clotting factor replacement, what is the most appropriate initial treatment strategy?

A. Continue with ATRA monotherapy
B. Add cytarabine to ATRA
C. Add daunorubicin and cytarabine (3+7) to ATRA
D. Add arsenic trioxide to ATRA

16. LEUKEMIAS RATIONALES

16-1 **C**

With a history of breast cancer with prior treatment with chemotherapy and radiation, this

woman has secondary AML. Based on the demonstration of complex cytogenetic abnormalities, she has adverse-risk disease based on the 2017 European LeukemiaNet classification. The patient otherwise has no known medical comorbidities and is per se a candidate for intensive chemotherapy. Chemotherapy with 3+7 has remained the standard remission-induction therapy for adults with newly diagnosed AML, outcomes in adults with secondary, adverse-risk disease are unsatisfactory with a treatment strategy that is based on chemotherapy alone. Thus, once a complete remission has been achieved, transplantation from an HLA-matched (related or unrelated) donor should be strongly considered as postremission treatment. Allogeneic transplantation is not typically performed as the first treatment modality.

Suggested Reading

Cornelissen JJ, Blaise D. Hematopoietic stem cell transplantation for patients with AML in first complete remission. *Blood.* 2016;127:62–70. PMID: 26660427.

Cornelissen JJ, Gratwohl A, Schlenk RF, et al. The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach. *Nat Rev Clin Oncol*. 2012;9:579–590. PMID: 22949046.

Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129:424–447. PMID: 27895058.

16-2 C

In this patient, the clinical and pathologic findings are diagnostic of a Philadelphia chromosome (Ph)–negative B-cell acute lymphoblastic leukemia (B-ALL). A subset of B-ALLs expresses CD20, a marker that in some, but not all, studies performed without the addition of CD20 antibodies was associated with a worse outcome. Standard induction therapy for younger adults with ALL most commonly involves combination chemotherapy; outcomes appear better with use of pediatric-inspired multi-agent chemotherapy. For younger adults with CD20-positive Ph-negative B-ALL, adding the CD20 antibody rituximab to combination chemotherapy improves event-free survival. The roles of blinatumomab and inotuzumab in front-line therapy of B-ALL are currently not defined.

Suggested Reading

Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia. *J Clin Oncol*. 2011;29:532–543. PMID: 21220592.

Faderl S, O'Brien S, Pui CH, et al. Adult acute lymphoblastic leukemia: concepts and strategies. *Cancer*. 2010;116:1165–1176. PMID: 20101737.

Maury S, Chevret S, Thomas X, et al. Rituximab in B-lineage adult acute lymphoblastic leukemia. *N Engl J Med*. 2016;375:1044–1053. PMID: 27626518.

16-3 D

Based on the pathologic data, this patient has acute myeloid leukemia (AML). Outcomes of patients with AML are highly variable. Cytogenetic and molecular abnormalities are the most important pretreatment factors that have been associated with failure to achieve remission with intensive chemotherapy and/or with shortened survival. According to the updated 2017 European LeukemiaNet risk classification, a patient with cytogenetically normal AML harboring a mutation in *NPM1* but not in *FLT3* is considered to be at favorable risk. Three days of an anthracycline such as daunorubicin in combination with 7 days of continuously infused cytarabine (3+7 regimen) has remained the standard remission induction therapy in such patients. One randomized study found no advantage of 90 over 60 mg/m^2/day of daunorubicin except for patients with *FLT3*/internal tandem duplication (ITD)–mutated AML. If a complete remission is achieved, the patient should receive additional postremission cytarabine-based

chemotherapy. Patients with a favorable cytogenetic/molecular risk profile are not typically considered for allogeneic hematopoietic stem cell transplantation during first remission because the benefit of transplantation in terms of reduction of relapse risk is offset by transplant-related (nonrelapse) mortality.

Suggested Reading

Burnett AK, Russell NH, Hills RK, et al. A randomized comparison of daunorubicin 90 mg/m^2 vs 60 mg/m^2 in AML induction: results from the UK NCRI AML17 trial in 1206 patients. *Blood*. 2015;125:3878–3885. PMID: 25833957.

Cornelissen JJ, Gratwohl A, Schlenk RF, et al. The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach. *Nat Rev Clin Oncol*. 2012;9:579–590. PMID: 22949046.

16-4 A

In this situation, chemotherapy with nelarabine can achieve complete remission rates of 30% or higher, although the drug has significant neurotoxic effects. T-ALL typically does not express the B-cell markers CD19 or CD22, and treatment with inotuzumab ozogamicin, blinatumomab, or CD19-directed CAR T cells would not be indicated. However, these treatments can be highly effective in relapsed or refractory B-ALL.

Suggested Reading

Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia. *J Clin Oncol*. 2011;29:532–543. PMID: 21220592.

Faderl S, O'Brien S, Pui CH, et al. Adult acute lymphoblastic leukemia: concepts and strategies. *Cancer*. 2010;116:1165–1176. PMID: 20101737.

Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med*. 2016;375:740–753. PMID: 27292104.

Sadelain M. CAR therapy: the CD19 paradigm. *J Clin Invest*. 2015;125:3392–3400. PMID: 26325036.

Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2015;16:57–66. PMID: 25524800.

16-5 B

This patient has CLL based on the peripheral-blood studies showing a clonal B-cell population expressing CD19, CD20, and CD23. Structural abnormalities of chromosome 17 occur in at least 15% of patients when FISH testing is performed; 17p13 deletions lead to disruption of the *TP53* gene, and del (17p) is now recognized as indicating very poor prognosis. CLL is not curable with currently available therapies, and several randomized studies found no improvement in survival with early versus delayed treatment for patients with early-stage disease. However, current indications to start therapy include evidence of progressive bone marrow failure (i.e., anemia, thrombocytopenia), massive or progressive symptomatic splenomegaly, massive or progressive symptomatic lymphadenopathy, progressive lymphocytosis (with lymphocyte doubling time of less than 6 months), autoimmune anemia or thrombocytopenia, and constitutional symptoms. This patient has several of these findings (e.g., anemia, thrombocytopenia, splenomegaly, and constitutional symptoms), and initiation of treatment is indicated. The oral Bruton tyrosine kinase (BTK) inhibitor ibrutinib was approved for first-line therapy of CLL with del(17p)/*TP53* mutation. Bendamustine plus rituximab can be considered for front-line therapy of patients with significant comorbidities or age over 65. Idelalisib (GS-1101) has shown high activity and durable disease control when used together with rituximab in older patients with treatment-naive CLL. Neither bendamustine plus rituximab nor idelalisib plus rituxan is typically used for front-line treatment of a younger adult with CLL

harboring a del(17p)/*TP53* mutation.

Suggested Reading

Stilgenbauer S. Prognostic markers and standard management of chronic lymphocytic leukemia. *Hematology Am Soc Hematol Educ Program*. 2015;2015:368–377. PMID: 26637745.

Zelenetz AD, Gordon LI, Wierda WG, et al. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 1.2015. *J Natl Compr Canc Netw.* 2015;13:326–362. PMID: 25736010.

16-6 D

The malignant cells in the classic cases of hairy cell leukemia are of B-cell origin, have no (or inconspicuous) nucleoli, and express CD19, CD20, CD123, and CD200 as well as the monocyte antigens CD11c and CD25. The most specific marker for this disease entity is CD103. Some studies have demonstrated that mutations in *BRAF*, specifically V600E, are present in virtually all cases of classic hairy cell leukemia. In contrast, the hairy cell variant often presents with significant leukocytosis. Cells are characterized by prominent nucleoli and lack of CD200 expression. They also typically do not express CD25 or CD123, and, molecularly, lack the *BRAF* V600E mutation. Mutations in *IDH1/2, RUNX1,* or overexpression of *BCL-2* are not hallmark findings of hairy cell leukemia.

Suggested Reading

Falini B, Martelli MP, Tiacci E. BRAF V600E mutation in hairy cell leukemia: from bench to bedside. *Blood*. 2016;128:1918–1927. PMID: 27554081.

Tiacci E, Park JH, De Carolis L, et al. Targeting mutant BRAF in relapsed or refractory hairy-cell leukemia. *N Engl J Med*. 2015;373:1733–1747. PMID: 26352686.

Tiacci E, Trifonov V, Schiavoni G, et al. *BRAF* mutations in hairy-cell leukemia. *N Engl J Med*. 2011;364:2305–2315. PMID: 21663470.

16-7 D

In this patient, the combination of *CALR* mutation and presence of grade 2 reticulin and collagen fibrosis as well as megakaryocytic proliferation and atypia in the bone marrow biopsy establish a diagnosis of primary myelofibrosis. In randomized trials, ruxolitinib provided substantial clinical benefits relative to standard therapy in intermediate or high DIPSS-plus risk myelofibrosis by reducing spleen size, ameliorating debilitating myelofibrosis-related symptoms, and perhaps improving OS. The benefit of ruxolitinib extends to patients in whom no *JAK2 V617F* mutations are found, such as this patient. In addition to treatment with ruxolitinib, for intermediate 2 or high DIPSS-plus risk or genetically high-risk disease (i.e., *CALR* mutation–negative and *ASXL1* mutation–positive), allogeneic hematopoietic stem cell transplantation should be considered, as many patients will experience a durable remission after transplantation with matched-related or matched-unrelated donors.

Suggested Reading

Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012;366:787–798. PMID: 22375970.

Passamonti F, Maffioli M, Cervantes F, et al. Impact of ruxolitinib on the natural history of primary myelofibrosis: a comparison of the DIPSS and the COMFORT-2 cohorts. *Blood*. 2014;123:1833–1835. PMID: 24443442.

Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med*. 2012;366:799–807. PMID: 22375971.

16-8 B

This woman presents with findings compatible with a diagnosis of a myeloproliferative

neoplasm, in particular polycythemia vera. The latter diagnosis is established if, besides an elevated hemoglobin or increased hematocrit, the bone marrow shows hypercellularity with trilineage hematopoiesis and prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes. While not diagnostic for this disorder, the vast majority of patients will have a *JAK2 V617F* mutation. If this mutation is absent, a diagnosis of polycythemia vera is still possible if there is a subnormal erythropoietin level. In this patient, the absence of a *JAK2 V617F* mutation and a high-normal erythropoietin level argue against a diagnosis of polycythemia vera, and the patient should be assessed for secondary causes of an elevated hematocrit (e.g., chronic pulmonary disease, right-to-left cardiac shunts, sleep apnea, high altitude, etc.). Treatment with low-dose aspirin and the use of intermittent phlebotomies to keep hematocrit < 42%, with or without the use of hydroxyurea, are indicated for the treatment of patients with polycythemia vera but have no role in patients with secondary causes of an elevated hematocrit.

Suggested Reading

Geyer HL, Mesa RA. Therapy for myeloproliferative neoplasms: when, which agent, and how? *Blood*. 2014;124:3529–3537. PMID: 25472969.

Lee G, Arcasoy MO. The clinical and laboratory evaluation of the patient with erythrocytosis. *Eur J Intern Med.* 2015;26:297–302. PMID: 25837692.

Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2017 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2017;92:94–108. PMID: 27991718.

Tefferi A, Pardanani A. Myeloproliferative neoplasms: a contemporary review. *JAMA Oncol*. 2015;1:97–105. PMID: 26182311.

16-9 D

This patient's AML is characterized by a t(9;11)(p21.3;q23.3) abnormality, possibly as a manifestation of prior exposure to topoisomerase II inhibitor–containing chemotherapy that was given for testicular cancer. The available cytogenetic/molecular findings classify his disease as intermediate (not favorable) risk. Based on assessments of relapse risk and transplantation-related morbidity/mortality, younger adults with AML in first complete remission—except those with a favorable cytogenetic/molecular risk profile—should be considered for allogeneic hematopoietic stem cell transplantation, particularly if comorbidity scores are low and an HLA-matched donor is available, as is the case for this man. Data from a recent randomized trial show significantly higher rates of relapse and shorter relapse-free survival with reduced-intensity as compared to myeloablative conditioning; myeloablative conditioning should therefore be prioritized if the patient is considered suitable. There is currently no established role for low-intensity maintenance therapy in AML.

Suggested Reading

Cornelissen JJ, Gratwohl A, Schlenk RF, et al. The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach. *Nat Rev Clin Oncol*. 2012;9:579–590. PMID: 22949046.

Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129:424–447. PMID: 27895058.

Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol*. 2017;35:1154–1161. PMID: 283830315.

16-10 D

APL is a distinct subtype of acute myeloid leukemia that has unique clinical, morphologic, and cytogenetic features and that is treated differently from all other acute leukemias. A unique feature of APL is its very high sensitivity to treatment with ATRA and arsenic trioxide (ATO). If

initiated promptly in patients with suspected APL, ATRA decreases the incidence of substantial bleeding complications, which represent the major cause of mortality in patients with APL. Some randomized trials have demonstrated that patients with lower-risk APL, defined as those presenting with a white blood cell count of less than 10,000/μL, can be treated with ATRA and ATO alone, with more sustained antileukemic efficacy and better survival than that seen with an ATRA/chemotherapy-based regimen.

Suggested Reading

Burnett AK, Russell NH, Hills RK, et al. Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2015;16:1295–1305. PMID: 26384238.

Platzbecker U, Avvisati G, Cicconi L, et al. Improved outcomes with retinoic acid and arsenic trioxide compared with retinoic acid and chemotherapy in non-high-risk acute promyelocytic leukemia: final results of the randomized Italian-German APL0406 trial. *J Clin Oncol*. 2017;35:605–612. PMID: 27400939.

Sanz MA, Lo-Coco F. Modern approaches to treating acute promyelocytic leukemia. *J Clin Oncol*. 2011;29:495–503. PMID: 21220600.

17 LYMPHOMAS
SELF-EVALUATION

17. LYMPHOMAS QUESTIONS

17-1 A 47-year-old man develops fatigue and a left axillary lymph node. He is evaluated by his primary care physician and found to have cervical and axillary adenopathy in addition to the left axillary lymph node. On review of systems, he has had mild night sweats. An excisional biopsy is performed and shows diffuse large B-cell lymphoma, CD20-positive, CD10-positive, BCL6-positive. Staging evaluation with a PET/CT confirms stage III disease. His lactate dehydrogenase (LDH) is normal, and hepatitis testing is positive for hepatitis B surface antigen (HBsAg) and negative for hepatitis B core antibody (HBcAb). He is scheduled to start R-CHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone) chemoimmunotherapy.

Which of the following is the most appropriate next step?

A. Start treatment with entecavir for 3 months.
B. Check weekly hepatitis B viral load for the duration of R-CHOP.
C. Check weekly hepatitis B viral load and give IVIG (intravenous immunoglobulin) monthly for the duration of oncology treatment.
D. Check confirmatory hepatitis B viral load and start entecavir prophylaxis for at least 6 months after oncology treatment ends.

17-2 A 74-year-old woman presents with diffuse adenopathy, a 10-pound weight loss, and mild thrombocytopenia. Excisional biopsy of an inguinal lymph node confirms follicular lymphoma, grade 1–2. She was treated with R-CHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone) chemotherapy for six cycles without significant toxic effects. The end-of-treatment CT scan shows no residual adenopathy. She is worried that her lymphoma will return, and has questions about maintenance rituximab.

Which of the following most appropriately describes the role of maintenance rituximab in this setting?

A. Maintenance rituximab every 12 weeks for 2 years will improve her overall survival.
B. Maintenance rituximab every 8 weeks for 2 years will improve her overall survival.
C. Maintenance rituximab every 8 weeks for 2 years will improve her progression-free but not overall survival.
D. Maintenance rituximab will not improve her progression-free or overall survival since she already received rituximab as part of initial treatment.

17-3 A 39-year-old man presents with sweats, cough, and pruritus. He is found to have palpable supraclavicular and left axillary lymph nodes. Imaging studies show a 6-cm mediastinal mass and hilar adenopathy. A biopsy confirms the presence of scattered

large binucleated cells with strong CD30 expression, CD15 expression, and no evidence of CD20 or CD45. His final diagnosis and stage is IIB classical Hodgkin lymphoma. He is treated with ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine) for six cycles and enters a complete metabolic remission. Seven months later, he self-palpates a right axillary lymph node. Biopsy confirms recurrent classical Hodgkin lymphoma and he receives ICE (ifosfamide/carboplatin/etoposide) salvage chemotherapy with a partial response. A second salvage regimen of gemcitabine/vinorelbine/doxil (GVD) is initiated, leading to a complete response.

What is the most appropriate next step?

A. High-dose chemotherapy and autologous stem cell transplantation followed by consolidative brentuximab vedotin for 16 doses
B. Consolidative brentuximab vedotin for 16 doses
C. High-dose chemotherapy and autologous stem cell transplantation followed by close observation
D. Combined nivolumab and brentuximab vedotin for 1 year

17-4 A 51-year-old man presents with asymptomatic enlargement of axillary lymph nodes. Staging evaluation with PET/CT shows bulky abdominal and inguinal involvement. Excisional biopsy shows rare large neoplastic cells within a vaguely nodular architectural background. The large cells have nuclei with a “popcorn” appearance and are CD20-positive and CD79a-positive, weakly positive for CD30, and CD15-negative. He is diagnosed with stage IIIA nodular lymphocyte–predominant Hodgkin lymphoma. He feels well and does not return to clinic despite repeated attempts to reach him. One year later, he presents with drenching night sweats, a 15-pound weight loss, and fatigue. Lab results are notable for an elevated white cell count of 14,000/mm^3, hemoglobin 11g/dL, absolute lymphocyte count 500/mm^3, lactate dehydrogenase (LDH) 300 U/L, and albumin 3.0 g/dL.

Which treatment is most appropriate at this time?

A. ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine)
B. Escalated BEACOPP (bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/predniso
C. ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine) for two cycles followed by interim PET. If the interim PET is positive, then change to escalated BEACOPP
D. R-CHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone)

17-5 A 69-year-old woman presents with fatigue, sweats, and diffuse arthralgias. Examination reveals diffuse cervical, axillary, and inguinal adenopathy. Laboratory tests are notable for polyclonal hypergammaglobulinemia and lactate dehydrogenase (LDH) twice the upper limit of normal. CT scans show hepatosplenomegaly in addition to widespread lymph node enlargement.

An excisional lymph node biopsy shows architectural effacement with an infiltrate of small to medium-sized lymphocytes clustering around endothelial venules with a background of plasma cells, histiocytes, and eosinophils. The lymphocytes express CD3, CD2, CD5,

CD4, and CD10 and are negative for CD7 and CD30. The lymph node is sent for genomic analysis and the report shows somatic mutations of *TET2*, *DNMT3A*, *RHOA*, and *IDH2.*

What is the most appropriate initial treatment plan?

A. CHOEP (cyclophosphamide/doxorubicin/vincristine/etoposide/prednisone)
B. CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) plus romidepsin
C. CHP (cyclophosphamide/doxorubicin/prednisone) plus brentuximab vedotin
D. CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone)

17-6 A 57-year-old woman was diagnosed with follicular lymphoma grade 1–2 almost 10 years ago. She was initially treated with R-CVP (rituximab/cyclophosphamide/vincristine/prednisone) and was in remission for 3 years. Since then, she has had two additional relapses requiring treatment with rituximab. Her most recent treatment was with bendamustine/rituximab for six cycles, completed 8 months ago. She now presents with progressive cervical and axillary adenopathy along with fatigue and weight loss.

A biopsy confirms recurrent follicular lymphoma grade 1–2 without evidence of transformation. She starts treatment with oral idelalisib 150 mg twice daily. She has quick resolution of her symptoms, and all palpable adenopathy begins to regress.

Three months later, persistent watery diarrhea and abdominal pain and cramping develops. She is seen in clinic and is hypotensive. She is admitted to the hospital for intravenous hydration.

In addition to holding idelalisib, what is the most appropriate next step?

A. Test for *Clostridium difficile* infection.
B. Start budesonide and oral steroids immediately.
C. Change treatment to ibrutinib.
D. Wait until diarrhea is resolved, then resume idelalisib 150 mg twice daily.

17-7 Progressive left upper quadrant abdominal pain and worsening fatigue develops in a 60-year-old woman. Blood tests demonstrate a leukocyte count of 3200/mm^3, hemoglobin 9 g/dL, and a platelet count of 40,000/µL. A bone marrow aspirate and biopsy demonstrate normal trilineage hematopoiesis with infiltration by 40% small to medium-sized neoplastic B-lymphocytes expressing CD20 and CD79a, but negative for CD5, CD10, CD11c, CD23, CD43, CD103, CD123, or cyclin D1. Staining of the marrow was negative for tartrate-resistant acid phosphatase (TRAP). Serologic tests were positive for hepatitis B surface antigen and hepatitis B core antibody. Tests for hepatitis C were negative. LDH is minimally elevated. Serum IgM is 1.8 g/dL.

Which test will best confirm the diagnosis?

A. Material from her bone marrow biopsy should be tested for *MYD88.*
B. Serum and urine immunoelectropheresis with quantitative immunoglobulins
C. A total-body FDG-PET/CT

D. Serum PCR for hepatitis B

17-8 A 61-year-old man with no comorbidities presents with left inguinal lymphadenopathy that grew quickly over the past 6 weeks. An inguinal lymph node biopsy shows sheets of intermediate-to-large sized cells that express CD20, CD19, CD10, and BCL2 (80% positivity). They lack expression of MUM1 and immunohistochemical staining for MYC shows that approximately 20% of the cells are positive. FISH testing is negative for a MYC rearrangement but is positive for t(14;18).

He undergoes a PET/CT which reveals widespread disease with diffuse adenopathy in the thorax and abdomen and uptake in the left ischium. Laboratory studies are notable for an elevated lactate dehydrogenase (LDH) of 400 U/L. A bone marrow biopsy is negative for lymphoma. The score on the International Prognostic Index (IPI) is 3.

What is the most appropriate treatment plan?

A. Dose-adjusted EPOCH-R (etoposide/prednisone/vincristine/cyclophosphamide/doxorubicin/rituximab)
B. R-CHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone) for six cycles plus autologous hematopoietic stem cell transplantation
C. R-CHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone) for six cycles
D. R-CHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone) for six cycles plus maintenance rituximab

17-9 A 61-year-old woman presents to her physician with malaise, unintentional weight loss of 15 pounds, and abdominal discomfort. Physical examination is notable for axillary and inguinal adenopathy. Laboratory studies show an elevated lactate dehydrogenase (LDH) and a creatinine clearance of 50 mL/hour, and CT scans confirm stage III disease. A biopsy shows DLBCL (diffuse large B-cell lymphoma), and she is treated with R-CHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone) for six cycles. An end-of-treatment PET/CT performed 6 weeks after her last cycle of chemotherapy shows a complete response. Following treatment, the patient is recovering well but is very anxious about recurrence. She wants to know how often she will be undergoing imaging tests.

What is the most appropriate plan for routine surveillance?

A. PET/CT every 6 months for 2 years, then annually for an additional 3 years
B. Physical examination and laboratory studies every 3 to 6 months for the first 2 years, then every 6 months for an additional 3 years
C. PET/CT annually for the first 5 years
D. CT scans every 6 months for 2 years, then annually for an additional 3 years

17-10 A 73-year-old man is seen by his primary care physician for an annual physical examination. He is noted to have an enlarged spleen. Laboratory studies show an elevated white cell count with lymphocytosis of approximately 60,000/µL. He has no constitutional or B symptoms.

Flow cytometry on peripheral blood shows a monoclonal B-cell population that has aberrant expression of CD5. The cells are positive for CD20 and cyclin D1 and negative for CD23.

CT scans of the chest, abdomen, and pelvis are performed and show moderate splenomegaly and a few small, scattered lymph nodes. A core needle biopsy of an iliac lymph node is performed and shows complete effacement by the same cells that were noted in the peripheral blood. Additional stains include SOX11, which is negative, and Ki-67 which shows 5 to 10% proliferation.

Which of the following is the most appropriate next step?

A. Start bendamustine and rituximab.
B. Recommend observation.
C. Start the Nordic regimen followed by an autologous stem cell transplantation.
D. Start rituximab plus CVP (cyclophosphamide/vincristine/prednisone).

17. LYMPHOMAS RATIONALES

17-1 D

Testing for hepatitis B is required prior to the use of rituximab and other anti-CD20 therapy because of the risk of viral reactivation and fatal hepatitis. Tests should include those for HBsAg and HBcAb for patients without risk factors; patients with risk factors or prior history of hepatitis B should also be tested for e-antigen. Patients who are seropositive for HBsAg or HBcAb should undergo measurement for quantitative viral load by polymerase chain reaction (PCR). Prophylactic antiviral therapy is recommended for any patient who is HBsAg-positive and receiving antilymphoma therapy. If the PCR is positive, the patient should be considered to have active disease. All patients with HBsAg positivity should be treated with entecavir (lamivudine has a higher risk of resistance) or other antivirals (adefovir, telbivudine, tenofovir), ideally for 6 to 12 months after R-CHOP. The hepatitis B viral load should be monitored monthly with PCR throughout treatment and every 3 months thereafter.

Suggested Reading

Huang H, Li X, Zhu J, et al. Entecavir vs lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy: a randomized clinical trial. *JAMA*. 2014;312:2521–2530. PMID: 25514302.

Huang YH, Hsiao LT, Hong YC, et al. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. *J Clin Oncol*. 2013;31:2765–2772. PMID: 23775967.

National Comprehensive Cancer Network. http://www.nccn.org. Accessed December 19, 2017.

17-2 C

Maintenance rituximab has been tested in several prospective trials as a means of prolonging response duration in patients with indolent lymphomas. Early studies found that maintenance rituximab following chemotherapy alone improves both progression-free and overall survival. However, the impact of maintenance rituximab following chemoimmunotherapy (i.e., chemotherapy plus an anti-CD20 monoclonal antibody) is different.

The large randomized international PRIMA trial addressed this question. Approximately 1200 patients with high tumor burden follicular lymphoma were treated with rituximab plus

chemotherapy (investigator's choice between CVP, CHOP, or fludarabine). Among 1019 responding patients, 505 received maintenance rituximab, with one dose every 8 weeks for 2 years while 513 were assigned to observation. Patients receiving maintenance rituximab had a superior progression-free survival (74.9% vs. 57.6%, $p < 0.0001$), but there was no difference in overall survival.

Both patients with a partial and a complete response according to CT criteria had a benefit for progression-free maintenance. PET scans were not routinely performed in this study.

Other maintenance schedules have also been tested, albeit in the relapsed setting. The European Organization for Research and Treatment of Cancer (EORTC) tested rituximab once every 12 weeks for 2 years and found improved progression-free survival, again without an overall survival advantage. A meta-analysis has shown a small overall survival advantage for patients with relapsed follicular lymphoma who were receiving maintenance rituximab, but our patient was treated in the first-line setting.

Suggested Reading

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van Oers MH, Van Glabbeke M, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. *J Clin Oncol*. 2010;28:2853–2858. PMID: 20439641.

Vidal L, Gafter-Gvili A, Salles G, et al. Rituximab maintenance for the treatment of patients with follicular lymphoma: an updated systematic review and meta-analysis of randomized trials. *J Natl Cancer Inst*. 2011;103:1799–1806. PMID: 22021664.

17-3 A

The standard of care for relapsed or primary refractory classical Hodgkin lymphoma (cHL) is high-dose chemotherapy followed by autologous stem cell transplantation. This recommendation is based on two randomized trials and several large single-arm studies and elicits a cure rate of approximately 50%. There are several key predictors of outcome, including time to relapse and chemosensitivity.

The AETHERA trial tested the impact of consolidative brentuximab vedotin, an antibody-drug conjugate against CD30, following high-dose chemotherapy and autologous stem cell transplantation on progression-free survival in patients with high-risk Hodgkin lymphoma. In this study, *high risk* was defined as primary refractory Hodgkin lymphoma (failure to achieve complete remission), relapsed Hodgkin lymphoma within 12 months after completion of initial chemotherapy, or extranodal involvement at the start of pretransplantation salvage chemotherapy. Following transplantation, patients were randomly assigned to either observation or 16 doses of consolidative brentuximab vedotin. With a median follow-up of 30 months, the brentuximab vedotin group had a superior progression-free survival of 42.9 months versus 24.1 months. Although nivolumab is now approved for relapsed Hodgkin lymphoma based on high single-agent response rates, it is not approved as a consolidation therapy.

Suggested Reading

Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372:311–319. PMID: 25482239.

Moskowitz CH, Matasar MJ, Zelenetz AD, et al. Normalization of pre-ASCT, FDG-PET imaging with second-line, non-cross-resistant, chemotherapy programs improves event-free survival in patients with Hodgkin lymphoma. *Blood.* 2012;119:1665–1670. PMID: 22184409.

Moskowitz CH, Nademanee A, Masszi T, et al: Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-

blind, placebo-controlled, phase 3 trial. *Lancet.* 2015;385:1853–1862. PMID: 25796459.

17-4 D

Nodular lymphocyte–predominant Hodgkin lymphoma (NLPHL) is an uncommon variant of Hodgkin lymphoma, accounting for 5% of cases. In contrast to classical Hodgkin lymphoma, NLPHL has strong CD20 expression and lacks CD15 and CD30. It has an overall favorable prognosis with a waxing and waning course, more analogous in behavior to a low-grade lymphoma than to classical Hodgkin lymphoma. Traditionally, NLPHL has been treated similarly to classical Hodgkin lymphoma, but late relapses and the observation that the most common cause of death is treatment-related toxicity has prompted many to recommend observation for advanced-stage disease or to consider less aggressive treatment. However, there is a risk of transformation to diffuse large B-cell lymphoma, usually of a T-cell–rich variant (TCR-DLBCL), and not to classical Hodgkin lymphoma. When transformation occurs, patients should be treated for TCR-DLBCL with R-CHOP chemotherapy. The Hodgkin lymphoma International Prognostic Score (male sex, > age 45, low albumin, anemia, leukocytosis, lymphopenia, stage IV disease) from Hasenclever and Diehl does not affect treatment for transformation to TCR-DLBCL.

Suggested Reading

Hasenclever D, Diehl V, A prognostic score for advanced Hodgkin's disease. *N Engl J Med.* 1998;339:1506–1514. PMID: 9819449.

Nogova L, Reineke T, Brillant C, et al. Lymphocyte-predominant and classical Hodgkin's lymphoma: a comprehensive analysis from the German Hodgkin Study Group. *J Clin Oncol*. 2008;26:434–439. PMID: 18086799.

Savage KJ, Mottok A, Fanale M. Nodular lymphocyte-predominant Hodgkin lymphoma. *Semin Hematol*. 2016;53:190–202. PMID: 27496311.

17-5 D

This patient has a nodal T-cell lymphoma most consistent with angioimmunoblastic T-cell lymphoma (AITL). AITL is a common type of peripheral T-cell lymphoma, accounting for 20 to 30% of cases. AITL often presents with generalized adenopathy, skin rash, systemic symptoms, hepatosplenomegaly, and polyclonal hypergammaglobulinemia.

In the past several years, the cell of origin has been discovered to be a CD4-positive T-follicular helper cell (TFH). Several other nodal peripheral T-cell lymphomas can also have malignant TFH cells and share biologic features with AITL. AITL has a strong epigenetic signature on genetic testing, with frequent mutations of *TET2* and *IDH2*, but this has not yet translated to a change in the standard treatment approach.

Instead, patients with nodal T-cell lymphomas (including PTCL-NOS, AITL, and ALK-negative ALCL) are treated similarly with CHOP induction therapy. The addition of etoposide to CHOP (the CHOEP regimen) improves event-free survival in younger patients with ALCL histology, but is toxic in patients over age 65 and did not have as much of an impact in non-ALCL subtypes. The addition of romidepsin to CHOP is feasible, and a randomized trial of the combination versus CHOP is ongoing. Brentuximab vedotin, an antibody-drug conjugate against CD30, plus CHP (omission of vincristine from CHOP) is being compared to standard CHOP chemotherapy in patients with ALCL, but our patient does not have CD30 expression and does not have the ALCL subtype.

CHOP chemotherapy is the current standard of care for newly diagnosed PTCL, including AITL. It is active in T-cell lymphomas, but only 40 to 60% of patients complete all six cycles and 70% of patients have a relapse within 12 months. If patients respond to CHOP induction,

consolidative autologous stem cell transplantation can be considered, although relatively few patients are cured. These dismal statistics should prompt all patients with T-cell lymphomas to be treated on a clinical trial if available.

Suggested Reading

Dupuis J, Morschhauser F, Ghesquieres H, et al. Combination of romidepsin with cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated patients with peripheral T-cell lymphoma: a non-randomised, phase 1b/2 study. *Lancet Haematol.* 2015;2:e160–e165. PMID: 26687958.

Iqbal J, Wright G, Wang C, et al. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. *Blood.* 2014;123:2915–2923. PMID: 24632715.

Schmitz N, Trumper L, Ziepert M, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. *Blood.* 2010;116:3418–3425. PMID: 20660290.

Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375–2390. PMID: 26980727.

Vose J, Armitage J, Weisenburger D, et al. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol*. 2008;26:4124–4130. PMID; 18626005.

17-6 A

Idelalisib is an oral inhibitor of phosphatidylinositol 3-kinase delta (PI3KΔ) approved for the use of relapsed/refractory indolent lymphomas and CLL following at least two prior regimens. A pivotal phase II trial showed an overall response rate of 57% in 125 patients with double-refractory indolent lymphomas, defined as progression within 6 months after treatment with an alkylating agent and rituximab. Patients were very heavily pretreated and had many high-risk features. The median duration of response was over 1 year and median overall survival was 20.3 months. The starting dose is 150 mg twice daily continued until progression, toxicity, or intolerance.

There are several treatment-related toxicities of note, including hepatotoxicity, pneumonitis, and fatal and/or severe diarrhea or colitis. Elevated AST (aspartate aminotransferase) or ALT (alanine aminotransferase) will develop in approximately 50% of patients, but this is mild and reversible in the majority of cases. Patients should have ALT and AST monitoring every 2 weeks for the first 3 months of treatment, every 4 weeks for the next 3 months, and then every 3 months while on treatment. The standard approach for hepatotoxicity is to hold idelalisib, and resume at a lower dose once the laboratory results are normalized.

There are two types of diarrhea associated with idelalisib therapy. However, before attributing diarrhea to idelalisib, all patients should have a thorough evaluation for infectious causes, so A is the correct answer here. If an infectious etiology is not identified, the patient may have idelalisib-associated diarrhea. The first type generally occurs within 8 weeks after starting treatment and is mild to moderate in nature and responds to antidiarrheal agents. The second type of diarrhea occurs late (usually at least 3 to 4 months after exposure) and is profuse and watery. A colonoscopy will show colonic infiltration by lymphocytes. Treatment consists of budesonide, systemic steroids, and supportive care. Resuming idelalisib requires a careful discussion, and many experts will discontinue treatment if a patient has idelalisib-related colitis that is severe. If idelalisib is to resume, a lower dose (100 mg twice daily) should be used.

Ibrutinib monotherapy has limited activity in relapsed follicular lymphoma and would not be an appropriate therapeutic choice.

Suggested Reading

Bartlett NL, LaPlant B, Qi J, et al. Ibrutinib monotherapy in relapsed/refractory follicular lymphoma (FL): preliminary results of a Phase 2 Consortium (P2C) trial. *Blood*. 2014;124:800.

Coutre SE, Barrientos JC, Brown JR, et al: Management of adverse events associated with idelalisib treatment: expert panel opinion. *Leuk Lymphoma*. 2015;56:2779–2786. PMID: 25726955.
Gopal AK, Kahl BS, de Vos S, et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014;370:1008–1018. PMID: 24450858.

17-7 A

Immunophenotypic analysis is a critical component of lymphoma diagnosis and can often distinguish subtypes with similar morphologic appearance. However, there are several lymphomas that have both a similar histopathologic appearances and similar immunophenotypes.

In this case, the differential diagnosis of a lymph node with a small cell infiltrate includes follicular lymphoma, marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LPL), small lymphocytic lymphoma (SLL), or even mantle cell lymphoma (MCL). The lack of CD10 typically excludes follicular lymphoma, which also would have a cleaved or elongated nuclear contour. The lack of CD5 excludes SLL and MCL, and the absence of cyclin D1 further supports that this is not MCL. Clinical distinction between the two remaining lymphoma subtypes, LPL/WM and MZL, can sometimes be difficult, as both are mature B-cell lymphomas lacking CD5 and CD10. Both can have an associated paraprotein (although usually higher in LPL/WM), both frequently have hepatosplenomegaly and limited adenopathy, and both have frequent marrow infiltration.

MYD88 has been discovered to be mutated in the vast majority of LPL/WM but rarely found in MZL, and is helpful in confirming the diagnosis.

This patient should have undergo serum and urine immunoelectrophoresis, measurement of quantitative immunoglobulin levels, and hepatitis B PCR as part of her evaluation, but these will not confirm the diagnosis. A staging FDG-PET is not indicated for indolent lymphomas, as the majority have very low metabolic uptake.[3]

Suggested Reading

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32:3059–3068. PMID: 25113753.
Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoetic and Lymphoid Tissues.* Lyon, France: IARC; 2008.
Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. *N Engl J Med.* 2012;367:826–833. PMID: 22931316.

17-8 C

This patient has diffuse large B-cell lymphoma (DLBCL), the most common lymphoma worldwide, accounting for approximately 30% of all cases. In the early part of the past decade, several pivotal trials clearly established R-CHOP as the standard of care compared to chemotherapy regimens without rituximab. However, DLBCL is now understood to be a very heterogeneous disease, and cure rates with R-CHOP are highly dependent on underlying clinical and biologic features. Patients who are less likely to be cured with R-CHOP include patients with a high International Prognostic Index (age > 60, poor performance status, elevated LDH, more than one extranodal site, and advanced stage), a nongerminal center cell-of-origin, double-hit lymphoma (co-rearrangement of the *MYC* and *BCL2* and/or *BCL6* genes), dual protein overexpression of MYC (> 40%) and BCL2 (> 50%), and advanced age.

Attempts to improve on R-CHOP have included dose dense delivery (i.e., R-CHOP every 14 days rather than every 21 days), consolidation with autologous stem cell transplantation, maintenance strategies, replacement of rituximab with newer monoclonal antibodies, and

infusional delivery of treatment. To date, none of these trials have shown a significant improvement in overall survival, and R-CHOP for six cycles thus remains the standard of care.
Some DLBCL subsets that might benefit from a different treatment approach include patients with a very high IPI and those with double-hit lymphoma. A randomized intergroup study in the United States evaluated the benefit of consolidative ASCT for patients with at least three risk factors in the IPI. Although the trial as a whole did not show an advantage to transplantation, patients with an IPI of 4 to 5 had an improved overall survival of 82% versus 64% favoring transplantation. Our patient has an IPI of 3.
Double-hit lymphoma is another subtype that does not fare well with R-CHOP and has less than 20% long-term survival in multiple retrospective series. Although there are no prospective data, large retrospective series suggest that augmented regimens improve outcomes, and this is an area of intense investigation. Our patient does not have double-hit lymphoma based on fluorescence in situ hybridization (FISH) results. It is important to distinguish double-hit lymphoma from dual protein expression of MYC and BCL2, which is an adverse prognostic factor, but not a distinct entity.

Suggested Reading

Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346:235–242. PMID: 11807147.

Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from the International DLBCL Rituximab-CHOP Consortium Program. *Blood*. 2013;121:4021–4131; quiz 4250. PMID: 23449635.

Nowakowski GS, Blum KA, Kahl BS, et al. Beyond RCHOP: a blueprint for diffuse large B cell lymphoma research. *J Natl Cancer Inst*. 2016;108. PMID: 27986884.

Oki Y, Noorani M, Lin P, et al. Double hit lymphoma: the MD Anderson Cancer Center clinical experience. *Br J Haematol*. 2014;166:891–901. PMID: 24943107.

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Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2006;7:379–391. PMID: 21940214.

Stiff PJ, Unger JM, Cook JR, et al: Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 2013;369:1681–1690. PMID: 24171516.

17-9 B

Despite an initial remission following R-CHOP, approximately 20 to 40% of patients with diffuse large B-cell lymphoma will have a recurrence and need second-line treatment. The risk of recurrence is highest in the first 2 years following treatment and is very low after 5 years, defining 5 years as the time when most patients are considered cured.
There are limited data supporting a specific surveillance schedule, but most series show limited value of routine imaging in the absence of symptoms. A large retrospective series found that 552 of 680 (81%) patients with DLBCL entered a remission after induction chemotherapy; 112 patients (20%) had a relapse but surveillance imaging detected relapse before clinical symptoms in only 1.6% of patients. A validation cohort similarly found that only 4 of 222 (1.8%) patients had relapse identified through routine imaging, whereas the remainder all had clinical signs or symptoms prompting an evaluation that led to a diagnosis of relapse.
A Danish–Swedish population-based study found similar results. Standard evaluation in Sweden following remission included clinical assessments every 3 to 4 months for 2 years without routine scans, whereas standard evaluation in Denmark included routine imaging every 6 months for 2 years. Imaging-based surveillance had no impact on survival, and the authors concluded that clinical surveillance should be the standard approach. Of note, patients with a

low IPI (0 to 2) had a relapse rate of only 6% if they achieved a complete response to treatment. Patients with a higher IPI had a relapse rate of 21%, but again, the use of routine imaging did not improve survival.

Suggested Reading

El-Galaly TC, Jakobsen LH, Hutchings M, et al. Routine imaging for diffuse large B-cell lymphoma in first complete remission does not improve post-treatment survival: a Danish–Swedish population-based study. *J Clin Oncol*. 2015;33:3993–3998. PMID: 26438115.

Thompson CA, Ghesquieres H, Maurer MJ, et al. Utility of routine post-therapy surveillance imaging in diffuse large B-cell lymphoma. *J Clin Oncol*. 2014;32:3506–3512. PMID: 25267745.

17-10 B

This patient has mantle cell lymphoma based on a clonal population of cells with CD20 expression, aberrant expression of CD5, and cyclin D1 expression. Further confirmation with FISH or cytogenetics for t(11;14) would be appropriate.

Mantle cell lymphoma is an uncommon subtype that occurs primarily in older males. It is incurable with standard approaches, but outcomes have dramatically improved over the past decade. Treatment is either aggressive or nonaggressive based on the patient's age and comorbidities. Patients who are young and fit are typically offered intensive induction chemotherapy followed by a consolidative autologous stem cell transplantation with prolonged response durations. Patients who are old and unfit are offered chemoimmunotherapy. Among chemoimmunotherapy options, two randomized trials have shown superior activity and decreased toxicity for bendamustine/rituximab compared to either R-CHOP or R-CVP.

However, this patient has a newly recognized clinical variant of MCL called indolent MCL. The indolent variant of MCL often presents similarly to CLL, with asymptomatic lymphocytosis and splenomegaly and less prominent adenopathy. SOX11, a transcription factor that is positive in classic and blastoid versions of MCL, is often negative in the indolent variant. Most patients are asymptomatic.

Although MCL is an incurable disease, many patients with asymptomatic disease and the indolent variant can be safely observed for several years without a negative impact on survival.

Suggested Reading

Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood*. 2014;123:2944–2952. PMID: 24591201.

Geisler CH, Kolstad A, Laurell A, et al. Nordic MCL2 trial update: six-year follow-up after intensive immunochemotherapy for untreated mantle cell lymphoma followed by BEAM or BEAC + autologous stem-cell support: still very long survival but late relapses do occur. *Br J Haematol*. 2012;158:355–362. PMID: 22640180.

Martin P, Chadburn A, Christos P, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. *J Clin Oncol*. 2009;27:1209–1213. PMID: 19188674.

Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381:1203–1210. PMID: 23433739.

18 MULTIPLE MYELOMA
SELF-EVALUATION

18. MULTIPLE MYELOMA QUESTIONS

18-1 A 65-year-old man is incidentally found to have a serum monoclonal protein of 2.5 g/dL during routine blood tests and IgA kappa on immunofixation. Urine protein immunofixation shows a monoclonal kappa M protein of 900 mg/24 hr. The serum free kappa level is 2000 mg/L, and serum free lambda is 10 g/L, with a serum FLC ratio of 200. There is no anemia, hypercalcemia, renal failure, or bone lesion on the skeletal survey. Bone marrow biopsy shows 35% plasma cells.

What is the most likely diagnosis?

A. Multiple myeloma
B. Smoldering multiple myeloma
C. Monoclonal gammopathy of undetermined significance
D. Solitary plasmacytoma

18-2 A 50-year-old woman is diagnosed with newly diagnosed myeloma. She has multiple lytic lesions and anemia.

All of the following will indicate the presence of high-risk disease except:

A. Deletion 17p
B. t(14;16)
C. t(14;20)
D. Trisomies 3, 7, and 9

18-3 A 60-year-old man diagnosed with myeloma is referred to you for treatment options. He is interested in the results of recent trials. He has standard-risk myeloma and has good performance status and no comorbidities.

What is the most appropriate initial therapy?

A. Bortezomib, lenalidomide, dexamethasone (VRd)
B. Lenalidomide plus low-dose dexamethasone (Rd)
C. Lenalidomide plus high-dose dexamethasone
D. Daratumumab, bortezomib, dexamethasone

18-4 A 68-year-old woman with myeloma has recently had the development of progressive disease while taking bortezomib, cyclophosphamide, dexamethasone. A trial of daratumumab was not effective. She is in good performance status. She has had no other therapy.

Which of the following agents is a proteasome inhibitor that has shown significant activity

even in patients for whom bortezomib therapy has failed?

A. Ixazomib
B. Elotuzumab
C. Panobinostat
D. Carfilzomib

18-5 A 70-year-old woman is about to start therapy for newly diagnosed myeloma. She has normal renal function. Her family wants a regimen that would help her function well, and they are particularly worried about neuropathy. You are contemplating bortezomib/lenalidomide/dexamethasone (VRd) as initial therapy.

Which of the following steps can minimize neuropathy associated with the VRd regimen?

A. Administer bortezomib twice weekly.
B. Prescribe aspirin once daily.
C. Administer bortezomib subcutaneously.
D. Increase the dose of dexamethasone.

18-6 A 64-year-old man is diagnosed with a monoclonal protein during a workup for neuropathy. His M protein is 0.3 g/dL, IgG kappa. The serum free light-chain ratio is normal. He has 8% plasma cells on bone marrow exam. A skeletal survey is negative. His physician diagnoses him as having monoclonal gammopathy of undetermined significance (MGUS).

Which of the following indicates that he has low-risk MGUS?

A. Age
B. Association with neuropathy
C. Normal serum free light-chain ratio
D. Bone marrow plasma cells less than 10%

18-7 A 52-year-old man with long-standing back pain undergoes a bone marrow biopsy for workup of indeterminate symptoms. Bone marrow shows 20% clonal lambda plasma cells. He has no anemia, hypercalcemia, or renal failure. His symptoms are later attributed to a renal stone. CT scan of the whole body reveals no lytic lesions. MRI of the spine is normal. He does have a serum monoclonal protein of 2.2 gm/dL, IgG lambda. The serum free light-chain ratio is increased at 9.

What is the most likely diagnosis?

A. Multiple myeloma
B. Smoldering multiple myeloma
C. Waldenström macroglobulinemia
D. POEMS syndrome

18. MULTIPLE MYELOMA RATIONALES

18-1 **A**

Based on the International Myeloma Working Group criteria this patient has multiple myeloma.

According to the revised criteria a diagnosis of multiple myeloma requires 10% or more plasma cells on bone marrow (or biopsy-proven plasmacytoma) plus one or more myeloma-defining events. This patient has an extremely high serum free light-chain level, with a ratio in excess of 100, which is a myeloma-defining event. The other myeloma-defining events are evidence of end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions) attributable to the underlying plasma cell disorder, 60% or more clonal plasma cells in the bone marrow, and > 1 focal lesion (≥5 mm) on magnetic resonance imaging.

Suggested Reading

Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15:e538–e548. PMID: 25439696.

18-2 D

The presence of trisomies t(11;14) and t(6;14) is not associated with high-risk myeloma. They generally have a good prognosis. All others listed are associated with more aggressive disease biology.

Suggested Reading

Kumar S, Fonseca R, Ketterling RP, et al. Trisomies in multiple myeloma: impact on survival in patients with high-risk cytogenetics. *Blood*. 2012;119:2100–2105. PMID: 22234687.

18-3 A

A randomized controlled trial by the Southwest Oncology group found improved progression-free survival and overall survival with VRd compared with Rd. This patient is a candidate for transplantation, and VRd is the most appropriate frontline therapy. Lenalidomide plus high-dose dexamethasone has been found to have increased mortality compared with Rd. Daratumumab/bortezomib/dexamethasone is used in relapsed myeloma, not as frontline therapy.

Suggested Reading

Durie BGM, Hoering A, Abidi MH, et al. Bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone induction followed by lenalidomide and dexamethasone maintenance in patients with newly diagnosed myeloma without intent for immediate autologous stem cell transplant: results of the randomised phase III SWOG trial S0777. *Lancet*. 2017;389:519–527. PMID: 28017406.

Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol.* 2010;11:29–37. PMID: 19853510.

18-4 D

Carfilzomib is a new proteasome inhibitor approved for the treatment of relapsed myeloma. It is effective in patients in whom both lenalidomide and bortezomib have failed. Ixazomib is a new proteasome inhibitor, but has not been shown to have meaningful activity in patients refractory to bortezomib. Elotuzumab is a SLAMF-7 monoclonal antibody, and not a proteasome inhibitor. Panobinostat is a deacetylase inhibitor.

Suggested Reading

Siegel DS, Martin T, Wang M, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. *Blood*. 2012;120:2817–2825. PMID: 22833546.

Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med.* 2015;372:142–152. PMID: 25482145.

18-5 C

Trials show that the risk of bortezomib-induced neuropathy can be reduced by administering the drug subcutaneously and once weekly. Aspirin reduces the risk of thrombosis, not neuropathy with VRd. Increasing the dose of dexamethasone is not an option and can increase toxicity.

Suggested Reading

Mateos MV, Oriol A, Martinez-Lopez J. Bortezomib/melphalan/prednisone (VMP) versus bortezomib/thalidomide/prednisone (VTP) as induction therapy followed by maintenance treatment with bortezomib/thalidomide (VT) versus bortezomib/prednisone (VP): a randomised trial in elderly untreated patients with multiple myeloma older than 65 years. *Lancet Oncol.* 2010;11:934–941. PMID: 20739218.

Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *Lancet Oncol.* 2011;12:431–440. PMID: 21507715.

18-6 C

The best predictors of progression of MGUS are the size and type of the M protein and an abnormal baseline serum free light-chain ratio. Patients with IgG MGUS less than 1.5 g/dL who have a normal serum free light-chain ratio are considered to have low-risk MGUS with a lifetime risk of progression of approximately 5%. Age, neuropathy, and bone marrow involvement of 8% do not indicate low-risk MGUS.

Suggested Reading

Rajkumar SV, Kyle RA, Therneau TM, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance (MGUS). *Blood*. 2005;106:812–817. PMID: 15855274.

18-7 B

By definition, smoldering multiple myeloma requires 10% or more plasma cells on bone marrow and/or 3 g/dl or more M protein on serum protein electrophoresis PLUS absence of anemia, hypercalcemia, renal failure, bone lesions, or other myeloma-defining events. This patient meets the criteria for smoldering multiple myeloma. The patient does not have MGUS because the bone marrow plasma cells are < 10% in MGUS. There is no evidence of POEMS syndrome or Waldenström macroglobulinemia.

Suggested Reading

Mateos M-V, Hernández M-T, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. *N Engl J Med.* 2013;369:438–447. PMID: 23902483.

Rajkumar SV, Landgren O, Mateos MV. Smoldering multiple myeloma. *Blood*. 2015;125:3069–3075. PMID: 25838344.

19 HEMATOPOIETIC CELL TRANSPLANATION

SELF-EVALUATION

19. HEMATOPOIETIC CELL TRANSPLANTATION QUESTIONS

19-1 A 44-year-old man with Philadelphia chromosome negative (Ph–) acute lymphocytic leukemia is to undergo a matched unrelated donor hematopoietic cell transplantation following a myeloablative preparative regimen.

Which of the following statements is most appropriate concerning differences between the use of bone marrow and granulocyte colony-stimulating factor (G-CSF)–mobilized peripheral blood as the stem cell source?

A. Engraftment is faster with bone marrow because bone marrow contains more hematopoietic stem cells than peripheral blood.
B. The incidence of graft rejection is lower with bone marrow because bone marrow contains more hematopoietic stem cells than peripheral blood.
C. The incidence of chronic graft-versus-host disease is higher with peripheral blood because mobilized peripheral blood contains more T cells than bone marrow.
D. The incidence of early fungal infections is reduced with the use of peripheral blood because mobilized peripheral blood contains more monocytes than bone marrow.

19-2 A search for an unrelated donor for a 59-year-old man with intermediate-2-risk myelodysplasia identifies a potential donor who is *HLA-A*, *HLA-B*, *HLA-C*, *HLA-DR*–matched, but is a multiparous woman whose ABO type is A and who has anti-B antibodies (IgG 1:256, IgM 1:64). The patient's ABO type is B, and he has anti-A antibody titers (IgG 1:128, IgM 1:32).

Which of the following statements is most appropriate?

A. If the stem cell product is depleted of both plasma and red cells, the donor can be used without any increased risk.
B. If the stem cell product is depleted of both plasma and red cells, the donor can be used but with a risk of both immediate and delayed hemolysis.
C. The donor should not be used because even with plasma and red cell depletion of the stem cell product, there is an unacceptable risk of severe and potentially fatal hemolysis.
D. The donor should not be used because even with plasma and red cell depletion of the stem cell product, there is an unacceptable risk of graft rejection.

19-3 On day 18 after receiving a myeloablative preparative regimen of cyclophosphamide plus 12 Gy total body irradiation (TBI) and a matched sibling peripheral-blood cell transplantation, a 50-year-old man has developed ascites, tender hepatomegaly, a bilirubin of 4.5 mg/dL, and a creatinine of 3.1 mg/dL that is increased from a pretransplantation level of 0.9. The patient has engrafted and has a white blood cell count

of 3500/mm^3 and a platelet count of 60,000/mm^3. The patient has no rash, nausea, vomiting, or diarrhea.

What therapy is most appropriate?

A. Supportive care only
B. Defibrotide 25 mg/kg/day
C. Prednisone 2 mg/kg/day
D. Heparin by continuous infusion 100 units/kg/day

19-4 A 35-year-old woman with *FLT3*-ITD mutated acute myeloid leukemia (AML) in first complete remission is planning to undergo a matched sibling peripheral-blood stem cell transplantation while in first remission. She has no identifiable comorbidities.

Which of the following preparative regimens is most appropriate?

A. Fludarabine 30 mg/m^2/day × 3 plus 200 cGy TBI (nonmyeloablative)
B. Cyclophosphamide 50 mg/kg/day × 4 days (reduced intensity)
C. Fludarabine 30 mg/m^2/day × 5 days plus busulfan 4 mg/kg/day × 2 days (reduced intensity)
D. Fludarabine 30 mg/m^2/day × 5 days plus busulfan 4 mg/kg/day × 4 days (myeloablative)

19-5 A 60-year-old woman received an allogeneic unmanipulated peripheral-blood stem cell graft from an HLA-matched unrelated donor for the treatment of AML in second complete remission 56 days ago. The patient engrafted promptly and has had no major complications. Today, a routine surveillance blood examination for cytomegalovirus (CMV) DNA comes back positive at a level of 250 IU/mL. Both the patient and donor were CMV-seropositive before transplantation.

What would you recommend?

A. Begin preemptive therapy with ganciclovir.
B. Begin preemptive therapy with foscarnet.
C. Continue to monitor peripheral-blood CMV DNA and consider preemptive therapy if the level rises above 1000 IU/mL.
D. Continue to monitor the patient carefully and begin therapy if evidence of CMV pneumonia or gastrointestinal disease develops.

19. HEMATOPOIEITIC CELL TRANSPLANTATION RATIONALES

19-1 C

In a prospective, randomized trial comparing bone marrow with G-CSF–mobilized peripheral blood as a stem cell source for matched unrelated donor transplantation following myeloablative preparative regimens, the use of mobilized peripheral blood was associated with somewhat faster engraftment but more chronic graft-versus-host disease (GVHD). Overall survival was equivalent, thus favoring the use of bone marrow in unrelated allogeneic transplantation unless there is a specific concern with slower engraftment. This differs from the results of bone

marrow versus mobilized peripheral blood in the matched sibling setting, where there may be a survival advantage to the use of peripheral blood.

Suggested Reading

Anasetti C, Logan BR, Lee SJ, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med*. 2012;367:1487–1496. PMID: 21075175.

Bensinger WI, Martin PJ, Storer B, et al. Transplantation of bone marrow as compared with peripheral-blood cells from HLA-identical relatives in patients with hematologic cancers. *N Engl J Med*. 2001;344:175–181. PMID: 11172139.

19-2 B

Since hematopoietic stem cells do not express ABO, HCT can be carried out across ABO blood group barriers by removing incompatible red blood cells (RBCs) and/or isoagglutinins from the donor graft. However, even with appropriate manipulations of the donor graft, a major ABO mismatch (e.g., recipient O, donor A) can result in immediate or delayed hemolysis of donor red cells by persistent recipient isohemagglutinins, and a minor mismatch (e.g., recipient B, donor O), can result in immediate hemolysis of recipient RBCs by donor-derived isohemagglutinins in the graft or delayed hemolysis of recipient RBCs by newly generated isohemagglutinins from donor lymphocytes (i.e., passenger lymphocytes).

Suggested Reading

Booth GS, Gehrie EA, Bolan CD, et al. Clinical guide to ABO-incompatible allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. 2013;19:1152–1158. PMID: 23571461.

O'Donnell MR. Blood group incompatibilities and hemolytic complications of hematopoietic cell transplantation. In Forman SJ, Negrin RS, Antin JH Appelbaum FR (eds.). *Thomas' Hematopoietic Cell Transplantation, 5th ed*. Oxford, UK: Wiley Blackwell, 2016.

19-3 B

This patient has sinusoidal obstruction syndrome (SOS) (formerly called "veno-occlusive disease") with multiorgan failure (MOF); if left untreated the mortality rate is greater than 80%. In a phase 3 trial, defibrotide improved day 100 survival from 25% to 38.2% and was well tolerated, leading to its approval by the FDA for the treatment of SOS. Although pilot studies of prednisone and heparin have been conducted, there are no phase III trials demonstrating a benefit for any other intervention.

Suggested Reading

Chao N. How I treat sinusoidal obstruction syndrome. *Blood.* 2014;123:4023–4026. PMID: 24833355.

Richardson PG, Riches ML, Kernan NA, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. *Blood*. 2016;127:1656–1665. PMID: 26825712.

19-4 D

A prospective, randomized phase III trial demonstrated lower relapse rates and improved OS with the use of myeloablative preparative regimens compared with reduced-intensity regimens in the treatment of AML and myelodysplastic syndromes (MDS). While reduced intensity regimens were associated with a lower rate of nonrelapse mortality, the markedly higher relapse rates seen with the lower-intensity regimens more than overwhelmed the safety advantage.

Suggested Reading

Ringdén O, Labopin M, Ehninger G, et al. Reduced intensity conditioning compared with myeloablative conditioning using

unrelated donor transplants in patients with acute myeloid leukemia. *J Clin Oncol.* 2009;27:4570–4577. PMID: 19652066.
Scott BL, Pasquini MC, Logan B, et al. Results of phase III randomized, multi-center study of allogeneic stem cell transplantation after high versus reduced intensity conditioning in patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML): Blood and Marrow Transplant Clinical Trial Network (BMT CTN) 0901. *Blood.* 2015;126 (suppl; abstr LBA-8).

19-5 A

Preemptive therapy with ganciclovir is indicated for the development of peripheral-blood levels of CMV > 125 IU/mL in patients who have undergone allogeneic transplantation. The trigger for starting preemptive therapy may be lower for recipients of cord-blood or T-cell–depleted stem cells, and for patients receiving > 1mg/kg prednisone for the treatment of GVHD. Foscarnet is generally reserved for patients who either have an intolerance to ganciclovir or who have CMV disease that fails to respond to initial ganciclovir treatment. Letermovir is a new antiviral agent with high activity against CMV.

Suggested Reading

Chemaly RF, Ullmann AJ, Stoelben S, et al. Letermovir for cytomegalovirus prophylaxis in hematopoietic-cell transplantation. *N Engl J Med.* 2014;370:1781–1789. PMID: 24806159.
Zaia, JA. Cytomegalovirus infection. In Forman SJ, Negrin RS, Antin JH Appelbaum FR (eds.). *Thomas' Hematopoietic Cell Transplantation, 5th ed*. Oxford, UK: Wiley Blackwell, 2016.

20 CANCER IN ELDERLY PATIENTS
SELF-EVALUATION

20. CANCER IN ELDERLY PATIENTS QUESTIONS

20-1 A 70–year-old man was found to have a large sigmoid colon mass during a screening colonoscopy, with the biopsy showing colonic adenocarcinoma. A staging CT scan revealed lung and liver metastases. He has a history of hypertension and diabetes and is taking amlodipine 5 mg daily and metformin 850 mg twice daily. He has an ECOG performance status of 1 and is able to carry out all activities of daily living (ADLs) and instrumental activities of daily living (IADLs). He lives with his wife, who is healthy and can care for him should he need further treatment.

Which of the following tools would be most appropriate to aid his oncologist in deciding whether or not he can tolerate chemotherapy?

A. G8 test
B. Hand grip strength test
C. The Cancer and Aging Research Group (CARG) score
D. Vulnerable Elders Survey (VES)-13 score

20-2 A 78-year-old man with a history of hypertension, hyperlipidemia, and diabetes presents to his urologist with lower urinary tract symptoms. He is found to have metastatic prostate cancer with multiple nodal and symptomatic bone metastases. His initial treatment was androgen-deprivation therapy with leuprolide acetate injections every 3 months. Despite initial response, his prostate specific antigen (PSA) began to rise after 12 months and his bone scan showed progressive bony metastatic disease. His serum calcium level was 9.0 mg/dL, and his creatinine clearance was 32mL/min.

Which of the following interventions would be appropriate, with the goal of reducing skeletal-related events?

A. Denosumab 120 mg every 6 months
B. Daily vitamin D and calcium supplements
C. Zoledronic acid given at 3 mg every 3 to 4 weeks
D. Pamidronate given at 90 mg monthly

20-3 A 75-year-old woman presents with a chronic cough, and she is found to have a central 3.4 cm x 2.8 cm proximal right lung mass on CT scan. A bronchoscopic biopsy reveals a moderately differentiated adenocarcinoma of the lung. No metastatic lesions are found on PET-CT scan. Past medical history is significant for well-controlled hypertension. Her ECOG performance status is 1, and she is independent and physically active prior to her current cough. She is deemed fit to undergo surgical resection of the tumor.

Which of the following should be considered by the surgeon prior to the surgery?

A. Preoperative antibiotic prophylaxis should be started at least 3 days before surgery.
B. In older adults undergoing nonemergent procedures, fasting from clear liquids for at least 6 hours before the procedure requiring general anesthesia is recommended.
C. Older patients should be evaluated for venous thromboembolism (VTE) and bleeding risk.
D. Nonessential medications should be continued perioperatively if deemed safe by the surgeon.

20-4 A 74-year-old man presents with a recent 10-lb weight loss and intermittent fever for 4 weeks. On examination he has palpable cervical lymphadenopathy. PET-CT reveals multiple FDG-avid enlarged lymph nodes above and below the diaphragm, but no extranodal disease sites. A cervical lymph node biopsy reveals a diffuse large B-cell lymphoma, which is CD5 and CD10 negative; BCL6 and IRF4/MUM1 are positive. Serum lactate dehydrogenase is 180 U/L. ECOG performance status is 1. He is started on full dose R-CHOP chemotherapy (every 21 days).

Which one of the following statements is correct with regard to this patient's subsequent risk of febrile neutropenia (FN)?

A. He has a high risk of FN and should be given prophylactic myeloid growth factor support due to his age.
B. He has low risk of FN but should be given prophylactic myeloid growth factor support due to his age.
C. He has high risk of FN and should be given prophylactic myeloid growth factor support due to his intermediate International Prognostic Index (IPI) score.
D. He has an intermediate risk of FN and should receive prophylactic myeloid growth factor support due to his age.

20-5 A 76-year-old woman found a firm nodular mass in the lower outer quadrant of her left breast on a breast self-exam. Mammography revealed a spiculated mass suggestive of malignancy. She underwent a lumpectomy, with pathology showing a 1.2 cm ductal adenocarcinoma that was ER-positive, PR-positive, and HER2-negative. The sentinel lymph node showed no evidence of malignancy. Surgical margins were negative. Her past medical history is significant for diabetes and hypertension, both of which are well controlled.

Which one of the following statements regarding her treatment options is most appropriate?

A. Adjuvant tamoxifen for 3 years is appropriate in view of her age and increased risk of venous thromboembolism.
B. Adjuvant radiation does not change her risk of distant recurrence, and thus is not needed.
C. Adjuvant chemotherapy with weekly docetaxel will improve disease-free survival compared to CMF (cyclophosphamide, methotrexate, 5-fluorouracil).
D. Disease-free survival is prolonged with or without adjuvant tamoxifen if adjuvant radiation therapy is given.

20. CANCER IN ELDERLY PATIENTS RATIONALES

20-1 C

The G8, VES-13, and handgrip strength tools are validated screening tools that are used widely to screen elderly cancer patients in order to determine which patients need a full comprehensive geriatric assessment (CGA). These tools do not predict risk of chemotherapy toxicity. The CARG and Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) utilize CGA factors to calculate the risk of grade 3 to 5 toxicity from chemotherapy. Both the scores have been validated in independent cohorts, and found to be valid chemotherapy toxicity assessment tools.

Suggested Reading

Decoster L, Van Puyvelde K, Mohile S, Wedding U, Basso U, Colloca G, Rostoft S, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations. *Ann Oncol*. 2015;26:288–300. PMID: 24936581.

Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, Levine RM, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. *Cancer.* 2012;118:3377–3386. PMID: 22072065.

Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, Lichtman SM, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol.* 2011;29:3457–3465. PMID: 21810685.

20-2 C

This elderly patient with metastatic prostate cancer has multiple comorbidities, including stage 3 chronic kidney disease. The SIOG task force on dosing adjustments for renal insufficiency recommends some form of geriatric assessment of older cancer patients, including with calculation of renal function, to adjust chemotherapy and supportive care medication dosages appropriately. With this patient's renal insufficiency, the zoledronic acid dose is reduced from the usual 4-mg dosage. For skeletal-related event (SRE) risk reduction, denosumab should be given at 120 mg every 4 weeks. Neither Vitamin D/calcium supplements nor pamidronate have been shown to reduce SREs.

Suggested Reading

Lichtman SM, Wildiers H, Launay-Vacher V, Steer C, Chatelut E, Aapro M. International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. *Eur J Cancer.* 2007;43:14–34. PMID: 17222747.

20-3 C

Older adults should be evaluated preoperatively for VTE and bleeding risk and given the appropriate VTE prophylaxis as VTE is more common in the elderly. Preoperative antibiotic prophylaxis should be started within 2 hours of the surgical incision. The guidelines recommend fasting from clear liquids at least 2 hours prior to an elective surgery requiring general anesthesia. Nonessential medication should be discontinued days before the surgery after a thorough medication review.

Suggested Reading

Mohanty S, Rosenthal RA, Russell MM, Neuman MD, Ko CY, Esnaola NF. Optimal Perioperative Management of the Geriatric Patient. Best Practice Guidelines from NSQIP / American Geriatrics Society 2015; 1–61. PMID: 27049783.

Silber JH, Rosenbaum PR, Trudeau ME, Chen W, Zhang X, Lorch SA, Kelz RR, et al. Preoperative antibiotics and mortality in the elderly. *Ann Surg.* 2005;242:107–114. PMID: 15973108.

20-4 D

He has intermediate risk (10 to 20%) of getting FN with q 21 d R-CHOP therapy. Based on National Comprehensive Cancer Network (NCCN) guidelines on the use of myeloid growth factors, the intermediate risk chemotherapy regimens do not require the use of prophylactic myeloid growth factor support. However, based on the additional risk factor of age > 65 years, he should receive prophylactic myeloid growth factor support. The use of R-CHOP given every 14 days would confer a high risk of FN. The IPI is a prognostic score and does not impact the risk of FN.

Suggested Reading

Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: a systematic review. *Crit Rev Oncol Hematol.* 2014;90:190–199. PMID: 24434034.

NCCN clinical practical guidelines in oncology. Myeloid Growth Factors. v2.2016.

20-5 B

Adjuvant tamoxifen for 5 years postoperatively will prolong her survival with her estrogen receptor positive status. CALGB 9343 study found that omission of radiotherapy for patients with stage 1 ER-positive disease resulted in a marginal increase in local recurrence but did not alter the OS or risk of distance disease recurrence. Adjuvant weekly docetaxel did not improve disease-free survival and contributed to poorer quality of life as compared to adjuvant CMF.

Suggested Reading

Hughes KS, Schnaper LA, Bellon JR, Cirrincione CT, Berry DA, McCormick B, Muss HB, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol.* 2013;31:2382–2387. PMID: 23690420.

Perrone F, Nuzzo F, Di Rella F, Gravina A, Iodice G, Labonia V, Landi G, et al. Weekly docetaxel versus CMF as adjuvant chemotherapy for older women with early breast cancer: final results of the randomized phase III ELDA trial. *Ann Oncol.* 2015;26:675–682. PMID: 25488686.

21 SYMPTOM MANAGEMENT SELF-EVALUATION

21. SYMPTOM MANAGEMENT QUESTIONS

21-1 A 48-year-old woman is about to begin a chemotherapy regimen that is rated as being highly emetogenic. She expresses significant concerns about nausea and vomiting, as she had significant morning sickness with her pregnancies. You plan to administer a 5-HT3 antagonist, dexamethasone, and an NK-1 antagonist as her standard antiemetic regimen.

Based on randomized phase III clinical trial data, which of the following would be the most effective agent to add to this combination?

A. Lorazepam
B. Metoclopramide
C. Chlorpromazine
D. Olanzapine

21-2 A 59-year-old postmenopausal woman with estrogen receptor (ER)–positive, progesterone receptor (PR)–positive, HER-2–negative breast cancer has been taking an aromatase inhibitor for 2 years. She has significant vaginal dryness and this is adversely affecting her marital relationship. Trials of vaginal lubricants have been unhelpful. She is reluctant to try intravaginal estrogen preparations because of the potential for systemic exposure to estrogen.

Which of the following is the most appropriate recommendation?

A. A trial of systemic testosterone
B. Intravaginal dehydroepiandrosterone (DHEA)
C. Marital counseling
D. Intravaginal estrogen

21-3 A 41-year-old premenopausal woman is taking tamoxifen for adjuvant treatment of resected stage II breast cancer. She reports severe hot flashes that are causing her to lose sleep and significantly interfere with her life.

Which of the following would be the most appropriate recommendation to try and reduce her symptoms?

A. Paroxetine
B. Venlafaxine
C. Amitriptyline
D. Fluoxetine

21-4 A 56-year-old postmenopausal woman is being treated with exemestane and everolimus

for metastatic ER-positive, HER2-negative breast cancer. She is tolerating the therapy relatively well, with the exception of significant oral mucositis.

Treatment with which of the following appears to provide significant relief of mammalian target of rapamycin (mTOR)–associated mucositis?

A. Oral dexamethasone solution, swish and spit
B. Nystatin, swish and swallow
C. Oral sucralfate
D. Benzydamine mouthwash
E. Palifermin

21-5 A 68-year-old man with metastatic non-small cell lung cancer is being followed in your clinic. His family is worried about his continued weight loss and lack of appetite. They ask about a new medicine they have heard about that can help lung cancer patients gain weight.

Which of the following cachexia treatments has been shown to improve lean body mass but not grip strength?

A. Anamorelin
B. Megestrol acetate
C. Dexamethasone
D. Medroxyprogesterone acetate

21-6 A 58-year-old man has been receiving ipilimumab for metastatic melanoma. His tumors have been significantly responding to treatment. After cycle four, he presents with severe diarrhea, with 10 or more stools per day, and is found to have significant intravascular volume depletion. The patient is hospitalized and rehydrated with IV fluids. Extensive evaluation for other causes of diarrhea, including infectious, are excluded and the patient is started on high-dose IV steroids as well as nonspecific low motility agents. After 3 days of steroids, the diarrhea continues with eight or more watery stools per day.

After excluding bowel perforation, what is the most appropriate next step in management of his diarrhea?

A. Octreotide
B. Metronidazole
C. Infliximab
D. Atropine

21-7 A 56-year-old woman is receiving platinum-based chemotherapy for non-small cell lung cancer. She has been having a good response to therapy and has been tolerating treatments well, with the exception of significant fatigue. Chemistry panel, blood counts, and evaluation of hormonal function all are within normal limits and cannot explain the fatigue. She is really bothered by this symptom and asks for something to help alleviate it.

You tell her that which of the following have been demonstrated in randomized, placebo-

controlled trials to reduce cancer-related fatigue?

A. Modafinil
B. Ginseng
C. Methylphenidate
D. Medical marijuana

21-8 A 63-year-old man is undergoing chemotherapy for advanced non-small cell lung cancer that does not harbor a driver mutation. After four cycles of therapy he presents to your office with symptoms of worsening dyspnea on exertion but no angina. Evaluation reveals a pale man with a resting tachycardia of 110 beats per minute, respiratory rate of 20 breaths per minute, blood pressure of 128/64 mmHg without orthostatic changes. CT scan shows continuing response of the cancer to therapy and no evidence of pleural effusion, infiltrate, or pulmonary embolism. Labs show a white blood cell count of 3500/mm^3 with 80% neutrophils, platelets of 100,000/mm^3, and hemoglobin of 7.6 g/dL with a mean corpuscular volume (MCV) of 95 fL.

What is the most appropriate next step in management of his symptomatic anemia?

A. Packed red blood cell (RBC) transfusion
B. Initiate IV iron therapy
C. Darbepoetin
D. Hold next cycle of chemotherapy and repeat labs in 1 week

21-9 A 48-year-old woman with history of ovarian cancer who has undergone a debulking operation with total abdominal hysterectomy/bilateral salpingo-oophorectomy (TAH/BSO) followed by adjuvant chemotherapy with a taxane and carboplatin now has no evidence of recurrent disease. During a routine follow-up visit, she mentions significant problems with intercourse and that this is having an effect on her relationship with her partner. Upon further questioning, she expresses a significant desire to pursue intercourse but that penetration is very painful. She is adamantly against using any estrogen, systemic or extravaginally.

Which of the following do you offer this patient?

A. Use of topical lidocaine applied to the introitus prior to intercourse
B. Referral to marriage counselor
C. Recommendation that she must avoid vaginal penetration due to her disease and treatment
D. Kegel exercises

21-10 A 65-year-old woman with ER-positive breast cancer has markedly bothersome hot flashes that have not been controlled with venlafaxine, citalopram, clonidine, gabapentin, or stellate ganglion blocks. She inquires whether there are any other nonhormonal agents that have been shown to decrease hot flashes more than does a placebo.

Which of the following should you recommend?

A. Doxepin
B. Oxybutynin

C. Atropine
D. Magnesium oxide

21. SYMPTOM MANAGEMENT RATIONALES

21-1 D

A phase III clinical trial in patients receiving highly emetogenic chemotherapy compared a standard regimen of a 5-HT3 antagonist, dexamethasone, and an NK-1 antagonist to the same regimen plus olanzapine. Those in the olanzapine group had significantly improved nausea control and less need for rescue medications. The National Comprehensive Cancer Network (NCCN) guidelines have now incorporated olanzapine into some of the recommended highly emetogenic chemotherapy regimens.

Suggested Reading

Navari RM, Qin R, Ruddy KJ, et al. Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. *N Engl J Med.* 2016; 375:134–142. PMID: 27410922.

NCCN Guidelines. Antiemesis. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed November 29, 2016.

21-2 B

Estrogen deprivation can cause significant changes in the vaginal epithelium. Topical estrogen therapy has been helpful in improving vaginal dryness in these settings, but concern is raised about systemic exposure to estrogen and its theoretical risk of increasing recurrence of the cancer. This risk is unknown and may be less when using the selective estrogen-receptor modulator (SERM) tamoxifen, as compared with using an aromatase inhibitor. Studies by Labrie et al. did demonstrate the efficacy of DHEA suppositories in patients without cancer. This product has been approved by the U.S. Food and Drug Administration. Data in breast cancer survivors also support that intravaginal DHEA was helpful for improving sexual function and that there were no increases in serum estrogen in women receiving aromatase inhibitors. Although no long-term data are available regarding risk of breast cancer recurrence, theoretically the risk should not be increased.

Suggested Reading

Barton DL, Sloan JA, Shuster LT, et al. Impact of vaginal dehydroepiandrosterone (DHEA) on vaginal symptoms in female cancer survivors: Trial N10C1 (Alliance*). J Clin Oncol.* 2014;32:5s (suppl; abstr 9507).

Labrie F, Archer D, Bouchard C, et al. Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. *Menopause.* 2009;16:923–931. PMID: 19424093.

Labrie F, Archer D, Bouchard C, et al. Serum steroid levels during 12-week intravaginal dehydroepiandrosterone administration. *Menopause.* 2009;16:897–906. PMID: 19436226.

21-3 B

Paroxetine is a known inhibitor of CYP2D6, which is required for activation of tamoxifen to its more active form, endoxifen. Fluoxetine has shown less efficacy when compared to other antidepressants for reducing hot flashes and also inhibits CYP2D6 to a moderate degree. Amitriptyline is a tricyclic antidepressant and has no real role in the treatment of hot flashes. Venlafaxine is a serotonin–norepinephrine reuptake inhibitor (SNRI) that does not strongly inhibit CYP2D6 and has been shown to reduce hot flashes by about 60% in placebo-controlled trials.

Suggested Reading

Archer DF, Seidman L, Constantine GD, et al. A double-blind, randomly assigned, placebo-controlled study of desvenlafaxine efficacy and safety for the treatment of vasomotor symptoms associated with menopause. *Am J Obstet Gynecol.* 2009;200:172.e1–e10. PMID: 19110224.

Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet.* 2000;356:2059–2063. PMID: 11145492.

Loprinzi CL, Sloan JA, Perez EA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. *J Clin Oncol.* 2002;20:1578–1583. PMID: 11896107.

21-4 A

Phase II trials have reported a significant decrease in mTOR-related mucositis in patients who used corticosteroid mouthwashes to be swished and spit out, compared to prior trials that did not use anything to try to prevent mucositis. Approximately 70 to 80% of patients in these trials have not reported any mucositis in the first 8 weeks of therapy, compared to only 33% in historical controls.

Nystatin is useful if an oral fungal infection is present, which would rarely be the case in patients receiving only an aromatase inhibitor plus an mTOR inhibitor. Oral sucralfate has not been shown to prevent mucositis. Benzydamine has not been evaluated in this situation. Palifermin has been shown to be helpful in patient undergoing myeloablative bone marrow transplantation.

Suggested Reading

Lalla RV, Bowen J, Barasch A, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer.* 2014;120:1453–1461. PMID: 24615748.

Loprinzi CL, Martenson JA. Keratinocyte growth factor: not yet ready for prime time. *J Clin Oncol.* 2003;21:1429–1430. PMID: 12697863.

Rugo HS, Seneviratne L, Beck JT, et al. Prevention of everolimus/exemestane (EVE/EXE) stomatitis in postmenopausal women with HR+ metastatic breast cancer using dexamethasone-based mouthwash (MW): results of the Swish trial. *J Clin Oncol.* 34, 2016 (suppl; abstr 525). PMID: 28156498.

Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med.* 2004;351:2590–2598. PMID: 15602019.

21-5 C

Two randomized, placebo controlled trials (ROMANA 1 and 2) were both done in patients with advanced lung cancer. Anamorelin (a ghrelin analog) did improve lean body mass in these patients, but not grip strength or performance status. As of 2016, this medication has not been approved in the United States for the treatment of cancer-associated anorexia or cachexia.

Suggested Reading

Temel JS, Abernethy AP, Currow DC, et al. Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomized, double-blind, phase 3 trials. *Lancet Oncol.* 2016;17:519–531. Epub 2016 Feb 20. PMID: 26906526.

21-6 C

Ipilimumab-induced diarrhea can be severe. It usually responds to holding the medication and the use of steroids to reduce the inflammatory response. It is important to rule out other causes such as superinfection with *C. difficile* or other agents, as well as to rule out bowel perforation. Steroids usually help to resolve the symptoms, but a minority of patients have persistent and refractory symptoms. This may be mediated by production of other inflammatory cytokines from the ipilimumab such as tumor necrosis factor (TNF). Infliximab is a monoclonal antibody directed against TNF-alpha and has been shown to be helpful in the management of steroid refractory ipilimumab-induced diarrhea.

Octreotide can be useful for treatment of cytotoxic chemotherapy– or radiation therapy–related diarrhea, but is not specific for ipilimumab-induced diarrhea. Metronidazole can be helpful for *C. difficile*–associated diarrhea. Atropine is often useful for the early diarrhea associated with irinotecan, but would not be indicated in this setting.

Suggested Reading

Pagès C, Gornet JM, Monsel G et al. Ipilimumab-induced acute severe colitis treated by infliximab. *Melanoma Res.* 2013;23:227–230. PMID: 23458760.

21-7 B

Cancer-related fatigue is a common problem. Several randomized, placebo-controlled clinical trials have failed to show any significant benefit to use of psychostimulants. However, two randomized, placebo-controlled clinical trials of ginseng have demonstrated patient-reported improvement in cancer-related fatigue.

Suggested Reading

Barton DL, Liu H, Dakhil SR, et al. Phase III evaluation of American ginseng (panax quinquefolius) to improve cancer-related fatigue: NCCTG Trial N07C2. *J Clin Oncol.* 2012;30 (suppl; abstr 9001).

Barton DL, Liu H, Dakhil SR, et al. Wisconsin Ginseng (Panax quinquefolius) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2. *J Natl Cancer Inst.* 2013;105:1230–1238. PMID: 23853057.

Bruera E, Yennurajalingam S, Palmer JL, et al. Methylphenidate and/or a nursing telephone intervention for fatigue in patients with advanced cancer: a randomized, placebo-controlled, phase II trial. *J Clin Oncol.* 2013;31:2421–2427. PMID: 23690414.

Moraska AR, Sood A, Dakhil SR, et al. Phase III, randomized, double-blind, placebo-controlled study of long-acting methylphenidate for cancer-related fatigue: North Central Cancer Treatment Group NCCTG-N05C7 trial. *J Clin Oncol.* 2010;28:3673–3679. PMID: 20625123.

Stankoff B, Waubant E, Confavreux C, et al. Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study. *Neurology.* 2005;64:1139–1143. PMID: 15824337.

21-8 A

A patient with symptomatic anemia should be transfused with red blood cells. This is the most rapid means of alleviating symptoms and has been shown to be safe. Transfusions should be limited to an amount that alleviates the symptoms and then stopped. Current guidelines suggest not using erythroid-stimulating agents, as the side effects, including an increased risk of thrombosis, as well as expense outweigh the benefits for most patients. As the patient has no evidence of iron deficiency, IV iron therapy is not indicated.

Suggested Reading

NCCN Guidelines. Cancer- and chemotherapy-induced anemia. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed November 29, 2016.

Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database Syst Rev.* 2012;12:CD003407. PMID: 23235597.

21-9 A

Dyspareunia is a common symptom for women who have undergone treatment for any one of a large number of cancers. Patients with pelvic, colorectal, bladder, and breast cancer frequently note such symptoms. One study investigated the use of 4% topical lidocaine applied to the introitus 3 minutes prior to intercourse. Patients reported significantly less dyspareunia and an improved ability to engage in intercourse. There seemed to be no adverse effects on the male partners. Ideally, this study should be repeated.

Kegel exercises are for bladder control, not for dyspareunia.

In addition, vaginal moisturizers can be recommended to try to increase vaginal health and vaginal lubricants can be used with intercourse. Of note, new data support that vaginal laser therapy can also be helpful to improve vaginal tissue.

Suggested Reading

Athanasiou S, Pitsouni E, Antonopoulou S, et al. The effect of microablative fractional CO2 laser on vaginal flora of postmenopausal women. *Climacteric.* 2016;19:512–518. PMID: 27558459.

Goetsch MF, Lim JY, Caughey AB. A practical solution for dyspareunia in breast cancer survivors: a randomized controlled trial. *J Clin Oncol.* 2015;33:3394–3400. PMID: 26215946.

Salvatore S, Leone Roberti Maggiore U, Athanasiou S, et al. Histological study on the effects of microablative fractional CO2 laser on atrophic vaginal tissue: an ex vivo study. *Menopause.* 2015;22:845–849. PMID: 25608269.

21-10 B

Pilot data, published in 2007, supported that oxybutynin was helpful for decreasing hot flashes. These findings were confirmed in a placebo-controlled, randomized, double-blind trial demonstrating that 15 mg of oxybutynin decreased hot flashes, to what appears to be a similar degree as is seen with several antidepressants and gabapentinoids. The main toxicity was mouth dryness. Magnesium oxide was studied in a placebo-controlled trial, which yielded negative results. There are no good data regarding doxepin or atropine in this situation.

Suggested Reading

Simon JA, Gaines T, LaGuardia KD. Extended-release oxybutynin therapy for vasomotor symptoms in women: a randomized clinical trial. *Menopause*. 2016;23:1214–1221. PMID: 27760081.

22 PALLIATIVE MEDICINE FOR CANCER

SELF-EVALUATION

22. PALLIATIVE MEDICINE FOR CANCER QUESTIONS

22-1 A 78-year-old man is receiving first-line therapy for metastatic pancreatic adenocarcinoma with single-agent gemcitabine. He receives close support from several family caregivers, including his wife, two siblings, and three adult children, who provide around-the-clock care. You recently note progression, and he and his family opt for hospice care.

Which one of the following statements is most appropriate?

A. Admission to hospice requires first changing the patient's code status from "Full Code" to "Do Not Resuscitate."
B. Eligibility requirements include prognosis of less than 6 months to live, determination of short prognosis by two physicians, and need for around-the-clock care.
C. Patients with advanced cancer may remain on hospice care as long as two physicians determine at any time that the prognosis is less than 6 months "if the disease runs its usual course."
D. Most patients receive hospice care in a special facility, like a hospice care house or a nursing home.

22-2 A 75-year-old man has recently been diagnosed with metastatic lung adenocarcinoma (ALK-negative). He is considering several options, including both cancer-directed treatments and pursuing hospice care. You are considering sending him to see a local outpatient palliative care specialist.

Which of the following is the most appropriate answer with regard to counseling the patient and family?

A. ASCO guidelines recommend integration of dedicated palliative care services when the patient has a very limited life expectancy.
B. Palliative care should be integrated as early in the care as possible in order to identify and manage complex areas of distress involving the patient and caregiver.
C. Data on the outcomes of palliative care integration in oncology are mixed, but a few high-profile trials show positive results.
D. The benefits achieved from integration of palliative care into oncology care are the same, irrespective of whether the patient is referred near the diagnosis of advanced disease or near the end of life.

22-3 A 56-year-old man's disease recently progressed on single-agent enzalutamide for hormone-refractory prostate cancer. He is currently receiving sustained-release morphine 60 mg every 8 hours scheduled with oxycodone 30 mg every 4 hours as needed with good pain control. His risk score by the Opioid Risk Tool is low, and he returns monthly to

receive prescriptions and has no history of aberrant behaviors with opioids.

Which one of the following statements is most accurate about the management of chronic cancer pain with opioids?

A. Assessment of risk of opioid diversion should be systematically performed only with patients who have a history of poor behaviors with opioids.
B. The patient's as-needed opioid dose is too high and should be revisited for a better dose.
C. Side effects of chronic opioid use that should be monitored and followed include constipation and excessive sedation.
D. Prescriptions and management of cancer-related pain should be slowly transitioned to other members of the cancer team, including anesthesia/pain and palliative care.

22-4 A 55-year-old postmenopausal woman with metastatic *ERBB2* nonoverexpressed, hormone receptor–negative breast cancer is beginning third-line chemotherapy. Her disease has progressed rapidly, with only 1 month of stable disease during second-line therapy. Now, her functional status has changed remarkably, from an ECOG 0 to an ECOG 2. She inquires about an immunotherapy phase I trial.

Which of the following statements is most appropriate regarding patient-centered communication?

A. The potential benefits of clinical trials matched with the patient's poor performance status often require difficult conversations; the oncologist should defer any conversations regarding "bad news" to avoid the patient losing hope.
B. Patients and clinicians are always aligned in terms of their understanding of the benefits of late-line chemotherapy for advanced disease.
C. Statements such, "I wish things were different," imply that the oncologist made a mistake in sequencing of chemotherapy and open her to an eventual lawsuit claiming negligence.
D. Expressing, "We're now in a different place," would subtly but clearly indicate to the patient and her caregivers that an important change in the clinical situation may require a conversation about future plans.

22-5 A 72-year-old woman with metastatic cholangiocarcinoma has significant abdominal pain. She is on a regimen of around-the-clock transdermal fentanyl patch daily, dosed at 50 µg and changing it every 72 hours. You decide to add a short-acting, breakthrough opioid for incident pain that occurs a few times per day.

Which of the following is the most appropriate breakthrough pain regimen?

A. Oxycodone/acetaminophen 5/500 mg one tablet every 4 hours as needed
B. Tramadol 25 mg every 6 hours as needed
C. Hydromorphone 4 mg every 4 hours as needed
D. Immediate-release morphine sulfate 30 mg every 4 hours as needed

22-6 A 72-year-old man receives a new diagnosis of metastatic pancreas cancer. He is accompanied by his primary caregiver, his wife of 50 years, to all his appointments. She

is tearful when you mention the word “cancer” but generally says very little during the appointments. The patient’s treatment plan includes gemcitabine, which is scheduled to begin next week.

Which of the following statements is most appropriate about supporting caregivers?

A. Caregiver distress and anxiety have no relationship to the utilization of acute care resources (e.g., emergency department visits, hospital admission) by patients.
B. Caregivers are often barriers to patients’ understanding of the clinical situation and often get in the way.
C. Adding a palliative care clinician to the patient’s care may improve emotional outcomes of the patient’s caregivers.
D. There is no relationship between the emotional state of caregivers and that of the patients for whom they care.

22. PALLIATIVE MEDICINE FOR CANCER RATIONALES

22-1 C

More than half of all patients who die with cancer in the United States receive some form of hospice care. For the vast majority of these patients, care is provided in familiar surroundings, such as the patient’s usual residence. This includes the patient’s home or other long-term care residential facility, such as a nursing home or assisted living facility. Because a patient’s Medicare Part A can pay for only one service at a time, concurrent use of hospice care and either hospitalization or skilled nursing facilities for acute rehabilitation are generally not covered.

Eligibility for patients with cancer to enroll in hospice care includes a two-physician certification of a prognosis of less than 6 months to live if the disease runs its usual course. Patients cannot be subjected to any coercion regarding changing code status to something other than “full code”; a patient can have any code status during enrollment and throughout the duration of hospice care. As prognostic uncertainty is a common problem in cancer, where certain cancers may stabilize after discontinuation of active treatments and patients may live longer than 6 months, physicians cannot be penalized for lengths of stay on hospice for greater than 6 months if documentation is in place that reflects an expected short prognosis if the disease runs its usual course.

Suggested Reading

Braveman C. Proposed Medicare Hospice Benefit Conditions of Participation changes profiled: Q & A. *Caring.* 2005;24:57. PMID: 16124223.

Centers for Medicare and Medicaid Services (CMS), HHS. Medicare and Medicaid programs: hospice conditions of participation: final rule. *Fed Regist.* 2008;73:32087–32220. PMID: 18677823.

22-2 B

ASCO guidelines recommend the early and regular integration of palliative care into routine oncology care for patients with advanced disease and those with high distress. Several high-profile studies have demonstrated the patient and caregiver benefits of early palliative care integration, especially around the time of diagnosis of advanced disease. In a randomized, controlled trial addressing the question of when integration should occur, Bakitas et al. demonstrated quality-of-life and potentially survival benefits earlier, around the time of

diagnosis, compared to up to 90 days later.
A systematic review and meta-analysis of eight studies involving patients with cancer demonstrated consistent benefits for early integration of palliative care, particularly with regard to quality-of-life and symptom-improvement outcomes. The study concluded that outcomes solely related to prolonging survival are somewhat mixed.

Suggested Reading

Bakitas MA, Tosteson TD, Li Z, et al. Early versus delayed initiation of concurrent palliative oncology care: patient outcomes in the ENABLE III randomized controlled trial. *J Clin Oncol.* 2015;33:1438–1445. PMID: 25800768.

Kavalieratos D, Corbelli J, Zhang D, et al. Association between palliative care and patient and caregiver outcomes: a systematic review and meta-analysis. *JAMA.* 2016;316:2104–2114. PMID: 27893131.

22-3 C

Cancer-related pain is a common syndrome, and it can be related to the cancer itself or present as a complication of cancer-directed treatments. It remains a core responsibility of oncology clinicians, even with the increasing scrutiny of prescribing habits by regulators and others, to provide appropriate pharmacologic management of pain. Sometimes, complexities among the patient's background, history of opioid use, or difficulties in managing pain require assistance by others, including pain specialists and palliative care teams.
Best practices for opioid prescribing include written and signed documentation of the patient's understanding of appropriate ways to handle opioids (sometimes referred to as "opioid contracts"), baseline assessments of risk of aberrant behaviors (performed on all patients with standardized tools such as the Opioid Risk Tool), and regular and risk-based assessments of prescribed- and illicit-drug use (through the use of urine drug screens). Long-term risks of opioid use include constipation and testosterone deficiency, which increasingly requires the use of testosterone replacement.

Suggested Reading

Benedetti C, Brock C, Cleeland C, et al. NCCN practice guidelines for cancer pain. *Oncology (Williston Park).* 2000;14:135–150. PMID: 11195407.

Dev R, Hui D, Dalal S, et al. Association between serum cortisol and testosterone levels, opioid therapy, and symptom distress in patients with advanced cancer. *J Pain Symptom Manage.* 2011;41:788–795. PMID: 21276699.

22-4 D

Effective, clear communication between clinicians and patients starts with asking permission to have the conversation. Then, it involves clearly assessing and addressing any issues in the patient's perceptions of his or her illness and ensuring that it aligns with that of the medical team. This requires frequently checking in regarding the patient's knowledge of the facts ("I have stage IV cancer."), the meaning of those facts ("Stage IV means this is not a curable cancer."), and the plan for care ("I am receiving chemotherapy to help me live a bit longer.").
A common misconception is that direct and open conversations with patients about bad news may take away their hope or fight. In fact, these conversations, performed in a timely way and prior to a medical crisis, can reduce unwanted, unnecessary, and overly aggressive end-of-life care that often impedes patients' meeting goals. These goals may include dying at home or spending the last days of life next to family and friends rather than in the hospital. Studies also demonstrate that patients may be overly optimistic in their estimations of life expectancy and achievable outcomes from chemotherapy in metastatic disease settings. Checking in frequently with patients to both clarify misperceptions and build rapport by demonstrating a concerted

interest in how care is aligning with their goals is important in these settings. Using phrases like "I wish things were different" and "We're in a different place" imply changes in the clinical condition alongside a shared mission to make the patient feel better. Importantly, it does not admit fault or malpractice, nor does it falsely imply that the cancer-directed treatment options may be better or more plentiful than what is actually true.

The proliferation of new and exciting therapies in oncology bring even more therapeutic and prognostic uncertainty to the clinician–patient visit. These complexities highlight the increasing importance of open and honest conversations regarding what is known, what is possible, best- and worst-case scenarios, and the role the oncologist plays throughout the spectrum of decisions that can be made.

Suggested Reading

Anselm AH, Palda V, Guest CB, et al. Barriers to communication regarding end-of-life care: perspectives of care providers. *J Crit Care.* 2005;20:214–223. PMID: 16253789.

Back AL, Trinidad SB, Hopley EK, Edwards KA. Reframing the goals of care conversation: "we're in a different place." *J Palliat Med.* 2014;17:1019–1024. PMID: 24932593.

Baile WF, Buckman R, Lenzi R, et al. SPIKES-A six-step protocol for delivering bad news: application to the patient with cancer. *Oncologist.* 2000;5:302–311. PMID: 10964998.

Glare P, Virik K, Jones M, et al. A systematic review of physicians' survival predictions in terminally ill cancer patients. *BMJ.* 2003;327:195–198. PMID: 12881260.

Lamont EB, Christakis NA. Prognostic disclosure to patients with cancer near the end of life. *Ann Intern Med.* 2001;134:1096–1105. PMID: 11412049.

22-5 D

It is standard of care and the subject of several quality measures to provide all patients with short-acting, breakthrough opioids to complement long-acting sustained-release products (e.g., sustained-release morphine). When opioids are prescribed, the breakthrough dose is usually 10 to 20% of the total daily around-the-clock sustained-release dose; the exceptions to this calculation are short-acting fentanyl products, for which the short-acting dose is typically the lowest dose in which the product is available (e.g., 200 µg transmucosal fentanyl). For the patient described, the current regimen of 50 µg transdermal fentanyl is equivalent to a total dose of about 150 mg of oral morphine per day; 10 to 20% of that total dose is 15 to 30 mg of morphine.

Thus, the other suggested answers are not correct, as their morphine equivalencies are much smaller than the 30-mg breakthrough dose suggested. For example, 4 mg of hydromorphone is equivalent to around 15 mg of morphine, too small a dose. The oxycodone 5-mg and tramadol 25-mg regimens are wholly inadequate, as they each convert to about 7 mg of morphine.

Suggested Reading

Davies AN. The management of breakthrough cancer pain. *Br J Nurs.* 2011;20:803–804, 806–807.

Dickman A. Integrated strategies for the successful management of breakthrough cancer pain. *Curr Opin Support Palliat Care* 2011;5:8–14. PMID: 21325998.

Zeppetella G. Opioids for the management of breakthrough cancer pain in adults: a systematic review undertaken as part of an EPCRC opioid guidelines project. *Palliat Med.* 2011;25(5):516–24. PMID: 21708858.

22-6 C

Increasing attention is being given to the role of caregivers in supporting positive outcomes for patients with cancer. Often, caregivers are the "front-line" members of the oncology team, reporting back to clinical professionals on issues of symptoms, performance status, and goals of care. Significant evidence demonstrates that caregivers suffer from the effects of poor

emotional states of their loved ones. This is observed as higher levels of depression among caregivers of patients who also exhibit depressive symptoms.

Oncology teams will need to further incorporate the needs and distress of caregivers into the comprehensive cancer care plan as the number of caregivers grow and their influence on patient outcomes is better understood, For example, higher intensity and frequency of caregiving practices are associated with lower hospital readmissions. Further, close support of caregivers, for example by a palliative care team, has also demonstrated improvement in emotional outcomes. Because of this, oncology teams are increasingly realizing that support of caregivers is an effective way to reduce unnecessary health care utilization while supporting patient-centered cancer care. This support of caregivers at its most basic level involves listening to caregivers, soliciting input and suggestions, and frequently reminding caregivers that their efforts are appreciated and valued.

Suggested Reading

Dionne-Odom JN, Azuero A, Lyons KD, et al. Benefits of early versus delayed palliative care to informal family caregivers of patients with advanced cancer: outcomes from the ENABLE III randomized controlled trial. *J Clin Oncol.* 2015;33:1446–1452. PMID: 25800762.

Dumont S, Turgeon J, Allard P, et al. Caring for a loved one with advanced cancer: determinants of psychological distress in family caregivers. *J Palliat Med.* 2006;9:912–921. PMID: 16910806.

Rabow MW, Hauser JM, Adams J. Supporting family caregivers at the end of life: “They don’t know what they don’t know.” *JAMA.* 2004;291:483–491. PMID: 14747506.

Rivera HR. Depression symptoms in cancer caregivers. *Clin J Oncol Nurs.* 2009;13:195–202. PMID: 19349266.

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