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GOLDMAN'S

CECIL MEDICINE

西氏内科学

第24版

肿瘤分册

LEE GOLDMAN
ANDREW I. SCHAFER

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Cecil

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GOLDMAN'S CECIL MEDICINE

24TH EDITION

西氏内科学

（第24版）

肿瘤分册

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PREFACE

The 24TH Edition of *Goldman's Cecil Medicine* symbolizes a time of extraordinary advances in medicine and in technological innovations for the dissemination of information. This textbook and its associated electronic products incorporate the latest medical knowledge in formats that are designed to appeal to learners who prefer to access information in a variety of ways.

The contents of *Cecil* have remained true to the tradition of a comprehensive textbook of medicine that carefully explains the *why* (the underlying normal physiology and pathophysiology of disease, now at the cellular and molecular as well as the organ level) and the *how* (now frequently based on Grade A evidence from randomized controlled trials). Descriptions of physiology and pathophysiology include the latest genetic advances in a practical format that strives to be useful to the nonexpert. Medicine has entered an era when the acuity of illness and the limited time available to evaluate a patient have diminished the ability of physicians to satisfy their intellectual curiosity. As a result, the acquisition of information, quite easily achieved in this era, is often confused with knowledge. We have attempted to counteract this tendency with a textbook that not only informs but also stimulates new questions and gives a glimpse of the future path to new knowledge. Grade A evidence is specifically highlighted in the text and referenced at the end of each chapter. In addition to the information provided in the textbook, the Cecil website supplies expanded content and functionality. In many cases, the full articles referenced in each chapter can be accessed from the Cecil website. The website is also continuously updated to incorporate subsequent Grade A information, other evidence, and new discoveries.

The sections for each organ system begin with a chapter that summarizes an approach to patients with key symptoms, signs, or laboratory abnormalities associated with dysfunction of that organ system. As summarized in Table 1-1, the text specifically provides clear, concise information regarding how a physician should approach more than 100 common symptoms, signs, and laboratory abnormalities, usually with a flow diagram, a table, or both for easy reference. In this way, *Cecil* remains a comprehensive text to guide diagnosis and therapy, not only for patients with suspected or known diseases but also for patients who may have undiagnosed abnormalities that require an initial evaluation.

Just as each edition brings new authors, it also reminds us of our gratitude to past editors and authors. Previous editors of *Cecil Medicine* include a short but remarkably distinguished group of leaders of American medicine: Russell Cecil, Paul Beeson, Walsh McDermott, James Wyngaarden, Lloyd H. Smith, Jr., Fred Plum, J. Claude Bennett, and Dennis Ausiello. As we welcome new associate editors—Wendy Levinson, Donald W. Landry, Anil Rustgi, and W. Michael Scheld—we also express our appreciation to Nicholas LaRusso and other associate editors from the previous editions on whose foundation we have built. Our returning associate editors—William P. Arend, James O. Armitage, David Clemmons, Jeffrey M. Drazen, and Robert C. Griggs—continue to make critical contributions to the selection of authors and the review and approval of all manuscripts. The editors, however, are fully responsible for the book as well as the integration among chapters.

The tradition of *Cecil Medicine* is that all chapters are written by distinguished experts in each field. We are also most grateful for the editorial assistance in New York of Theresa Considine and Silva Sergenian. These individuals and others in our offices have shown extraordinary dedication and equanimity in working with authors and editors to manage the unending flow of manuscripts, figures, and permissions. We also thank Faten Aberra, Reza Akari, Robert C. Brunham, Ivan Ciric, Seema Daulat, Gregory F. Erikson, Kevin Ghassemi, Jason H. Huang, Caron Jacobson, Lisa Kachnic, Bryan T. Kelly, Karen Krok, Heather Lehman, Keiron Leslie, Luis Marcos, Michael Overman, Eric Padron, Bianca Maria Piraccini, Don W. Powell, Katy Ralston, James M. Swain, Tania Thomas, Kirsten Tillisch, Ali Turabi, Mark Whiteford, and Y. Joseph Woo, who contributed to various chapters. At Elsevier, we are most indebted to Dolores Meloni and Linda McKinley, and also thank Cathy Carroll, Taylor Ball, Virginia Wilson, Linda Van Pelt, Suzanne Fannin, and Steve Stave, who have been critical to the planning and production process under the direction of Mary Gatsch. Many of the clinical photographs were supplied by Charles D. Forbes and William F. Jackson, authors of *Color Atlas and Text of Clinical Medicine*, Third Edition, published in 2003 by Elsevier Science Ltd. We thank them for graciously permitting us to include their pictures in our book. We have been exposed to remarkable physicians in our lifetimes and would like to acknowledge the mentorship and support of several of those who exemplify this paradigm—Robert H. Gifford, Lloyd H. Smith, Jr., Frank Gardner, and William Castle. Finally, we would like to thank the Goldman family—Jill, Jeff, Abigail, Mira, Daniel, and Robyn Goldman—and the Schafer family—Pauline, Eric, Pam, John, Evan, and Kate—for their understanding of the time and focus required to edit a book that attempts to sustain the tradition of our predecessors and to meet the needs of today's physician.

LEE GOLDMAN, MD
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SECTION XV: ONCOLOGY

XV

ONCOLOGY

182 APPROACH TO THE PATIENT WITH CANCER

MICHAEL C. PERRY

DIAGNOSIS

Few diagnoses produce such emotional responses as *cancer* or *leukemia,* and in the first few moments after those words are uttered, the patient often experiences a storm of feelings that limit useful discussion. When the time is right, however, the physician and the patient must discuss the diagnosis, its implications, and the therapeutic alternatives. It is often best for the patient if family members or close friends are present in the consulting room, both to provide emotional support and to be another "set of ears." It is often useful to ask, "What do you understand about your diagnosis?"

If the physician is not familiar with the latest treatments, consultation in advance with, for example, the National Cancer Institute's Physician Data Query will make the interview more meaningful. Prompt referral to a specialist, whether a surgical oncologist, radiation oncologist, or medical oncologist, is imperative. The generalist should not be a therapeutic nihilist unless he or she is intimately involved in the field and knows about all the current therapies and clinical trials.

The consulting medical oncologist, often advised by a local tumor board comprising medical, surgical, and radiation oncologists, usually outlines the prognosis and the alternatives: standard therapy, possible clinical trials, a second opinion, or no treatment. Many oncologists actively participate in clinical trials and may have investigational drugs available, or they may suggest referral to a tertiary cancer center as appropriate.

Diagnostic Procedures

In most settings, a lesion has been found on physical examination or by abnormal laboratory or radiographic studies, and a biopsy has confirmed the diagnosis. It is critical that the biopsy be representative of the entire tumor and that appropriate investigations (e.g., special stains, flow cytometry, cytogenetics, hormone assays) be performed before treatment is initiated. If there is a question whether the lesion is benign or malignant or about its proper classification, consideration should be given to additional biopsies, and consultation with a reference pathologist may be indicated. There is seldom a need for such rapid therapy that appropriate pretreatment evaluations cannot be performed. For many tumor sites, such as the colon (Chapter 199), there is one predominant histology; in others, such as the lung (Chapter 197), the distinction between small cell lung cancer and non–small cell lung cancer is critical for treatment. For breast cancer (Chapter 204), the treating physician is interested in a variety of factors, such as histology, tumor grade, the presence or absence of estrogen and progesterone receptors, and the presence of ERBB2 (HER2/neu) overexpression.

Staging and Work-up

After a diagnosis has been established, staging is next. The American Joint Committee on Cancer staging system is considered the standard in the United States and is based on the TNM (tumor, node, metastasis) system. The approach to staging depends on the type of cancer, but it commonly includes plain films such as chest radiographs, computed tomography (CT), magnetic resonance imaging (MRI), radionuclide scans, and, increasingly, positron emission tomography (PET). These studies are typically supplemented by routine hematologic and chemistry profiles, tumor markers, and, in some cases, bone marrow aspiration and biopsies.

The keys to the work-up are to identify sites of metastases and to establish an indicator lesion or lesions to monitor therapy. Thus, for most solid tumors, a CT scan and perhaps a bone scan can accomplish both goals, with brain CT or MRI reserved for cases in which central nervous system metastases are most likely (e.g., small cell lung cancer). PET scans supplement CT scans by establishing that a given lesion is likely to be malignant and by clarifying other sites of disease. In patients with known, established advanced disease, they are seldom needed.

TREATMENT Rx

Development of a Treatment Plan

For cancers amenable to surgery, resection is usually the best alternative if the patient is a suitable candidate for anesthesia (Chapter 440) and is otherwise in acceptable condition in terms of concomitant or comorbid illnesses. A joint discussion among the internist, oncologist, surgeon, and anesthesiologist is often very useful in this regard. Determination of the patient's performance score (Table 182-1) is a simple means of assessing functional status. If life expectancy is limited or if the patient is not a good candidate for surgery, radiation therapy is usually considered the next best "local" therapy, with chemotherapy reserved for patients whose disease is extensive or metastatic. The increasing effectiveness of chemotherapy has resulted in its earlier incorporation into therapy, often as part of an "organ-sparing" approach. Ideally, the discussion of treatment with the patient should take a multidisciplinary approach, with clarification of the diagnosis, prognosis, treatment goals, alternatives, side effects, and risks and benefits.

Surgical Therapy

Surgery is used to biopsy a suspected lesion, to remove the primary tumor, to bypass obstructions, and to provide palliation. A preoperative discussion may determine the requirement for placement of a venous access device at the time of surgery, thus eliminating the need for a second anesthesia.

Surgery remains the most common method to cure localized cancers, such as breast cancer (Chapter 204), colorectal cancer (Chapter 199), and lung cancer (Chapter 197), but it is limited by the location of the tumor, its extension, and distant metastases. Even if a tumor cannot be removed, a biopsy provides confirmation of the diagnosis. Occasionally, an obstructing lesion can be bypassed to provide palliation.

Surgical staging also establishes the extent of the disease. For ovarian cancer (Chapter 205), surgical "debulking" aims to remove all visible disease, leaving minimal residual disease, to enhance chemotherapy.

In rare circumstances when the primary tumor is controlled, removal of a single metastasis (metastasectomy) can result in long-term survival; an example is resection of a single liver metastasis found at the time of colectomy for colorectal cancer. A variety of surgical techniques, such as radio frequency ablation or cryoablation, can treat hepatic metastases in carefully selected patients. Adjuvant chemotherapy is often given after surgery in this situation to treat microscopic metastases.

Reconstruction after a disfiguring procedure is critical to long-term physical and emotional functioning. Examples include post-mastectomy breast reconstruction (Chapter 204) and plastic surgery procedures to correct deformities after head and neck surgery (Chapter 196).

Radiation Therapy

Ionizing radiation (Chapter 19) can be delivered using high-energy rays, known as *teletherapy*, via a linear accelerator; by brachytherapy, through the application of radioactive implants, seeds, wires, or plaques; and intravenously by using radioisotopes. Radiation interacts with molecular oxygen, inducing the formation of superoxide, hydrogen peroxide, or hydroxyl radicals that damage DNA, leading to cell death. Like chemotherapy, radiation therapy is most effective against rapidly dividing cells.

As "local" therapies, both surgery and radiation therapy are limited in their effectiveness by the inapparent extension of disease, the location of tumors next to normal structures that must be preserved, and the presence of distant metastases. Normal tissue tolerance, which varies among the different organs and tissues, often prevents the use of radiation doses that could uniformly eradicate cancers. Radiation therapy is also limited by tumor hypoxia: large, bulky tumors are frequently relatively radioresistant, whereas well-oxygenated tumors can be more effectively treated at lower doses.

Radiation therapy can be used as the primary treatment, as part of multimodality therapy, in the adjuvant setting, and for palliation. As a single modality, radiation therapy can be curative for early-stage malignancies such as laryngeal cancer (Chapter 196), cervical cancer (Chapter 205), and prostate cancer (Chapter 207). Breast-conserving surgery (Chapter 204) requires the use of radiation to treat the remaining breast. Partial irradiation techniques using three-dimensional planning with external beam radiation or with a balloon catheter have recently been developed and used in selected patients with appropriately placed and sized breast cancers. For localized prostate cancer (Chapter 207), implanted radioactive seeds of gold or palladium offer an alternative to surgery or external beam radiation therapy, again in carefully selected patients.

It is important to note that the combination of chemotherapy and radiation therapy may result in synergistic toxicities, such as esophagitis (Chapter 140) in the treatment of lung cancer (Chapter 197) or mucositis in the treatment of head and neck cancer (Chapter 196).

Newer techniques, such as intensity-modulated radiation therapy, permit more exact tailoring of the dose to the target, thereby reducing damage to the surrounding normal tissues. Stereotactic radiation therapy or gamma knife techniques allow the treatment of primary or metastatic brain tumors (Chapter 195) measuring up to 3 cm with pinpoint accuracy, minimizing damage to normal brain. Proton therapy has only limited applicability at this time; it is

TABLE 182-1 KARNOFSKY AND ZUBROD PERFORMANCE SCALES

Karnofsky Performance Status Scale	
VALUE	**LEVEL OF FUNCTIONAL CAPACITY**
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity, minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self, unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization is indicated although death is not imminent
20	Hospitalization is necessary, very sick, active supportive treatment necessary
10	Moribund, fatal processes progressing rapidly
0	Dead

Eastern Cooperative Oncology Group (Zubrod) Performance Scale	
PERFORMANCE STATUS	**DEFINITION**
0	Asymptomatic
1	Symptomatic; fully ambulatory
2	Symptomatic; in bed <50% of day
3	Symptomatic; in bed >50% of day
4	Bedridden

used for some uveal melanomas, skull base tumors, and a few pediatric malignancies.

Low- to moderate-dose palliative radiation is used to ameliorate symptomatic cancer when cure is no longer the goal. For instance, radiation therapy can improve brain metastases (Chapter 195), relieve pain from bone lesions (Chapter 208), relieve obstructing lesions, and sometimes relieve hemoptysis caused by lung cancer (Chapter 197) or bleeding from a gynecologic malignancy (Chapter 205). Bone-seeking radioisotopes such as samarium or strontium may relieve pain from bone metastases in prostate cancer (Chapter 207) or breast cancer (Chapter 204).

Systemic Therapy

Chemotherapy

Pharmacogenomics, the study of inherited interindividual differences in drug disposition and effects, is becoming important in cancer therapy because genetic polymorphisms in drug-metabolizing enzymes are often responsible for the variations in efficacy and toxicity observed with many chemotherapeutic agents. Drugs potentially affected by polymorphisms identified to date include the thiopurines, 5-fluorouracil, irinotecan, and the platinum agents. In patients who are heterozygous or homozygous for deficiencies in metabolizing enzymes, toxicity can be dramatically enhanced.

Currently available tests cannot reliably assess the likelihood of response to therapy, so treatment is largely empirical and based on predictive factors from the tumor itself. Gene expression microarrays currently under development may reliably predict responses in the future. Gene profiles are increasingly used to determine the necessity of therapy, such as the adjuvant therapy of breast or lung cancer.

Assessing Treatment

Assessment of the response to therapy depends largely on tumor size, determined by either direct measurement or diagnostic imaging studies. The categories of response are complete response, with total absence of tumor and correction of tumor-associated changes; partial response, defined as greater than 50% reduction in tumor size; stable disease, defined as greater than 25% but less than 50% reduction in tumor size; and progressive disease, characterized by either tumor growth or the development of new tumors. Leukemias can be assessed by bone marrow aspirates, and multiple myeloma is typically assessed by the measurement of monoclonal proteins, peripheral blood counts, and percentages of malignant plasma cells in bone marrow samples, as well as radiographs of bone lesions.

Chemotherapy is now used in a variety of settings with or without and before, during, or after surgery and radiation therapy (Table 182-2). Considerable experimental evidence suggests that cancers are most sensitive to

TABLE 182-2 EXAMPLES OF TIMING OF CHEMOTHERAPY

ADJUVANT THERAPY	NEOADJUVANT THERAPY	ORGAN-SPARING THERAPY	COMBINATION CHEMOTHERAPY
Stage I and II breast cancer	Stage III breast cancer	Anal cancer	Metastatic solid tumors*
Stage III colorectal cancer		Laryngeal cancer	Hematologic malignancies
Stage III melanoma		Esophageal cancer	
Stage I–III lung cancer			

*Usually palliative.

chemotherapy during the early stages of growth, as a result of the high growth fraction and shorter cell cycle times. Thus, a given dose of drug exerts a greater therapeutic effect against a rapidly growing tumor than against a larger, quiescent tumor.

Neoadjuvant Chemotherapy

Neoadjuvant therapy, also called *primary* or *induction chemotherapy*, is used before surgery or radiation therapy to decrease the size of locally advanced cancers, thereby permitting better surgical resection, and to eradicate undetectable metastases. It also affords an opportunity to evaluate the effectiveness of treatment by histologic analysis of resected tissue. This approach is most often used for locally advanced breast cancer (Chapter 204), although other primary tumors can be targeted. Disadvantages include the initially incomplete pathologic staging and the possibility that ineffective chemotherapy will permit the tumor to grow beyond the point of resection.

Organ-sparing therapy is the use of chemotherapy, radiation therapy, or both to salvage organs that would have been surgically removed if cure were the intended result. This technique is often effective in patients with cancers of the larynx (Chapter 196), esophagus (Chapter 198), bladder (Chapter 203), and anus (Chapter 199).

Adjuvant Chemotherapy

Adjuvant chemotherapy is used in patients whose primary tumor and all evidence of cancer (e.g., regional lymph nodes) have been surgically removed or treated definitively with radiation but in whom the risk of recurrence is high because of involved lymph nodes or certain morphologic or biologic characteristics of the cancer. Common examples include cancers of the breast (Chapter 204) and colon (Chapter 199). The typical end points of clinical chemotherapy, such as shrinkage of measurable tumor on serial radiographic studies, are not available in this situation; instead, relapse-free survival and overall survival are the principal measures of treatment effect. For an individual patient receiving adjuvant therapy, there is no way to determine whether such therapy is beneficial or necessary, so decisions are generally based on evidence from clinical trials.

Adjuvant therapy has been used in a wide variety of tumors, with variable success. In the case of breast cancer (Chapter 204) and colon cancer (Chapter 199), the number of lives saved by the use of adjuvant therapy is significant because of the large number of affected patients, despite the modest absolute differences between treated and control patients with current treatment programs. Resectable lung cancer (Chapter 197) has recently been added to this list.

Palliative Chemotherapy

Chemotherapy rarely cures cancers that remain after surgical or radiation treatment or that recur after such therapy. Pancreatic cancer (Chapter 200) is perhaps the best example of this scenario, because few patients are deemed eligible for surgery, and most have recurrent cancer after surgery. Most adult patients with recurrent or metastatic disease are considered for palliative therapy if there is no realistic chance of cure but the potential for prolongation of useful life and/or relief of tumor-related symptoms makes such therapy reasonable.

Combination Chemotherapy

Virtually all the curative chemotherapy regimens developed for hematologic malignancies or solid tumors use combinations of active agents. Combination chemotherapy is usually superior to the use of single agents in adjuvant and neoadjuvant therapy as well. The improved results achieved by combination chemotherapy can be explained in several ways. Resistance to any single agent is almost always present at diagnosis, even in clinically responsive tumors. Tumors that are initially "sensitive" to chemotherapy rapidly acquire resistance to single agents, either as a result of selection of a preexisting clone of resistant tumor cells or because of an increased rate of mutation leading to drug resistance. Combination chemotherapy theoretically addresses both phenomena by providing a broader range of coverage against initially

resistant clones of cells and preventing or slowing the development of resistant clones.

Combination chemotherapy follows a set of principles. All drugs must be active against the tumor, and all drugs must be given at an optimal dose and on an optimal schedule. The drugs should have different mechanisms of antitumor activity as well as different toxicity profiles, and the drugs should be given at consistent intervals for the shortest possible treatment time.

Hormonal Therapy

Endocrine or hormonal therapy for cancer (Table 182-3), the earliest form of systemic therapy, is almost entirely limited to breast cancer (Chapter 204) and prostate cancer (Chapter 207). Many premenopausal breast cancers are thought to be under the influence of estrogens, and hormonal deprivation (ablation) may produce long-term responses in properly selected patients (those with estrogen and/or progesterone receptor positivity who have predominantly soft tissue or bone disease). This hormonal ablation may take the form of surgical removal of the ovaries, ablative radiation therapy, or the use of luteinizing hormone–releasing hormone antagonists. The antiestrogen tamoxifen is effective against breast cancer, and it may decrease the incidence of contralateral breast cancers in both premenopausal and postmenopausal women with breast cancer. It also has an estrogen-like activity that is responsible for an increased rate of endometrial cancers. Somewhat paradoxically, postmenopausal women who are candidates for hormonal therapy may also respond to tamoxifen.

Aromatase Inhibitors

Patients who have experienced a prolonged objective response or stable disease with hormonal therapy may be candidates for second-, third-, or fourth-line hormonal therapy. However, such responses tend to become less frequent and shorter, and many patients eventually need chemotherapy. Recently, aromatase inhibitors (e.g., anastrozole, letrozole, exemestane), which decrease the conversion of metabolites in fat and muscle into estrogen, have been found to be more effective than tamoxifen as first-line therapy in both the adjuvant and metastatic settings, although the optimal schedule for tamoxifen and the aromatase inhibitors in the adjuvant setting is still under study (Chapter 204).

Prostate cancer (Chapter 207) is androgen dependent, and androgen deprivation through castration or antiandrogens can produce meaningful responses. Estrogen therapy is now used infrequently because of its cardiovascular side effects and the availability of better alternatives. Once prostate cancer becomes androgen independent, second-line hormonal therapy rarely produces useful responses.

Corticosteroids

The corticosteroids (Chapter 34), typically prednisone or dexamethasone, are widely used in the treatment of hematologic and oncologic cancers. In Hodgkin's disease (Chapter 192), the non-Hodgkin's lymphomas (Chapter 191), and multiple myeloma (Chapter 193), corticosteroids have antitumor activity. In solid tumors, they are used as antiemetics and, rarely, for the treatment of hypercalcemia of cancer (Chapter 186), for symptomatic relief of cerebral edema in cases of central nervous system metastases (Chapter 195), or as an adjunct to radiation therapy for spinal cord metastases. Megestrol acetate (Megace) is often used in an attempt to relieve anorexia, which is common among cancer patients.

Immunotherapy

Two cancers characterized by often unpredictable clinical behavior, melanoma (Chapter 210) and renal cell carcinoma (Chapter 203), are treated with interferon, interleukin-2, or both (Table 182-4). Dramatic responses are uncommon, and immunotherapy is only a minor component of cancer therapy.

Molecularly Targeted Agents

Targeted agents (Table 182-5) are drugs directed at a specific molecular point, such as a protein tyrosine kinase, or at the presence of a specific antigen on a tumor cell. The first tyrosine kinase inhibitors were imatinib and erlotinib. The best example of the success of tyrosine kinase inhibitor therapy is the dramatic response of chronic myelogenous leukemia (Chapter 190) to imatinib (Gleevec). Imatinib also has activity against gastrointestinal stromal cell tumors.

Erlotinib, directed against the epidermal growth factor receptor (EGFR), has antitumor effects in patients whose non–small cell lung cancers (Chapter 197) have EGFR mutations. Current research aims to identify the specific types of mutations so that patients can be prospectively selected for therapy, analogous to the measurement of estrogen receptors to select breast cancer patients for hormonal therapy.

The vascular endothelial growth factor receptor (VEGFR) stimulates the formation of new blood vessels that are critical for tumor growth. Anti-VEGFR agents, such as the monoclonal antibody bevacizumab, prevent VEGF from transducing its signal in endothelial cells, thereby preventing their division. Bevacizumab has antitumor effects in metastatic colorectal cancer, non–small cell lung cancer, and breast cancer. Thalidomide inhibits angiogenesis through an unknown mechanism and is used against multiple myeloma (Chapter 193).

Bortezomib (Velcade), a unique drug, is a reversible inhibitor of the proteasome pathway that normally regulates the intracellular concentration of specific proteins, thus controlling homeostasis. It has been effective in the treatment of refractory multiple myeloma (Chapter 193) and non-Hodgkin's lymphomas (Chapter 191).

The development of monoclonal antibodies directed against antigens found on cancer cells represents an additional treatment modality, often complementary to conventional chemotherapy. Examples include alemtuzumab, cetuximab, rituximab, and trastuzumab. Trastuzumab has recently been shown to add significantly to disease-free survival time in patients positive for HER2/neu who receive adjuvant therapy for early-stage breast cancer (Chapter 204). These monoclonal antibodies can be used alone ("naked") or, in some cases,

TABLE 182-3 HORMONAL THERAPY

Corticosteroids
Prednisone
Dexamethasone (Decadron)
Androgens
Fluoxymesterone (Halotestin)
Estrogens
Diethylstilbestrol (DES)
Antiandrogens
Bicalutamide (Casodex)
Flutamide (Eulexin)
Nilutamide (Nilandron)
Antiestrogens
Tamoxifen (Nolvadex)
Toremifene (Fareston)
Progestational agents
Megestrol acetate (Megace)
Luteinizing hormone–releasing hormone analogues
Leuprolide (Lupron)
Goserelin (Zoladex)
Degarelix
Aromatase inhibitors
Anastrozole (Arimidex)
Exemestane (Aromasin)
Letrozole (Femara)
Estrogen receptor antagonist
Fulvestrant (Faslodex)

TABLE 182-4 IMMUNOTHERAPY

Interferon-α (Intron A, Roferon)
Interleukin-2 (Proleukin)

TABLE 182-5 MOLECULARLY TARGETED AGENTS AND MONOCLONAL ANTIBODIES

MOLECULARLY TARGETED AGENTS
Imatinib (Gleevec)
Dasatinib (Sprycel)
Nilotinib (Tasigna)
Erlotinib (Tarceva)—EGFR TKI
Antiangiogenesis agents
Bevacizumab (Avastin)—VEGF inhibitor
Thalidomide (Thalomid)
Lenalidomide (Revlimid)
Multikinase inhibitor
Sorafenib (Nexavar)
Sunitinib (Sutent)
Temosirolimus (Torisel)
Everloimus (Affinitor)
Pazopanib (Votrient)
Lapatinib (Tykerb)
Bortezomib (Velcade)—proteasome inhibitor
MONOCLONAL ANTIBODIES
Trastuzumab (Herceptin)
Rituximab (Rituxan)
Gemtuzumab ozogamicin (Mylotarg)
Alemtuzumab (Campath)
Cetuximab, C-225 (Erbitux)
Tositumomab iodine-131 (Bexxar)
Panitumumab (Vectibex)
Ofatumumab (Arzerra)
Ibritumomab tiuxetan Y 90 (Zevalin)

EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

labeled with a radioactive molecule to enhance cell killing. This radioimmunoconjugate approach has been most effective in the treatment of non-Hodgkin's lymphomas (Chapter 191) and chronic lymphocytic leukemia (Chapter 190). The effectiveness of monoclonal antibodies is limited by changes in the antigenic composition of neoplastic cells, called *antigenic drift*.

Individual Agents

A list of the most commonly used chemotherapeutic agents (Table 182-6) can help in understanding the key issues each one raises. In all cases, the most current information from the manufacturer should be sought before therapy is initiated. The number of new drugs continues to increase, and some older drugs included in previous editions of this textbook have been omitted.

The administration of chemotherapy is best done by specifically trained individuals because of the dual risks of hypersensitivity reactions and extravasation. No doses or schedules are suggested because these agents are often used in combination, and the doses must be reduced in many cases. End-organ function also affects dosing. The administration of chemotherapy during pregnancy is an especially difficult circumstance and requires a particularly high level of expertise.

Unless otherwise specified, all chemotherapeutic agents are capable of producing some degree of nausea and vomiting, myelosuppression, alopecia, mucositis, and/or diarrhea after treatment. Most agents are also teratogenic, mutagenic, and carcinogenic, so these toxicities are not repeated for each agent. Drugs used routinely to offset agent-specific toxicities are also included in Table 182-6.

Bone Marrow or Stem Cell Transplantation

Because the major dose-limiting toxicity of most chemotherapeutic agents is myelosuppression, approaches have been developed to harvest the pluripotent stem cells found in bone marrow, peripheral blood, or, less often, cord blood before marrow-damaging chemotherapy so that the stem cells can be reinfused later (Chapter 181). This technique is most effective for acute leukemias (Chapter 189), relapsed lymphomas (Chapter 191), and germ cell tumors (Chapter 206). The effectiveness of this approach is limited more by the inability to eradicate cancer cells than by the inability to achieve engraftment. Transplants may be syngeneic (from an identical twin), autologous (from oneself), allogeneic (from a matched donor, such as a sibling or parent), or from a matched unrelated donor. Nonablative hematopoietic transplants that do not completely abolish myelopoiesis reduce toxicity and allow the treatment of older and medically infirm patients.

Special Circumstances: Pregnant and Geriatric Patients

Pregnancy

Cancer during pregnancy is not uncommon, with breast, cervical, ovarian, melanoma, thyroid, and hematologic malignancies being most common. This is obviously an emotionally charged time, as the joy of a new birth is contrasted with the possible loss of the mother. Clinical decision making is complicated by ethical, moral, cultural, and religious issues. This is not an area for the inexperienced. If surgery can be safely accomplished, this may be the best course, even if it is only a temporizing measure. Radiation therapy carries the very real risk of radiation exposure to the fetus, and staging is almost always suboptimal and confined to ultrasound examinations. When the disease requires chemotherapy, changes in both the mother and the fetus must be taken into account; for instance, there are major changes is pharmacokinetics during pregnancy, along with changes in renal function and plasma volume, plasma protein levels, hepatic metabolism, gastrointestinal absorption, and placental transfer, not to mention fetal pharmacokinetics and placental excretion. Many of the commonly used chemotherapeutic drugs are classified by the Food and Drug Administration as category D (positive human fetal risk, but the benefits in pregnant women may be acceptable despite the risk) or category X (studies in humans and animal have shown fetal malformations or there is evidence of fetal risk based on human evidence). If the mother's condition permits, it is advisable to defer chemotherapy during the first and perhaps the second trimesters and to treat life-threatening situations during the third trimester after extensive counseling with the parents.

Geriatrics

The aging U.S. population has brought an increasing number of older patients with cancer to the attention of oncologists, and the field of geriatric oncology is a new area of specialization. An increasing proportion of cancers occurs in the older population. The changes that develop with age are covered in another chapter, but they can be briefly summarized here as decreased excretion of drugs and metabolites from the kidneys, decreased volume of distribution of water-soluble drugs, and increased susceptibility to myelosuppression, cardiomyopathy, and neuropathy. Many older adults also have comorbid illnesses that must be taken into account. As a general rule, the suitability of an older patient for therapy can be determined by a comprehensive geriatric assessment (CGA) that evaluates the patient's function, comorbidity, nutrition, medications, and resources. By itself, age is not a barrier to surgery; rather, the patient's performance status and the CGA should determine the likelihood of a good recovery. Tolerance of radiation therapy seems to remain largely intact with increasing age. Chemotherapy decisions are also based on the performance status and CGA, with the use of growth factors to increase the white blood cell count and to maintain a hemoglobin sufficient to minimize symptoms. Dosage adjustments are also made for individual glomerular filtration rates for patients aged 65 and older. The use of lower chemotherapy doses based on age alone is probably not advisable and may result in ineffective therapy.

Management of Complications

Supportive Care

Nutrition is always a concern for patients newly diagnosed with cancer, even if they have not experienced weight loss. In fact, significant weight loss is an adverse prognostic factor for several cancers, especially lung cancer. Patients are often concerned about whether their diet contributed to development of the cancer and whether diet can influence the results of therapy. In most settings, neither of these scenarios is the case. Malnourished patients should be evaluated by a dietitian to determine whether they are ingesting sufficient calories and whether dietary supplements might be needed. Some patients, such as those with head and neck cancers (Chapter 196) or esophageal cancers (Chapter 198), may require parenteral nutrition through a percutaneous endoscopic gastrostomy tube. Total parenteral nutrition (Chapter 224) is rarely indicated, is not particularly helpful, and is likely to produce an ethical dilemma when therapy fails and the decision to discontinue it must be discussed. Corticosteroids increase appetite but have many undesirable side effects. Megestrol acetate (Megace) at a dose of 800 mg/day improves appetite and allows weight gain in many patients; it is expensive, although the suspension is less costly than the tablets. The synthetic cannabinoid dronabinol (Marinol) stimulates appetite and reduces nausea in some patients, but it can produce dysphoria, particularly in older patients. A multiple vitamin with zinc may help with abnormal taste and provide trace minerals. Larger than recommended doses of vitamins are not helpful and may be toxic. It is always useful to inquire what over-the-counter and alternative medications (Chapter 38) are being contemplated or used by the patient.

Symptom Management

Symptom management is key to successful treatment and the patient's quality of life. Pain control (Chapter 29) can be accomplished with a variety of analgesics, both non-narcotic and narcotic. Oncologists use a 10-point scale for evaluating pain control (Fig. 182-1) and start with nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and acetaminophen, progress through ibuprofen and related drugs, and then through combinations of NSAIDs and narcotics to stronger narcotics.[1] Newer narcotics are available in both short-duration and long-duration forms; some patches last 72 hours, which are ideal for patients who have severe pain and are unable to take oral medications. Oral transmucosal fentanyl is more effective than standard-release morphine in this setting. Oral mucositis, a common complication of intensive therapy for hematologic malignancies, can be treated with local measures or with recombinant human keratinocyte growth factor.[2,3] Oral anti-*Candida* drugs that are absorbed or partially absorbed from the gastrointestinal tract can help prevent oral candidiasis.[4]

Many patients still fear chemotherapy because of the risk of nausea and vomiting. New antiemetics, used in combination, have made this side effect much less common. Chemotherapeutic drugs can be ranked according to their probability of causing nausea and vomiting, with prophylactic treatment given accordingly. The availability of the serotonin 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists (dolasetron, granisetron, ondansetron) has dramatically improved the ability to completely control nausea and vomiting. Although prochlorperazine may be adequate for mildly emetogenic chemotherapy, more emetogenic regimens require combination therapy with a corticosteroid (usually dexamethasone), a 5-HT_3 antagonist, and a benzodiazepine (e.g., lorazepam). A newer antiemetic, aprepitant, is particularly useful for the treatment of delayed nausea and vomiting. Treating patients before the development of nausea and vomiting is much more effective and helps patients adhere to their treatment schedules.

Growth factors, such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), permit the more rapid recovery of white blood cell nadirs, thus permitting chemotherapy to be given on schedule, without reducing the dosage in many cases.[5] However, such therapy does not decrease hospitalizations or improve survival. It is possible to determine which individuals are at greatest risk for febrile neutropenia (Chapters 170 and 289) and treat them in advance, based on published guidelines.[6,7] Anemia induced by chemotherapy can be alleviated, the need for transfusions reduced, and quality of life improved by the use of either erythropoietin (Procrit) or darbepoetin (Aranesp).

The bisphosphonates pamidronate (Aredia) and zoledronate (Zometa) are very effective not only to treat tumor-induced hypercalcemia (Chapter 186) but also to reduce pathologic fractures in bones with metastatic lesions, particularly from breast cancer (Chapter 204), prostate cancer (Chapter 207), and myeloma (Chapter 193). They are also used to treat osteoporosis caused by chemotherapy-induced premature menopause in young women with breast cancer. Denosumab (Xgeva) is a human monoclonal antibody that binds to

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TABLE 182-6

AGENT	CLASS	ACTION	EXCRETION	UNIQUE SIDE EFFECTS	DRUG INTERACTIONS	INDICATIONS
ALKYLATING AGENTS						
Bendamustine (Treanda)	Alkylating agent	Bifunctional with both alkylating and purine-like antimetabolite action	Biotransformation in liver	None	Synergistic with rituximab	CLL, myeloma, Hodgkin's and non-Hodgkin's lymphoma
Carboplatin (Paraplatin)	Platinum coordination compound	Produces interstrand DNA cross-links, similar to those with bifunctional alkylating agents; cell cycle nonspecific	Renal	Nephrotoxicity, ototoxicity, neuropathy, hypomagnesemia, hypersensitivity reactions, hepatotoxicity	Avoid other nephrotoxic or ototoxic drugs	Ovarian cancer, testicular cancer, lung cancer, head and neck cancer, breast cancer
Chlorambucil (Leukeran)	Bifunctional alkylating agent	Formation of interstrand DNA cross-links with resultant inactivation of DNA; cell cycle nonspecific	Hepatic biotransformation, renal excretion	Hepatotoxicity, pulmonary toxicity	None	CLL, Waldenström's macroglobulinemia, Hodgkin's and non-Hodgkin's lymphomas, myeloproliferative disorders, ovarian cancer
Cisplatin (Platinol)	Platinum coordination compound	Produces interstrand DNA cross-links similar to bifunctional alkylating agents; cell cycle nonspecific	Renal	Nephrotoxicity, ototoxicity, neuropathy, hypomagnesemia, hypersensitivity reactions, hemolytic anemia, SIADH	Avoid other nephrotoxic or ototoxic drugs	Testicular cancer, other germ cell tumors, ovarian cancer, bladder cancer, prostate cancer, lung cancer, sarcomas, cervical cancer, endometrial cancer, gastric cancer, breast cancer, adrenal cancer, head and neck cancer
Cyclophosphamide (Cytoxan, Neosar)	Alkylating agent of nitrogen mustard type	Cross-linking of DNA and RNA, inhibits protein synthesis; cell cycle nonspecific	Hepatic biotransformation, renal excretion	Hemorrhagic cystitis, SIADH	Phenobarbital increases rate of metabolism and leukopenia; cyclophosphamide potentiates effects of succinylcholine and may increase oral anticoagulant activity	Breast cancer, ovarian cancer, Hodgkin's and non-Hodgkin's lymphomas, leukemias, neuroblastoma, retinoblastoma, other sarcomas, bladder cancer, lung cancer, cervical cancer, endometrial cancer, prostate cancer, osteogenic sarcoma, Wilms' tumor
Dacarbazine (DTIC-Dome)	Nonclassic alkylating agent	Inhibits DNA and RNA synthesis via formation of carbonium ions; cell cycle nonspecific	Hepatic biotransformation, renal excretion	Pain on injection, flu-like syndrome, hepatic veno-occlusive disease, photosensitivity	Heparin, lidocaine, hydrocortisone, phenytoin, phenobarbital, interleukin-2	Melanoma, Hodgkin's disease, sarcomas
Ifosfamide (Ifex)	Alkylating agent of nitrogen mustard type	Alkylated metabolites interact with DNA; cell cycle nonspecific	Hepatic biotransformation, renal elimination	Hemorrhagic cystitis, nephrotoxicity, CNS toxicity	None	Germ cell tumors, sarcomas, non-Hodgkin's lymphomas, cervical cancer, Ewing's sarcoma, lung cancer
Mechlorethamine, nitrogen mustard (Mustargen)	Bifunctional alkylating agent	Cross-links strands of DNA and RNA, inhibits protein synthesis; cell cycle nonspecific	Rapidly deactivated in body fluids and tissues	Extravasation	None	Hodgkin's disease, intracavitary treatment of effusions; topically for mycosis fungoides
Melphalan (Alkeran)	Alkylating agent of nitrogen mustard type	Forms interstrand, intrastrand, or DNA protein cross-links; cell cycle nonspecific	Deactivated in body fluids and tissues, renal elimination 50%	Pulmonary toxicity	Cimetidine decreases oral bioavailability; cyclosporine enhances risk of renal toxicity	Multiple myeloma, breast cancer, ovarian cancer, rhabdomyosarcoma, bone marrow ablation for stem cell transplantation
Mitomycin (Mutamycin)	Antitumor antibiotic	Acts as bifunctional alkylating agent, inhibiting DNA synthesis; cell cycle nonspecific, but most active in G and S phases	Hepatic biotransformation, renal elimination	Cumulative myelosuppression, extravasation, renal toxicity, pulmonary toxicity, cardiac toxicity, hemolytic-uremic syndrome	Prior treatment with vinca alkaloids may predispose to pulmonary toxicity; if used with doxorubicin, may potentiate cardiotoxicity	Gastric cancer, pancreatic cancer, anal cancer, lung cancer, head and neck cancer, cervical cancer

Oxaliplatin (Eloxatin)	Platinum coordination compound	Produces interstrand DNA cross-links similar to bifunctional alkylating agents; cell cycle nonspecific	Renal	Nephrotoxicity, neurotoxicity (worse with cold), allergic reactions	Avoid other nephrotoxic drugs, incompatible with 5-fluorouracil	Colorectal cancer
Procarbazine (Matulane)	Nonclassic alkylating agent and MAO inhibitor	Unknown; metabolism produces highly active free radicals that may alkylate and methylate DNA; cell cycle specific, S phase	Renal 70% after hepatic biotransformation	Disulfiram (Antabuse)-like side effects with alcohol ingestion; patients should avoid foods containing tyramine due to the drug's MAO inhibitory effects; central and peripheral neurotoxicity, hepatotoxicity, pulmonary toxicity	>100, including alcohol, antihistamines, anticoagulants, anticonvulsants, hypoglycemics, certain antihypertensives, caffeine-containing preparations, narcotics, methyldopa, metrizamide, sympathomimetics, tyramine or other high pressor amine-containing foods	Hodgkin's disease, brain tumors
Streptozocin (Zanosar)	Nitrosourea	Inhibits DNA synthesis	Renal	Cumulative, dose-related renal toxicity, hepatotoxicity, glucose intolerance	None	Islet cell tumors of pancreas, carcinoid tumors
Temozolomide (Temodar)	Nonclassic alkylating agent	Inhibits DNA and RNA synthesis via formation of carbonium ions; cell cycle nonspecific	Hepatic biotransformation, renal excretion	Photosensitivity	None	Melanoma, brain tumors
DIFFERENTIATING AGENTS						
All-*trans*-retinoic acid (ATRA)	Retinoid	Induces differentiation and/or inhibition of clonogenicity	Conjugation to glucuronic acid with subsequent biliary excretion and enterohepatic circulation	Mucocutaneous toxicity, ocular toxicity, musculoskeletal toxicity, neurologic toxicity, hepatotoxicity, lipid toxicity	None	Acute progranulocytic leukemia
Arsenic trioxide (Trisenox)	Natural product	Induces differentiation of acute progranulocytic leukemia cells	Hepatic metabolism, excreted in urine	Prolonged QT interval, acute progranulocytic leukemia differentiation syndrome, leukocytosis, peripheral neuropathy	Medications that increase QT interval, such as antiarrhythmics and amphotericin	Acute progranulocytic leukemia
ENZYMES						
L-Asparaginase (Elspar)	Enzyme	Hydrolyzes l-asparagine to aspartic acid and ammonia, resulting in cellular deficiency of l-asparagine; sensitive tumor cells lack asparagine synthetase; interferes with protein, DNA, and RNA synthesis; cell cycle specific for G1 phase of cell division	Metabolized in liver	Hypersensitivity reactions, inhibitory effects on protein synthesis with resultant decreases in hepatic synthesis of coagulation factors, pancreatitis, hyperglycemia, CNS depression, hepatotoxicity	Abolishes effects of methotrexate on malignant cells; concurrent vincristine may enhance hyperglycemic effects of asparaginase and increase risk of neuropathy	Acute lymphoblastic leukemia
ANTIMETABOLITES						
5-Azacitidine (Vidaza)	Antimetabolite; pyrimidine nucleoside analogue of cytidine	Causes hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells	Hepatic metabolism, excreted in urine	Renal toxicity, low serum bicarbonate levels	None	Myelodysplasia
Capecitabine (Xeloda)	Antimetabolite of pyrimidine analogue type	Fluoropyrimidine carbamate prodrug form of 5-fluorouracil; given orally; inactive as itself; inhibits DNA and RNA synthesis; cell cycle specific, S phase	Hepatic catabolism	Hand and foot syndrome, angina	Warfarin potentiation, phenytoin, antacids, leucovorin, thymidine	Breast cancer, colorectal cancer

TABLE 182-6

AGENT	CLASS	ACTION	EXCRETION	UNIQUE SIDE EFFECTS	DRUG INTERACTIONS	INDICATIONS
Cladribine (Leustatin), 2-chloro-2-deoxy-D-adenosine	Antimetabolite	Purine nucleoside analogue, inhibits both DNA synthesis and repair	Uncertain	Bone marrow suppression, fever, paralysis, and/or acute renal failure when used at very high doses for BMT	None known	Hairy cell leukemia
Clofarabine (Clofar)	Purine nucleoside antimetabolite	Inhibits DNA synthesis and DNA repair	Excreted in urine and other?	Bone marrow suppression, hepatotoxicity	Other renal and hepatotoxic drugs	Relapsed acute lymphoblastic leukemia
Cytarabine (Cytosar-U, Tarabine PFS)	Antimetabolite	Activated to cytarabine triphosphate in tissues, inhibits DNA synthesis; cell cycle specific, S phase	Deaminated in blood and tissues	Pancreatitis; with high doses, cerebral dysfunction, GI damage, hepatotoxicity, pulmonary edema, corneal damage, "Ara-C syndrome"	With high-dose cyclophosphamide, may increase cardiotoxicity	Acute granulocytic leukemia and its variants, non-Hodgkin's lymphoma, myelodysplasia*
Fludarabine phosphate (Fludara)	Antimetabolite of purine type	2-Fluoro-ara-ATP inhibits DNA synthesis by inhibition of ribonucleotide reductase and the DNA polymerases; cell cycle specific, S phase	Renal	Neurologic, pulmonary toxicity	None	CLL
Fluorouracil (5-FU, Adrucil)	Antimetabolite of pyrimidine analogue type	Inhibits DNA and RNA synthesis; cell cycle specific, S phase	Respiratory, small renal elimination	Cerebellar ataxia, myocardial ischemia	None	Breast cancer, GI cancers, head and neck cancer, bladder cancer, ovarian cancer, endometrial cancer, effusions
Floxuridine (FUDR)	Antimetabolite of pyrimidine analogue type	Inhibits DNA and RNA synthesis; cell cycle specific, S phase	Respiratory, small renal elimination	Cerebellar ataxia, myocardial ischemia, hepatotoxicity	Leucovorin enhances activity and toxicity; thymidine rescues toxic effects	Intra-arterial therapy for hepatic malignancies
Hydroxyurea (Hydrea)	Antimetabolite	Inhibits ribonucleotide reductase, causing inhibition of DNA synthesis; cell cycle specific, S phase	Renal after hepatic biotransformation	Megaloblastosis	May enhance effects of anti-HIV drugs	Myeloproliferative neoplasms, ovarian cancer, head and neck cancer, cervical cancer (with radiation therapy)
Mercaptopurine (Purinethol, 6-MP)	Antimetabolite of purine analogue type	Inhibits DNA synthesis; cell cycle specific, S phase	Metabolic alteration by xanthine oxidase, renal excretion	Hepatotoxicity, skin rashes	Dose must be reduced when used with allopurinol; concomitant methotrexate enhances bioavailability of 6-MP; inhibits warfarin (Coumadin) effects	Acute lymphoblastic leukemia
Methotrexate (Folex, Mexate)	Antimetabolite of folic acid analogue type	Inhibits DNA, RNA, thymidylate, and protein synthesis as a result of binding to dihydrofolate reductase; cell cycle specific, S phase	Renal	Hepatotoxicity, lung disease; in high doses, acute renal failure, acute neurologic dysfunction; avoid use with ascites, pleural effusions	Salicylates, NSAIDs, folic acid–containing vitamins, oral nonabsorbable broad-spectrum antibiotics, trimethoprim/sulfamethoxazole, other nephrotoxic drugs	Breast cancer, head and neck cancer, choriocarcinoma, acute lymphoblastic leukemia, non-Hodgkin's lymphomas, osteosarcoma, intrathecal treatment of meningeal leukemia, bladder cancer, lung cancer
Pemetrexed (Alimta)	Antimetabolite of folic acid analogue type	Inhibits thymidylate synthetase, dihydrofolate reductase, and de novo purine synthesis; cell cycle specific, S phase	Renal, after hepatic metabolism	Must be given with folic acid and vitamin B_{12}; avoid use with ascites, pleural effusions	Salicylates, NSAIDs	Mesothelioma, breast cancer, lung cancer
Pentostatin (Nipent)	Purine antagonist	Inhibits adenosine deaminase; also inhibits RNA synthesis	Renal	Fever, fatigue, rash, pain, hepatotoxicity, chronic immunosuppression	Enhances effects of vidarabine, a purine nucleoside with antiviral activity; must not be given with fludarabine because of fatal pulmonary toxicity	Hairy cell leukemia, CLL
Pralatrexate (Fotolyn)	Antimetabolite type		Renal	Requires vitamin B_{12} and folate supplementation	Myelosuppression	Relapsed peripheral T-cell lymphomas

NONCOVALENT DNA-BINDING DRUGS						
Bleomycin (Blenoxane)	Antitumor antibiotic	Inhibition of DNA synthesis; most effective in G2 phase of cell division	Renal	Dose-related pulmonary fibrosis, hypersensitivity reactions, skin and mucocutaneous toxicity, including Raynaud's phenomenon (in combination with other agents), fever, chills; usually considered nonmyelosuppressive	Cisplatin may decrease renal clearance; high oxygen concentrations may enhance pulmonary toxicity, even after therapy	Testicular cancer and other germ cell tumors; Hodgkin's and non-Hodgkin's lymphomas; mycosis fungoides; squamous cell carcinomas of head and neck, cervix, and vulva; pleural effusions
Daunorubicin (Cerubidine)	Antitumor antibiotic	Binds to DNA by intercalation between base pairs and inhibits DNA and RNA synthesis by template disordering and steric obstruction; most active in S phase but not cell cycle phase specific	Hepatic biotransformation with 40% biliary excretion	Dose-related cardiotoxicity, extravasation, red urine	None	Acute granulocytic leukemia and its variants, acute lymphoblastic leukemia
Doxorubicin (Adriamycin, Rubex)	Antitumor antibiotic	Binds to DNA by intercalation between base pairs and inhibits DNA and RNA synthesis by template disordering and steric obstruction; cell cycle specific, S phase	Hepatic biotransformation with 50% biliary excretion	Dose-related cardiotoxicity, extravasation, red urine	None	Acute granulocytic leukemia and its variants, acute lymphoblastic leukemia, breast cancer, bladder cancer, ovarian cancer, thyroid cancer, lung cancer, Hodgkin's and non-Hodgkin's lymphomas, sarcomas, gastric cancer, multiple myeloma, endometrial cancer, bladder cancer, prostate cancer, Wilms' tumor, neuroblastoma
Doxorubicin liposomal (Doxil)	Anthracycline antibiotic	Topoisomerase inhibitor	Liver	Dose-related cardiotoxicity, extravasation, hand-foot syndrome	None	Ovarian cancer, myeloma, Kaposi's sarcoma
Epirubicin (Ellence)	Antitumor antibiotic	Intercalates with DNA	Liver	Dose-related cardiotoxicity	None	Breast cancer adjuvant therapy
Idarubicin (Idamycin)	Anthracycline glycoside	Intercalates DNA and inhibits DNA synthesis, interacts with RNA polymerases, and inhibits topoisomerase II	Hepatic biotransformation, biliary excretion	Dose-related cardiotoxicity, extravasation	None	Acute granulocytic leukemia and its variants
Mitoxantrone (Novantrone)	Antitumor antibiotic	Binds to DNA by intercalation between base pairs and nonintercalative electrostatic interaction, resulting in inhibition of DNA and RNA synthesis; not cell cycle specific, but most active in late S phase	Hepatic biotransformation, biliary/fecal excretion	Dose-related cardiotoxicity, extravasation, blue-green urine	None	Prostate cancer, acute myelogenous leukemia and its variants, breast cancer, non-Hodgkin's lymphomas
INHIBITORS OF CHROMATIN FUNCTION						
Docetaxel (Taxotere)	Mitotic spindle poison	Unique mitotic spindle inhibitor; cell cycle specific, M phase	Hepatic metabolism, biliary	Hypersensitivity reactions, fluid retention syndrome, nail discoloration, neuropathy, arthralgias	Inhibitors or activators of liver cytochrome P-450 CYP34A enzyme system may affect metabolism	Breast cancer, prostate cancer, lung cancer, ovarian cancer, esophageal cancer, gastric cancer, head and neck cancer, bladder cancer
Etoposide (VP-16, VePesid)	Epipodophyllo toxin	Inhibits DNA synthesis; cell cycle dependent and phase specific, with maximum effect in S and G2 phases	Hepatic biotransformation, renal elimination	Allergic reactions, hepatotoxicity, CNS toxicity, hypotension	None	Testicular cancer, lung cancer, Hodgkin's and non-Hodgkin's lymphomas, choriocarcinoma, Ewing's sarcoma, acute granulocytic leukemia
Irinotecan (Camptosar)	Topoisomerase I inhibitor	Binds to topoisomerase I–DNA complex and prevents relegation of these single-strand breaks	Metabolized in liver	Early and late diarrhea may be severe	None	Colorectal cancer, small cell lung cancer

TABLE 182-6

AGENT	CLASS	ACTION	EXCRETION	UNIQUE SIDE EFFECTS	DRUG INTERACTIONS	INDICATIONS
Paclitaxel (Taxol)	Mitotic spindle poison	Unique mitotic spindle inhibitor; cell cycle specific, M phase	Hepatic metabolism, biliary	Hypersensitivity reactions, neuropathy, arthralgias, cardiotoxicity	Enhanced myelosuppression with doxorubicin	Lung cancer, ovarian cancer, breast cancer, esophageal cancer, gastric cancer, head and neck cancer
Paclitaxel protein-bound particles (Abraxane)	Mitotic spindle poison	Unique mitotic spindle inhibitor; cell cycle specific, M phase	Hepatic metabolism, biliary	Hypersensitivity reactions, neuropathy, arthralgias/myalgias, cardiotoxicity	Enhanced myelosuppression with doxorubicin	Metastatic breast cancer
Topotecan (Hycamtin)	Topoisomerase I inhibitor	Binds to topoisomerase I–DNA complex and prevents relegation of these single-strand breaks	Excreted unchanged in urine	—	None	Relapsed ovarian cancer, small cell lung cancer
Vinblastine (Velban)	Vinca alkaloid	Blocks mitosis by arresting cells in metaphase; cell cycle specific, M phase	Biliary/fecal	Extravasation, neurotoxicity	None	Testicular cancer, breast cancer, choriocarcinoma, Hodgkin's and non-Hodgkin's lymphomas, Kaposi's sarcoma, bladder cancer, neuroblastoma, renal carcinoma
Vincristine (Oncovin)	Vinca alkaloid	Blocks mitosis by arresting cells in metaphase; cell cycle specific, M phase	Biliary/fecal	Extravasation, neurotoxicity, constipation, SIADH	Concurrent use with L-asparaginase may increase neurotoxicity	Acute lymphocytic leukemia, neuroblastoma, Wilms' tumor, Hodgkin's and non-Hodgkin's lymphomas, rhabdomyosarcoma, Ewing's sarcoma, breast cancer, small cell lung cancer, multiple myeloma
Vinorelbine (Navelbine)	Vinca alkaloid	Inhibits tubulin polymerization, disrupting formation of microtubule assembly during mitosis; cell cycle specific, M phase	Biliary/fecal	Extravasation, neurotoxicity, constipation, SIADH	Drugs metabolized by liver P-450 system, phenytoin	Non–small cell lung cancer, breast cancer, non- Hodgkin's lymphomas
HORMONAL AGENTS						
Anastrozole (Arimidex)	Nonsteroidal aromatase inhibitor	Inhibits synthesis of estrogens by inhibiting conversion of adrenal androgens to estrogens	Metabolized in liver	Hot flashes, arthralgias	None	Adjuvant and metastatic breast cancer in postmenopausal women
Bicalutamide (Casodex)	Nonsteroidal antiandrogen	Binds to androgen receptors in prostate	Hepatic metabolism	Worsening bone pain, gynecomastia, hot flashes	None	Prostate cancer (usually in conjunction with LHRH antagonist)
Degarelix (Firmagon)	GnRH receptor antagonist	Binds to GnRH receptors in pituitary		Injection site reactions, increased LFTs, QT interval prolongation	None	Prostate cancer
Dexamethasone (Decadron)	Corticosteroid	Multiple	Renal excretion of inactive metabolites	Cushingoid appearance, hyperglycemia, fluid retention, osteoporosis, muscular weakness, peptic ulcer disease, cataracts, psychosis, aseptic necrosis	Efficacy impaired by phenytoin	Acute lymphoblastic leukemia, Hodgkin's and non-Hodgkin's lymphomas, CLL, multiple myeloma, Waldenström's macroglobulinemia, cerebral edema, hypercalcemia, lymphangitic metastases, antiemetic
Diethylstilbestrol (DES)	Estrogen	Stimulation of autocrine growth factors	Renal	Feminization in men, fluid retention, thromboembolic phenomena, induction of endometrial cancer	None	Breast cancer, prostate cancer

Estradiol	Estrogen	Stimulation of autocrine growth factors	Renal	Feminization in men, fluid retention, thromboembolic phenomena, induction of endometrial cancer	None	Breast cancer, prostate cancer
Estramustine (Emcyt)	Phosphorylated combination of estradiol and nitrogen mustard	Inhibits microtubule structure and function; cell cycle specific, M-phase	Biliary/fecal	Feminization, fluid retention	None	Prostate cancer
Estrogens (conjugated or esterified)	Estrogen	Stimulation of autocrine growth factors, inhibition of pituitary secretion of LH, resulting in decreased serum testosterone concentration	Primarily renal	Feminization in men, fluid retention, thromboembolic phenomena, induction of endometrial cancer	None	Breast cancer, prostate cancer
Exemestane (Aromasin)	Steroidal aromatase inhibitor	Permanently binds to and irreversibly inhibits aromatase, inhibits synthesis of estrogens by inhibiting conversion of adrenal androgens to estrogens	Metabolized in liver	Hot flashes, arthralgias	None	Metastatic breast cancer in postmenopausal women
Fluoxymesterone (Halotestin)	Androgen	Suppresses GnRH, LH, and FSH through negative feedback mechanism involving hypothalamus and anterior pituitary	Renal	Masculinization in women, hepatotoxicity	May increase anticoagulant effects of warfarin (Coumadin); decreased blood glucose, resulting in potential for hypoglycemia in diabetics	Breast cancer
Flutamide (Eulexin)	Antiandrogen	Inhibition of androgen uptake and/or inhibition of nuclear binding of androgen in target tissues; its interference with testosterone at cellular level complements "medical castration" produced by LHRH analogues	Renal	Worsening bone pain, hot flashes, gynecomastia	None	Prostate cancer (usually in conjunction with LHRH antagonist)
Fulvestrant (Faslodex)	Estrogen receptor antagonist	Competitively binds to estrogen receptor and downregulates estrogen receptor protein in breast cancer cells	Cleared by hepatobiliary route	Arthralgias	None	Recurrent breast cancer in postmenopausal women
Goserelin (Zoladex)	Synthetic decapeptide analogue of LHRH	Suppresses pituitary gonadotropins, with fall of serum testosterone into castrate range	Metabolism	Worsening bone pain, hot flashes	None	Breast cancer, prostate cancer
Letrozole (Femara)	Nonsteroidal competitive inhibitor of aromatase	Inhibits synthesis of estrogens by inhibiting conversion of adrenal androgens to estrogens	Metabolized in liver	Hot flashes, arthralgias	None	Adjuvant and metastatic breast cancer in postmenopausal women
Leuprolide (Lupron, Lupron Depot)	Synthetic LHRH analogue	Suppresses secretion of GnRH, with resultant fall in testosterone secretion, producing "medical castration"	Metabolized in liver	Increased bone pain, hot flashes, thromboembolic phenomena	None	Prostate cancer, breast cancer
Medroxyprogesterone (Provera, Depo- Provera)	Progestational drug	Inhibition of pituitary gonadotropin production with resultant decrease in estrogen secretion	Renal	Weight gain, thromboembolic phenomena, fetal hazard	None	Breast cancer, endometrial cancer
Megestrol acetate (Megace)	Progestational drug	Inhibition of pituitary gonadotropin production, with resultant decrease in estrogen secretion	Renal	Weight gain, thromboembolic phenomena, fetal hazard	None	Breast cancer, endometrial cancer

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