**Piperazine** (generic, Vermizine)

Oral: piperazine citrate tablets equivalent to 250 mg of the hexahydrate; piperazine citrate syrup equivalent to 500 mg of the hexahydrate per 5 mL

**Praziquantel** (Biltricide; others outside the USA)

Oral: 600 mg tablets (other strengths outside the USA)

**Pyrantel pamoate** (Antiminth, Combantrin, Pin-rid, Pin-X)

Oral: 50 mg (base)/mL suspension; 62.5 mg (base) capsules (available without prescription in the USA)

**Suramin** (Bayer 205, others)

Parenteral: ampules containing 0.5 or 1 g powder to be reconstituted as a 10% solution and used immediately

*Note:* Suramin is not marketed in the USA but can be obtained from the Parasitic Disease Drug Service, Centers for Disease Control, Atlanta, 404-639-3670.

**Thiabendazole** (Mintezol)

Oral: 500 mg chewable tablets; suspension, 500 mg/mL

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**Chapter 55. Cancer Chemotherapy**

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Cancer Chemotherapy: Introduction

**Acronyms**

- **ABVD:** Doxorubicin (adriamycin), bleomycin, vinblastine, dacarbazine
- **CHOP:** Cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (oncovin), prednisone
- **CMF:** Cyclophosphamide, methotrexate, fluorouracil
- **COP:** Cyclophosphamide, vincristine (oncovin), prednisone
- **FAC:** Fluorouracil, doxorubicin (adriamycin), cyclophosphamide
- **FEC:** Fluorouracil, epirubicin, cyclophosphamide
- **IFL:** Irinotecan, fluorouracil, leucovorin
- **MP:** Melphalan, prednisone
- **MOPP:** Mechlorethamine, vincristine (oncovin), procarbazine, prednisone
- **PCV:** Procarbazine, lomustine, vincristine
- **PEB:** Cisplatin (platinum), etoposide, bleomycin
- **VAD:** Vincristine, doxorubicin (adriamycin), dexamethasone

**General**
Cancer is basically a disease of cells characterized by a shift in the control mechanisms that govern cell proliferation and differentiation. Cells that have undergone neoplastic transformation usually express cell surface antigens that may be of normal fetal type, may display other signs of apparent immaturity, and may exhibit qualitative or quantitative chromosomal abnormalities, including various translocations and the appearance of amplified gene sequences. Such cells proliferate excessively and form local tumors that can compress or invade adjacent normal structures. A small subpopulation of cells within the tumor can be described as tumor stem cells. They retain the ability to undergo repeated cycles of proliferation as well as to migrate to distant sites in the body to colonize various organs in the process called metastasis. Such tumor stem cells thus can express clonogenic or colony-forming capability. Tumor stem cells often have chromosome abnormalities reflecting their genetic instability, which leads to progressive selection of subclones that can survive more readily in the multicellular environment of the host. Quantitative abnormalities in various metabolic pathways and cellular components accompany this neoplastic progression. The invasive and metastatic processes as well as a series of metabolic abnormalities resulting from the cancer cause illness and eventual death of the patient unless the neoplasm can be eradicated with treatment.

Causes of Cancer

The incidence, geographic distribution, and behavior of specific types of cancer are related to multiple factors, including sex, age, race, genetic predisposition, and exposure to environmental carcinogens. Of these factors, environmental exposure is probably most important. Chemical carcinogens (particularly those in tobacco smoke) as well as azo dyes, aflatoxins, asbestos, and benzene have been clearly implicated in cancer induction in humans and animals. Identification of potential carcinogens in the environment has been greatly simplified by the widespread use of the Ames test for mutagenic agents. Ninety percent of carcinogens can be shown to be mutagenic with this assay. Ultimate identification of potential human carcinogens, however, requires testing in at least two animal species.

Certain herpes and papilloma group DNA viruses and type C RNA viruses have also been implicated as causative agents in animal cancers and are responsible for some human cancers as well. Oncogenic RNA viruses all appear to contain a reverse transcriptase enzyme that permits translation of the RNA message of the tumor virus into the DNA code of the infected cell. Thus, the information governing transformation can become a stable part of the genome of the host cell. Expression of virus-induced neoplasia probably also depends on additional host and environmental factors that modulate the transformation process. A specific human retrovirus (HTLV-I) has been identified as being the causative agent for a specific type of human T cell leukemia. The virus that causes AIDS (HIV-1) is closely related. Cellular genes are known that are homologous to the transforming genes of the retroviruses, a family of RNA viruses, and induce oncogenic transformation. These mammalian cellular genes, known as oncogenes, have been shown to code for specific growth factors and their receptors and may be amplified (increased number of gene copies) or modified by a single nucleotide in malignant cells. The \textit{bcl-2} oncogene may be a generalized cell death suppressor gene that directly regulates apoptosis, a pathway of programmed cell death.

Another class of genes, tumor suppressor genes, may be deleted or damaged, with resulting neoplastic change. A single gene in this class, the \textit{p53} gene, has been shown to have mutated from a tumor suppressor gene to an oncogene in a high percentage of cases of several human tumors, including liver, breast, colon, lung, cervix, bladder, prostate, and skin. The normal wild form of this gene appears to play an important role in suppressing neoplastic transformation; mutations in this gene place the cell at high risk.
Cancer Therapeutic Modalities

Cancer is the second most common cause of death in the USA, after heart disease, causing over 500,000 fatalities annually. With present methods of treatment, one third of patients are cured with local modalities (surgery or radiation therapy), which are quite effective when the tumor has not metastasized by the time of treatment. Earlier diagnosis might lead to increased cure rates with such local treatment; however, in the remaining cases, early micrometastasis is a characteristic feature of the neoplasm, indicating that a systemic approach such as chemotherapy is required (often along with surgery or radiation) for effective cancer management. At present, about 50% of patients with cancer can be cured, with chemotherapy contributing to cure in 10–15% of patients.

Cancer chemotherapy, as currently employed, can be curative in certain disseminated neoplasms that have undergone either gross or microscopic spread by the time of diagnosis. These cancers include testicular cancer, non-Hodgkin's lymphoma, Hodgkin's disease, and choriocarcinoma as well as childhood cancers such as acute lymphoblastic leukemia, Burkitt's lymphoma, Wilms' tumor, and embryonal rhabdomyosarcoma. There are also growing numbers of cancers in which the use of chemotherapy combined with initial surgery can increase the cure rate in locally advanced early-stage breast cancer, esophageal cancer, rectal cancer, and osteogenic sarcoma.

For many other forms of disseminated cancer, chemotherapy provides palliative rather than curative therapy at present. Effective palliation results in temporary improvement of the symptoms and signs of cancer and enhancement in the overall quality of life. In the past decade, advances in cancer chemotherapy have also begun to provide evidence that chemical control of neoplasia may become a reality for many forms of cancer. This will probably be achieved through a combined-modality approach in which optimal combinations of surgery, radiotherapy, and chemotherapy are used to eradicate both the primary neoplasm and its occult micrometastases before gross spread can be detected on physical or x-ray examination. Use of hormonal agents to modulate tumor growth is playing an increasing role in hormone-responsive tumors thanks to the development of hormone antagonists and partial agonists. Several recombinant biologic agents have been identified as being active for cancer therapy, including interferon alfa and interleukin-2.

Anticancer Drug Development

A major effort to develop anticancer drugs through both empiric screening and rational design of new compounds has been under way for over 3 decades. Recent advances in this field have included the synthesis of peptides and proteins with recombinant DNA techniques and monoclonal antibodies. The drug development program has employed testing in a few well-characterized transplantable animal tumor systems. Simple in vitro assays for measuring drug sensitivity of a battery of human tumor cells augment and shorten the testing program and are used currently as the primary screening tests for new agents by the National Cancer Institute and many pharmaceutical firms. After new drugs with potential anticancer activity are identified, they are subjected to preclinical toxicologic and limited pharmacologic studies in animals as described in Chapter 5: Basic & Clinical Evaluation of New Drugs. Promising agents that do not have excessive toxicity are then advanced to phase I clinical trials, wherein their pharmacologic and toxic effects are usually tested in patients with advanced cancer. Other features of clinical testing are similar to the procedure for other drugs but may be accelerated.

Ideal anticancer drugs would eradicate cancer cells without harming normal tissues. Unfortunately, no currently available agents meet this criterion, and clinical use of these drugs involves a weighing of benefits against toxicity in a search for a favorable therapeutic index.
Classes of drugs that have recently entered clinical development include signal transduction inhibitors, focused on critical signaling pathways essential for cell growth and proliferation; microtubule inhibitors, directed against the mitotic spindle apparatus; differentiation agents, intended to force neoplastic cells past a maturation block to form end-stage cells with little or no proliferative potential; antimetastatic drugs, designed to perturb surface properties of malignant cells and thus alter their invasive and metastatic potential; antiangiogenic agents, designed to inhibit the formation of tumor vasculature; hypoxic tumor stem cell-specific agents, designed to exploit the greater capacity for reductive reactions in these often therapeutically resistant cells; tumor radiosensitizing and normal tissue radioprotecting drugs, aimed at increased therapeutic effectiveness of radiation therapy; cytoprotective agents, focused on protecting certain normal tissues against the toxic effects of chemotherapy; and biologic response modifiers, which alter tumor-host metabolic and immunologic relationships.

Importance of Neoplastic Cell Burden

Patients with widespread cancer may have up to $10^{12}$ tumor cells throughout the body at the time of diagnosis (Figure 55–1). If tolerable dosing of an effective drug is capable of killing 99.99% of clonogenic tumor cells, treatment would induce a clinical remission of the neoplasm associated with symptomatic improvement. However, there would still be up to 8 logs of tumor cells ($10^8$) remaining in the body, including those that might be inherently resistant to the drug because of tumor heterogeneity. There may also be other tumor cells that reside in pharmacologic sanctuary sites (eg, the central nervous system, testes), where effective drug concentrations may be difficult to achieve. When cell cycle-specific drugs are used, the tumor stem cells must also be in the sensitive phase of the cell cycle (not in G0). For this reason, scheduling of these agents is particularly important. In common bacterial infections, a three-log reduction in microorganisms might be curative because host resistance factors can eliminate residual bacteria through immunologic and microbicidal mechanisms; however, host mechanisms for eliminating even moderate numbers of cancer cells appear to be generally ineffective.

Figure 55–1.
The log-kill hypothesis. Relationship of tumor cell number to time of diagnosis, symptoms, treatment, and survival. Three alternative approaches to drug treatment are shown for comparison with the course of tumor growth when no treatment is given (dashed line). In the protocol diagrammed at top, treatment (indicated by the arrows) is given infrequently and the result is manifested as prolongation of survival but with recurrence of symptoms between courses of treatment and eventual death of the patient. The combination chemotherapy treatment diagrammed in the middle section is begun earlier and is more intensive. Tumor cell kill exceeds regrowth, drug resistance does not develop, and "cure" results. In this example, treatment has been continued long after all clinical evidence of cancer has disappeared (1–3 years). This approach has been established as effective in the treatment of childhood acute leukemia, testicular cancers, and Hodgkin's disease. In the treatment diagrammed near the bottom of the graph, early surgery has been employed to remove the primary tumor and intensive adjuvant chemotherapy has been administered long enough (up to 1 year) to eradicate the remaining tumor cells that comprise the occult micrometastases.

Combinations of agents with differing toxicities and mechanisms of action are often employed to overcome the limited log kill of individual anticancer drugs. If drugs display nonoverlapping toxicities, they can be used at almost full dosage, and at least additive cytotoxic effects can be achieved with combination chemotherapy; furthermore, subclones resistant to only one of the agents can potentially be eradicated. Some combinations of anticancer drugs also appear to exert true synergism, wherein the effect of the two drugs is greater than additive. The efficacy of combination chemotherapy has now been validated in many forms of human cancer, and the scientific rationale appears to be sound. As a result, combination chemotherapy is now the standard approach to curative treatment of testicular cancer and lymphomas and to palliative treatment of many other tumor types. This important therapeutic approach was first formulated by Skipper and Schabel and described as the log-kill hypothesis (Figure 55–1).
Growth of acute leukemias and aggressive lymphomas closely follows exponential cell kinetics. In contrast, most human solid tumors do not grow in such a manner; instead, they follow a Gompertzian model of tumor growth and regression. Under Gompertzian kinetics, the growth fraction of the tumor is not constant and peaks when the tumor is about one third of its maximum size.

Importance of Cell Cycle Kinetics

Information on cell and population kinetics of cancer cells explains, in part, the limited effectiveness of most available anticancer drugs. A schematic summary of cell cycle kinetics is presented in Figure 55–2. This information is relevant to the mode of action, indications, and scheduling of cell cycle-specific (CCS) and cell cycle-nonspecific (CCNS) drugs. Agents falling into these two major classes are summarized in Table 55–1.

<table>
<thead>
<tr>
<th>Cell Cycle-Specific (CCS) Agents</th>
<th>Cell Cycle-Nonspecific (CCNS) Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimetabolites</td>
<td>Alkylation agents</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Busulfan</td>
</tr>
<tr>
<td>Cladribine</td>
<td>Carmustine</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>Lomustine</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Mechloretamine</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Melphalan</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>Thiotepa</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Anthracyclines</td>
</tr>
<tr>
<td>Thioguanine</td>
<td>Daunorubicin</td>
</tr>
<tr>
<td>Antitumor antibiotic</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Epirubicin</td>
</tr>
<tr>
<td>Epipodophyllotoxins</td>
<td>Idarubicin</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Mitoxantrone</td>
</tr>
<tr>
<td>Teniposide</td>
<td>Antitumor antibiotics</td>
</tr>
<tr>
<td>Taxanes</td>
<td>Dactinomycin</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Mitomycin</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Camptothecins</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>Irinotecan</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Topotecan</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Platinum analogs</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Carboplatin</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
</tr>
</tbody>
</table>
Figure 55–2.

The cell cycle and cancer. A conceptual depiction of the cell cycle phases that all cells—normal and neoplastic—must traverse before and during cell division. The percentages given represent the approximate percentage of time spent in each phase by a typical malignant cell; the duration of G1, however, can vary markedly. Many of the effective anticancer drugs exert their action on cells traversing the cell cycle and are called cell cycle-specific (CCS) drugs (Table 55–1). A second group of agents called cell cycle-nonspecific (CCNS) drugs can sterilize tumor cells whether they are cycling or resting in the G0 compartment. CCNS drugs can kill both G0 and cycling cells (although cycling cells are more sensitive).

In general, CCS drugs are most effective in hematologic malignancies and in solid tumors in which a relatively large proportion of the cells are proliferating or are in the growth fraction. CCNS drugs (many of which bind to cellular DNA and damage these macromolecules) are particularly useful in low growth fraction solid tumors as well as in high growth fraction tumors. In all instances, effective agents sterilize or inactivate tumor stem cells, which are often only a small fraction of the cells within a tumor. Non-stem cells (eg, those that have irreversibly differentiated) are considered sterile by definition and are not a significant component of the cancer problem.

Resistance to Cytotoxic Drugs

A major problem in cancer chemotherapy is drug resistance. Some tumor types, eg, malignant melanoma, renal cell cancer, and brain cancer, exhibit primary resistance, ie, absence of response on the first exposure, to currently available standard agents. The presence of inherent drug resistance is felt to be tightly associated with the genomic instability associated with the development of most cancers. Acquired resistance develops in a number of drug-sensitive tumor types. Experimentally, drug resistance can be highly specific to a single drug and usually is based on a change in the genetic apparatus of a given tumor cell with amplification or increased expression of one or more specific genes. In other instances, a multidrug-resistant phenotype occurs—resistance to a variety of natural product anticancer drugs of differing structures developing after exposure to a single agent. This form of multidrug resistance is often associated
with increased expression of a normal gene (the \textit{MDRI} gene) for a cell surface glycoprotein (P-glycoprotein) involved in drug efflux. This transport molecule requires ATP to expel a variety of foreign molecules (not limited to antitumor drugs) from the cell. It is expressed constitutively in normal tissues such as the epithelial cells of the kidney, large intestine, and adrenal gland as well as in a variety of tumors. Multidrug resistance can be reversed experimentally by calcium channel blockers, such as verapamil, and a variety of other drugs, which inhibit the transporter. Other mechanisms of multiple drug resistance involve overexpression of the multidrug resistance protein 1 (MRP1), a member of the ATP-binding cassette transmembrane transporter superfamily that now consists of nine members (MRP1-MRP9). MRP1, the most extensively studied, increases resistance to natural product drugs such as anthracyclines, vinca alkaloids, taxanes, and epipodophyllotoxins by functioning as a drug export pump.

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Basic Pharmacology of Cancer Chemotherapeutic Drugs

Polyfunctional Alkylating Agents

The major clinically useful alkylating agents (Figure 55–3) have a structure containing a bis(chloroethyl)amine, ethyleneimine, or nitrosourea moiety. Among the bis(chloroethyl)amines, cyclophosphamide, mechlorethamine, melphalan, and chlorambucil are the most useful. Ifosfamide is closely related to cyclophosphamide but has a somewhat different spectrum of activity and toxicity. Thiotapec and busulfan are used for specialized purposes for ovarian cancer and chronic myeloid leukemia, respectively. The major nitrosoureas are carmustine (BCNU), lomustine (CCNU), and semustine (methyl-CCNU). A variety of investigational alkylating agents have been synthesized that link various carrier molecules such as amino acids, nucleic acid bases, hormones, or sugar moieties to a group capable of alkylation; however, successful site-directed alkylation has not been achieved to date.
Structures of major classes of alkylating agents.

As a class, the alkylating agents exert cytotoxic effects via transfer of their alkyl groups to various cellular constituents. Alkylations of DNA within the nucleus probably represent the major interactions that lead to cell death. However, these drugs react chemically with sulfhydryl, amino, hydroxyl, carboxyl, and phosphate groups of other cellular nucleophiles as well. The general mechanism of action of these drugs involves intramolecular cyclization to form an ethyleneimonium ion that may directly or through formation of a carbonium ion transfer an alkyl group to a cellular constituent. In addition to alkylation, a secondary mechanism that occurs with nitrosoureas involves carbamoylation of lysine residues of proteins through formation of isocyanates.

The major site of alkylation within DNA is the N7 position of guanine (Figure 55–4); however, other bases are also alkylated to lesser degrees, including N1 and N3 of adenine, N3 of cytosine,
and O6 of guanine, as well as phosphate atoms and proteins associated with DNA. These interactions can occur on a single strand or on both strands of DNA through cross-linking, as most major alkylating agents are bifunctional, with two reactive groups. Alkylation of guanine can result in miscoding through abnormal base pairing with thymine or in depurination by excision of guanine residues. The latter effect leads to DNA strand breakage through scission of the sugar-phosphate backbone of DNA. Cross-linking of DNA appears to be of major importance to the cytotoxic action of alkylating agents, and replicating cells are most susceptible to these drugs. Thus, although alkylating agents are not cell cycle-specific, cells are most susceptible to alkylation in late G1 and S phases of the cell cycle and express block in G2.

**Figure 55–4.**

[Diagram showing the mechanism of alkylation of DNA guanine. A bis(chloroethyl)amine forms an ethyleneimonium ion and a carbonium ion that react with a base such as N7 of guanine in DNA, producing an alkylated purine. Alkylation of a second guanine residue, through the illustrated mechanism, results in cross-linking of DNA strands.]

**Drug Resistance**

The mechanism of acquired resistance to alkylating agents may involve increased capability to repair DNA lesions, decreased permeability of the cell to the alkylating drug, and increased production of glutathione, which inactivates the alkylating agent through conjugation or through increased glutathione S-transferase activity, which catalyzes the conjugation.

**Pharmacologic Effects**

Active alkylating agents have direct vesicant effects and can damage tissues at the site of injection as well as produce systemic toxicity. Toxicities are generally dose-related and occur particularly in
rapidly growing tissues such as bone marrow, the gastrointestinal tract, and the reproductive system. After intravenous injection, nausea and vomiting usually occur within 30–60 minutes with mechlorethamine, cyclophosphamide, or carmustine. The emetogenic effects are mediated by the central nervous system and can be reduced by pretreatment with 5-HT₃ (serotonin) receptor antagonists such as ondansetron or granisetron. Subcutaneous injection of mechlorethamine or carmustine leads to tissue necrosis and sloughing.

Cyclophosphamide in its parent form does not have direct cytotoxic effects, and it must be activated to cytotoxic forms by microsomal enzymes (Figure 55–5). The liver microsomal cytochrome P450 mixed-function oxidase system converts cyclophosphamide to 4-hydroxycyclophosphamide, which is in equilibrium with aldophosphamide. These active metabolites are believed to be delivered by the bloodstream to both tumor and normal tissue, where nonenzymatic cleavage of aldophosphamide to the cytotoxic forms—phosphoramide mustard and acrolein—occurs. The liver appears to be protected through the enzymatic formation of the inactive metabolites 4-ketocyclophosphamide and carboxyphosphamide.

The major toxicities of alkylating agents are set forth in Table 55–2 and discussed below.
<table>
<thead>
<tr>
<th>Alkylating Agent</th>
<th>Single-Agent Dosage</th>
<th>Acute Toxicity</th>
<th>Delayed Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechlorethamine</td>
<td>0.4 mg/kg IV in single or divided doses</td>
<td>Nausea and vomiting, myelosuppression</td>
<td>Moderate depression of peripheral blood count; excessive doses produce severe bone marrow depression with leukopenia, thrombocytopenia, and bleeding; alopecia and hemorrhagic cystitis occasionally occur with cyclophosphamide; cystitis can be prevented with adequate hydration; busulfan is associated with skin pigmentation, pulmonary fibrosis, and adrenal insufficiency</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>0.1–0.2 mg/kg/d orally; 6–12 mg/d</td>
<td>Nausea and vomiting, myelosuppression</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>3.5–5 mg/kg/d orally for 10 days; 1 g/m² IV as single dose</td>
<td>Nausea and vomiting, myelosuppression</td>
<td></td>
</tr>
<tr>
<td>Melphalan</td>
<td>0.25 mg/kg/d orally for 4 days every 4–6 weeks</td>
<td>Nausea and vomiting, myelosuppression</td>
<td></td>
</tr>
<tr>
<td>Thiotepa (triethylenethiophosphoramide)</td>
<td>0.2 mg/kg IV for 5 days</td>
<td>Nausea and vomiting, myelosuppression</td>
<td></td>
</tr>
<tr>
<td>Busulfan</td>
<td>2–8 mg/d orally; 150–250 mg/course</td>
<td>Nausea and vomiting, myelosuppression</td>
<td></td>
</tr>
<tr>
<td>Carmustine (BCNU)</td>
<td>200 mg/m² IV every 6 weeks</td>
<td>Nausea and vomiting</td>
<td>Leukopenia, thrombocytopenia, and rarely hepatitis</td>
</tr>
<tr>
<td>Lomustine (CCNU)</td>
<td>150 mg/m² orally every 6 weeks</td>
<td>Nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td>Altretamine</td>
<td>10 mg/kg/d for 21 days</td>
<td>Nausea and vomiting</td>
<td>Leukopenia, thrombocytopenia, and peripheral neuropathy</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>50–200 mg/d orally</td>
<td>Nausea and vomiting, flu-like syndrome, drug interactions</td>
<td>Bone marrow depression, central nervous system depression, leukemogenic</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>300 mg/m² daily IV for 5</td>
<td>Nausea and vomiting</td>
<td>Bone marrow depression</td>
</tr>
</tbody>
</table>
Cisplatin

- 20 mg/m²/d IV for 5 days or 50–70 mg/m² as single dose every 3 weeks
- Nausea and vomiting, myelosuppression
- Nephrotoxicity, peripheral sensory neuropathy, ototoxicity, nerve dysfunction.

Carboplatin

- AUC 5–7 mgxmin/mL
- Myelosuppression, nausea and vomiting
- Rarely: peripheral neuropathy, renal toxicity, and hepatic dysfunction

Oxaliplatin

- 130 mg/m² IV every 3 weeks or 85 mg/m² IV every 2 weeks
- Nausea and vomiting, laryngopharyngeal dysesthesias
- Peripheral sensory neuropathy, diarrhea, myelosuppression, and renal toxicity

Oral administration of alkylating agents has been of great value, and this approach has been developed using relatively less reactive alkylating drugs. Cyclophosphamide, melphalan, chlorambucil, busulfan, and, more recently, temozolomide are those most commonly given via the oral route, and their cytotoxic effects are similar to those observed with parenteral administration. In general, if a tumor is resistant to one alkylating agent, it will be relatively resistant to other agents of this class (though not necessarily to nitrosoureas); however, there are exceptions to this rule depending on the specific tumor. Cyclophosphamide is the most widely used alkylating agent. The oral drug busulfan has a major degree of specificity for the granulocyte series and is therefore of particular value in therapy of chronic myelogenous leukemia. With all oral alkylating agents, some degree of leukopenia is necessary to provide evidence that the drug has been absorbed adequately. Frequent monitoring of blood counts is essential during administration of these agents as the development of severe leukopenia or thrombocytopenia necessitates immediate interruption of therapy.

Nitrosoureas

These drugs appear to be non-cross-resistant with other alkylating agents; all require biotransformation, which occurs by nonenzymatic decomposition, to metabolites with both alkylating and carbamoylating activities. The nitrosoureas are highly lipid-soluble and cross the blood-brain barrier, making them useful in the treatment of brain tumors. The nitrosoureas appear to function by cross-linking through alkylation of DNA. The drugs may be more effective against plateau phase cells than exponentially growing cells, though within a cycling cell population these agents appear to slow cell progression through the DNA synthetic phase. After oral administration of lomustine, peak plasma levels of metabolites appear within 1–4 hours; central nervous system concentrations reach 30–40% of the activity present in the plasma. While the initial plasma half-life is in the range of 6 hours, a second half-life is in the range of 1–2 days. Urinary excretion appears to be the major route of elimination from the body. One naturally occurring sugar-containing nitrosourea, streptozocin, is interesting because it has minimal bone marrow toxicity. This agent has activity in the treatment of insulin-secreting islet cell carcinoma of the pancreas.
Related Drugs Probably Acting As Alkylating Agents

A variety of other compounds have mechanisms of action that involve alkylation. These include procarbazine, dacarbazine, altretamine (hexamethylmelamine), cisplatin, and carboplatin. Dosages and major toxicities are listed in Table 55–2.

Procarbazine

The oral agent procarbazine is a methylhydrazine derivative, and it is commonly used in combination regimens for Hodgkin's disease, non-Hodgkin's lymphoma, and brain tumors. The drug is also leukemogenic and has teratogenic and mutagenic properties.

The mechanism of action of procarbazine is uncertain; however, the drug inhibits the synthesis of DNA, RNA, and protein; prolongs interphase; and produces chromosome breaks. Oxidative metabolism of this drug by microsomal enzymes generates azoprocabcarine and H2O2, which may be responsible for DNA strand scission. A variety of other metabolites of the drug are formed that may be cytotoxic. One metabolite is a weak monoamine oxidase (MAO) inhibitor, and adverse side effects can occur when procarbazine is given with other MAO inhibitors.

There is an increased risk of secondary cancers in the form of acute leukemia, and the carcinogenic potential of procarbazine is felt to be higher than that of most other alkylating agents.

Dacarbazine

Dacarbazine is a synthetic compound that functions as an alkylating agent following metabolic activation by liver microsomal enzymes by oxidative N-demethylation to the monomethyl derivative. This metabolite spontaneously decomposes to 5-aminomimidazole-4-carboxamide, which is excreted in the urine, and diazomethane. The diazomethane generates a methyl carbonium ion that is believed to be the likely cytotoxic species. Dacarbazine is administered parenterally and is not schedule-dependent. It produces marked nausea, vomiting, and myelosuppression. Its major applications are in melanoma, Hodgkin's disease, and soft tissue sarcomas.

Altretamine (Hexamethylmelamine)

Altretamine is structurally similar to triethylenemelamine. It is relatively insoluble and available only in oral form. It is rapidly biotransformed in the liver by demethylation to the pentamethylmelamine and tetramethylmelamine metabolites. This agent is approved for use in ovarian cancer patients who have progressed despite treatment with a regimen based on platinum or an alkylating agent (or both). The main dose-limiting toxicities include nausea, vomiting, and myelosuppression. Neurotoxicity in the form of somnolence, mood changes, and peripheral neuropathy is also observed.

Cisplatin, Carboplatin, & Oxaliplatin

Cisplatin (cis-diamminedichloroplatinum [II]) is an inorganic metal complex discovered through the serendipitous observation that neutral platinum complexes inhibited division and induced filamentous growth of Escherichia coli. Several platinum analogs have been subsequently synthesized. While the precise mechanism of action of cisplatin is still undefined, it is thought to act in somewhat the same way as alkylating agents. It kills cells in all stages of the cell cycle, inhibits DNA biosynthesis, and binds DNA through the formation of interstrand cross-links. The primary binding site is the N7 of guanine, but covalent interaction with adenine and cytosine also occurs.
The platinum complexes appear to synergize with certain other anticancer drugs. Aggressive hydration with intravenous saline infusion alone or with saline and mannitol or other diuretics appears to significantly reduce the incidence of nephrotoxicity.

Cisplatin has major antitumor activity in a broad range of solid tumors, including non-small cell and small cell lung cancer, esophageal and gastric cancer, head and neck cancer, and genitourinary cancers, particularly testicular, ovarian, and bladder cancer. When used in combination regimens with vinblastine and bleomycin or etoposide and bleomycin, cisplatin-based therapy has led to the cure of nonseminomatous testicular cancer.

Carboplatin is a second-generation platinum analog that exerts its cytotoxic effects exactly as cisplatin and has activity against the same spectrum of solid tumors. Its main dose-limiting toxicity is myelosuppression, and it has significantly less renal toxicity and gastrointestinal toxicity than cisplatin. Moreover, vigorous intravenously hydration is not required. As a result, carboplatin is now being used in place of cisplatin in combination chemotherapy.

Oxaliplatin is a third generation diaminocyclohexane platinum analog. Its mechanism of action is identical to that of cisplatin and carboplatin. However, it is not cross-resistant to cancer cells that are resistant to cisplatin or carboplatin on the basis of mismatch repair defects. This agent was recently approved for use as second-line therapy in metastatic colorectal cancer following treatment with the combination of fluorouracil-leucovorin and irinotecan, and it is now widely used as first-line therapy of this disease as well. Neurotoxicity is dose-limiting and characterized by a peripheral sensory neuropathy, often triggered or worsened upon exposure to cold. While this neurotoxicity is cumulative, it tends to be reversible—in contrast to cisplatin-induced neurotoxicity.

Clinical Uses of the Alkylating Agents

The alkylating agents are used in the treatment of a wide variety of hematologic and solid cancers, generally as part of a combination regimen. They are discussed along with various specific tumors (below).

Antimetabolites (Structural Analogs)

The development of drugs with actions on intermediary metabolism of proliferating cells has been important both clinically and conceptually. While biochemical properties unique to all cancer cells have yet to be discovered, neoplastic cells do have a number of quantitative differences in metabolism from normal cells that render them more susceptible to a number of antimetabolites or structural analogs. Many of these agents have been rationally designed and synthesized based on knowledge of cellular processes, and a few have been discovered as antibiotics.

Mechanisms of Action

The biochemical pathways that have thus far proved to be most vulnerable to antimetabolites have been those relating to nucleotide and nucleic acid synthesis. In a number of instances, when an enzyme is known to have a major effect on pathways leading to cell replication, inhibitors of the
reaction it catalyzes have proved to be useful anticancer drugs.

These drugs and their doses and toxicities are shown in Table 55–3. The principal drugs are discussed below.

<table>
<thead>
<tr>
<th>Chemotherapeutic Agent</th>
<th>Single-Agent Dosage</th>
<th>Delayed Toxicity$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>1250 mg/m²/bid orally for 14 days followed by 1 week of rest. Repeat every 3 weeks.</td>
<td>Diarrhea, hand-and-foot syndrome,$^2$ myelosuppression, nausea and vomiting</td>
</tr>
<tr>
<td>Cladribine</td>
<td>0.09 mg/kg/d for 7 days by continuous IV infusion in sterile saline</td>
<td>Myelosuppression, nausea and vomiting, and immunosuppression</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>100 mg/m²/d for 5–10 days, either by continuous IV infusion or SC every 8 hours.</td>
<td>Nausea and vomiting, bone marrow depression, stomatitis, and cerebellar ataxia</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>25 mg/m²/d for 5 days every 28 days (administer IV over 30 minutes)</td>
<td>Myelosuppression, immunosuppression, fever, myalgias, and arthralgias</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>15 mg/kg/d IV for 5 days by 24-hour infusion; 15 mg/kg weekly IV</td>
<td>Nausea, mucositis, diarrhea, myelosuppression, hand and foot syndrome, and neurotoxicity</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>1000 mg/m² IV weekly for up to 7 weeks followed by 1 week of rest</td>
<td>Nausea, vomiting, diarrhea, myelosuppression</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>2.5 mg/kg/d orally</td>
<td>Myelosuppression, immunosuppression, and hepatotoxicity</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>2.5–5 mg/d orally (Rheumatrex); 10 mg intrathecally (Folex) once or twice weekly</td>
<td>Mucositis, diarrhea, bone marrow depression with leukopenia and thrombocytopenia</td>
</tr>
<tr>
<td>Thioguanine</td>
<td>2 mg/kg/d orally</td>
<td>Myelosuppression, immunosuppression, and hepatotoxicity</td>
</tr>
</tbody>
</table>

$^1$These drugs do not cause acute toxicity.

$^2$Hand and foot syndrome is a form of erythromelalgia manifested as tingling, numbness, pain, erythema, swelling, and increased pigmentation.

Methotrexate
Methotrexate (MTX) is a folic acid antagonist that binds to the active catalytic site of dihydrofolate reductase (DHFR), interfering with the synthesis of the reduced form that accepts one-carbon units. Lack of this cofactor interrupts the synthesis of thymidylate, purine nucleotides, and the amino acids serine and methionine, thereby interfering with the formation of DNA, RNA, and proteins. The enzyme binds methotrexate with high affinity, and at pH 6.0, virtually no dissociation of the enzyme-inhibitor complex occurs (inhibition constant about 1 nmol/L). At physiologic pH, reversible competitive kinetics occur (inhibition constant about 1 μmol/L). Intracellular formation of polyglutamate derivatives appears to be important in the therapeutic action of methotrexate. The polyglutamates of methotrexate are selectively retained within cancer cells and have increased inhibitory effects on enzymes involved in folate metabolism, making them important determinants of the duration of action of methotrexate.

Drug Resistance

Tumor cell resistance to methotrexate has been attributed to (1) decreased drug transport, (2) decreased polyglutamate formation, (3) synthesis of increased levels of DHFR through gene amplification, and (4) altered DHFR with reduced affinity for methotrexate. Recent studies have also suggested that decreased accumulation of drug through activation of the multidrug resistance P170 glycoprotein transporter may also result in drug resistance.

Dosage & Toxicity

Methotrexate is administered by the intravenous, intrathecal, or oral route. Up to 90% of an oral dose is excreted in the urine within 12 hours. The drug is not subject to metabolism, and serum levels are therefore proportionate to dose as long as renal function and hydration status are adequate. Dosages and toxic effects are listed in Table 55–3. The effects of methotrexate can be reversed by administration of leucovorin (citrovorum factor). Leucovorin rescue has been used with accidental overdose or experimentally along with high-dose methotrexate therapy in a protocol intended to rescue normal cells while still leaving the tumor cells subject to its cytotoxic action.
Other Applications

Methotrexate is also used in the treatment of rheumatoid arthritis (Chapter 36: Nonsteroidal Anti-Inflammatory Drugs, Disease-Modifying Antirheumatic Drugs, Nonopioid Analgesics, & Drugs Used in Gout) and psoriasis.

Purine Antagonists

6-Thiopurines

**Mercaptopurine (6-MP)** was the first of the thiopurine series found useful as an anticancer drug. Like other thiopurines, it must be metabolized by hypoxanthine-guanine phosphoribosyl transferase (HGPRT) to the nucleotide form (6-thioinosinic acid), which in turn inhibits a number of the enzymes of purine nucleotide interconversion. Significant amounts of thioguanylic acid and 6-methylmercaptopurine ribotide (MMPR) are also formed from 6-MP. These metabolites may also contribute to the action of the mercaptopurine. Mercaptopurine is used primarily in the treatment of childhood acute leukemia, and a closely related analog, azathioprine, is used as an immunosuppressive agent (see Chapter 56: Immunopharmacology).

**Thioguanine (6-TG)** inhibits several enzymes in the purine nucleotide pathway. A variety of metabolic lesions are associated with the cytotoxic action of the purinethiols. These include inhibition of purine nucleotide interconversion; decrease in intracellular levels of guanine nucleotides, which leads to inhibition of glycoprotein synthesis; interference with the formation of DNA and RNA; and incorporation of thiopurine nucleotides into both DNA and RNA. 6-TG has a synergistic action when used together with cytarabine in the treatment of adult acute leukemia.

Drug Resistance

Resistance to both 6-MP and 6-TG occurs most commonly by decrease in HGPRT activity; an alternative mechanism in acute leukemia involves elevation of levels of alkaline phosphatase, which results in dephosphorylation of thiopurine nucleotide and cellular loss of the resulting ribonucleoside.

Dosage & Toxicity

Mercaptopurine and thioguanine are both given orally (Table 55–3) and excreted mainly in the urine. However, 6-MP is converted to an inactive metabolite (6-thiouric acid) by an oxidation catalyzed by xanthine oxidase, whereas 6-TG requires deamination before it is metabolized by this enzyme. This factor is important because the purine analog allopurinol, a potent xanthine oxidase inhibitor, is frequently used with chemotherapy in hematologic cancers to prevent hyperuricemia after tumor cell lysis. It does this by blocking purine oxidation, allowing excretion of cellular purines that are relatively more soluble than uric acid. Nephrotoxicity and acute gout produced by excessive uric acid are thereby prevented. Simultaneous therapy with allopurinol and 6-MP results in excessive toxicity unless the dose of mercaptopurine is reduced to 25% of the usual level. This effect does not occur with 6-TG, which can be used in full doses with allopurinol.
Fludarabine Phosphate

Fludarabine phosphate (2-fluoro-arabinofuranosyladenine monophosphate) is rapidly dephosphorylated to 2-fluoro-arabinofuranosyladenine and then phosphorylated intracellularly by deoxycytidine kinase to the triphosphate. This metabolite interferes with DNA synthesis through inhibition of DNA polymerase-\(\alpha\) and ribonucleotide reductase, and it also induces apoptosis. Fludarabine phosphate is used chiefly in the treatment of low-grade non-Hodgkin's lymphoma and chronic lymphocytic leukemia (CLL). Fludarabine phosphate is given parentally and is excreted primarily in the urine; its dose-limiting toxicity is myelosuppression.

Cladribine

Cladribine (2-chlorodeoxyadenosine) achieves high intracellular concentrations because of its resistance to adenosine deaminase; it is phosphorylated by deoxycytidine kinase and is incorporated into DNA. Cladribine causes DNA strand breaks (presumably through interference with DNA repair) and loss of NAD (through activation of poly[ADP-ribose]synthase). Cladribine is indicated for the treatment of hairy cell leukemia and is also used for CLL and low-grade non-Hodgkin's lymphoma. It is normally administered as a single continuous 7-day infusion; under these conditions, its toxicity usually consists of transient myelosuppression. In addition, it is an immunosuppressive agent, and a decrease in CD4 and CD8 cells, lasting for over 1 year, occurs in most patients.

Pyrimidine Antagonists

Fluorouracil

5-Fluorouracil (5-FU) is a prodrug and undergoes a complex series of biotransformation reactions to ribosyl and deoxyribosyl nucleotide metabolites. One of these metabolites, 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP), forms a covalently bound ternary complex with the enzyme thymidylate synthase and the reduced folate \(N^5,10\)-methylenetetrahydrofolate, a reaction critical for the synthesis of thymidylate. This results in inhibition of DNA synthesis through "thymineless death." 5-FU is converted to 5-fluorouridine-5'-triphosphate (FUTP), which is then incorporated into RNA, where it interferes with RNA processing and mRNA translation. In
addition, 5-FU is converted to 5-fluorodeoxyuridine-5'-triphosphate (FdUTP), which can be incorporated into cellular DNA, resulting in inhibition of DNA synthesis and function. Thus, the cytotoxicity of fluorouracil is felt to be the result of effects on both DNA- and RNA-mediated events.

Fluorouracil is normally given intravenously (Table 55–3) and has a short metabolic half-life on the order of 15 minutes. It is not administered by the oral route because its bioavailability is erratic due to the high levels of the breakdown enzyme dihydropyrimidine dehydrogenase present in the gut mucosa. Floxuridine (5-fluoro-2'-deoxyuridine, FUDR) has an action similar to that of fluorouracil, and it is only used for hepatic artery infusions. A cream incorporating fluorouracil is used topically for treating basal cell cancers of the skin.

Fluorouracil is the most widely used agent for the treatment of colorectal cancer, both as adjuvant therapy as well as for advanced disease. In addition, it has activity against a wide variety of solid tumors, including cancers of the breast, stomach, pancreas, esophagus, liver, head and neck, and anus. Its major toxicities are listed in Table 55–3.

Capecitabine

Capecitabine is a fluoropyrimidine carbamate prodrug that has nearly 70–80% oral bioavailability. It undergoes extensive metabolism in the liver by the enzyme carboxylesterase to an intermediate, 5'-deoxy-5-fluorocytidine. This in turn is converted to 5'-deoxy-5-fluorouridine by the enzyme cytidine deaminase. The 5'-deoxy-5-fluorouridine metabolite is then hydrolyzed by thymidine phosphorylase to fluorouracil in the tumor. (The expression of thymidine phosphorylase is significantly higher in a broad range of solid tumors than in corresponding normal tissue.) Peak plasma levels are achieved in about 1.5 hours, and peak fluorouracil levels are reached at 2 hours after oral administration.

Capecitabine is used in the treatment of metastatic breast cancer as either a single agent or in combination with the taxane docetaxel. It has recently been approved for use in the treatment of metastatic colorectal cancer as monotherapy, and significant efforts are now directed at using this agent in combination with either irinotecan or oxaliplatin. The main toxicities of capecitabine are listed in Table 55–3. While myelosuppression, nausea and vomiting, and mucositis can be observed with this agent, the incidence is significantly less than that seen with intravenous fluorouracil.

Cytarabine

Cytarabine (cytosine arabinoside, ara-C) is an S phase-specific antimetabolite that is converted by deoxycytidine kinase to the 5'-mononucleotide (AraCMP). AraCMP is further metabolized to the triphosphate (AraCTP), which competitively inhibits DNA polymerase and results in blockade of DNA synthesis. Cytarabine is also incorporated into RNA and DNA. Incorporation into DNA leads to interference with chain elongation and defective ligation of fragments of newly synthesized
DNA. The cellular retention time for AraCTP appears to correlate with its lethality to malignant cells.

After intravenous administration (Table 55–3), the drug is cleared rapidly, with most being deaminated to an inactive form. The ratio of the anabolic enzyme deoxycytidine kinase to the inactivating catalyst cytidine deaminase is important in determining the cytotoxicity of cytarabine.

In view of cytarabine's S phase specificity, the drug is highly schedule-dependent and must be given either by continuous infusion or every 8–12 hours for 5–7 days. Its activity is limited almost entirely to treatment of acute myelogenous leukemia, for which it is a major drug. Adverse effects are listed in Table 55–3.

Gemcitabine

Gemcitabine is phosphorylated initially by the enzyme deoxycytidine kinase and then by other nucleoside kinases to the di- and triphosphate nucleotide forms, which then inhibit DNA synthesis. Inhibition is considered to result from two actions: inhibition of ribonucleotide reductase by gemcitabine diphosphate, which reduces the level of deoxyribonucleoside triphosphates required for the synthesis of DNA; and incorporation of gemcitabine triphosphate into DNA. Following incorporation of gemcitabine nucleotide, only one additional nucleotide can be added to the growing DNA strand, resulting in chain termination.
Gemcitabine was initially approved for use in pancreatic cancer but is now widely used in the treatment of non-small cell lung cancer and bladder cancer. Myelosuppression is the principal dose-limiting toxicity.

Plant Alkaloids

Vincristine

Vincristine is an alkaloid derived from *Vinca rosea*, the periwinkle plant. Its mechanism of action involves depolymerization of microtubules, which are an important part of the cytoskeleton and the mitotic spindle. The drug binds specifically to the microtubule protein tubulin in dimeric form; the drug-tubulin complex adds to the forming end of the microtubules to terminate assembly, and depolymerization of the microtubules then occurs. This results in mitotic arrest at metaphase, dissolution of the mitotic spindle, and interference with chromosome segregation. Toxicity includes nausea and vomiting, bone marrow suppression, and alopecia. It has clinical activity in the treatment of Hodgkin's disease, non-Hodgkin's lymphomas, breast cancer, and germ cell cancer. See clinical section below and Table 55–4.

![Chemical structure of Vincristine and Vinblastine](image)

Table 55–4. Natural Product Cancer Chemotherapy Drugs: Dosages and Toxicities.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Single-Agent Dosage</th>
<th>Acute Toxicity</th>
<th>Delayed Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>Up to 15 units/m² IV twice weekly to a total dose of 200–250 units</td>
<td>Allergic reactions, fever, hypotension</td>
<td>Skin toxicity, pulmonary fibrosis, mucositis, alopecia</td>
</tr>
<tr>
<td>Dactinomycin (actinomycin D)</td>
<td>0.04 mg/kg IV weekly</td>
<td>Nausea and vomiting</td>
<td>Stomatitis, gastrointestinal tract upset, alopecia, bone marrow depression</td>
</tr>
<tr>
<td>Daunorubicin (daunomycin)</td>
<td>30–60 mg/m² daily IV for 3 days, or 30–60 mg/m² IV weekly</td>
<td>Nausea, fever, red urine (not hematuria)</td>
<td>Cardiotoxicity (see text), alopecia, bone marrow depression</td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage and Administration</td>
<td>Side Effects</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Docetaxel</strong></td>
<td>100 mg/m² IV over 1 hour every 3 weeks</td>
<td>Hypersensitivity, rash</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurotoxicity, fluid retention, neutropenia</td>
<td></td>
</tr>
<tr>
<td><strong>Doxorubicin</strong> (Adriamycin)</td>
<td>60 mg/m² daily IV for 3 days, or 30–60 mg/m² IV weekly</td>
<td>Nausea, red urine (not hematuria)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiotoxicity (see text), alopecia, bone marrow depression, stomatitis</td>
<td></td>
</tr>
<tr>
<td><strong>Etoposide (VP-16)</strong></td>
<td>50–100 mg/m² daily for 5 days</td>
<td>Nausea, vomiting, hypotension</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alopecia, bone marrow depression</td>
<td></td>
</tr>
<tr>
<td><strong>Idarubicin</strong></td>
<td>12 mg/m² IV daily for 3 days (with cytarabine)</td>
<td>Nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone marrow depression, mucositis, cardiotoxicity</td>
<td></td>
</tr>
<tr>
<td><strong>Irinotecan</strong></td>
<td>125 mg/m² IV once weekly for 4 weeks; repeat every 6 weeks or 300–350 mg/m² IV every 3 weeks</td>
<td>Diarrhea, nausea, vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhea, bone marrow depression, nausea and vomiting, liver function abnormalities</td>
<td></td>
</tr>
<tr>
<td><strong>Mitomycin</strong></td>
<td>20 mg/m² IV every 6 weeks</td>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thrombocytopenia, anemia, leukopenia, mucositis</td>
<td></td>
</tr>
<tr>
<td><strong>Paclitaxel</strong></td>
<td>130–170 mg/m² IV over 3 or 24 hours every 3–4 weeks</td>
<td>Nausea, vomiting, hypotension, arrhythmias, hypersensitivity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone marrow depression, peripheral sensory neuropathy</td>
<td></td>
</tr>
<tr>
<td><strong>Topotecan</strong></td>
<td>1.5 mg/m² IV for 5 days, repeat every 21 days for 4 courses</td>
<td>Nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone marrow depression, arthralgias</td>
<td></td>
</tr>
<tr>
<td><strong>Vinblastine</strong></td>
<td>0.1–0.2 mg/kg IV weekly</td>
<td>Nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alopecia, loss of reflexes, bone marrow depression</td>
<td></td>
</tr>
<tr>
<td><strong>Vincristine</strong></td>
<td>1.5 mg/m² IV (maximum: 2 mg weekly)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Areflexia, muscle weakness, peripheral neuritis, paralytic ileus, mild bone marrow depression, alopecia</td>
<td></td>
</tr>
<tr>
<td><strong>Vinorelbine</strong></td>
<td>30 mg/m² IV weekly</td>
<td>Nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone marrow depression, fatigue, constipation, hyporeflexia, paresthesias</td>
<td></td>
</tr>
</tbody>
</table>

Vincristine

Vincristine is also an alkaloid derivative of Vinca rosea and is closely related in structure to vinblastine. Its mechanism of action is considered to be identical to that of vinblastine in that it functions as a mitotic spindle poison leading to arrest of cells in the M phase of the cell cycle. Despite these similarities to vinblastine, vincristine has a strikingly different spectrum of clinical
activity and qualitatively different toxicities.

Vincristine has been effectively combined with prednisone for remission induction in acute lymphoblastic leukemia in children. It is also active in various hematologic malignancies such as Hodgkin's and non-Hodgkin's lymphoma and multiple myeloma and in several pediatric tumors including rhabdomyosarcoma, neuroblastoma, Ewing's sarcoma, and Wilms' tumor. The main dose-limiting toxicity is neurotoxicity, usually expressed as a peripheral sensory neuropathy, although autonomic nervous system dysfunction—with orthostatic hypotension, sphincter problems, and paralytic ileus—cranial nerve palsies, ataxia, seizures, and coma have been observed. While myelosuppression can occur, it is generally milder and much less significant than with vinblastine. The other potential side effect that can develop is the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

Vinorelbine

Vinorelbine is a semisynthetic vinca alkaloid whose mechanism of action is identical to that of vinblastine and vincristine, i.e., inhibition of mitosis of cells in the M phase through inhibition of tubulin polymerization. Despite its similarities in mechanism of action, vinorelbine has activity in non-small cell lung cancer and in breast cancer. Myelosuppression with neutropenia is the dose-limiting toxicity, but nausea and vomiting, transient elevations in liver function tests, neurotoxicity, and SIADH are also reported.

Epipodophyllotoxins

Two compounds, VP-16 (etoposide) and a related drug, VM-26 (teniposide), are semisynthetic derivatives of podophyllotoxin, which is extracted from the mayapple root (Podophyllum peltatum). Both an intravenous and an oral formulation of etoposide are approved for clinical use in the USA. Etoposide and teniposide are similar in chemical structure and in their effects—they block cell division in the late S-G2 phase of the cell cycle. Their primary mode of action involves inhibition of topoisomerase II, which results in DNA damage through strand breakage induced by the formation of a ternary complex of drug, DNA, and enzyme. The drugs are water-insoluble and need to be formulated in a Cremophor vehicle for clinical use. These agents are administered via the intravenous route (Table 55–4) and are rapidly and widely distributed throughout the body except for the brain. Up to 90–95% of drug is protein-bound, mainly to albumin. Dose reduction is required in the setting of renal dysfunction. Etoposide has clinical activity in germ cell cancer, small cell and non-small cell lung cancer, Hodgkin's and non-Hodgkin's lymphomas, and gastric cancer and as high-dose therapy in the transplant setting for breast cancer and lymphomas. Teniposide's use is limited to acute lymphoblastic leukemia.

Camptothecins

The camptothecins are natural products that are derived from the Camptotheca acuminata tree, and they inhibit the activity of topoisomerase I, the key enzyme responsible for cutting and religating single DNA strands. Inhibition of the enzyme results in DNA damage. Topotecan is indicated in the treatment of patients with advanced ovarian cancer who have failed platinum-based chemotherapy and is also approved as second-line therapy of small cell lung cancer. The main route of elimination is renal excretion, and for this reason caution must be exercised in patients with abnormal renal function, with dosage reduction being required.

Irinotecan is a prodrug that is converted mainly in the liver by the carboxylesterase enzyme to the
SN-38 metabolite, which is a potent inhibitor of topoisomerase I. In contrast to topotecan, irinotecan and SN-38 are mainly eliminated in bile and feces, and dose reduction is required in the setting of liver dysfunction. Irinotecan is indicated as second-line monotherapy in patients with metastatic colorectal cancer who have failed fluorouracil-based therapy and as first-line therapy when used in combination with fluorouracil and leucovorin. Myelosuppression and diarrhea are the two most common adverse events. There are two forms of diarrhea: an early form that occurs within 24 hours after administration and is felt to be a cholinergic event effectively treated with atropine, and a late form which usually occurs 3–10 days after treatment. The late diarrhea can be severe, leading to significant electrolyte imbalance and dehydration in some cases.

**Taxanes**

**Paclitaxel** is an alkaloid ester derived from the Western yew (*Taxus brevifolia*) and the European yew (*Taxus baccata*). The drug functions as a mitotic spindle poison through high-affinity binding to microtubules with enhancement of tubulin polymerization. This promotion of microtubule assembly by paclitaxel occurs in the absence of microtubule-associated proteins and guanosine triphosphate and results in inhibition of mitosis and cell division.

Paclitaxel has significant activity in a wide variety of solid tumors, including ovarian, advanced breast, non-small cell and small cell lung, head and neck, esophageal, prostate, and bladder cancer and AIDS-related Kaposi's sarcoma. It is metabolized extensively by the liver P450 system, and nearly 80% of the drug is excreted in feces. For this reason, dose reduction is required in the setting of liver dysfunction. The primary dose-limiting toxicities are listed in Table 55–4. Hypersensitivity reactions may be observed in up to 5% of patients, but the incidence can be reduced by premedication with dexamethasone, diphenhydramine, and an H2 blocker.

**Docetaxel** is a semisynthetic taxane derived from the European yew tree. Its mechanism of action, metabolism, and elimination are identical to those of paclitaxel. It is approved for use as second-line therapy in advanced breast cancer and non-small cell lung cancer, and it also has major activity in head and neck cancer, small cell lung cancer, gastric cancer, advanced platinum-refractory ovarian cancer, and bladder cancer. Its major toxicities are listed in Table 55–4.

**Antitumor Antibiotics**

Screening of microbial products has led to the discovery of a number of growth inhibiting compounds that have proved to be clinically useful in cancer chemotherapy. Many of these antibiotics bind to DNA through intercalation between specific bases and block the synthesis of RNA, DNA, or both; cause DNA strand scission; and interfere with cell replication. All of the anticancer antibiotics now being used in clinical practice are products of various strains of the soil microbe *Streptomyces*. These include the anthracyclines, dactinomycin, bleomycin, and mitomycin.

**Anthracyclines**

The anthracycline antibiotics, isolated from *Streptomyces peucetius var caesius*, are among the most widely used cytotoxic anticancer drugs. Two congeners, doxorubicin and daunorubicin, are FDA-approved, and their structures are shown below. Several other anthracycline analogs have entered clinical practice, including idarubicin, epirubicin, and mitoxantrone. Daunorubicin was the first agent in this class to be isolated, and it is still used in the treatment of acute myeloid leukemia. Doxorubicin has a broad spectrum of clinical activity against hematologic malignancies as well as a wide range of solid tumors. The entire class of anthracyclines exert their cytotoxic action through four major mechanisms. These are (1) inhibition of topoisomerase II; (2) high-affinity binding to
DNA through intercalation, with consequent blockade of the synthesis of DNA and RNA, and DNA strand scission; (3) binding to cellular membranes to alter fluidity and ion transport; and (4) generation of semiquinone free radicals and oxygen free radicals through an enzyme-mediated reductive process. This latter mechanism has now been established as being the cause of the drug's cardiac toxicity.

In the clinical setting, anthracyclines are administered via the intravenous route (Table 55–4). The anthracyclines are metabolized extensively in the liver, with reduction and hydrolysis of the ring substituents. The hydroxylated metabolite is an active species, whereas the aglycone is inactive. Up to 50% of drug is eliminated in the feces via biliary excretion, and for this reason dose reduction is required in the setting of liver dysfunction. Although anthracyclines are usually administered on an every-3-week schedule, alternative schedules of administration such as low-dose weekly or 72–96 hour continuous infusions have been shown to yield equivalent clinical efficacy with reduced overall toxicity.

Doxorubicin is one of the most important anticancer drugs, with major clinical activity in carcinomas of the breast, endometrium, ovary, testicle, thyroid, stomach, bladder, liver, and lung; in soft tissue sarcomas; and in several childhood cancers, including neuroblastoma, Ewing's sarcoma, osteosarcoma, and rhabdomyosarcoma. It is also widely used in hematologic malignancies, including acute lymphoblastic leukemia, multiple myeloma, and Hodgkin's and non-Hodgkin's lymphomas. It is generally used in combination with other anticancer agents (eg, cyclophosphamide, cisplatin, and fluorouracil), and responses and remission duration tend to be improved with combination regimens as opposed to single-agent therapy. Daunorubicin has a far narrower spectrum of activity than doxorubicin. Daunorubicin has been mainly used for the treatment of acute myeloid leukemia, although there has been a shift in clinical practice toward using idarubicin, an analog of daunorubicin. Its efficacy in solid tumors appears to be limited.

Idarubicin is a semisynthetic anthracycline glycoside analog of daunorubicin and is approved for use in combination with cytarabine for induction therapy of acute myeloid leukemia. When combined with cytarabine, idarubicin appears to be more active than daunorubicin in producing complete remissions and in improving survival in patients with acute myelogenous leukemia.

Epirubicin is a doxorubicin analog whose mechanism of action is identical to that of all other anthracyclines. It was initially approved for use as a component of adjuvant therapy of early-stage,
node-positive breast cancer but is now also used for the treatment of metastatic breast cancer.

The main dose-limiting toxicity of all anthracyclines is myelosuppression, with neutropenia more commonly observed than thrombocytopenia. In some cases, mucositis is dose-limiting. Two forms of cardiotoxicity are observed. The acute form occurs within the first 2–3 days and presents as arrhythmias or conduction abnormalities, other electrocardiographic changes, pericarditis, and myocarditis. This form is usually transient and is asymptomatic in most cases. The chronic form results in a dose-dependent, dilated cardiomyopathy associated with heart failure. The chronic cardiac toxicity appears to result from increased production of free radicals within the myocardium. This effect is rarely seen at total doxorubicin dosages below 500–550 mg/m². Use of lower weekly doses or continuous infusions of doxorubicin appear to reduce the incidence of cardiac toxicity. In addition, treatment with the iron-chelating agent dexrazoxane (ICRF-187) is currently approved to prevent or reduce anthracycline-induced cardiotoxicity in women with metastatic breast cancer who have received a total cumulative dose of doxorubicin of 300 mg/m². All anthracyclines can produce "radiation recall reaction," with erythema and desquamation of the skin observed at sites of prior radiation therapy.

Mitoxantrone

Mitoxantrone (dihydroxyanthracenedione, DHAD) is an anthracene compound whose structure resembles the anthracycline ring. It binds to DNA to produce strand breakage and inhibits both DNA and RNA synthesis. It is currently used for treatment of advanced, hormone-refractory prostate cancer and low-grade non-Hodgkin's lymphoma. It is also indicated in breast cancer as well as in pediatric and adult acute myeloid leukemias. The plasma half-life of mitoxantrone in patients is approximately 75 hours, and it is predominantly excreted via the hepatobiliary route in feces. Myelosuppression with leukopenia is the dose-limiting toxicity, and mild nausea and vomiting, mucositis, and alopecia also occur. While the drug is felt to be less cardiotoxic than doxorubicin, both acute and chronic cardiac toxicity are reported. A blue discoloration of the fingernails, sclera, and urine can be observed up to 1–2 days after drug therapy.

Dactinomycin

Dactinomycin is an antitumor antibiotic isolated from a Streptomyces organism. It binds tightly to double-stranded DNA through intercalation between adjacent guanine-cytosine base pairs and inhibits all forms of DNA-dependent RNA synthesis, with ribosomal RNA formation being most sensitive to drug action. Dactinomycin is mainly used to treat pediatric tumors such as Wilms' tumor, rhabdomyosarcoma, and Ewing's sarcoma, but it has activity also against germ cell tumors and gestational trophoblastic disease. Dactinomycin can also induce a "radiation recall reaction." See Table 55–4 for other toxicities.

Mitomycin

Mitomycin (mitomycin C) is an antibiotic isolated from Streptomyces caespitosus. It is an alkylating agent that undergoes metabolic activation through an enzyme-mediated reduction to generate an alkylating agent that cross-links DNA. Hypoxic tumor stem cells of solid tumors exist in an environment conducive to reductive reactions and are more sensitive to the cytotoxic actions of mitomycin than normal cells and oxygenated tumor cells. It is thought to be a CCNS alkylating agent, and it is the best available drug for use in combination with radiation therapy to attack hypoxic tumor cells. Its main clinical use is in the treatment of squamous cell cancer of the anus.
along with fluorouracil and radiation therapy. In addition, it is used in combination chemotherapy for squamous cell carcinoma of the cervix and for adenocarcinomas of the stomach, pancreas, and lung. One special application of mitomycin has been in the intravesical treatment of superficial bladder cancer. Because virtually none of the agent is absorbed systemically, there is little or no systemic toxicity.

See Table 55–4 for common toxicities. The hemolytic-uremic syndrome, manifested as microangiopathic hemolytic anemia, thrombocytopenia, and renal failure, as well as occasional instances of interstitial pneumonitis have been reported.

**Bleomycin**

Bleomycin is a small peptide that contains a DNA-binding region and an iron-binding domain at opposite ends of the molecule. It acts by binding to DNA, which results in single-strand and double-strand breaks following free radical formation, and inhibition of DNA biosynthesis. The fragmentation of DNA is due to oxidation of a DNA-bleomycin-Fe(II) complex and leads to chromosomal aberrations. Bleomycin is a CCS drug that causes accumulation of cells in the G2 phase of the cell cycle.

Bleomycin is indicated for the treatment of Hodgkin's and non-Hodgkin's lymphomas, germ cell tumor, head and neck cancer, and squamous cell cancer of the skin, cervix, and vulva. In addition, it can be used as a sclerosing agent for malignant pleural effusions and ascites. One advantage of this agent is that it can be given subcutaneously, intramuscularly, or intravenously (Table 55–4). Peak blood levels of bleomycin after intramuscular injection appear within 30–60 minutes. Intravenous injection of similar dosages yields higher peak concentrations and a terminal half-life of about 2.5 hours. Elimination of bleomycin is mainly via renal excretion; for this reason, dose modification is recommended in the setting of renal dysfunction.

Pulmonary toxicity is dose-limiting for bleomycin and usually presents as pneumonitis with cough, dyspnea, dry inspiratory crackles on physical examination, and infiltrates on chest x-ray. The incidence of this adverse event is increased in patients older than 70 years of age and with cumulative doses greater than 400 units. In rare cases, pulmonary toxicity can be fatal. Other toxicities are listed in Table 55–4.

**Hormonal Agents**

**Steroid Hormones & Antisteroid Drugs**

The relationship between hormones and hormone-dependent tumors was initially demonstrated in 1896 when Beatson showed that oophorectomy produced improvement in women with advanced breast cancer. Sex hormones and adrenocortical hormones are employed in the management of
several other types of cancer. Since sex hormones are actively involved in the stimulation and control of proliferation and function of certain tissues, including the mammary and prostate glands, cancers arising from these tissues may be inhibited or stimulated by appropriate changes in hormonal balance. Cancer of the breast and cancer of the prostate can be effectively treated with sex hormone therapy or ablation of appropriate endocrine organs.

Corticosteroids have been useful in the treatment of acute leukemia, lymphoma, multiple myeloma, and other hematologic malignancies as well as in advanced breast cancer. In addition, they are effective as supportive therapy in the management of cancer-related hypercalcemia. The steroid hormones and related agents most useful in cancer therapy are listed in Table 55–5.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Adult Dosage</th>
<th>Acute Toxicity</th>
<th>Delayed Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiandrogen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flutamide</td>
<td>250 mg/tid orally</td>
<td>Mild nausea</td>
<td>Hot flushes, transient elevations in liver function tests</td>
</tr>
<tr>
<td><strong>Antiestrogen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>20 mg/d orally</td>
<td>Transient flare of tumor symptoms</td>
<td>Menopausal symptoms, fluid retention and edema, thromboembolic events, increased incidence of endometrial hyperplasia and cancer</td>
</tr>
<tr>
<td><strong>Progestins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>40 mg orally 4 times daily</td>
<td>None</td>
<td>Fluid retention</td>
</tr>
<tr>
<td><strong>Adrenocorticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>40–200 mg/d orally</td>
<td>None</td>
<td>Fluid retention, hypertension, diabetes, increased susceptibility to infection, moon facies</td>
</tr>
<tr>
<td>Prednisone</td>
<td>20–100 mg/d orally</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Gonadotropin-releasing hormone agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goserelin acetate</td>
<td>3.6 mg SC monthly</td>
<td>Transient flare of tumor symptoms, pain at injection site</td>
<td>Hot flushes, impotence, gynecomastia</td>
</tr>
<tr>
<td>Leuprolide</td>
<td>7.5 mg SC monthly</td>
<td>Transient flare of tumor symptoms, pain at injection site</td>
<td>Hot flushes, impotence, gynecomastia</td>
</tr>
<tr>
<td><strong>Aromatase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aminoglutethimide  250 mg orally twice daily and hydrocortisone 20 mg twice daily  Fatigue, mild nausea  Skin rash, adrenal insufficiency, myelosuppression

Anastrozole  1 mg orally daily  Mild nausea, headache  Fatigue, hot flushes, arthralgias

Exemestane  25 mg orally daily  Mild nausea, headache  Fatigue, hot flushes

Letrozole  2.5 mg orally daily  Mild nausea, headache  Fatigue, hot flushes, arthralgias

The mechanisms of action of steroid hormones on lymphoid, mammary, and prostatic cancer have been partially clarified. Specific cell surface receptors have been identified for estrogen, progesterone, corticosteroids, and androgens in neoplastic cells in these tissues. As in normal cells, steroid hormones also form an intracellular steroid-receptor complex that ultimately binds directly to nuclear proteins associated with DNA to activate transcription of a broad range of cellular genes involved in cell growth and proliferation (see Chapter 39: Adrenocorticosteroids & Adrenocortical Antagonists).

Most steroid-sensitive cancers express specific cell surface receptors. Prednisone-sensitive lymphomas, estrogen-sensitive breast cancers, and prostatic cancers express specific receptors for corticosteroids, estrogens, and androgens, respectively. It is now possible to assay tumor specimens for steroid receptor content and to identify which individual patients are likely to benefit from hormonal therapy. Measurement of the estrogen receptor (ER) and progesterone receptor (PR) proteins in breast cancer tissue is now standard clinical practice. ER or PR positivity predicts response to hormonal therapy, whereas patients whose tumors are ER-negative generally fail to respond to such treatment.

The sex hormones are used in the treatment of cancers of the breast, prostate, and endometrium. With replacement doses, estrogen can stimulate the growth of breast and endometrial cancer. Surprisingly, high-dose estrogen is useful therapeutically in metastatic breast cancer but has been largely replaced by antiestrogen therapy. In prostate cancer, androgens stimulate growth while estrogen administration results in suppression of androgen production. Drugs that reduce androgen secretion or block the effect of androgens at the receptor level are also effective in prostate cancer.

The toxicities of adrenocortical hormones are presented in Chapter 39: Adrenocorticosteroids & Adrenocortical Antagonists and those of estrogens and androgens in Chapter 40: The Gonadal Hormones & Inhibitors.

Estrogen & Androgen Inhibitors

The antiestrogen tamoxifen has proved to be extremely useful for the treatment of both early-stage and metastatic breast cancer. It is now approved as a chemopreventive agent in women at high risk for breast cancer. In addition, this hormonal agent has activity in endometrial cancer. Tamoxifen functions as a competitive partial agonist-inhibitor of estrogen and binds to the estrogen receptors of estrogen-sensitive tumors. However, tamoxifen has a tenfold lower affinity for ER than does estradiol, indicating the importance of ablation of endogenous estrogen for optimal antiestrogen effect. In addition to its direct antiestrogen effects on tumor cells, tamoxifen also suppresses serum levels of insulin-like growth factor-1 and up-regulates local production of transforming growth factor-β.
Tamoxifen is given orally and is rapidly and completely absorbed. High plasma levels of tamoxifen are obtained within 4–6 hours after oral administration, and the agent has a much longer biologic half-life than estradiol—on the order of 7–14 days. It is extensively metabolized by the liver P450 system, and the main metabolites also possess antitumor activity similar to that of the parent drug. Tamoxifen is well tolerated, and its side effects are generally quite mild (Table 55–5).

Flutamide and bicalutamide are nonsteroidal antiandrogen agents that bind to the androgen receptor and inhibit androgen effects. They are administered orally and are rapidly and completely absorbed by the gastrointestinal tract. At present they are used in combination with radiation therapy for the treatment of early-stage prostate cancer and in the setting of metastatic prostate cancer. Toxicities are listed in Table 55–5.

Gonadotropin-Releasing Hormone Agonists

**Leuprolide** and goserelin are synthetic peptide analogs of naturally occurring gonadotropin-releasing hormone (GnRH, LHRH). They are described in further detail in Chapters 37 and 40. These analogs are more potent than the natural hormone and function as LHRH agonists. When given as depot preparations, these agents lead to a transient release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) followed by inhibition of the release of these gonadotropins. In men, this results in castration levels of testosterone after 2–4 weeks of therapy.

Leuprolide and goserelin are indicated in the treatment of advanced prostate cancer and more recently these agents have been incorporated as part of neoadjuvant therapy of early-stage prostate cancer. Leuprolide and goserelin are now formulated in long-acting depot forms, which allows for administration once every 3 months. The main side effects include hot flushes, impotence, and gynecomastia. Other toxicities are given in Table 55–5.

Aromatase Inhibitors

**Aminoglutethimide** is a nonsteroidal inhibitor of corticosteroid synthesis at the first step involving the conversion of cholesterol to pregnenolone; see Chapter 39: Adrenocorticosteroids & Adrenocortical Antagonists). Aminoglutethimide also inhibits the extra-adrenal synthesis of estrone and estradiol. Aside from its direct effects on adrenal steroidogenesis, aminoglutethimide is an inhibitor of an aromatase enzyme that converts the adrenal androgen androstenedione to estrone (Figure 40–2). This aromatization of an androgenic precursor into an estrogen occurs in body fat. Since estrogens promote the growth of breast cancer, estrogen synthesis in adipose tissue can be important in breast cancer growth in postmenopausal women.

Aminoglutethimide is primarily used in the treatment of metastatic breast cancer in women whose tumors express significant levels of estrogen or progesterone receptors. It also has activity in
advanced prostate cancer that is hormone-responsive. Aminoglutethimide is normally administered with hydrocortisone to prevent symptoms of adrenal insufficiency. Hydrocortisone is preferable to dexamethasone because the latter agent accelerates the rate of catabolism of aminoglutethimide. Adverse effects of aminoglutethimide are listed in Table 55–5.

**Anastrozole** is a selective nonsteroidal inhibitor of aromatase that has no inhibitory effect on adrenal glucocorticoid or mineralocorticoid synthesis. It is presently approved for first-line treatment of postmenopausal women with metastatic breast cancer that is ER-positive, for treatment of postmenopausal women with metastatic breast cancer that is ER-positive and has progressed while on tamoxifen therapy, and as adjuvant therapy of postmenopausal women with hormone-positive, early-stage breast cancer. **Letrozole** is a nonsteroidal competitive inhibitor of aromatase that is significantly more potent than aminoglutethimide and acts in the same way as anastrozole. It is also indicated for first-line treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer and for second-line treatment of postmenopausal women with advanced breast cancer after progression on tamoxifen therapy. **Exemestane** is a steroidal hormonal agent that binds to and irreversibly inactivates aromatase. There appears to be a lack of cross-resistance between exemestane and nonsteroidal aromatase inhibitors. This agent is indicated for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed on tamoxifen therapy. Each of these aromatase inhibitors exhibits a similar side effect profile (Table 55–5, see also Chapter 40: The Gonadal Hormones & Inhibitors).

**Miscellaneous Anticancer Drugs**

See Table 55–6.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dosage</th>
<th>Acute Toxicity</th>
<th>Delayed Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic trioxide</td>
<td>0.15 mg/kg/d IV for 60 days as induction therapy; 0.15 mg/kg/d IV for 5 days per week for a total of 5 weeks as consolidation therapy</td>
<td>Headache and lightheadedness</td>
<td>Fatigue, cardiac dysrhythmias, fever, dyspnea, fluid retention and weight gain</td>
</tr>
<tr>
<td>Asparaginase</td>
<td>20,000 IU/m² daily IV for 5–10 days</td>
<td>Nausea, fever, and allergic reactions</td>
<td>Hepatotoxicity, mental depression, pancreatitis</td>
</tr>
<tr>
<td>Imatinib</td>
<td>400–600 mg/d orally</td>
<td>Nausea and vomiting</td>
<td>Fluid retention with ankle and periorbital edema, diarrhea, myalgias</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>300 mg/m² orally for 5 days</td>
<td>Nausea and vomiting</td>
<td>Bone marrow depression</td>
</tr>
<tr>
<td>Mitotane</td>
<td>6–15 g/d orally</td>
<td>Nausea and vomiting</td>
<td>Diarrhea, lethargy, adrenal insufficiency, transient skin rash</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>10–12 mg/m² IV every 3–4 weeks</td>
<td>Nausea</td>
<td>Bone marrow depression, occasional cardiac toxicity, mild alopecia</td>
</tr>
</tbody>
</table>
Trastuzumab is a monoclonal antibody that is described in Chapter 56: Immunopharmacology. Imatinib (STI571) is an inhibitor of the tyrosine kinase domain of the Bcr-Abl oncoprotein and prevents the phosphorylation of the kinase substrate by ATP. It is indicated for the treatment of chronic myelogenous leukemia (CML), a pluripotent hematopoietic stem cell disorder characterized by the t(9:22) Philadelphia chromosomal translocation. This translocation results in the Bcr-Abl fusion protein, the causative agent in CML, and is present in up to 95% of patients with this disease. This agent inhibits other activated receptor tyrosine kinases for platelet-derived growth factor receptor (PDGFR), stem cell factor (SCF), and c-kit.

Imatinib is administered orally and is well absorbed; it is highly protein-bound in plasma. The drug is metabolized in the liver, and elimination of metabolites occurs mainly in feces via biliary excretion. This agent is approved for use as first-line therapy in chronic phase CML, in blast crisis, and as second-line therapy for chronic phase CML that has progressed on prior interferon-α therapy. Imatinib is effective also for treatment of gastrointestinal stromal tumors expressing the c-kit tyrosine kinase. Dosage and toxicities are listed in Table 55–6.

Asparaginase (L-asparagine amidohydrolase) is an enzyme that is isolated from various bacteria for clinical use. The drug is used to treat childhood acute lymphocytic leukemia. It hydrolyzes circulating L-asparagine to aspartic acid and ammonia. Because tumor cells lack asparagine synthetase, they require an exogenous source of L-asparagine. Thus, depletion of L-asparagine results in effective inhibition of protein synthesis. In contrast, normal cells can synthesize L-asparagine and thus are less susceptible to the cytotoxic action of asparaginase. The main side effect of this agent is a hypersensitivity reaction manifested by fever, chills, nausea and vomiting, skin rash, and urticaria. Severe cases can present with bronchospasm, respiratory failure, and hypotension. Other toxicities include an increased risk of both clotting and bleeding as a result of alterations in various clotting factors, pancreatitis, and neurologic toxicity with lethargy, confusion, hallucinations, and coma.

Hydroxyurea (HONHCONH₂) is an analog of urea whose mechanism of action involves the inhibition of DNA synthesis in the S phase by inhibiting the enzyme ribonucleotide reductase, resulting in depletion of deoxynucleoside triphosphate pools. The drug is administered orally and has nearly 100% oral bioavailability. It is mainly used in chronic myelogenous leukemia and treatment of the blast crisis of acute myeloid leukemia. However, it is also effective as an adjunct with radiation therapy for head and neck cancer and in treating essential thrombocytosis and polycythemia vera. Myelosuppression is the dose-limiting toxicity, but nausea and vomiting, mucositis and diarrhea, headache and increased lethargy, and a maculopapular skin rash with pruritus are also observed.
Mitotane

This drug (Figure 39–5) is a dichloro analog of the insecticide DDT that was first found to be adrenolytic in dogs. Subsequently, it was found to be useful in the treatment of an adrenocortical carcinoma, and it is labeled for this clinical indication. The drug produces tumor regression and reduces the excessive adrenal steroid secretion that often occurs with this malignancy. Toxicities are listed in Table 55–6.

Retinoic Acid Derivatives

**All-trans-Retinoic acid (tretinoin)** produces remissions in patients with acute promyelocytic leukemia (APL) through the induction of terminal differentiation, in which the leukemic promyelocytes lose their ability to proliferate. APL is associated with a t(15;17) chromosomal translocation, which disrupts the gene for the nuclear receptor-α for retinoic acid and fuses it to a gene called *PML*. This chimeric gene, which expresses aberrant forms of the retinoic acid receptor-α, is present in virtually all patients with promyelocytic leukemia and appears to be responsible for sensitivity to all-trans-retinoic acid. This agent is approved for use in APL following progression or relapse with anthracycline-based chemotherapy and for patients in whom anthracycline-based chemotherapy is contraindicated. However, a number of serious adverse events have been observed, and they include vitamin A toxicity manifesting as headache, fever, dry skin and mucous membranes, skin rash, pruritus, and conjunctivitis; retinoic acid syndrome with fever, leukocytosis, dyspnea, weight gain, diffuse pulmonary infiltrates, and pleural or pericardial effusions; increased serum cholesterol and triglyceride levels; central nervous system toxicity in the form of dizziness, anxiety, depression, confusion, and agitation; abdominal pain and diarrhea; and transient elevations in liver function tests. Finally, this retinoid has been shown to be teratogenic.

**13-cis-Retinoic acid (isotretinoin)** is used for the treatment of severe cystic acne (Chapter 62: Dermatologic Pharmacology). It also appears to have significant clinical activity as an adjuvant to prevent second primary tumors in patients with head and neck squamous cell carcinoma and may also have activity in the chemoprevention of non-small cell lung cancer. However, it remains an investigational agent for cancer chemotherapy in the USA, and further clinical studies are under way to confirm its true clinical benefit.

Arsenic Trioxide

Arsenic trioxide (AS$_2$O$_3$) is used for induction of remission in patients with acute promyelocytic leukemia with the t(15;17) chromosomal translocation refractory to or relapsed following first-line therapy with all-trans-retinoic acid- and anthracycline-based chemotherapy. It functions by inducing differentiation through degradation of the chimeric PML/RAR-alpha protein. In addition, it induces apoptosis through a mitochondrion-dependent process, resulting in subsequent release of cytochrome C with caspase activation. This drug is administered via the intravenous route and it is widely distributed in the body. The main toxicities are fatigue, electrocardiographic changes with QT prolongation, arrhythmias, and a syndrome characterized by fever, dyspnea, skin rash, fluid retention, and weight gain.

Bone Marrow Growth Factors

Use of bone marrow-stimulating factors with chemotherapy can reduce the frequency and severity of neutropenic sepsis and other complications. Two recombinant bone marrow growth factors that stimulate neutrophil growth are available: granulocyte colony-stimulating factor (G-CSF, filgrastim; and pegfilgrastim, long-acting filgrastim) and granulocyte-macrophage colony-stimulating factor
Both sargramostim and filgrastim can reduce the incidence of neutropenia and prevent the onset of infection when used as an adjunct to chemotherapy and can also shorten hospitalization after bone marrow transplantation. There are currently two colony-stimulating growth factors for red blood cells: darbopoetin alfa and erythropoietin. They are indicated for chemotherapy-induced anemia in patients with nonmyeloid cancer, as well as for anemia associated with chronic renal failure.

Amifostine

Amifostine (WR-2721) is an organic thiophosphate analog designed to produce preferential cytoprotection of normal tissues from cytotoxic therapies. The preferential cytoprotection is due to the activation of amifostine by membrane-bound alkaline phosphatase to the free thiol, WR-1065, the active form. This activation occurs to a greater extent in normal tissue sites than in tumor cells. The free thiol acts as a potent scavenger of free radicals and superoxide anions to inactivate the reactive species of cisplatin and radiation therapy. At present, this agent is approved to reduce the incidence of nephrotoxicity in ovarian cancer and non-small cell lung cancer in conjunction with cisplatin-based chemotherapy and to reduce the incidence of xerostomia in patients undergoing radiation therapy for head and neck cancer. Amifostine does not appear to adversely affect the antitumor activity of cisplatin or radiation therapy. Recent studies suggest that amifostine can reduce the incidence of pneumonitis and esophagitis secondary to combined modality therapy for non-small cell lung cancer, and there is also evidence that it can stimulate bone marrow growth in patients with marrow disorders such as the myelodysplastic syndrome.

Investigational Agents

Several of the drugs mentioned in the text remain investigational in the USA until their clinical efficacy and safety can be fully established. In specific instances where treatment with one of these agents seems warranted, it usually can be arranged through a compassionate use program either by contacting the pharmaceutical sponsor of the drug or by contacting the Division of Cancer Treatment of the National Cancer Institute and the Food and Drug Administration, which can provide further information and identify investigators who are authorized to administer these drugs. This status applies to gefitinib, a small molecule inhibitor of the tyrosine kinase domain of the epidermal growth factor (EGF) receptor; cetuximab, a chimeric monoclonal antibody directed specifically against the EGF receptor; pemetrexed, an inhibitor of thymidylate synthase, dihydrofolate reductase, and enzymes involved in de novo purine synthesis; suramin, an inhibitor of various growth factors including basic fibroblast growth factor; and several others.

Katzung PHARMACOLOGY, 9e > Section VIII. Chemotherapeutic Drugs > Chapter 55. Cancer Chemotherapy >
A thorough knowledge of the kinetics of tumor cell proliferation along with an enhanced understanding of the pharmacology and mechanism of action of cancer chemotherapeutic agents is critically important in designing optimal regimens for patients with cancer (Table 55–7). The strategy for developing drug regimens requires a knowledge of the particular characteristics of specific tumors—eg, Is there a high growth fraction? Is there a high spontaneous cell death rate? Are most of the cells in G0? Is a significant fraction of the tumor composed of hypoxic stem cells? Are their normal counterparts under hormonal control? Similarly, knowledge of the pharmacology of specific drugs is equally important—eg, Does the drug have a particular affinity for uptake by the tumor cells (streptozocin)? Are the tumor cells sensitive to the drug? Is the drug cell cycle-specific? Does the drug require activation in certain normal tissue such as the liver, or is it activated in the tumor tissue itself (capecitabine)? Similarly, for some tumor types, knowledge of receptor expression is important. For example, in patients with breast cancer, analysis of the tumor for expression of estrogen or progesterone receptors—or overexpression of HER-2 receptors—is important in guiding therapy. Knowledge of specific pathway abnormalities (eg, Ras pathway) for intracellular signaling may prove important for the next generation of anticancer drugs.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Current Treatment of Choice</th>
<th>Other Valuable Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphocytic leukemia</td>
<td>Induction: vincristine plus prednisone. Remission maintenance: mercaptopurine, methotrexate, and cyclophosphamide in various combinations</td>
<td>Asparaginase, daunorubicin, carmustine, doxorubicin, cytarabine, allopurinol,1 craniospinal radiotherapy</td>
</tr>
<tr>
<td>Acute myelocytic and myelomonocytic leukemia</td>
<td>Combination chemotherapy: cytarabine and mitoxantrone or daunorubicin or idarubicin</td>
<td>Methotrexate, thioguanine, mercaptopurine, allopurinol,1 mitoxantrone, azacitidine,2 amsacrine,2 etoposide</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>Chlorambucil and prednisone (if indicated), fludarabine</td>
<td>Allopurinol,1 doxorubicin, cladribine</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>Imatinib, busulfan, or interferon, bone marrow transplantation (selected patients)</td>
<td>Vincristine, mercaptopurine, hydroxyurea, melphalan, interferon, allopurinol1</td>
</tr>
<tr>
<td>Hodgkin's disease (stages III and IV)</td>
<td>Combination chemotherapy: vinblastine, doxorubicin, dacarbazine, bleomycin</td>
<td>Lomustine, etoposide, ifosfamide, interferon, mechlorethamine, vincristine, procarbazine, prednisone</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>Combination chemotherapy: cyclophosphamide, doxorubicin, vincristine, prednisone</td>
<td>Bleomycin, lomustine, Carmustine, etoposide, interferon, mitoxantrone, ifosfamide, rituximab</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Melphalan plus prednisone or multiagent combination chemotherapy</td>
<td>Cyclophosphamide, vincristine, carmustine, interferon, doxorubicin, epoetin alfa1</td>
</tr>
<tr>
<td>Macroglobulinemia</td>
<td>Chlorambucil or fludarabine</td>
<td>Prednisone</td>
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<tr>
<td>Polycythemia vera</td>
<td>Busulfan, chlorambucil, or cyclophosphamide</td>
<td>Radioactive phosphorus 32</td>
</tr>
<tr>
<td>Carcinoma of adrenal</td>
<td>Mitotane</td>
<td>Suramin²</td>
</tr>
<tr>
<td>Carcinoma of breast</td>
<td>(1) Adjuvant chemotherapy or tamoxifen after primary breast surgery</td>
<td>Cyclophosphamide, doxorubicin, vincristine, methotrexate, fluorouracil, paclitaxel, mitoxantrone, prednisone,¹ megestrol, androgens,¹ aminoglutethimide, trastuzumab</td>
</tr>
<tr>
<td></td>
<td>(2) Combination chemotherapy or hormonal manipulation for late recurrence</td>
<td></td>
</tr>
<tr>
<td>Carcinoma of cervix</td>
<td>Radiation plus cisplatin (localized), cisplatin, carboplatin (metastatic)</td>
<td>Lomustine, cyclophosphamide, doxorubicin, methotrexate, mitomycin, bleomycin, vincristine, interferon, 13-cis-retinoic acid</td>
</tr>
<tr>
<td>Carcinoma of colon</td>
<td>Fluorouracil plus leucovorin plus irinotecan</td>
<td>Oxaliplatin</td>
</tr>
<tr>
<td>Carcinoma of endometrium</td>
<td>Progestins or tamoxifen</td>
<td>Doxorubicin, cisplatin, carboplatin</td>
</tr>
<tr>
<td>Carcinoma of lung</td>
<td>Cisplatin plus taxane</td>
<td>Methotrexate, vincristine, vinblastine, doxorubicin, mitomycin C</td>
</tr>
<tr>
<td>Carcinoma of ovary</td>
<td>Cisplatin or carboplatin plus paclitaxel</td>
<td>Cyclophosphamide, doxorubicin, melphalan, fluorouracil, vincristine, altretamine, bleomycin</td>
</tr>
<tr>
<td>Carcinoma of pancreas</td>
<td>Gemcitabine</td>
<td>Docetaxel, fluorouracil</td>
</tr>
<tr>
<td>Carcinoma of prostate</td>
<td>GnRH agonist plus androgen antagonist</td>
<td>Aminoglutethimide, doxorubicin, cisplatin, prednisone,¹ estramustine, fluorouracil, progestins, suramin²</td>
</tr>
<tr>
<td>Carcinoma of stomach</td>
<td>Fluorouracil plus cisplatin</td>
<td>Hydroxyurea, lomustine</td>
</tr>
<tr>
<td>Carcinoma of testis</td>
<td>Combination chemotherapy: cisplatin, bleomycin, and etoposide</td>
<td>Methotrexate, dactinomycin, plicamycin, vinblastine, doxorubicin, cyclophosphamide, etoposide, ifosfamide plus mesna¹</td>
</tr>
<tr>
<td>Carcinoma of thyroid</td>
<td>Radioiodine (¹³¹I), doxorubicin, cisplatin</td>
<td>Bleomycin, fluorouracil, melphalan</td>
</tr>
<tr>
<td>Carcinomas of head and neck</td>
<td>Fluorouracil plus cisplatin, cisplatin plus paclitaxel</td>
<td>Methotrexate, bleomycin, hydroxyurea, doxorubicin, vincristine, vinorelbine</td>
</tr>
<tr>
<td>Disease</td>
<td>Treatment Options</td>
<td></td>
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<tr>
<td>Choriocarcinoma (trophoblastic neoplasms)</td>
<td>Methotrexate alone or etoposide and cisplatin</td>
<td></td>
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<tr>
<td></td>
<td>Vinblastine, mercaptopurine, chlorambucil, doxorubicin</td>
<td></td>
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<tr>
<td>Wilms' tumor</td>
<td>Vincristine plus dactinomycin after surgery and radiotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methotrexate, cyclophosphamide, doxorubicin</td>
<td></td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Cyclophosphamide plus doxorubicin and vincristine</td>
<td></td>
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<tr>
<td></td>
<td>Dactinomycin, daunorubicin, cisplatin</td>
<td></td>
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<tr>
<td>Carcinoid</td>
<td>Doxorubicin plus cyclophosphamide, fluorouracil, octreotide</td>
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<td></td>
<td>Interferon, dactinomycin, methysergide, streptozocin</td>
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<tr>
<td>Insulinoma</td>
<td>Streptozocin, interferon</td>
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<tr>
<td></td>
<td>Doxorubicin, fluorouracil, mitomycin, streptozocin</td>
<td></td>
</tr>
<tr>
<td>Osteogenic sarcoma</td>
<td>Doxorubicin, or methotrexate with leucovorin rescue initiated after surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide, dacarbazine, interferon, ifosfamide plus mesna&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous sarcomas</td>
<td>Doxorubicin plus dacarbazine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methotrexate, dactinomycin, ifosfamide plus mesna, vincristine, vinblastine</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>Dacarbazine, cisplatin, temozolomide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lomustine, hydroxyurea, mitomycin, dactinomycin, interferon, tamoxifen</td>
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</tbody>
</table>

<sup>1</sup> Supportive agent, not oncolytic.

<sup>2</sup> Investigational agent. Treatment available through qualified investigators and centers authorized by National Cancer Institute and Cooperative Oncology Groups.

Drugs that affect cycling cells can often be used most effectively after treatment with a cell cycle-nonspecific agent (eg, alkylating agents); this principle has been tested in a few human tumors with increasing success. Similarly, recognition of true drug synergism (tumor cell kill by the drug combination greater than the additive effects of the individual drugs) or antagonism is important in the design of combination chemotherapeutic programs. The combination of cytarabine with an anthracycline in acute myelogenous leukemia and the use of vinblastine or etoposide along with cisplatin and bleomycin in testicular tumors are good examples of true drug synergism against cancer cells but not against normal tissues.

In general, it is preferable to use cytotoxic chemotherapeutic agents in intensive pulse courses every 3–4 weeks rather than to use continuous daily dosage schedules. This allows for maximum effects against neoplastic cell populations with complete hematologic and immunologic recovery between courses rather than leaving the patient continuously suppressed with cytotoxic therapy. This approach reduces adverse effects but does not reduce therapeutic efficacy.

The application of these principles is well illustrated in the current approach to the treatment of acute leukemia, lymphomas, Wilms' tumor, and testicular neoplasms.

Adjuvant Chemotherapy
One of the most important roles for effective cancer chemotherapy is as an adjuvant to initial or primary field treatment with other methods such as surgery or radiation therapy. Failures with primary field therapy are due principally to occult micrometastases outside the primary field. With the currently available treatment modalities, this form of combined-modality therapy appears to offer the greatest chance of curing patients with solid tumors.

Distant micrometastases are usually present in patients with one or more positive lymph nodes at the time of surgery (eg, in breast cancer) and in patients with tumors having a known propensity for early hematogenous spread (eg, osteogenic sarcoma, Wilms’ tumor). The risk of recurrent or metastatic disease in such patients is extremely high (80%). Only systemic therapy can adequately attack micrometastases. Chemotherapy regimens that are at least moderately effective against advanced cancer may have curative potential (at the right dosage and schedule) when combined with primary therapy such as surgery. Several studies show that adjuvant chemotherapy prolongs both disease-free and overall survival in patients with osteogenic sarcoma, rhabdomyosarcoma, or breast cancer. Similar comments apply to the use of three cycles of combination chemotherapy (eg, MOPP) prior to total nodal radiation in stage IIB Hodgkin’s disease.

In breast cancer, premenopausal women with positive lymph nodes at the time of mastectomy have benefited from combination chemotherapy. It has been established that several programs of cytotoxic chemotherapy achieve prolonged disease-free and overall survival times; this method of treatment has increased the cure rate in high-risk primary breast cancer. In general, regimens with at least three active drugs have been useful. The results produced by combination chemotherapy are superior to those produced by single agents because combination chemotherapy copes better with tumor cell heterogeneity and produces a greater tumor cell log kill. Full protocol doses of cytotoxic agents are required to maximize the likelihood of efficacy. Clinical trials have proved tamoxifen to be an effective adjuvant in postmenopausal women with positive estrogen receptor tests on the primary tumor. Because it is cytostatic rather than cytocidal, adjuvant therapy with tamoxifen is usually administered for 5 years. A recent trial in women with node-negative disease showed no additional advantage with 10 years of tamoxifen therapy. Tamoxifen adjuvant chemotherapy is now standard in node-positive postmenopausal women with positive ER or PR tests on tumor specimens. Tamoxifen has also received regulatory approval for reducing the incidence of breast cancer in women who are at high risk for developing the disease.

Other applications of adjuvant chemotherapy include colorectal cancer, testicular cancer, head and neck cancer, and gynecologic neoplasms. In a recent large-scale trial in patients with primary melanoma at high risk of metastases, intensive administration of interferon alfa improved disease-free survival. Thus, adjuvant chemotherapy (with curative intent) should now be considered for patients who undergo primary surgical staging and therapy and are found to have a stage and histologic type of cancer with a high risk of micrometastasis. This policy is germane to those tumor types for which palliative chemotherapy has already been developed and has been shown to induce complete remissions in advanced stages of the disease. In each instance, the benefit:risk ratio must be closely examined.

Combined-modality therapy—radiation plus cisplatin—for localized carcinoma of the cervix has recently proved to achieve long-term survival rates superior to those reported with radiation alone.

Primary chemotherapy (prior to local surgery) is now extensively used in patients with osteogenic sarcoma and has facilitated limb-sparing procedures. Primary chemotherapy is also being evaluated in breast cancer to “downstage” patients prior to surgery.

The Leukemias
Acute Leukemia

Childhood Leukemia

Acute lymphoblastic leukemia (ALL) is the predominant form of leukemia in childhood, and it is the most common form of cancer in children. Children with this disease have a relatively good prognosis. A subset of patients with neoplastic lymphocytes expressing surface antigenic features of T lymphocytes have a poor prognosis (see Chapter 56: Immunopharmacology). A cytoplasmic enzyme expressed by normal thymocytes, terminal deoxycytidylyl transferase (terminal transferase), is also expressed in many cases of ALL. T cell ALLs also express high levels of the enzyme adenosine deaminase (ADA). This led to interest in the use of the ADA inhibitor pentostatin (deoxycoformycin) for treatment of such T cell cases. Until 1948, the median length of survival in ALL was 3 months. With the advent of the folic acid antagonists, the length of survival was greatly increased. Subsequently, corticosteroids, mercaptopurine, cyclophosphamide, vincristine, daunorubicin, and asparaginase were all found to act against this disease. A combination of vincristine and prednisone plus other agents is currently used to induce remission. Over 90% of children enter complete remission with this therapy with only minimal toxicity. However, circulating leukemic cells often migrate to sanctuary sites located in the brain and testes. The value of prophylactic intrathecal methotrexate therapy for prevention of central nervous system leukemia (a major mechanism of relapse) has been clearly demonstrated. Intrathecal therapy with methotrexate should therefore be considered as a standard component of the induction regimen for children with ALL.

Adult Leukemia

Acute myelogenous leukemia (AML) is the most common leukemia seen in adults. The single most active agent for AML is cytarabine; however, it is best used in combination with an anthracycline, in which case complete remissions occur in about 70% of patients. Idarubicin has now replaced daunorubicin as the preferred anthracycline.

Patients often require intensive supportive care during the period of induction chemotherapy. Such care includes platelet transfusions to prevent bleeding, filgrastim to shorten periods of neutropenia, and antibiotics to combat infections. Younger patients (eg, < age 55) who are in complete remission and have an HLA-matched donor are candidates for allogeneic bone marrow transplantation. The transplant procedure is preceded by high-dose chemotherapy and total body irradiation followed by immunosuppression. This approach may cure up to 35–40% of eligible patients. Patients over age 60 respond less well to chemotherapy, primarily because their tolerance for aggressive therapy and their resistance to infection is lower.

Once remission of AML is achieved, consolidation chemotherapy is required to maintain a durable remission and to induce cure. The usual approach is to administer up to four courses of high-dose cytarabine.

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) arises from a chromosomally abnormal hematopoietic stem cell in which a balanced translocation between the long arms of chromosomes 9 and 22, t(9;22), is observed in 90–95% of cases. This translocation results in expression of the Ber-Abl fusion oncoprotein with a molecular weight of 210 kDa, which is constitutively expressed. The clinical symptoms and course are related to the white blood cell count and its rate of increase. Most patients with white cell counts over 50,000/μL should be treated. The goals of treatment are to reduce the
granulocytes to normal levels, to raise the hemoglobin concentration to normal, and to relieve
disease-related symptoms. There has been a significant change in the management of this disease.
Recently, the signal transduction inhibitor imatinib was approved for use as first-line therapy in
previously untreated patients with chronic phase CML. Imatinib is also recommended in patients
with chronic phase disease who have failed prior interferon alfa therapy. Nearly all patients treated
with imatinib exhibit a complete hematologic response, and up to 40–50% of patients will show a
complete cytogenetic response. The usual dose for chronic phase disease is 400 mg/d, and an
advantage of this drug is that it is given orally. As described previously, this drug is extremely well
tolerated and is associated with relatively minor side effects. Other treatment options include
interferon alfa, busulfan, other oral alkylating agents, and hydroxyurea.

Chronic Lymphocytic Leukemia

Patients with early-stage chronic lymphocytic leukemia (CLL) have a relatively good prognosis,
and therapy has not changed the course of the disease. However, in the setting of high-risk disease
or in the presence of disease-related symptoms, treatment is indicated.

The purine nucleoside analog fludarabine is rapidly becoming the treatment of choice in CLL.
Fludarabine can be given alone or used in combination with cyclophosphamide and with
mitoantrone and dexamethasone. The most commonly used single chemotherapeutic agent has
been the alkylating agent chlorambucil. The dosage is usually 0.1 mg/kg/d, with monitoring of
blood counts at weekly intervals. Chlorambucil is frequently combined with prednisone, although
there is no clear evidence that the combination yields better response rates or survival compared
with chlorambucil alone. Alternatively, cyclophosphamide can be given, usually in dosages of 1–2
g/m² every 3–4 weeks. In most cases, cyclophosphamide is given in combination with vincristine
and prednisone (CHOP protocol), or it can also be given with these same drugs along with
doxorubicin (CHOP).

Monoclonal antibody-targeted therapies are being more widely used in CLL, especially in relapsed
or refractory disease. Alemtuzumab is a chimeric monoclonal antibody directed against the CD52
antigen and is approved for use in CLL that is refractory to alkylating agent or fludarabine therapy.
Response rates up to 30–35% are observed, with disease stabilization in another 30% of patients.
Rituximab is an anti-CD20 antibody that also has clinical activity in this setting.

The Lymphomas

Hodgkin's Disease

The treatment of Hodgkin's disease has undergone dramatic evolution over the last 30 years.
Hodgkin's disease is now recognized as a B cell neoplasm in which the malignant Reed-Sternberg
cells have rearranged VH genes. In addition, the Epstein-Barr virus genome has been identified in
up to 80% of tumor specimens.

Complete staging evaluation is required before a definitive treatment plan can be made. For patients
with stage I and stage IIA disease, there has been a significant change in the treatment approach.
Initially, these patients were treated with extended-field radiation therapy. However, given the late
effects of radiation therapy, which include hypothyroidism and an increased risk of secondary
cancers and coronary artery disease, combined-modality therapy with a brief course of combination
chemotherapy and involved field radiation therapy is now the recommended approach. The main
advance for patients with advanced stage III and IV Hodgkin's disease came with the development
of MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) chemotherapy in the 1960s.
This regimen resulted initially in high complete response rates—on the order of 80–90%, with cures in up to 60% of patients. Over the past few years, the anthracycline-containing regimen ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) has been shown to be more effective and less toxic than MOPP, especially with regard to the incidence of sterility and secondary malignancies. This regimen uses four cycles of ABVD. The Stanford group has developed an alternative regimen wherein a 12-week course of combination chemotherapy, termed Stanford V (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone) is followed by involved radiation therapy.

With all these regimens, over 80% of previously untreated patients with advanced Hodgkin's disease (stages III and IV) are expected to go into complete remission, with disappearance of all disease-related symptoms and objective evidence of disease. Approximately 50–60% of all patients with Hodgkin's disease are cured of their disease.

Non-Hodgkin's Lymphomas

Over the past 25 years, there has been a dramatic increase, by over 80%, in the incidence of non-Hodgkin's lymphoma. This is a heterogeneous disease, and the clinical characteristics of non-Hodgkin's lymphoma subsets are related to the underlying histopathologic features and the extent of disease involvement. In general, the nodular (or follicular) lymphomas have a far better prognosis, with a median survival up to 7 years, compared with the diffuse lymphomas, which have a median survival of about 1–2 years.

Combination chemotherapy is the treatment standard for patients with diffuse non-Hodgkin's lymphoma. The anthracycline-containing regimen CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) has been considered the best treatment in terms of initial therapy. Recently, randomized phase III clinical studies have shown that the combination of CHOP with the anti-CD20 monoclonal antibody rituximab results in improved response rates, disease-free survival, and overall survival compared with CHOP chemotherapy alone.

The nodular follicular lymphomas are low-grade, indolent tumors that tend to present in an advanced stage and are usually confined to lymph nodes, bone marrow, and spleen. This form of non-Hodgkin's lymphomas, when presenting at an advanced stage, is considered incurable, and treatment is generally palliative. To date, there is no evidence that immediate treatment with combination chemotherapy offers clinical benefit over close observation and "watchful waiting" with initiation of chemotherapy at the time of disease symptoms.

Multiple Myeloma

This plasma cell malignancy is one of the models of neoplastic disease in humans because it arises from a single tumor stem cell, and the tumor cells produce a marker protein (myeloma immunoglobulin) that allows the total body burden of tumor cells to be quantified. Multiple myeloma principally involves the bone marrow and the surrounding bone, causing bone pain, lytic lesions, bone fractures, and anemia as well as an increased susceptibility to infection.

Most patients with multiple myeloma are symptomatic at the time of initial diagnosis and require treatment with cytotoxic chemotherapy. Treatment with the combination of the alkylating agent melphalan and prednisone (MP protocol) remains a standard regimen. About 40% of patients respond to the MP combination, and the median remission is on the order of 2–2.5 years. While a host of studies have investigated the efficacy of combination of multiple alkylating agents, none of these regimens have as yet been shown to be superior to MP.
Melphalan and other alkylating agents should be avoided in patients who are felt to be candidates for high-dose therapy with stem cell transplantation, as prior therapy will affect the success of stem cell harvesting. In this setting, the nonalkylator combination of vincristine, doxorubicin, and dexamethasone (VAD) has been used.

Thalidomide is now a well-established agent for treating refractory or relapsed disease, and about 30% of patients will achieve a response to this therapy. More recently, thalidomide has been used in combination with dexamethasone, and response rates on the order of 65% have been observed. Studies are now under way to directly compare VAD with the combination of thalidomide and dexamethasone. In some patients, especially those with poor performance status, single-agent pulse dexamethasone administered on a weekly basis can be effective in palliating symptoms.

Significant efforts are currently focused on developing novel agents for multiple myeloma. These include CC5013, a small molecule analog of thalidomide with immunomodulatory effects; the proteasome inhibitor PS341; and arsenic trioxide.

Breast Cancer

Stage I & Stage II Disease

The management of primary breast cancer has undergone a remarkable evolution as a result of major efforts at early diagnosis (through encouragement of self-examination as well as through the use of cancer detection centers) and the implementation of combined modality approaches incorporating systemic chemotherapy as an adjuvant to surgery and radiation therapy. Women with stage I disease (small primaries and negative axillary lymph node dissections) are currently treated with surgery alone, and they have an 80% chance of cure.

Women with node-positive disease have a high risk of both local and systemic recurrence. Thus, lymph node status directly indicates the risk of occult distant micrometastasis. In this situation, postoperative use of systemic cytotoxic chemotherapy with six cycles of cyclophosphamide-methotrexate-fluorouracil (CMF protocol) or of fluorouracil, doxorubicin, and cyclophosphamide (FAC) has been shown to significantly reduce the relapse rate and prolong survival. Alternative regimens with equivalent clinical benefit include four cycles of doxorubicin and cyclophosphamide and six cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC). Each of these chemotherapy regimens has benefited women with stage II breast cancer with one to three involved lymph nodes. Women with four or more involved nodes have had limited benefit thus far from adjuvant chemotherapy. High-dose chemotherapy with autologous stem cell rescue and growth factor support is presently being evaluated in women with ten or more involved nodes. Long-term analysis has clearly shown improved survival rates in node-positive premenopausal women who have been treated aggressively with multiagent combination chemotherapy.

Tamoxifen is beneficial in postmenopausal women when used alone or when combined with cytotoxic chemotherapy. The present recommendation is to administer tamoxifen for 5 years of continuous therapy after surgical resection. Longer durations of tamoxifen therapy do not appear to add additional clinical benefit. Results from several randomized trials for breast cancer have established that adjuvant chemotherapy for premenopausal women and adjuvant tamoxifen for postmenopausal women are of benefit to women with stage I (node-negative) breast cancer. While this group of patients has the lowest overall risk of recurrence after surgery alone (about 35–50% over 15 years), this risk can be further reduced with adjuvant therapy.

Stage III & Stage IV Disease
The approach to women with advanced breast cancer remains a major problem, as current treatment options are only palliative. Combination chemotherapy, endocrine therapy, or a combination of both results in overall response rates of 40–50%, with only a 10–20% complete response rate. Breast cancers expressing estrogen receptors (ER) or progesterone receptors (PR), retain the intrinsic hormonal sensitivities of the normal breast—including the growth-stimulatory response to ovarian, adrenal, and pituitary hormones. Patients who show improvement with hormonal ablative procedures also respond to the addition of tamoxifen. The aromatase inhibitors anastrozole and letrozole have recently been approved as first-line therapy in women with advanced breast cancer whose tumors are hormone-receptor positive. In addition, these agents and exemestane are approved as second-line therapy following treatment with tamoxifen.

Patients with significant visceral involvement of the lung, liver, or brain and those with rapidly progressive disease rarely benefit from hormonal maneuvers, and initial systemic chemotherapy is indicated in such cases. For the 25–30% of breast cancer patients whose tumors express the HER-2/neu cell surface receptor, a humanized monoclonal anti-HER-2/neu antibody, trastuzumab, is available for therapeutic use alone or in combination chemotherapy.

Systemic Chemotherapy

About 50–60% of patients with metastatic disease respond to initial chemotherapy. A broad range of anticancer agents have activity in this disease, including the anthracyclines (doxorubicin, mitoxantrone, and epirubicin), the taxanes (docetaxel and paclitaxel), navelbine, capecitabine, gemcitabine, cyclophosphamide, methotrexate, and cisplatin. Doxorubicin and the taxanes are the most active cytotoxic drugs. Combination chemotherapy has been found to induce higher and more durable remissions in up to 50–80% of patients. Anthracycline-containing regimens including fluorouracil, doxorubicin, and cyclophosphamide or epirubicin, cyclophosphamide, and fluorouracil are now considered standard first-line regimens. With most combination regimens, partial remissions have a median duration of about 10 months and complete remissions have a duration of about 15 months. Unfortunately, only 10–20% of patients achieve complete remissions with any of these regimens, and as noted, complete remissions are usually not long-lasting. The addition of tamoxifen to combination chemotherapy yields only modest additional improvement.

Prostate Cancer

Prostate cancer was the second type of cancer shown to be responsive to hormonal manipulation. The treatment of choice for patients with advanced prostate cancer is elimination of testosterone production by the testes either through surgical or chemical castration. Bilateral orchectomy or estrogen therapy in the form of diethylstilbestrol were previously used as first-line therapy. However, at present, the use of LHRH agonists—including leuprolide and goserelin agonists, alone or in combination with an antiandrogen (eg, flutamide, bicalutamide, or nilutamide)—has become the preferred approach. There appears to be no survival advantage of total androgen blockade using a combination of LHRH agonist and antiandrogen agent compared with single-agent therapy. Hormonal treatment reduces symptoms—especially bone pain—in 70–80% of patients and may cause a significant reduction in the PSA level, which is now widely accepted as a surrogate marker for response to treatment in prostate cancer. Although initial hormonal manipulation is able to control symptoms for up to 2 years, patients usually present with progressive disease. Second-line hormonal therapies include aminoglutethimide plus hydrocortisone, the antifungal agent ketoconazole plus hydrocortisone, or hydrocortisone alone.

Unfortunately, nearly all patients with advanced prostate cancer eventually become refractory to hormone therapy. A regimen of mitoxantrone and prednisone is approved in patients with hormone-
refractory prostate cancer since it provides effective palliation in those who experience significant bone pain. Estramustine is an antimicrotubule agent that produces an almost 20% response rate as a single agent. However, when used in combination with either etoposide or a taxane such as docetaxel or paclitaxel, response rates are more than doubled to 40–50%. To date, no combination regimen has resulted in improved survival benefit. For this reason, intense efforts are focused on identifying novel agents and treatment regimens for patients with hormone-refractory prostate cancer.

Gastrointestinal Cancers

Colorectal adenocarcinoma is the most common type of gastrointestinal malignancy. There are approximately 145,000 new cases diagnosed each year in the USA; worldwide, there are nearly one million cases diagnosed each year. At the time of initial presentation, only about 40–45% of cases are potentially curable with surgery. Patients presenting with high-risk stage II disease and stage III disease with involvement of regional lymph nodes are candidates for adjuvant chemotherapy with fluorouracil plus leucovorin and are generally treated for up to 6–8 months following surgical resection. Treatment with this combination regimen reduces the recurrence rate after surgery by 35% in these patients and clearly improves overall patient survival compared with surgery alone. For patients with rectal carcinoma, surgical adjuvant therapy with protracted intravenous infusion of fluorouracil along with pelvic irradiation provides a modest albeit significant improvement in both relapse-free and overall survival.

As a single agent, the topoisomerase I inhibitor irinotecan is approved as second-line therapy in patients who are no longer responding to fluorouracil. The combination of irinotecan, fluorouracil, and leucovorin (IFL protocol) when given either in a weekly bolus fashion or via a biweekly infusion schedule has now been shown to provide significant clinical benefit in terms of overall response rates, time to disease progression, and survival when compared with treatment with the combination of fluorouracil and leucovorin. Oxaliplatin has recently received approval in the USA for use in combination with a biweekly infusion schedule of fluorouracil and leucovorin as second-line therapy in patients who have failed the IFL regimen.

The incidence of gastric cancer, esophageal cancer, and pancreatic cancer is much lower than for colorectal cancer, but these malignancies are more aggressive. In most cases, they cannot be completely resected surgically, as most patients present with either locally advanced or metastatic disease at the time of their initial diagnosis. Fluorouracil-based chemotherapy has been the usual approach for gastroesophageal cancers. Recently, there has been a shift toward incorporating cisplatin-based regimens in combination with either the topoisomerase I inhibitor irinotecan or with one of the taxanes, paclitaxel or docetaxel, and response rates in the range of 40–50% are now being reported. In addition, neoadjuvant approaches with combination chemotherapy and radiation therapy prior to surgery appear to have some promise in selected patients. Although gemcitabine is approved for use as a single-agent in metastatic pancreas cancer, the overall response rate is less than 10%, with no complete responses. Intense efforts are now being placed on incorporating gemcitabine into various combination regimens and on identifying novel agents that target signal transduction pathways felt to be critical for the growth of pancreatic cancer.

Lung Cancer

Lung cancer can be divided into two main histopathologic subtypes, non-small cell and small cell. Non-small cell lung cancer (NSCLC) makes up about 75–80% of all cases of lung cancer, and this group includes adenocarcinoma, squamous cell cancer, and large cell cancer, while small cell lung cancer (SCLC) makes up the remaining 20–25%. When NSCLC is diagnosed in an advanced stage
with metastatic disease, the prognosis is extremely poor, with a median survival of about 8 months. It is clear that prevention (primarily through avoidance of cigarette smoking) and early detection remain the most important means of control. When diagnosed at an early stage, surgical resection can result in patient cure. However, in most cases, distant metastases have occurred at the time of diagnosis. In certain instances, radiation therapy can be offered for palliation of pain, airway obstruction, or bleeding and to treat patients whose performance status would not allow for more aggressive treatments.

Patients with small cell lung cancer (the most aggressive type) show the best responses to platinum-based combination regimens, including cisplatin and etoposide or cisplatin and irinotecan. The topoisomerase I inhibitor topotecan is used as second-line monotherapy in patients who have failed a platinum-based regimen.

Ovarian Cancer

In the majority of patients, this cancer remains occult and becomes symptomatic after it has already metastasized to the peritoneal cavity. At this stage, it usually presents with malignant ascites. It is important to accurately stage this cancer with laparoscopy, ultrasound, and CT scanning. Patients with stage I disease appear to benefit from whole-abdomen radiotherapy and may receive additional benefit from combination chemotherapy with cisplatin and cyclophosphamide.

Combination chemotherapy is the standard approach to stage III and stage IV disease. Randomized clinical studies have shown that the combination of paclitaxel and cisplatin provides survival benefit compared with the previous standard combination of cisplatin plus cyclophosphamide. More recently, several studies have shown that carboplatin and paclitaxel yields clinical results similar to what is achieved with the cisplatin plus paclitaxel combination; however, because of reduced toxicity and greater ease of administration, carboplatin plus paclitaxel has now become the treatment of choice. In patients who present with recurrent disease, the topoisomerase I inhibitor topotecan, the alkylating agent altretamine, and liposomal doxorubicin are used as single agent monotherapy.

Testicular Cancer

The introduction of platinum-based combination chemotherapy has made an impressive change in the treatment of patients with advanced testicular cancer. At present, chemotherapy is recommended for patients with stage IIC or stage III seminomas and nonseminomatous disease. Over 90% of patients respond to chemotherapy, and, depending upon the extent and severity of disease, complete remissions up to 70–80% are observed. Over 50% of patients achieving complete remission are cured with chemotherapy. In patients with good-risk features, three cycles of cisplatin, etoposide, and bleomycin (PEB protocol) or four cycles of cisplatin and etoposide give virtually identical results. In patients with high-risk disease, the combination of cisplatin, etoposide, and ifosfamide can be used as well as etoposide and bleomycin with high-dose cisplatin. Clinical studies are ongoing to determine the role of high-dose therapy and bone marrow transplantation in this setting.

Malignant Melanoma

Malignant melanoma is one of the most difficult neoplasms to treat because it is relatively resistant to drugs. Dacarbazine, temozolomide, and cisplatin are the most active cytotoxic agents for this disease. Biologic agents, including interferon alfa and interleukin-2 (IL-2), may have greater activity than traditional anticancer agents, and treatment with high-dose IL-2 has led to cures in a small subset of patients. Several clinical studies are actively investigating the combination of
biologic therapy with combination chemotherapy in what has been labeled biochemotherapy regimens. Thus far, overall response rates as well as complete response rates appear to be much higher with biochemotherapy regimens compared with chemotherapy alone. Unfortunately, treatment toxicity also seems to be increased. This approach remains investigational, and further studies are required to determine whether this approach can lead to improved patient survival.

Brain Cancer

Chemotherapy has only limited efficacy in the treatment of malignant gliomas. In general, the nitrosoureas, because of their ability to cross the blood-brain barrier, are the most active agents in this disease. Carmustine (BCNU) can be used a single agent, or lomustine (CCNU) can be used in combination with procarbazine and vincristine. In addition, the nonclassic alkylating agent temozolomide has activity in the setting of recurrent disease, and it is approved for this indication. The histopathologic subtype oligodendroglialoma has now been shown to be especially chemosensitive, and the combination of procarbazine, lomustine, and vincristine (PCV protocol) is the treatment of choice for this disease.

Choriocarcinoma

This rare tumor arises from fetal trophoblastic tissue and was the first metastatic cancer cured with chemotherapy. Single-agent methotrexate produced complete regression of metastatic lesions, resulting in a high percentage of cures. At present, treatment with single-agent methotrexate or dactinomycin is recommended for low-risk disease, while intense combination regimens including methotrexate and leucovorin rescue, etoposide, dactinomycin, vincristine, and cyclophosphamide are recommended for intermediate or high-risk disease.

Evaluation of Clinical Response

Since cancer chemotherapy can induce clinical improvement, significant toxicity, or both, it is critically important to carefully assess the effects of treatment. The goal of therapy in most cancers is to palliate symptoms and to improve the overall quality of life.

Shrinkage in tumor size is a useful measure of clinical response, and this effect can be demonstrated by physical examination, chest film or other x-ray, or special scanning procedures such as bone scanning (breast, prostate cancer), CT scan, magnetic resonance imaging (MRI), or ultrasonography.

Another sign of therapeutic response is a significant decrease in the quantity of a tumor product or marker substance that reflects the amount of tumor in the body.

Normalization of organ function is another useful indicator of drug effectiveness. Examples of such improvement include the normalization of liver function (eg, increased serum albumin) in patients known to have liver metastases and improvement in neurologic findings in patients with cerebral metastases.

Finally, a valuable sign of clinical improvement is the general well-being of the patient. Although this finding is a combination of subjective and objective factors and may be subject to placebo effects, it nonetheless serves as an obvious and useful sign of clinical improvement and can be used to reassess some of the objective observations listed above. Factors to be considered in determining general well-being include improved appetite, weight gain, and improved performance status (eg, ambulatory versus bedridden).
Secondary Malignancies & Cancer Chemotherapy

The development of secondary malignancies is a late complication of some types of cancer chemotherapy. The most frequent secondary malignancy is acute myelogenous leukemia (AML). The alkylating agents, procarbazine, etoposide, and ionizing radiation are all considered to be leukemogenic. AML has been observed in up to 15% of patients with Hodgkin's disease who have received radiotherapy plus MOPP chemotherapy and in patients with multiple myeloma, ovarian carcinoma, or breast carcinoma treated with melphalan. The risk of AML is observed as early as 2–4 years after the initiation of chemotherapy and peaks at 5 and 9 years. With improvements in the clinical efficacy of various combination chemotherapy regimens resulting in prolonged survival and in some cases actual cure of cancer, the issue of how second cancers may affect long-term survival assumes greater importance. There is already evidence that certain alkylating agents (eg, cyclophosphamide) may be less carcinogenic than others (eg, melphalan). Systematic testing of the carcinogenicity of anticancer drugs in several animal models should allow less toxic agents to be identified and substituted for other more carcinogenic ones in chemotherapy regimens.

Preparations Available

The reader is referred to the manufacturers' literature for the most recent information.

Chapter 56. Immunopharmacology

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Immunopharmacology: Introduction

Acronyms

- ADA Adenosine deaminase
- ALG Antilymphocyte globulin
- APC Antigen-presenting cell
- ATG Antithymocyte globulin
- CD Cluster of differentiation
- CSF Colony-stimulating factor
- CTL Cytotoxic T lymphocyte
- DC Dendritic cell
- DTH Delayed-type hypersensitivity
- FKBP FK-binding protein
- HAMA Human antimouse antibody
- IFN Interferon
- IL Interleukin
- IGIV Immunoglobulin intravenous
- LAK cell Lymphokine-activated killer cell
- LFA Lymphocyte functional antigen
- MAb Monoclonal antibody
- MHC Major histocompatibility complex
- MCP-1 Macrophage chemotactic protein-1
- MIP-1 Macrophage inflammatory protein-1
- NK cell Natural killer cell