56 Antineoplastic Agents

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DRUG LIST

ALKYLATING AGENTS

The alkylating agents are the largest class of anticancer agents, comprising five subgroups: nitrogen mustards, alkyl sulfonates, nitrosoureas, ethyleneimine, and thiazines (Table 56.1). Several other agents, including procarbazine, hexamethylmelamine, dacarbazine, estramustine, and mitomycin C, are thought to act at least in part by alkylation.

By definition, *alkylating agents* are compounds that are capable of introducing alkyl groups into nucleophilic sites on other molecules through the formation of *covalent bonds*. These nucleophilic targets for alkylation include the sulfhydryl, amino, phosphate, hydroxyl, carboxyl, and imidazole groups that are present in macromolecules and low-molecular-weight compounds within cells.

The macromolecular sites of alkylation damage include DNA, RNA, and various enzymes. The inhibition of DNA synthesis occurs at drug concentrations that are lower than those required to inhibit RNA and protein synthesis, and *the degree of DNA alkylation correlates especially well with the cytotoxicity* of these drugs. This interaction also accounts for the mutagenic and carcinogenic properties of the alkylating agents. The reactions of various alkylating agents with DNA have been studied in detail, and the 7-nitrogen (N7) and 6-oxygen (O6) of guanine have been shown to be particularly

TABLE 56.1 Classification of the Anticancer Drugs

I. Alkylating agents
  A. Nitrogen mustards
    1. Mechlorethamine hydrochloride (*Mustargen,* HN_2, nitrogen mustard)
    2. Cyclophosphamide (*Cytoxan*)
    3. Chlorambucil (*Leukeran*)
    4. Melphalan (*Alkeran, L-PAM,* L-phenylalanine mustard)
    5. Ifosfamide (*Ifex*)
  B. Alkyl sulfonates
    1. Busulfan (*Myleran*)
  C. Nitrosoureas
    1. Carmustine (BCNU, *BiCNU*)
    2. Lomustine (CCNU, *CeeNU*)
    3. Semustine (methyl-CCNU)
    4. Streptozocin (*Zanosar,* streptozotocin)
  D. Ethylenimines
    1. Thiotepa
  E. Triazenes
    1. Dacarbazine (*DTIC-Dome*)

II. Antimetabolites
  A. Folate antagonist
    1. Methotrexate (*Folex, Mexate*)
  B. Purine analogues
    1. Thioguanine (6-TG, 6-thioguanine)
    2. Mercaptopurine (6-MP, *Purinethol*)
    3. Fludarabine (*Fludara*)
    4. Pentostatin (deoxycoformycin, *Nipent*)
    5. Cladribine (2-chloro-deoxyadenosine, *Leustatin*)
  C. Pyrimidine analogues
    1. Cytarabine (cytosine arabinoside, *Cytosar-U,* ara-C)
    2. Fluorouracil (5-FU, 5-fluorouracil)

III. Antibiotics
  A. Anthracyclines
    1. Doxorubicin hydrochloride (*Adriamycin*)
    2. Daunorubicin (daunomycin, *Cerubidine*)
    3. Idarubicin (*Idamycin*)
  B. Bleomycins
    1. Bleomycin sulfate (*Blenoxane*)
  C. Mitomycin (mitomycin C, *Mutamycin*)
  D. Dactinomycin (actinomycin D, *Cosmegen*)
  E. Plicamycin (*Mithracin*)

IV. Plant-derived products
  A. Vinca alkaloids
    1. Vincristine (*Oncovin*)
    2. Vinblastine (*Velban*)
  B. Epipodophyllotoxins
    1. Etoposide (VP-16, *Vepesid*)
    2. Teniposide (VM-26, *Vumon*)
  C. Taxanes: paclitaxel *Taxol*)

V. Enzymes
  A. L-Asparaginase (*Elspar*)

VI. Hormonal agents
  A. Glucocorticoids
  B. Estrogens, antiestrogens
    1. Tamoxifen citrate (*Nolvadex*)
    2. Estramustine phosphate sodium (*Emcyt*)
  C. Androgens, antiandrogens
    1. Flutamide (*Eulexin*)
  D. Progestins
  E. Luteinizing hormone–releasing hormone (LH-RH) antagonists
    1. Buserelin (*Suprefact*)
    2. Leuprolide (*Lupron*)
  F. Octreotide acetate (*Sandostatin*)

VII. Miscellaneous agents
  A. Hydroxyurea (*Hydrea*)
  B. Procarbazine (*N*-methylhydrazine, *Matulane, Natulan*)
  C. Mitotane (o,p′-DDD, *Lysodren*)
  D. Hexamethylmelamine (HMM)
  E. Cisplatin (*cis*-platinum II; *Platinol*)
  F. Carboplatin (*Paraplatin*)
  G. Mitoxantrone (*Novantrone*)

VIII. Monoclonal antibodies

IX. Immunomodulating agents
  A. Levamisole (*Ergamisol*)
  B. Interferons
    1. Interferon alfa-2a (*Roferon-A*)
    2. Interferon alfa-2b (*Intron A*)
  C. Interleukins: aldesleukin (interleukin-2, IL-2, *Proleukin*)

X. Cellular growth factors
  A. Filgrastim (G-CSF; *Neupogen*)
  B. Sargramostim (GM-CSF, *Leukine, Prokine*)

Proprietary (*italics*) and other names are given in parentheses.

susceptible to attack by electrophilic compounds. There are several possible consequences of N7 guanine alkylation:

1. *Cross-linkage.* Bifunctional alkylating agents, such as the nitrogen mustards, may form covalent bonds with each of two adjacent guanine residues. Such interstrand cross-linkages will *inhibit DNA replication and transcription.* Intrastrand cross-links also may be produced between DNA and a nearby protein.
2. *Mispairing of bases.* Alkylating at N7 changes the O6 of guanine to its enol tautomer, which can then form base pairs with thymine. This may lead to gene miscoding, with adenine–thymine pairs replacing guanine–cytosine. The result is the production of *defective proteins.*
3. *Depurination.* N7 alkylation may cause cleavage of the imidazole ring and excision of the guanine residue, leading to *DNA strand breakage.*

Although all alkylating agents can cause the kinds of genetic damage just discussed, individual drugs differ from one another in their electrophilic reactivity, the structure of their reactive intermediates, and their pharmacokinetic properties. These differences will be reflected in the spectrum of their antitumor activities and in the toxicities they produce in normal tissues.

Nitrogen Mustards

Mechlorethamine

Mechlorethamine (nitrogen mustard; *Mustargen*), a derivative of the war gas sulfur mustard, is considered to be the first modern anticancer drug. In the early 1940s it was discovered to be effective in the treatment of human lymphomas.

Mechlorethamine in aqueous solution loses a chloride atom and forms a cyclic ethylenimmonium ion. This carbonium ion interacts with nucleophilic groups, such as the N7 and O6 of guanine, and leads to an interstrand cross-linking of DNA. Although there is great variation among normal and tumor tissues in their sensitivity to mechlorethamine, the drug is generally more toxic to proliferating cells than to resting or plateau cells. Mechlorethamine has a chemical and biological half-life in plasma of less than 10 minutes after intravenous injection. Little or no intact drug is excreted in urine.

The major indication for mechlorethamine is Hodgkin's disease; the drug is given in the MOPP regimen (mechlorethamine, vincristine, procarbazine, prednisone; see Chapter 55). Other less reactive nitrogen mustards are now preferred for the treatment of non-Hodgkin's lymphomas, leukemias, and various solid tumors.

The dose-limiting toxicity of mechlorethamine is *myelosuppression;* maximal leukopenia and thrombocytopenia occur 10 to 14 days after drug administration, and recovery is generally complete at 21 to 28 days. Lymphopenia and immunosuppression may lead to activation of latent herpes zoster infections, especially in patients with lymphomas. Mechlorethamine will affect rapidly proliferating normal tissues and cause alopecia, diarrhea, and oral ulcerations. *Nausea and vomiting* may occur 1 to 2 hours after injection and can last up to 24 hours. Since mechlorethamine is a potent blistering agent, care should be taken to avoid extravasation into subcutaneous tissues or even spillage onto the skin. Reproductive toxicity includes amenorrhea and inhibition of oogenesis and spermatogenesis. About half of premenopausal women and almost all men treated for 6 months with MOPP chemotherapy become permanently infertile. The drug is teratogenic and carcinogenic in experimental animals.

Cyclophosphamide

Cyclophosphamide (*Cytoxan*) is the most versatile and useful of the nitrogen mustards. Preclinical testing showed it to have a favorable therapeutic index and to possess the broadest spectrum of antitumor activity of all alkylating agents. As with the other nitrogen mustards, cyclophosphamide administration results in the formation of cross-links within DNA due to a reaction of the two chloroethyl moieties of cyclophosphamide with adjacent nucleotide bases. Cyclophosphamide must be activated metabolically by microsomal enzymes of the cytochrome P450 system before ionization of the chloride atoms and formation of the cyclic ethylenimmonium ion can occur. The metabolites phosphoramide mustard and acrolein are thought to be the ultimate active cytotoxic moiety derived from cyclophosphamide.

Cyclophosphamide can be given orally, intramuscularly, or intravenously. The plasma half-life of intact cyclophosphamide is 6.5 hours. Only 10 to 15% of the circulating parent drug is protein bound, whereas 50% of the alkylating metabolites are bound to plasma proteins. Since cyclophosphamide and its metabolites are eliminated primarily by the kidneys, renal failure will greatly prolong their retention.

Cyclophosphamide has a wide spectrum of antitumor activity. In lymphomas, it is frequently used in combination with vincristine and prednisone (CVP [or COP] regimen) or as a substitute for mechlorethamine in the MOPP regimen (C-MOPP). High dosages of intravenously administered cyclophosphamide are often curative in Burkitt's lymphoma, a childhood malignancy with a very fast growth rate. Oral daily dosages are useful for less aggressive tumors, such as nodular lymphomas, myeloma, and chronic leukemias.

Cyclophosphamide is a component of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) and other drug combinations used in the treatment of breast cancer. Cyclophosphamide in combination may produce complete remissions in some patients with ovarian cancer and oat cell (small cell) lung cancer. Other tumors in which beneficial results have been reported include non–oat cell lung cancers, various sarcomas, neuroblastoma, and carcinomas of the testes, cervix, and bladder. Cyclophosphamide also can be employed as an alternative to azathioprine in suppressing immunological rejection of transplant organs.

Bone marrow suppression that affects white blood cells more than platelets is the major dose-limiting toxicity. Maximal suppression of blood cell count occurs 10 to 14 days after drug administration; recovery is generally seen 21 to 28 days after injection. Cyclophosphamide reduces the number of circulating lymphocytes and impairs the function of both humoral and cellular (i.e., B and T cell) aspects of the immune system. Chronic therapy increases the risk of infections. Nausea may occur a few hours after administration. *Alopecia* is more common than with other mustards.

A toxicity that is unique to cyclophosphamide and ifosfamide is cystitis. Dysuria and decreased urinary frequency are the most common symptoms. Rarely, fibrosis and a permanently decreased bladder capacity may ensue. The risk of development of carcinoma of the bladder also is increased. Large intravenous doses have resulted in impairment of renal water excretion, hyponatremia, and increased urine osmolarity and have been associated with hemorrhagic subendocardial necrosis, arrhythmias, and congestive heart failure. Interstitial pulmonary fibrosis may also result from chronic treatment. Other effects of chronic drug treatment include infertility, amenorrhea, and possible mutagenesis and carcinogenesis.

Ifosfamide

Ifosfamide (*Ifex*) is an analogue of cyclophosphamide that requires metabolic activation to form 4-hydroxyifosfamide. In general, the metabolism, serum half-life, and excretion of ifosfamide are similar to those of cyclophosphamide.

Ifosfamide is active against a broad spectrum of tumors, including germ cell cancers of the testis, lymphomas, sarcomas, and carcinomas of the lung, breast, and ovary. It is thought to be more active than cyclophosphamide in germ cell cancers and sarcomas.

Ifosfamide is less myelosuppressive than cyclophosphamide but is more toxic to the bladder. It also may produce alopecia, nausea, vomiting, infertility, and second tumors, particularly acute leukemias. Neurological symptoms including confusion, somnolence, and hallucinations have also been reported. It is recommended that ifosfamide be coadministered with the thiol compound mesna (*Mesnex*) to avoid hemorrhagic cystitis.

Melphalan

Melphalan (*Alkeran*) is an amino acid derivative of mechlorethamine that possesses the same general spectrum of antitumor activity as do the other nitrogen mustards. However, the bioavailability of the oral preparation is quite variable (25–90%) from one patient to another.

The major indications for melphalan are in the palliative therapy of multiple myeloma and cancers of the breast or ovary. Because it does not produce alopecia, melphalan is occasionally substituted for cyclophosphamide in the CMF regimen for breast cancer.

Melphalan produces less nausea and vomiting than does cyclophosphamide; however, its bone marrow suppression tends to be more prolonged and affects both white cells and platelets. Peak suppression of blood counts occurs 14 to 21 days after a 5-day course of drug therapy; recovery is generally complete within 3 to 5 weeks.

Chlorambucil

Chlorambucil (*Leukeran*) is an aromatic nitrogen mustard that is intermediate in chemical reactivity between mechlorethamine and melphalan. Its mechanisms of action and range of antitumor activity are similar to theirs. It is well absorbed orally, but detailed information concerning its metabolic fate in humans is lacking.

Chlorambucil is used primarily as daily palliative therapy for chronic lymphocytic leukemia, Waldenströom's macroglobulinemia, myeloma, and other lymphomas.

Bone marrow toxicity is the major side effect of chlorambucil. Nausea is uncommon or mild, and hair loss does not occur. Chlorambucil shares the immunosuppressive, teratogenic, and carcinogenic properties of the nitrogen mustards.

Nitrosoureas

Carmustine, Lomustine, and Semustine

The nitrosoureas are alkylating agents that are highly lipid soluble and share similar pharmacological and clinical properties. Carmustine (BCNU), lomustine (CCNU), and semustine (methyl-CCNU) are chemically unstable, forming highly reactive decomposition products. The chemical half-life of these drugs in plasma is only 5 to 15 minutes. Their marked lipid solubility facilitates distribution into the brain and cerebrospinal fluid (CSF).

The chloroethyl moiety of these nitrosoureas is capable of alkylating nucleic acids and proteins and producing single-strand breaks and interstrand cross-linkage

of DNA. *Both alkylation and carbamoylation* contribute to the therapeutic and toxic effects of the nitrosoureas. These agents can kill cells in *all* phases of the cell cycle.

Oral absorption of lomustine and semustine is complete, but degradation and metabolism are so rapid that the parent drug cannot be detected after oral administration. Although the plasma half-lives of the parent drugs are only a few minutes, degradation products with antitumor activity may persist for longer periods.

Carmustine and lomustine can produce remissions that last from 3 to 6 months in 40 to 50% of patients with primary brain tumors. Both drugs also are used as secondary treatment of Hodgkin's disease and in experimental combination chemotherapy for various types of lung cancer. Other tumors in which remission rates of 10 to 30% have been obtained are non-Hodgkin's lymphomas, multiple myeloma, melanoma, renal cell carcinoma, and colorectal cancer.

The nitrosoureas produce severe nausea and vomiting in most patients 4 to 6 hours after administration. The major site of dose-limiting toxicity is the bone marrow; leukopenia and thrombocytopenia occur after 4 to 5 weeks. Less frequent side effects include alopecia, stomatitis, and mild abnormalities of liver function. Pulmonary toxicity, manifested by cough, dyspnea, and interstitial fibrosis, is becoming increasingly recognized as a complication of long-term nitrosourea treatment. As alkylating agents, these drugs are potentially mutagenic, teratogenic, and carcinogenic.

Streptozocin

Streptozocin (*Zanosar*), a water-soluble nitrosourea produced by the fungus *Streptomyces achromogenes,* acts through methylation of nucleic acids and proteins. In addition, it produces rapid and severe depletion of the pyridine nucleotides nicotinamide adenine dinucleotide (NAD) and its reduced form (NADH) in liver and pancreatic islets.

Streptozocin is not well absorbed from the gastrointestinal tract and must be administered intravenously or intraarterially. In preclinical studies, the plasma half-life was 5 to 10 minutes.

Streptozocin produces remission in 50 to 60% of patients with islet cell carcinomas of the pancreas. It is also useful in malignant carcinoid tumors.

Almost all patients have nausea and vomiting. The major toxicity is *renal tubular damage,* which may be severe in 5 to 10% of patients taking streptozocin. Treatment of metastatic insulinomas may result in the release of insulin from the tumor and subsequent hypoglycemic coma. Less severe toxicities include diarrhea, anemia, and mild alterations in glucose tolerance or liver function tests.

Alkyl Sulfonates

Busulfan

Busulfan (*Myleran*) is a bifunctional methanesulfonic ester that forms intrastrand cross-linkages with DNA. The drug is well absorbed after oral administration and has a plasma half-life of less than 5 minutes. Metabolites and degradation products are excreted primarily in the urine.

Busulfan is used in the palliative treatment of chronic granulocytic leukemia. Daily oral therapy results in decreased peripheral white blood cells and improved symptoms in almost all patients during the chronic phase of the disease. Excessive uric acid production from rapid tumor cell lysis should be prevented by coadministration of allopurinol.

At usual therapeutic dosages, busulfan is selectively toxic to granulocyte precursors rather than lymphocytes. Thrombocytopenia and anemia and less commonly, nausea, alopecia, mucositis, and sterility also may occur. Unusual side effects of busulfan include gynecomastia, a general increase in skin pigmentation, and interstitial pulmonary fibrosis.

Ethylenimines

Thiotepa

Although thiotepa is chemically less reactive than the nitrogen mustards, it is thought to act by similar mechanisms. Its oral absorption is erratic. After intravenous injection, the plasma half-life is less than 2 hours. Urinary excretion accounts for 60 to 80% of eliminated drug.

Thiotepa has antitumor activity against ovarian and breast cancers and lymphomas. However, it has been largely supplanted by cyclophosphamide and other nitrogen mustards for treatment of these diseases. It is used by direct instillation into the bladder for multifocal local bladder carcinoma.

Nausea and myelosuppression are the major toxicities of thiotepa. It is not a local vesicant and has been safely injected intramuscularly and even intrathecally.

Triazenes

Dacarbazine

Dacarbazine (*DTIC-Dome*) is activated by photodecomposition and by enzymatic *N*-demethylation. Eventual formation of a methyl carbonium ion results in methylation of DNA and RNA and inhibition of nucleic acid and protein synthesis. *As with other alkylating agents, cells in all phases of the cell cycle are susceptible to dacarbazine.*

The plasma half-life of dacarbazine is biphasic, with a distribution phase of 19 minutes and an elimination phase of 5 hours. The drug is not appreciably protein bound, and it does not enter the central nervous system

(CNS). Urinary excretion of unchanged drug is by renal tubular secretion. Dacarbazine metabolism and decomposition is complex.

Dacarbazine is the most active agent used in metastatic melanoma, producing a 20% remission rate. It is also combined with doxorubicin and other agents in the treatment of various sarcomas and Hodgkin's disease.

Dacarbazine may cause severe nausea and vomiting. Leukopenia and thrombocytopenia occur 2 weeks after treatment, with recovery by 3 to 4 weeks. Less common is a flulike syndrome of fever, myalgias, and malaise. Alopecia and transient abnormalities in renal and hepatic function also have been reported.

ANTIMETABOLITES

Folate Antagonists

In general, antimetabolites used in cancer chemotherapy are drugs that are *structurally related to naturally occurring compounds,* such as vitamins, amino acids, and nucleotides. These drugs can compete for binding sites on enzymes or can themselves become incorporated into DNA or RNA and thus interfere with cell growth and proliferation. The antimetabolites in clinical use include the folic acid analogue methotrexate, the pyrimidines (fluorouracil and cytarabine), and the purines (thioguanine, mercaptopurine, fludarabine, pentostatin, and cladribine).

Methotrexate

Methotrexate competitively inhibits the binding of folic acid to the enzyme dihydrofolate reductase. This enzyme catalyzes the formation of tetrahydrofolate, as follows:

$$\text{Folic acid } (FH_2) \xrightarrow{\text{dihydrofolate reductase}} \text{tetrahydrofolate } (FH_4)$$

Tetrahydrofolate is in turn converted to N^5,N^{10}-methylenetetrahydrofolate, which is an essential cofactor for the synthesis of thymidylate, purines, methionine, and glycine. The major mechanism by which methotrexate brings about cell death appears to be inhibition of DNA synthesis through a blockage of the biosynthesis of thymidylate and purines.

Cells in S-phase are most sensitive to the cytotoxic effects of methotrexate. RNA and protein synthesis also may be inhibited to some extent and may delay progression through the cell cycle, particularly from G_1 to S.

Resistance

Mammalian cells have several mechanisms of resistance to methotrexate. These include an increase in intracellular dihydrofolate reductase levels, appearance of altered forms of dihydrofolate reductase with decreased affinity for methotrexate, and a decrease in methotrexate transport into cells (see Chapter 55). The relative importance of each of these mechanisms of resistance in various human tumors is not known.

Cellular uptake of the drug is by carrier-mediated active transport. Drug resistance due to decreased transport can be overcome by greatly increasing extracellular methotrexate concentration, which provides a rationale for high-dose methotrexate therapy. Since bone marrow and gastrointestinal cells do not have impaired folate methotrexate transport, these normal cells can be selectively rescued with reduced folate, bypassing the block of dihydrofolate reductase. Leucovorin (citrovorum factor, folinic acid, 5-formyltetrahydrofolate) is the agent commonly used for rescue.

Absorption, Metabolism, and Excretion

Methotrexate is well absorbed orally and at usual dosages is 50% bound to plasma proteins. The plasma decay that follows an intravenous injection is triphasic, with a distribution phase, an initial elimination phase, and a prolonged elimination phase. The last phase is thought to reflect slow release of methotrexate from tissues. The major routes of drug excretion are glomerular filtration and active renal tubular secretion.

The formation of polyglutamic acid conjugates of methotrexate has been observed in tumor cells and in the liver and may be an important determinant of cytotoxicity. These methotrexate polyglutamates are retained in the cell and are also potent inhibitors of dihydrofolate reductase.

Clinical Uses

Methotrexate is part of curative combination chemotherapy for acute lymphoblastic leukemias, Burkitt's lymphoma, and trophoblastic choriocarcinoma. It is also useful in adjuvant therapy of breast carcinoma; in the palliation of metastatic breast, head, neck, cervical, and lung carcinomas; and in mycosis fungoides.

High-dose methotrexate administration with leucovorin rescue has produced remissions in 30% of patients with metastatic osteogenic sarcoma.

Methotrexate is one of the few anticancer drugs that can be safely administered intrathecally for the treatment of meningeal metastases. Its routine use as prophylactic intrathecal chemotherapy in acute lymphoblastic leukemia has greatly reduced the incidence of recurrences in the CNS and has contributed to the cure rate in this disease. Daily oral doses of methotrexate are used for severe cases of the nonneoplastic skin disease psoriasis (see Chapter 41), and methotrexate has been used as an immunosuppressive agent in severe rheumatoid arthritis.

Adverse Effects

Myelosuppression is the major dose-limiting toxicity associated with methotrexate therapy. Gastrointestinal toxicity may appear in the form of ulcerative mucositis and diarrhea. Nausea, alopecia, and dermatitis are common with high-dose methotrexate. The greatest danger of high-dose therapy is renal toxicity due to precipitation of the drug in the renal tubules, and the drug should not be used in patients with renal impairment. Intrathecal administration may produce neurological toxicity ranging from mild arachnoiditis to severe and progressive myelopathy or encephalopathy. Chronic low-dose methotrexate therapy, as used for psoriasis, may result in cirrhosis of the liver. Occasionally methotrexate produces an acute, potentially lethal lung toxicity that is thought to be allergic or hypersensitivity pneumonitis. Additionally, methotrexate is a potent teratogen and abortifacient.

Drug Interactions

Salicylates, probenecid, and sulfonamides inhibit the renal tubular secretion of methotrexate and may displace it from plasma proteins. Asparaginase inhibits protein synthesis and may protect cells from methotrexate cytotoxicity by delaying progression from G_1-phase to S-phase. Methotrexate may either enhance or inhibit the action of fluorouracil, depending on its sequence of administration.

Gemcitabine

Gemcitabine (*Gemzar*), an antimetabolite, undergoes metabolic activation to difluorodeoxycytidine triphosphate, which interferes with DNA synthesis and repair. It is the single most active agent for the treatment of metastatic pancreatic cancer, and it is used as a first-line treatment for both pancreatic and small cell lung cancer. It is administered by intravenous infusion. The dose-limiting toxicity is bone marrow suppression.

Purine Analogues

Thioguanine (6-Thioguanine)

Thioguanine is an analogue of the natural purine guanine in which a hydroxyl group has been replaced by a sulfhydryl group in the 6-position. Two major mechanisms of cytotoxicity have been proposed for 6-thioguanine: (1) incorporation of the thio nucleotide analogue into DNA or RNA and (2) feedback inhibition of purine nucleotide synthesis. Both of these actions require initial activation of the drug by the enzyme hypoxanthine guanine–phosphoribosyltransferase (HGPRTase), as follows:

$$\text{6-Thioguanine (6-TG)} \xrightarrow{\text{HGPRTase}} \text{6-thioguanosine-5-monophosphate (6-TGMP)}$$

The product of this reaction, 6-TGMP, can eventually be converted to deoxy-6-thioguanosine-triphosphate (dTGTP), which has been shown to be incorporated into DNA. *Resistance* of human leukemia cells to thioguanine has been correlated with decreased activity of HGPRTase and to increased inactivation of the thio nucleotides by alkaline phosphatase.

Thioguanine is slowly absorbed after oral administration; parent drug levels are barely detectable, and peak levels of metabolites occur only after 6 to 8 hours. Total urinary excretion of metabolites in the first 24 hours is 24 to 46% of the administered dose.

Thioguanine is used primarily as part of a combined induction of chemotherapy in acute myelogenous leukemia.

Myelosuppression, with leukopenia and thrombocytopenia appearing 7 to 10 days after treatment, and mild nausea are the most common adverse effects. Liver toxicity with jaundice has been reported in some patients but appears to be less common than with mercaptopurine.

Mercaptopurine (6-Mercaptopurine)

Mercaptopurine (*Purinethol*) is an analogue of hypoxanthine and was one of the first agents shown to be active against acute leukemias. It is now used as part of maintenance therapy in acute lymphoblastic leukemia. Mercaptopurine must be activated to a nucleotide by the enzyme HGPRTase. This metabolite is capable of inhibiting the synthesis of the normal purines adenine and guanine at the initial aminotransferase step and inhibiting the conversion of inosinic acid to the nucleotides adenylate and guanylate at several steps. Some mercaptopurine is also incorporated into DNA in the form of thioguanine. The relative significance of these mechanisms to the antitumor action of mercaptopurine is not clear.

Resistance to mercaptopurine may be a result of decreased drug activation by HGPRTase or increased inactivation by alkaline phosphatase.

The plasma half-life of an intravenous bolus injection of mercaptopurine is 21 minutes in children and 47 minutes in adults. After oral administration, peak plasma levels are attained within 2 hours. The drug is 20% bound to plasma proteins and does not enter the CSF. Xanthine oxidase is the primary enzyme involved in the metabolic inactivation of mercaptopurine.

Mercaptopurine is used in the maintenance therapy of acute lymphoblastic leukemia. It also displays activity against acute and chronic myelogenous leukemias.

The major toxicities of mercaptopurine are myelosuppression, nausea, vomiting, and hepatic toxicity.

Fludarabine

Fludarabine (*Fludara*) is a fluorinated purine analogue of the antiviral agent vidarabine. The active metabolite,

2-fluoro-ara-adenosine triphosphate, inhibits various enzymes involved in DNA synthesis, including DNA polymerase-α, ribonucleotide reductase, and DNA primase. Unlike most antimetabolites, it is toxic to nonproliferating as well as dividing cells, primarily lymphocytes and lymphoid cancer cells.

The drug is highly active in the treatment of chronic lymphocytic leukemia, with approximately 40% of patients achieving remissions after previous therapy with alkylating agents has failed. Activity is also seen in the low-grade lymphomas.

The major side effect is myelosuppression, which contributes to fevers and infections in as many as half of treated patients. Nausea and vomiting are mild. Occasional neurotoxicity has been noted at higher doses, with agitation, confusion, and visual disturbances.

Pentostatin

Pentostatin (*Nipent,* deoxycoformycin) is a purine isolated from fermentation cultures of the microbe *Streptomyces antibioticus.* Its mechanism of action involves inhibition of the enzyme adenosine deaminase, which plays an important role in purine salvage pathways and DNA synthesis. The resulting accumulation of deoxyadenosine triphosphate (dATP) is highly toxic to lymphocytes.

Pentostatin is effective in the therapy of hairy cell leukemia, producing remissions in 80 to 90% of patients and complete remissions in more than 50%. The major toxic effects of the drug include myelosuppression, nausea, and skin rashes.

Cladribine

Cladribine (*Leustatin*) is a synthetic purine nucleoside that is converted to an active cytotoxic metabolite by the enzyme deoxycytidine kinase. Like the other purine antimetabolites, it is relatively selective for both normal and malignant lymphoid cells and kills resting as well as dividing cells by mechanisms that are not completely understood.

The drug is highly active against hairy cell leukemia, producing complete remissions in more than 60% of patients treated with a single 7-day course. Activity has also been noted in other low-grade lymphoid malignancies. The major side effect is myelosuppression.

Pyrimidine Analogues

Cytarabine

Cytarabine (cytosine arabinoside, ara-C, *Cytosar-U*) is an analogue of the pyrimidine nucleosides cytidine and deoxycytidine. It is one of the most active agents available for the treatment of acute myelogenous leukemia. *Cytarabine kills cells in the S-phase of the cycle by competitively inhibiting DNA polymerase.* The drug must first be activated by pyrimidine nucleoside kinases to the triphosphate nucleotide ara-cytosine triphosphate (ara-CTP). The susceptibility of tumor cells to cytarabine is thought to be a reflection of their ability to activate the drug more rapidly (by kinases) than to inactivate it (by deaminases).

Cytarabine is rapidly metabolized in the liver, kidney, intestinal mucosa, and red blood cells and has a half-life in plasma of only 10 minutes after intravenous bolus injection. The major metabolite, uracil arabinoside (ara-U), can be detected in the blood shortly after cytarabine administration. About 80% of a given dose is excreted in the urine within 24 hours, with less than 10% appearing as cytarabine; the remainder is ara-U. When the drug is given by continuous infusion, cytarabine levels in CSF approach 40% of those in plasma.

Cytarabine is used in the chemotherapy of acute myelogenous leukemia, usually in combination with an anthracycline agent, thioguanine, or both. It is less useful in acute lymphoblastic leukemia and the lymphomas and has no known activity against other tumors. It has been used intrathecally in the treatment of meningeal leukemias and lymphomas as an alternative to methotrexate.

Myelosuppression is a major toxicity, as is severe bone marrow hypoplasia. Nausea and mucositis also may occur. Intrathecal administration occasionally produces arachnoiditis or more severe neurological toxicity.

Fluorouracil

Fluorouracil (5-fluorouracil, 5-fluorouracil, *Efudex, Adrucil*) is a halogenated pyrimidine analogue that must be activated metabolically. The active metabolite that inhibits DNA synthesis is the deoxyribonucleotide 5-fluoro-2′deoxyuridine-S′-phosphate (FdUMP). *5-Fluorouracil is selectively toxic to proliferating rather than non-proliferating cells and is active in both the G_1- and S-phases.* The target enzyme inhibited by 5-fluorouracilfluorouracil is thymidylate synthetase, which catalyzes the following reaction:

$$\begin{array}{ccc} \text{Uridylate} & \xrightarrow{\text{thymidylate synthetase}} & \text{thymidylate} \\ \text{(dUMP)} & & \text{(dTMP)} \\ \text{methylenetetrahydrofolate} & \longrightarrow & \text{dihydrofolate} \end{array}$$

The carbon-donating cofactor for this reaction is N^5,N^{10} methylenetetrahydrofolate, which is converted to dihydrofolate. The reduced folate cofactor occupies an allosteric site on thymidylate synthetase, which allows for the covalent binding of 5-FdUMP to the active site of the enzyme.

Another action proposed for 5-fluorouracil may involve the incorporation of the nucleotide 5-fluorouridine triphosphate (5-FUTP) into RNA. The cytotoxic

role of these "fraudulent" 5-fluorouracil-containing RNAs is not well understood.

Several possible mechanisms of resistance to 5-fluorouracil have been identified, including increased synthesis of the target enzyme, altered affinity of thymidylate synthetase for FdUMP, depletion of enzymes (especially uridine kinase) that activate 5-fluorouracil to nucleotides, an increase in the pool of the normal metabolite deoxyuridylic acid (dUMP), and an increase in the rate of catabolism of 5-fluorouracil.

The drug has been administered orally, but absorption by this route is erratic. The plasma half-life of 5-fluorouracil after intravenous injection is 10 to 20 minutes. It readily enters CSF. Less than 20% of the parent compound is excreted into the urine, the rest being largely metabolized in the liver.

5-Fluorouracil is used in several combination regimens in the treatment of breast cancer. It also has palliative activity in gastrointestinal adenocarcinomas, including those originating in the stomach, pancreas, liver, colon, and rectum. Other tumors in which some antitumor effects have been reported include carcinomas of the ovary, cervix, oropharynx, bladder, and prostate. Topical 5-fluorouracil cream has been useful in the treatment of premalignant keratoses of the skin and superficial basal cell carcinomas, but it should not be used in invasive skin cancer.

Floxuridine (*FUDR*) is the nucleoside of 5-fluorouracil that is readily converted into 5-fluorouracil in vivo. It has similar pharmacological effects but is preferred to 5-fluorouracil for hepatic arterial infusions because it is more extensively metabolized in the liver than 5-fluorouracil, with less systemic toxicity.

The toxicities of 5-fluorouracil vary with the schedule and mode of administration. Nausea is usually mild if it occurs at all. Myelosuppression is most severe after intravenous bolus administration, with leukopenia and thrombocytopenia appearing 7 to 14 days after an injection. Daily injection or continuous infusion is most likely to produce oral mucositis, pharyngitis, diarrhea, and alopecia. Skin rashes and nail discoloration have been reported, as have photosensitivity and increased skin pigmentation on sun exposure. Neurological toxicity is manifested as acute cerebellar ataxia that may occur within a few days of beginning treatment.

ANTIBIOTICS

Doxorubicin and Daunorubicin

The anthracycline antibiotics are fermentation products of *Streptomyces peucetius.* Daunorubicin (*Cerubidine*) is used to treat acute leukemias, while its structural analogue, doxorubicin (*Adriamycin*) is extensively employed against a broad spectrum of cancers. Although the two drugs have similar pharmacological and toxicological properties, doxorubicin is more potent against most animal and human tumors and will be discussed in greater detail.

Doxorubicin binds tightly to DNA by its ability to *intercalate* between base pairs and therefore is preferentially concentrated in nuclear structures. Intercalation results in steric hindrance, hence production of single-strand breaks in DNA and inhibition of DNA synthesis and DNA-dependent RNA synthesis. The enzyme topoisomerase II is thought to be involved in the generation of DNA strand breaks by the anthracyclines. *Cells in S-phase are most sensitive to doxorubicin,* although cytotoxicity also occurs in other phases of the cell cycle.

In addition to the intercalation mechanism described, the anthracycline ring of doxorubicin can undergo a one-electron reduction to form free radicals and participate in further electron transfer. These highly active substances can then react with tissue macromolecules. This type of interaction suggests an alternative mechanism of cytotoxicity for the anthracyclines. In particular, the cardiac toxicity of anthracyclines may result from the generation of free radicals of oxygen.

Resistance to the anthracyclines usually involves decreased drug accumulation due to *enhanced active efflux* of drug. This form of drug resistance is common among the large, heterocyclic naturally derived anticancer agents. It is termed *multidrug resistance* because of the high degree of cross-resistance among the anthracyclines, vinca alkaloids, dactinomycin, and podophyllotoxins (see Chapter 55).

Doxorubicin is not absorbed orally, and because of its ability to cause tissue necrosis must not be injected intramuscularly or subcutaneously. Distribution studies indicate rapid uptake in all tissues except the CNS. Extensive tissue binding, primarily intranuclear, accounts for the prolonged elimination half-life. The drug is extensively metabolized in the liver to hydroxylated and conjugated metabolites and to aglycones that are primarily excreted in the bile.

Doxorubicin is one of the most effective agents used in the treatment of carcinomas of the breast, ovary, endometrium, bladder, and thyroid and in oat cell cancer of the lung. It is included in several combination regimens for diffuse lymphomas and Hodgkin's disease. Doxorubicin can be used as an alternative to daunorubicin in acute leukemias and is useful in Ewing's sarcoma, osteogenic sarcoma, soft-tissue sarcomas, and neuroblastoma. Some activity has been reported in non–oat cell lung cancer, multiple myeloma, and adenocarcinomas of the stomach, prostate, and testis.

The most important toxicities caused by doxorubicin involve the heart and bone marrow. Acutely, doxorubicin may cause transient cardiac arrhythmias and depression of myocardial function. Doxorubicin may

cause radiation recall reactions, with flare-ups of dermatitis, stomatitis, or esophagitis that had been produced previously by radiation therapy. Less severe toxicities include phlebitis and sclerosis of veins used for injection, hyperpigmentation of nail beds and skin creases, and conjunctivitis. Because of its intense red color, doxorubicin will impart a reddish color to the urine for 1 or 2 days after administration.

Idarubicin

Idarubicin (*Idamycin*) differs from its parent compound, daunorubicin, by the absence of the methoxy group in the anthracycline ring structure. Its mechanisms of action and resistance are similar to those of doxorubicin and daunorubicin; however, it is more lipophilic and more potent than these other anthracyclines. Idarubicin undergoes extensive hepatic metabolism and biliary excretion. Adverse reactions of idarubicin are similar to those of its congeners.

Bleomycin

The bleomycins are a group of glycopeptides that are isolated from *Streptomyces verticillus*. The clinical preparation, bleomycin sulfate (*Blenoxane*), is a mixture of several components. Bleomycin binds to DNA, in part through an intercalation mechanism, without markedly altering the secondary structure of the nucleic acid. The drug produces both single- and double-strand scission and fragmentation of DNA. It is thought that the bleomycins, which are avid metal-chelating agents, form a bleomycin–Fe^{++} complex that can donate electrons to molecular oxygen, thus forming the superoxide and hydroxyl free radicals. It is these highly reactive intermediates that attack DNA and produce DNA strand breakage and maximum cytotoxicity in the late G_2 and early M-phases of the cell cycle.

Bleomycin is poorly absorbed orally, but it can be given by various parenteral routes. Its plasma half-life is not affected by renal dysfunction as long as creatinine clearance is greater than 35 mL/minute.

Bleomycin hydrolase, which inactivates bleomycin, is an enzyme that is abundant in liver and kidney but virtually absent in lungs and skin; the latter two organs are the major targets of bleomycin toxicity. It is thought that bleomycin-induced dermal and pulmonary toxicities are related to the persistence of relatively high local concentrations of active drug.

Bleomycin, in combination with cisplatin or etoposide, is important as part of the potentially curative combination chemotherapy of advanced testicular carcinomas. Bleomycin is used in some standard regimens for the treatment of Hodgkin's and non-Hodgkin's lymphomas, and it is useful against squamous cell carcinomas of the head and neck, cervix, and skin.

A potentially fatal lung toxicity occurs in 10 to 20% of patients receiving bleomycin. Patients particularly at risk are those who are over 70 years of age and have had radiation therapy to the chest. Rarely, bleomycin also may cause allergic pneumonitis. Bleomycin skin toxicity is manifested by hyperpigmentation, erythematosus rashes, and thickening of the skin over the dorsum of the hands and at dermal pressure points, such as the elbows. Many patients develop a low-grade transient fever within 24 hours of receiving bleomycin. Less common adverse effects include mucositis, alopecia, headache, nausea, and arteritis of the distal extremities.

Mitomycin

Mitomycin (mitomycin C, *Mitocin-C, Mutamycin*) is an antibiotic that is derived from a species of *Streptomyces*. It is sometimes classified as an alkylating agent because it can covalently bind to and cross-link DNA. Mitomycin is thought to inhibit DNA synthesis through its ability to alkylate double-strand DNA and bring about interstrand cross-linking. There is evidence that enzymatic reduction by a reduced nicotinamide–adenine dinucleotide phosphate (NADPH) dependent reductase is necessary to activate the drug.

The drug is rapidly cleared from serum after intravenous injection but is not distributed to the brain.

Mitomycin has limited palliative effects in carcinomas of the stomach, pancreas, colon, breast, and cervix.

The major toxicity associated with mitomycin therapy is unpredictably long and cumulative myelosuppression that affects both white blood cells and platelets. A syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure also has been described. Renal, hepatic, and pulmonary toxicity may occur. The drug is teratogenic and carcinogenic, and it can cause local blistering.

Dactinomycin

Dactinomycin (actinomycin D, *Cosmegen*) is one of a family of chromopeptides produced by *Streptomyces*. It is known to bind noncovalently to double-strand DNA by partial intercalation, inhibiting DNA-directed RNA synthesis. The drug is most toxic to proliferating cells, but it is not specific for any one phase of the cell cycle. *Resistance* to dactinomycin is caused by decreased ability of tumor cells to take up and retain the drug, and it is associated with cross-resistance to vinca alkaloids, the anthracyclines, and certain other agents (multidrug resistance).

Dactinomycin is cleared rapidly from plasma, does not enter the brain, is not appreciably metabolized or protein bound, and is gradually excreted in both bile and urine. Virtually no drug is detected in CSF.

Dactinomycin is used in curative combined treatment of Wilms' tumor, Ewing's sarcoma, rhabdomyosarcoma, and gestational choriocarcinoma. It is active in testicular tumors, lymphomas, melanomas, and sarcomas, although its use in most of these malignancies has been supplanted by other agents.

The major side effects of dactinomycin are severe nausea, vomiting, and myelosuppression. Mucositis, diarrhea, alopecia, and radiation recall reactions may occur. The drug is immunosuppressive and carcinogenic.

Plicamycin

Plicamycin (mithramycin, *Mithracin*) is one of the chromomycin group of antibiotics produced by *Streptomyces tanashiensis.* Plicamycin binds to DNA and inhibits transcription. It also inhibits resorption of bone by osteoblasts, thus lowering serum calcium levels. Very little is known about its distribution, metabolism, and excretion. Because of its severe toxicity, plicamycin has limited clinical utility. The major indication for plicamycin therapy is in the treatment of life-threatening hypercalcemia associated with malignancy. Plicamycin also can be used in the palliative therapy of metastatic testicular carcinoma when all other known active drugs have failed.

PLANT-DERIVED PRODUCTS

Three classes of plant-derived drugs, the vinca alkaloids (vincristine, vinblastine, and vinorelbine), the epipodophyllotoxins (etoposide and teniposide), and the taxanes (paclitaxel and taxotere), are used in cancer chemotherapy. These classes differ in their structures and mechanisms of action but share the multidrug resistance mechanism, since they are all substrates for the multidrug transporter P-glycoprotein.

Vinca Alkaloids

Vincristine, Vinblastine, and Vinorelbine

Vincristine (*Oncovin*) and vinblastine (*Velban*) are both produced by the leaves of the periwinkle plant. Despite their structural similarity, there are significant differences between them in regard to clinical usefulness and toxicity.

The vinca alkaloids *bind avidly to tubulin,* a class of proteins that form the mitotic spindle during cell division. The drugs cause cellular arrest in metaphase during mitosis, and cell division cannot be completed. Although the vinca alkaloids usually have been regarded as phase specific in the cell cycle, some mammalian cells are most vulnerable in the late S-phase.

Resistance to vinca alkaloids has been correlated with a decreased rate of drug uptake or an increased drug efflux from these tumor cells. Cross-resistance usually occurs with anthracyclines, dactinomycin, and podophyllotoxins.

Both vincristine and vinblastine are extensively bound to tissues, and only small amounts of the drug are distributed to the brain or CSF. The plasma disappearance of vinblastine and vinorelbine is triphasic. Similar clinical pharmacokinetics have been noted with vincristine and vinorelbine. Biliary excretion is the major route of drug excretion.

Vincristine is an important component of the curative combination chemotherapy for acute lymphoblastic leukemia, Hodgkin's disease (the MOPP regimen), and non-Hodgkin's lymphomas. It is also used in several regimens for pediatric solid tumors, including Wilms' tumor, Ewing's sarcoma, rhabdomyosarcoma, and neuroblastoma; in adult tumors of the breast, lung, and cervix; and in sarcomas. Its relative lack of myelosuppression makes it more attractive than vinblastine for use in combination with myelotoxic drugs. Vinblastine is especially useful in testicular carcinomas and is also active in Hodgkin's disease, other types of lymphomas, breast cancer, and renal cell carcinoma.

Vinorelbine is particularly useful in the treatment of advanced non–small cell lung cancer and can be administered alone or in combination with cisplatin. It is thought to interfere with mitosis in dividing cells through a relatively specific action on mitotic microtubules.

Neurological toxicity is the major dose-limiting toxicity of vincristine, whereas bone marrow toxicity is limiting for vinblastine. Severe neutropenia occurs in approximately half of the patients receiving vinorelbine. Severe leukopenia is the major side effect of vinblastine. These drugs are potent local blistering agents and will produce tissue necrosis if extravasated.

Epipodophyllotoxins

Etoposide

Etoposide (*VePesid*) is a semisynthetic derivative of podophyllotoxin that is produced in the roots of the American mandrake, or May apple. Unlike podophyllotoxin and vinca alkaloids, etoposide does not bind to microtubules. It forms a complex with the enzyme topoisomerase II, which results in a single-strand breakage of DNA. It is most lethal to cells in the S- and G_2-phases of the cell cycle. Drug *resistance* to etoposide is thought to be caused by decreased cellular drug accumulation.

Etoposide is most useful against testicular and ovarian germ cell cancers, lymphomas, small cell lung cancers, and acute myelogenous and lymphoblastic leukemia. Toxicities include mild nausea, alopecia, allergic reaction, phlebitis at the injection site, and bone marrow toxicity.

Teniposide

Teniposide (VM-26, *Vumon*) is closely related to etoposide in structure, mechanisms of action and resistance,

and adverse effects. It is more lipophilic and approximately threefold more potent than etoposide. Its major uses have been in pediatric cancers, particularly in acute lymphoblastic leukemias.

Taxanes

Paclitaxel

Paclitaxel (*Taxol*) is a highly complex, organic compound isolated from the bark of the Pacific yew tree. It binds to tubulin dimers and microtubulin filaments, promoting the assembly of filaments and preventing their depolymerization. This increase in the stability of microfilaments results in disruption of mitosis and cytotoxicity and disrupts other normal microtubular functions, such as axonal transport in nerve fibers.

The major mechanism of resistance that has been identified for paclitaxel is transport out of tumor cells, which leads to decreased intracellular drug accumulation. This form of resistance is mediated by the multidrug transporter P-glycoprotein.

Paclitaxel's large volume of distribution indicates significant tissue binding. The drug is extensively metabolized by the liver, and doses must be reduced in patients with abnormal liver function or with extensive liver metastases. Very little of the drug is excreted in the urine.

Paclitaxel is among the most active of all anticancer drugs, with significant efficacy against carcinomas of the breast, ovary, lung, head, and neck. It is combined with cisplatin in the therapy of ovarian and lung carcinomas and with doxorubicin in treating breast cancer.

Myelosuppression is the major side effect of paclitaxel. Alopecia is common, as is reversible dose-related peripheral neuropathy. Most patients have mild numbness and tingling of the fingers and toes beginning a few days after treatment. Mild muscle and joint aching also may begin 2 or 3 days after initiation of therapy. Nausea is usually mild or absent. Severe hypersensitivity reactions may occur. Cardiovascular side effects, consisting of mild hypotension and bradycardia, have been noted in up to 25% of patients.

ENZYMES

L-Asparaginase

The enzyme L-asparaginase (*Elspar*) is derived from the bacteria *Escherichia coli* and *Erwinia carotovora.* It catalyzes the hydrolysis of L-asparagine to aspartic acid and ammonia. L-Glutamine also can undergo hydrolysis by this enzyme, and during therapy, the plasma levels of both amino acid substrates fall to zero. Tumor cells sensitive to L-asparaginase are deficient in the enzyme asparagine synthetase and therefore cannot synthesize asparagine. *Depletion of exogenous asparagine and glutamine inhibits protein synthesis in cells lacking asparagine synthetase,* which leads to inhibition of nucleic acid synthesis and cell death.

The half-life of L-asparaginase in human plasma is 6 to 30 hours. The drug remains primarily in the intravascular space, so its volume of distribution is only slightly greater than that of the plasma. Metabolism and disposition are thought to occur through serum proteases, the reticuloendothelial system, and especially in patients with prior exposure to the drug, binding by antibodies. The drug is not excreted in urine, and very little appears in the CSF.

The major indication for L-asparaginase is in the treatment of acute lymphoblastic leukemia; complete remission rates of 50 to 60% are possible. Lack of cross-resistance and bone marrow toxicity make the enzyme particularly useful in combination chemotherapy. L-Asparaginase also can be used in the treatment of certain types of lymphoma. It has no role in the treatment of nonlymphocytic leukemias or other types of cancer.

Since it is a foreign protein, L-asparaginase may produce hypersensitivity reactions, including urticarial skin rashes and severe anaphylactic reactions. One-third of patients have nausea, anorexia, weight loss, and mild fever. Almost all patients develop elevated serum transaminases and other biochemical indices of hepatic dysfunction. Severe hepatic toxicity occurs in fewer than 5% of cases. Patients receiving L-asparaginase may develop symptoms of CNS toxicity, including drowsiness, confusion, impaired mentation, and even coma. Pancreatitis occurs in 5 to 10% of cases. Hyperglycemia, possibly due to inhibition of insulin synthesis, also may occur. *L-Asparaginase differs from most cytotoxic drugs in its lack of toxicity to bone marrow, gastrointestinal tract, and hair follicles.*

HORMONE DERIVATIVES

Tamoxifen

Tamoxifen (*Nolvadex*) is a synthetic antiestrogen (see Chapter 63) used in the treatment of breast cancer. Normally, estrogens act by binding to a cytoplasmic protein receptor, and the resulting hormone–receptor complex is then translocated into the nucleus, where it induces the synthesis of ribosomal RNA (rRNA) and messenger RNA (mRNA) at specific sites on the DNA of the target cell. *Tamoxifen also avidly binds to estrogen receptors and competes with endogenous estrogens for these critical sites.* The drug–receptor complex has little or no estrogen agonist activity. Tamoxifen directly inhibits growth of human breast cancer cells that contain estrogen receptors but has little effect on cells without such receptors.

Tamoxifen is slowly absorbed, and maximum serum levels are achieved 4 to 7 hours after oral administration.

The drug is concentrated in estrogen target tissues, such as the ovaries, uterus, vaginal epithelium, and breasts. Hydroxylation and glucuronidation of the aromatic rings are the major pathways of metabolism; excretion occurs primarily in the feces.

The presence of estrogen receptors (ER) in biopsies of breast cancers is a good predictor of responsiveness to tamoxifen therapy: 60% of women with ER-positive tumors will have a remission, as opposed to fewer than 10% with ER-negative tumors. Overall, 35 to 40% of women with breast cancer will respond to some degree, with antitumor effects lasting an average of 9 to 12 months. Complete remissions may occur in 10 to 15% of patients and may last several months to a few years. Therapy should be continued for at least 6 weeks to establish efficacy.

Tamoxifen administration is associated with few toxic side effects, most frequently hot flashes (in 10–20% of patients) and occasionally vaginal dryness or discharge. Mild nausea, exacerbation of bone pain, and hypercalcemia may occur.

Estramustine

Estramustine phosphate sodium (*Emcyt*) is a hybrid structure combining estradiol and a nitrogen mustard in a single molecule. The drug has been approved for use in prostatic carcinomas and will produce clinical remissions in one-third of patients who have failed to respond to previous estrogen therapy. The mechanism of action of estramustine is not well defined, but it does not appear to require either alkylation of DNA or the presence of estrogen receptors in tumor cells. Nonetheless, the toxicities of the drug are similar to those of estrogen therapy: breast tenderness and enlargement (gynecomastia), fluid retention, mild nausea, and an increased risk of thrombophlebitis and pulmonary embolism. The drug is not myelosuppressive.

Flutamide

Flutamide (*Eulexin*) is a nonsteroidal antiandrogen (see Chapter 63) compound that competes with testosterone for binding to androgen receptors. The drug is well absorbed on oral administration. It is an active agent in the hormonal therapy of cancer of the prostate and has been shown to complement the pharmacological castration produced by the gonadotropin-releasing hormone (GnRH) agonist leuprolide. Flutamide prevents the stimulation of tumor growth that may occur as a result of the transient increase in testosterone secretion after the initiation of leuprolide therapy. The most common side effects of flutamide are those expected with androgen blockade: hot flashes, loss of libido, and impotence. Mild nausea and diarrhea occur in about 10% of patients.

Buserelin and Leuprolide

Buserelin (*Suprefact*) and leuprolide (*Lupron*) are peptide analogues of the hypothalamic hormone LH-RH (luteinizing hormone–releasing hormone). Chronic exposure of the pituitary to these agents abolishes gonadotropin release and results in markedly decreased estrogen and testosterone production by the gonads. Their major clinical use is in the palliative hormonal therapy of cancer of the prostate.

Leuprolide is a potent LH-RH agonist for the first several days to a few weeks after initiation of therapy, and therefore, it initially stimulates testicular and ovarian steroidogenesis. Because of this initial stimulation of testosterone production, it is recommended that patients with prostatic cancer be treated concurrently with leuprolide and the antiandrogen flutamide (discussed earlier). Leuprolide is generally well tolerated, with hot flashes being the most common side effect.

Somatostatin Analogue

Octreotide acetate (*Sandostatin*) is a synthetic peptide analogue of the hormone somatostatin. Its actions include inhibition of the pituitary secretion of growth hormone and an inhibition of pancreatic islet cell secretion of insulin and glucagon. Unlike somatostatin, which has a plasma half-life of a few minutes, octreotide has a plasma elimination half-life of 1 to 2 hours. Excretion of the drug is primarily renal.

Octreotide is useful in inhibiting the secretion of various autacoids and peptide hormones by metastatic carcinoid tumors (serotonin) and islet cell carcinomas of the pancreas (gastrin, glucagon, insulin, vasoactive intestinal peptide). The diarrhea and flushing associated with the carcinoid syndrome are improved in 70 to 80% of the patients treated with octreotide. Its side effects, which are usually mild, include nausea and pain at the injection site. Mild transient hypoglycemia or hyperglycemia may result from alterations in insulin, glucagon, or growth hormone secretion.

MISCELLANEOUS AGENTS

Hydroxyurea

Hydroxyurea (*Hydrea*) inhibits the enzyme *ribonucleotide reductase* and thus depletes intracellular pools of deoxyribonucleotides, resulting in a specific impairment of DNA synthesis. The drug therefore is an S-phase specific agent whose action results in an accumulation of cells in the late G_1- and early S-phases of the cell cycle.

Hydroxyurea is rapidly absorbed after oral administration, with peak plasma levels achieved approximately 1 to 2 hours after drug administration; its elimi-

nation half-life is 2 to 3 hours. The primary route of excretion is renal, with 30 to 40% of a dose excreted unchanged.

Hydroxyurea is used for the rapid lowering of blood granulocyte counts in patients with chronic granulocytic leukemia. The drug also can be used as maintenance therapy for patients with the disease who have become resistant to busulfan. Only a small percentage of patients with other malignancies have had even brief remissions induced by hydroxyurea administration.

Hematological toxicity, with white blood cells affected more than platelets, may occur. Megaloblastosis of the bone marrow also may be observed. Recovery is rapid, generally within 10 to 14 days after discontinuation of the drug. Some skin reactions, including hyperpigmentation and hyperkeratosis, have been reported with chronic treatment.

Procarbazine

Procarbazine (*Matulane*) may autooxidize spontaneously, and during this reaction hydrogen peroxide and hydroxyl free radicals are generated. These highly reactive products may degrade DNA and serve as one mechanism of procarbazine-induced cytotoxicity. Cell toxicity also may be the result of a transmethylation reaction that can occur between the *N*-methyl group of procarbazine and the N7 position of guanine.

Procarbazine is rapidly absorbed after oral administration and has a plasma half-life of only 10 minutes. The drug crosses the blood-brain barrier, reaching levels in CSF equal to those obtained in plasma. Metabolism is extensive and complex. Urinary excretion accounts for 70% of the procarbazine and its metabolites lost during the first 24 hours after drug administration.

When originally tested as a single agent in advanced Hodgkin's disease, procarbazine produced tumor regression responses that were brief, usually lasting only 1 to 3 months. The combination of procarbazine with mechlorethamine, vincristine, and prednisone in the MOPP regimen, however, resulted in an 81% complete remission rate in Hodgkin's disease. Most of these patients are considered cured. Procarbazine is also used in various combination chemotherapy protocols for non-Hodgkin's lymphomas and small cell anaplastic (oat cell) carcinoma of the lung. Limited antitumor effects have been observed against multiple myeloma, melanoma, and non–oat cell lung cancers.

The major side effects associated with procarbazine therapy are nausea and vomiting, leukopenia, and thrombocytopenia. Skin rashes have been reported, as have rare cases of allergic interstitial pneumonia. Procarbazine administration produces a high degree of chromosomal breakage, and the compound is mutagenic, teratogenic, and carcinogenic in experimental systems.

Procarbazine may potentiate the effects of tranquilizers and hypnotics. Hypertensive episodes can result if procarbazine is administered simultaneously with adrenomimetic drugs or with tyramine-containing foods. Rarely, a reaction to alcohol similar to that provoked by disulfiram may occur.

Mitotane

The observation that mitotane (*Lysodren*) could produce adrenocortical necrosis in animals led to its use in the palliation of inoperable adrenocortical adenocarcinomas. A reduction in both tumor size and adrenocortical hormone secretion can be achieved in about half of the patients taking the drug. Because normal adrenocortical cells also are affected, endogenous glucocorticoid production should be monitored and replacement therapy administered when appropriate.

Mitotane is incompletely absorbed from the gastrointestinal tract after oral administration. However, once absorbed, it tends to accumulate in adipose tissue. Mitotane is slowly excreted and will appear in the urine for several years. The major toxicities associated with its use are anorexia, nausea, diarrhea, lethargy, somnolence, dizziness, and dermatitis.

Hexamethylmelamine

Although both DNA and RNA synthesis are inhibited in cells exposed to hexamethylmelamine (*Hexalen*), the molecular mechanisms of these effects are not known.

Hexamethylmelamine is readily absorbed after oral administration, with peak plasma levels achieved after 1 hour. The drug is readily metabolized to form a number of demethylated metabolites. Urinary elimination is the primary route of drug excretion.

Hexamethylmelamine is useful for the treatment of ovarian adenocarcinoma and is frequently combined with cyclophosphamide, cisplatin, and doxorubicin in the treatment of this tumor. It also has some activity against small cell lung cancer.

Nausea and vomiting are the major toxicities associated with hexamethylmelamine administration. Myelosuppression and a peripheral neuropathy also may occur.

Cisplatin

Cisplatin (*Platinol*) is an inorganic coordination complex with a broad range of antitumor activity. It is especially useful in the treatment of testicular and ovarian cancer. It binds to DNA at nucleophilic sites, such as the N7 and O6 of guanine, producing alterations in DNA structure and inhibition of DNA synthesis. Adjacent guanine residues on the same DNA strand are preferentially cross-linked. This platinating activity is analogous

to the mode of action of alkylating agents. Cisplatin also binds extensively to proteins. It does not appear to be phase specific in the cell cycle.

Cisplatin shows biphasic plasma decay with a distribution phase half-life of 25 to 49 minutes and an elimination half-life of 2 to 4 days. More than 90% of the drug is bound to plasma proteins, and binding may approach 100% during prolonged infusion. Cisplatin does not cross the blood-brain barrier. Excretion is predominantly renal and is incomplete.

Cisplatin, combined with bleomycin and vinblastine or etoposide, produces cures in most patients with metastatic testicular cancer or germ cell cancer of the ovary. Cisplatin also shows some activity against carcinomas of the head and neck, bladder, cervix, prostate, and lung.

Renal toxicity is the major potential toxicity of cisplatin. Severe nausea and vomiting that often accompany cisplatin administration may necessitate hospitalization. Cisplatin has mild bone marrow toxicity, yielding both leukopenia and thrombocytopenia. Anemia is common and may require transfusions of red blood cells. Anaphylactic allergic reactions have been described. Hearing loss in the high frequencies (4000 Hz) may occur in 10 to 30% of patients. Other reported toxicities include peripheral neuropathies with paresthesias, leg weakness, and tremors. Excessive urinary excretion of magnesium also may occur.

Carboplatin

Carboplatin (*Paraplatin*) is an analogue of cisplatin. Its plasma half-life is 3 to 5 hours, and it has no significant protein binding. Renal excretion is the major route of drug elimination.

Despite its lower chemical reactivity, carboplatin has antitumor activity that is similar to that of cisplatin against ovarian carcinomas, small cell lung cancers, and germ cell cancers of the testis. Most tumors that are resistant to cisplatin are cross-resistant to carboplatin.

The major advantage of carboplatin over cisplatin is a markedly reduced risk of toxicity to the kidneys, peripheral nerves, and hearing; additionally, it produces less nausea and vomiting. It is, however, more myelosuppressive than cisplatin. Other adverse effects include anemia, abnormal liver function tests, and occasional allergic reactions.

Mitoxantrone

Mitoxantrone (*Novantrone*) is a synthetic anthraquinone that is structurally and mechanistically related to the anthracyclines. It intercalates with DNA and produces single-strand DNA breakage. It is cross-resistant with doxorubicin in multidrug-resistant cells and in patients who have failed to respond to doxorubicin therapy.

Mitoxantrone is active against breast carcinomas, leukemias, and lymphomas. Its antitumor efficacy in patients with breast cancer is slightly lower than that of doxorubicin. Its major toxicity is myelosuppression; mucositis and diarrhea also may occur. Mitoxantrone produces less nausea, alopecia, and cardiac toxicity than does doxorubicin.

IMMUNOMODULATING AGENTS

Levamisole

Levamisole (*Ergamisol*) is an antiparasitic drug that has been found to enhance T-cell function and cellular immunity. The drug improves survival of patients with resected colorectal cancers when combined with 5-fluorouracil; the mechanism of this interaction is not known. Levamisole does not have antitumor activity against established or metastatic cancer and has not been found useful in the adjuvant therapy of cancers other than colorectal cancer.

The major adverse effects of levamisole are nausea and anorexia. Skin rashes, itching, flulike symptoms, and fevers also have been observed.

Interferon Alfa-2b

Interferon alfa-2b (*Intron A*) is a recombinant DNA product derived from the interferon alfa-2b gene of human white blood cells. Its mechanism of antitumor action involves binding to a plasma membrane receptor but is otherwise poorly understood. Its serum half-life is 2 to 3 hours after parenteral administration.

Interferon alfa-2b is useful in the treatment of a rare form of chronic leukemia, hairy cell leukemia, in which it produces remissions in 60 to 80% of patients. However, it has minimal antitumor activity in most human cancers. Remissions lasting a few months have been observed in 10 to 20% of patients with lymphomas, multiple myeloma, melanoma, renal cell carcinoma, and ovarian carcinoma.

The adverse effects of interferon alfa-2b include fever and a flulike syndrome of muscle ache, fatigue, headache, anorexia, and nausea. Other less common side effects include leukopenia, diarrhea, dizziness, and skin rash.

Interleukins

Aldesleukin

Aldesleukin (IL-2, *Proleukin*) is a human recombinant interleukin-2 protein. Its antitumor action is thought to include multiple effects on the immune system, such as

enhancement of T-lymphocyte cytotoxicity, induction of natural killer cell activity, and induction of interferon-γ production. Aldesleukin has been used alone and in combination with lymphokine activated killer (LAK) cells or tumor-infiltrating lymphocytes (TIL).

The drug produces remissions in 15% of patients with renal cell carcinoma, with median durations of remission of 18 to 24 months.

Several serious toxicities have been observed, with a fatality rate of 5% in the initial studies. The major adverse effect is severe hypotension in as many as 85% of patients, which may lead to myocardial infarctions, pulmonary edema, and strokes. This hypotension is thought to be due to a capillary leak syndrome resulting from extravasation of plasma proteins and fluid into extravascular space and a loss of vascular tone. Patients with significant cardiac, pulmonary, renal, hepatic, or CNS conditions should not receive therapy with aldesleukin. Other adverse reactions include nausea and vomiting, diarrhea, stomatitis, anorexia, altered mental status, fevers, and fatigue.

CELLULAR GROWTH FACTORS

Filgrastim

Filgrastim (*Neupogen*) is a human recombinant granulocyte colony–stimulating factor (rG-CSF) produced using recombinant DNA technology. It acts on precursor hematopoietic cells in the bone marrow by binding to specific receptors that stimulate cellular proliferation and differentiation into neutrophils. It also enhances some neutrophil functions, including phagocytosis and antibody-dependent killing.

Filgrastim is used to accelerate recovery of neutrophils after chemotherapy, both to prevent infections and to shorten the duration of neutropenia in patients in whom infections have developed.

The drug is generally well tolerated, with the major adverse reaction being mild to moderate bone pain secondary to stimulation of bone marrow proliferation.

Sargramostim

Sargramostim (GM-CSF, *Leukine, Prokine*) is a human recombinant granulocyte and macrophage colony–stimulating factor that stimulates the production and potentiates the function of both granulocytes and macrophages from hematopoietic progenitor cells. It is used to accelerate bone marrow repopulation after high-dose chemotherapy, radiation therapy, and bone marrow transplantation. Adverse effects associated with sargramostim use include bone pain (similar to that of filgrastim), fatigue, fevers, skin rash, malaise, and fluid retention.

NEW DRUG THERAPIES FOR CANCER

Imantinib

Imantinib mesylate (*Gleevec*) is a rationally designed inhibitor of the tumor-specific bcr-abl kinase. The Philadelphia chromosome, present in nearly all patients with chronic myelogenous leukemia (CML), is produced by a chromosomal rearrangement linking the bcr and the abl genes. The bcr-able kinase is therefore a unique drug target in leukemic cells, and imantinib selectively and potently inhibits this kinase. Remissions in CML patients are achieved with high frequency and very low toxicity, and this compound may become a front-line agent for treating this cancer. Unfortunately, drug resistance has already been observed in the clinic as a result of mutations in the bcr-abl kinase, and this magic bullet does not appear to be curative for CML patients. Extension of the use of imantinib to other tumor types with overexpression of c-kit kinase or platelet-derived growth factor kinase is undergoing development because of its observed activity against these kinases.

Herceptin

The introduction of herceptin (*Trastuzumab*) into clinical practice for the treatment of breast cancer marks a major advance in the use of monoclonal antibody cancer therapy. Herceptin is a humanized antibody directed against the HER-2 antigen that is overexpressed on the tumor cell surface in approximately 25% of breast cancer patients. HER-2/neu/erbB2 overexpression marks an aggressive estrogen receptor–negative form of breast cancer. Therefore, a therapeutic agent selective for this target is particularly valuable. Herceptin is administered by intravenous infusion and in conjunction with paclitaxel can extend survival in patients with HER-2/neu/erbB2 overexpressing metastatic breast cancer. Herceptin use is associated with infusion- related hypotension, flushing and bronchoconstriction, and skin rash but no bone marrow toxicity. Herceptin appears to sensitize patients to cardiotoxicity, an important concern in patients also receiving doxorubicin.

Iressa

Iressa (ZD1839) is an orally active tyrosine kinase inhibitor selective for the epidermal growth factor (EGF) receptor tyrosine kinase. Iressa is undergoing clinical trials in the treatment of various solid tumors, including head and neck cancer, breast cancer and non-small cell lung cancer. Its antitumor activity is derived from the fact that the EGF receptor and EGF signaling are

frequently overactivated in sensitive tumors. The major side effects include diarrhea and skin rash. Bone marrow toxicity has not been a dose-limiting problem.

A summary of the principal clinical uses of most of the drugs mentioned in this chapter can be found in Table 56.2.

TABLE 56.2 Major Clinical Uses of the Anticancer Drugs

Drugs	Therapeutic Uses
Aldesleukin	**Renal cell carcinoma**
L-Asparaginase	Acute lymphocytic leukemia, lymphomas
Bleomycin	Advanced testicular carcinoma; Hodgkin's and non-Hodgkin's lymphomas; squamous cell carcinoma of head, neck, cervix, skin
Buserelin, estramustine, flutamide, leuprolide	Prostatic cancer
Busulfan	Chronic granulocytic leukemia
Carboplatin, cisplatin	Testicular and ovarian cancer
Carmustine, lomustine, semustine	CNS tumors, Hodgkin's disease, lymphomas, melanoma, colorectal and renal cell cancer
Chlorambucil	Chronic lymphocytic leukemia, myeloma, lymphomas
Cladribine, pentostatin	Hairy cell leukemia
Cyclophosphamide	Lymphoma, breast and ovarian cancer, oat cell lung cancer
Cytarabine	Acute myelogenous and acute lymphoblastic leukemia, lymphomas
Dacarbazine	Metastatic melanoma, sarcomas, Hodgkin's disease
Dactinomycin	Wilms' tumor, Ewing's sarcoma, rhabdomyosarcoma, gestational choriocarcinoma, testicular tumors, lymphomas, melanomas
Daunorubicin, doxorubicin, idarubicin	Breast, ovarian, endometrial, bladder, thyroid cancers; oat cell cancer of the lung
Etoposide, teniposide	Testicular, ovarian germ cell cancers, small-cell lung cancer, acute myelogenous and lymphoblastic leukemia
Filgrastim	Promotes recovery of neutrophils after chemotherapy
Fludarabine	Chronic lymphocytic leukemia, low-grade lymphomas
Fluorouracil	Breast, ovarian, cervical, bladder and prostate cancer; gastrointestinal adenocarcinomas
Gemcitabine	Metastatic pancreatic cancer; small cell lung cancer
Gleevec	Leukemia
Herceptin	Breast cancer
Hexamethylmelamine	Ovarian adenocarcinoma, small-cell lung cancer
Hydroxyurea	Chronic myelogenous leukemia
Ifosfamide	Multiple myeloma, breast and ovarian cancer
Interferon alfa-2b	Hairy cell leukemia
Iressa	Head, neck, breast, and lung cancer
Levamisole	Colorectal cancer
Mechlorethamine	Hodgkin's disease
Melphalan	Multiple myeloma, breast and ovarian cancer
Mercaptopurine	Acute lymphoblastic leukemia; acute and chronic myelogenous leukemias
Methotrexate	Acute lymphoblastic leukemia; Burkitt's lymphoma; trophoblastic choriocarcinoma; breast cancer; head, neck, cervical, lung carcinomas
Mitomycin	Stomach, pancreatic, colon, breast, cervical carcinomas
Mitotane	Adrenocortical adenocarcinoma
Mitoxantrone	Breast carcinoma, leukemia, lymphomas
Octreotide	Metastatic carcinoid, islet cell carcinomas
Paclitaxel	Breast, ovarian, lung, head, neck tumors
Plicamycin	Hypercalcemia of malignancy, metastatic testicular carcinoma
Procarbazine	Lymphomas, small cell anaplastic lung cancers
Sargramostim	Stimulates granulocyte and macrophage production after chemotherapy
Streptozocin	Islet cell pancreatic carcinoma, malignant carcinoid tumor
Tamoxifen	Breast cancer
Thioguanine	Acute myelogenous leukemia
Thiotepa	Breast, ovarian cancer, lymphomas
Vincristine, vinblastine, vinorelbine	Acute lymphoblastic leukemia, Hodgkin's disease, pediatric solid tumors (e.g., Wilms', Ewing's), neuroblastoma

Study Questions

1. The nitrogen mustard with the broadest spectrum of antitumor activity in its class is
   (A) Ifosfamide
   (B) Cyclophosphamide
   (C) Mechlorethamine
   (D) Chlorambucil
   (E) Melphalan
2. The first demonstration of the curative potential of chemotherapy in human cancer was the use of which agent in trophoblastic choriocarcinoma in women?
   (A) Chlorambucil
   (B) Thiotepa
   (C) Methotrexate
   (D) Melphalan
   (E) Carmustine
3. Which class of drugs bind avidly to tubulin and cause arrest of cells in metaphase?
   (A) Vinca alkaloids
   (B) Nitrogen mustards
   (C) Alkylating agents
   (D) Antiestrogens
   (E) Antimetabolites
4. You see a patient with breast cancer whose cancer is ER positive. You prescribe tamoxifen. The patient inquires about her chances for remission. What do you tell her?
   (A) You indicate that you do not have a good idea and that only time will tell.
   (B) You indicate that her chances are not too good.
   (C) You indicate that her chances of remission are about 95%.
   (D) You indicate that her chances are somewhat better than 50%.
   (E) You indicate that her chances would be better if her tumor were ER negative.
5. Interferon alfa-2b has been somewhat of a disappointment as an anticancer drug. However, it has proved useful in the treatment of which of the following tumors?
   (A) Oat cell tumors of the lung
   (B) Melanoma
   (C) Wilms' tumor
   (D) ER-positive breast cancer
   (E) Hairy cell leukemia

ANSWERS

1. **B.** Although all of the compounds are nitrogen mustards and have the same basic mechanism of action, differences in the toxicity profile, duration of action, metabolism, and distribution within the body account for the fact that differences in the spectrum of antitumor activity and clinical indications differ for agents within the same class. Ifosfamide also has a broad spectrum of antitumor activity although it is not as broad as that of cyclophosphamide. Mechlorethamine is indicated for use only in Hodgkin's disease. Bone marrow toxicity limits the usefulness of chlorambucil. The effectiveness of melphalan is limited because a substituted phenyl ring in the molecule reduces its reactivity.
2. **C.** The long-term complete remissions of trophoblastic choriocarcinoma in women was the first demonstration of the curative potential of chemotherapy in human cancer. The other choices are all nitrogen mustard compounds. Although carmustine has been shown to produce long-lasting remission in patients with primary brain tumor, the toxicity of nitrogen mustards limits their use. They are usually used in combination with other agents.
3. **A.** The mechanism of action of nitrogen mustards is to form covalent bonds with adjacent guanine residues and inhibit DNA replication and transcription. The nitrogen mustards are also alkylating agents. Antiestrogens inhibit in vitro growth of human breast cancer cells that contain estrogen receptors. Antimetabolites are drugs that are structurally related to naturally occurring compounds, such as vitamins, amino acids, or nucleotides. They can compete for binding sites on enzymes or can become incorporated into DNA or RNA and thus interfere with cell growth and proliferation.
4. **D.** Actually the chances of remission are about 60%. The presence of ER-positive tumors is much more favorable for tamoxifen therapy than if the tumors were ER negative.
5. **E.** The discovery that the endogenous proteins known as interferons were capable of containing viral infections led to the hope that they would have many beneficial results, including anticancer activity. Although they are effective in the treatment of hairy cell leukemia and AIDS-associated Kaposi's sarcoma, they have not been shown to be the panacea that was originally envisioned.

SUPPLEMENTAL READING

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CASE Study Treatment of Leukemic Meningitis

A 15-year-old girl moves into your neighborhood and makes an appointment to see you. She is being treated for acute lymphoblastic leukemia. She tells you that she has been doing well, but recently she has had frequent severe headaches, and her mother said she has stumbled a couple of times during the past week for no apparent reason. She is being treated with cytarabine. If leukemic meningitis is suspected, what should be done next?

ANSWER: Immediately arrange for an evaluation of the CSF. If the CSF reveals leukemic cells, you can consider administering methotrexate 12 mg intrathecally every day for 4 days. With such a regimen, subsequent evaluations of the CSF often indicate no leukemic cells present. The headaches and balance problems typically disappear. Six months later, most patients show no evidence of leukemia.