**Anticancer Drugs**

I**. OVERVIEW**

It is estimated that 25 percent of the population of the United States will face a diagnosis of cancer during their lifetime, with 1.3 million new cancer patients diagnosed each year. Less than a quarter of these patients will be cured solely by surgery and/or local radiation. Most of the remain- der will receive systemic chemotherapy at some time during their illness. In a small fraction (approximately 10 percent) of patients with cancer rep- resenting selected neoplasms, the chemotherapy will result in a cure or a prolonged remission. However, in most cases, the drug therapy will produce only a regression of the disease, and complications and/or relapse may eventually lead to death. Thus, the overall 5-year survival rate for cancer patients is about 65 percent, ranking cancer second only to cardiovascular disease as a cause of mortality. See Figure 39.1 for a list of the anticancer agents discussed in this chapter.

II**. PRINCIPLES OF CANCER CHEMOTHERAPY**

Cancer chemotherapy strives to cause a lethal cytotoxic event or apoptosis in the cancer cell that can arrest a tumor’s progression. The attack is generally directed toward DNA or against metabolic sites essential to cell replication, for example, the availability of purines and pyrimidines that are the building blocks for DNA or RNA synthesis (Figure 39.2). Ideally, these anticancer drugs should interfere only with cellular processes that are unique to malignant cells. Unfortunately, most currently avail- able anticancer drugs do not specifically recognize neoplastic cells but, rather, affect all kinds of proliferating cells, both normal and abnormal. Therefore, almost all antitumor agents have a steep dose-response curve for both toxic and therapeutic effects.

A**. Treatment strategies**

1. **Goals of treatment**: The ultimate goal of chemotherapy is a cure (that is, long-term, disease-free survival). A true cure requires the eradication of every neoplastic cell. If a cure is not attainable, then the goal becomes control of the disease (stop the cancer from enlarging and spreading) to extend survival and maintain the best quality of life. Thus, the individual maintains a “normal” existence, with the cancer being treated as a chronic disease. In either case, the neoplastic cell burden is initially reduced (debulked), either by surgery and/or by radiation, followed by chemo- therapy, immunotherapy, or a combination of these treatment modalities (Figure 39.3). In advanced stages of cancer, the likelihood of controlling the cancer is far from reality and the goal is palliation (that is, alleviation of symptoms and avoidance of life-threatening toxicity). This means that chemotherapeutic drugs may be used to relieve symptoms caused by the cancer and improve the quality of life, even though the drugs may not lengthen life.

**2. Indications for treatment**: Chemotherapy is indicated when neoplasms are disseminated and are not amenable to surgery. Chemotherapy is also used as a supplemental treatment to attack micrometastases following surgery and radiation treatment, in which case it is called adjuvant chemotherapy. Chemotherapy given prior to the surgical procedure in an attempt to shrink the cancer is referred to as neoadjuvant chemotherapy, and chemotherapy given in lower doses to assist in prolonging a remission is known as maintenance chemotherapy.

**3. Tumor susceptibility** and the growth cycle: The fraction of tumor cells that are in the replicative cycle (“growth fraction”) influences their susceptibility to most cancer chemotherapeutic agents. Rapidly dividing cells are generally more sensitive to anticancer drugs, whereas slowly proliferating cells are less sensitive to chemo therapy. In general, nonproliferating cells (those in the G0 phase; Figure 39.4) usually survive the toxic effects of many of these agents.

**a. Cell-cycle specificity of drugs**:

 Both normal cells and tumor cells go through growth cycles (see Figure 39.4). However, the number of cells that are in various stages of the cycle may differ in normal and neoplastic tissues. Chemotherapeutic agents that are effective only against replicating cells (that is, those cells that are cycling) are said to be cell-cycle specific (see Figure 39.4), whereas other agents are said to be cell-cycle nonspecific. The nonspecific drugs, although having generally more toxicity in cycling cells, are also useful against tumors that have a low percentage of replicating cells.

**b. Tumor growth rate**

The growth rate of most solid tumors in vivo is initially rapid, but growth rate usually decreases as the tumor size increases (see Figure 39.3). This is due to the unavailability of nutrients and oxygen caused by inadequate vascularization and lack of blood circulation. Reducing the tumor burden through surgery or radiation often promotes the recruitment of the remaining cells into active proliferation and increases their susceptibility to chemotherapeutic agents.

**B. Treatment regimens and scheduling**

Drugs are usually administered on the basis of body surface area, with an effort being made to tailor the medications to each patient.

**1. Log kill**: Destruction of cancer cells by chemotherapeutic agents follows first-order kinetics (that is, a given dose of drug destroys a constant fraction of cells). The term “log kill” is used to describe this phenomenon. For example, a diagnosis of leukemia is generally made when there are about 109 (total) leukemic cells. Consequently, if treatment leads to a 99.999-percent kill, then 0.001 percent of 109 cells (or 104 cells) would remain. This is defined as a five-log kill (reduction of 105 cells). At this point, the patient will become asymptomatic, and the patient is in remission (see Figure 39.3). For most bacterial infections, a fi ve-log (100,000-fold) reduction in the number of microorganisms results in a cure, because the immune system can destroy the remaining bacterial cells. However, tumor cells are not as readily eliminated, and additional treatment is required to totally eradicate the leukemic cell population.

2**. Pharmacologic sanctuaries**: Leukemic or other tumor cells fi nd sanctuary in tissues such as the central nervous system (CNS), where transport constraints prevent certain chemotherapeutic agents from entering. Therefore, a patient may require irradiation of the craniospinal axis or intrathecal administration of drugs to eliminate the leukemic cells at that site. Similarly, drugs may be unable to penetrate certain areas of solid tumors.

**3. Treatment protocols**: Combination-drug chemotherapy is more successful than single-drug treatment in most of the cancers for which chemotherapy is effective.

**a. Combinations of drugs**: Cytotoxic agents with qualitatively different toxicities, and with different molecular sites and mechanisms of action, are usually combined at full doses. This results in higher response rates, due to additive and/ or potentiated cytotoxic effects, and nonoverlapping host toxicities. In contrast, agents with similar dose-limiting toxicities, such as myelosuppression, nephrotoxicity, or cardiotoxicity, can be combined safely only by reducing the doses of each.

**b. Advantages of drug combinations**: The advantages of such drug combinations are that they 1) provide maximal cell killing within the range of tolerated toxicity, 2) are effective against a broader range of cell lines in the heterogeneous tumor population, and 3) may delay or prevent the development of resistant cell lines.

**c. Treatment protocols**: Many cancer treatment protocols have been developed, and each one is applicable to a particular neoplastic state. They are usually identified by an acronym. For example, a common regimen called POMP, used for the treatment of acute lymphocytic leukemia, consists of prednisone, oncovin (vincristine), methotrexate, and purinethol (mercapto purine). Therapy is scheduled intermittently (approximately 21 days apart) to allow recovery of the patient’s immune system, which is also affected by the chemotherapeutic agent, thus reducing the risk of serious infection.

**C. Problems associated with chemotherapy**

Cancer drugs are toxins that present a lethal threat to the cells. It is, therefore, not surprising that cells have evolved elaborate defense mechanisms to protect themselves from chemical toxins, including chemotherapeutic agents.

 1**. Resistance**: Some neoplastic cells (for example, melanoma) are inherently resistant to most anticancer drugs. Other tumor types may acquire resistance to the cytotoxic effects of a medication by mutating, particularly after prolonged administration of suboptimal drug doses. The development of drug resistance is minimized by short-term, intensive, intermittent therapy with combinations of drugs. Drug combinations are also effective against a broader range of resistant cells in the tumor population. A variety of mechanisms are responsible for drug resistance, each of which is considered separately in the discussion of a particular drug.

**2. Multidrug resistance**: Stepwise selection of an amplified gene that codes for a transmembrane protein (P-glycoprotein for “permeability” glycoprotein; Figure 39.5) is responsible for multidrug resistance. This resistance is due to adenosine triphosphate–dependent pumping of drugs out of the cell in the presence of P-glycoprotein. Cross- resistance following the use of structurally unrelated agents also occurs. For example, cells that are resistant to the cytotoxic effects of the vinca alkaloids are also resistant to dactinomycin and to the anthracycline antibiotics as well as to colchicine, and vice versa. These drugs are all naturally occurring substances, each of which has a hydrophobic aromatic ring and a positive charge at neutral pH. [Note: P-glycoprotein is normally expressed at low levels in most cell types, but higher levels are found in the kidney, liver, pancreas, small intestine, colon, and adrenal gland. It has been suggested that the presence of P-glycoprotein may account for the intrinsic resistance to chemo therapy observed with adenocarcinomas.] Certain drugs at high concentrations (for example, verapamil) can inhibit the pump and, thus, interfere with the efflux of the anticancer agent. However, these drugs are undesirable because of adverse pharmacologic actions of their own. Pharmacologically inert pump blockers are being sought.

**3. Toxicity**: Therapy aimed at killing rapidly dividing cancer cells also affects normal cells undergoing rapid proliferation (for exam- ple, cells of the buccal mucosa, bone marrow, gastrointestinal [GI] mucosa, and hair follicles), contributing to the toxic manifestations of chemotherapy.

**a. Common adverse effects**: Most chemotherapeutic agents have a narrow therapeutic index. Severe vomiting, stomatitis, bone marrow suppression, and alopecia occur to a lesser or greater extent during therapy with all antineoplastic agents. Vomiting is often controlled by administration of antiemetic drugs. Some toxicities, such as myelosuppression that predisposes to infection, are common to many chemotherapeutic agents (Figure 39.6), whereas other adverse reactions are confined to specific agents, such as, bladder toxicity with cyclophosphamide, cardiotoxicity with doxorubicin, and pulmonary fibrosis with bleomycin. The duration of the side effects varies widely. For example, alopecia is transient, but the cardiac, pulmonary, and bladder toxicities are irreversible.

**b. Minimizing adverse effects**: Some toxic reactions may be ameliorated by interventions, such as the use of cytoprotectant drugs, perfusing the tumor locally (for example, a sarcoma of the arm), removing some of the patient’s marrow prior to intensive treatment and then reimplanting it, or promoting intensive diuresis to prevent bladder toxicities. The megaloblastic anemia that occurs with methotrexate can be effectively counteracted by administering folinic acid (leucovorin, 5-formyltetrahydrofolic acid; see below). With the availability of human granulocyte colony–stimulating factor (filgrastim), the neutropenia associated with treatment of cancer by many drugs can be partially reversed.

**4. Treatment-induced tumors**: Because most antineoplastic agents are mutagens, neoplasms (for example, acute nonlymphocytic leukemia) may arise 10 or more years after the original cancer was cured. [Note: Treatment-induced neoplasms are especially a problem after therapy with alkylating agents.]

**III. ANTIMETABOLITES**

Antimetabolites are structurally related to normal compounds that exist within the cell. They generally interfere with the availability of normal purine or pyrimidine nucleotide precursors, either by inhibiting their synthesis or by competing with them in DNA or RNA synthesis. Their maximal cytotoxic effects are in S-phase (and are, therefore, cell-cycle specific).

**A.Methotrexate**

The vitamin folic acid plays a central role in a variety of metabolic reactions involving the transfer of one-carbon units1 and is essential for cell replication. Methotrexate [meth-oh-TREK-sate] (MTX) is structurally related to folic acid and acts as an antagonist of that vitamin by inhibiting dihydrofolate reductase2 (DHFR), which is the enzyme that converts folic acid to its active, coenzyme form, tetrahydrofolic acid (FH4).

**1. Mechanism of action**: Folic acid is obtained from dietary sources or from that produced by intestinal flora. It undergoes reduction to FH4 via a reaction catalyzed by intracellular nicotinamideade- nine dinucleotide phosphate–dependent DHFR (Figure 39.7). MTX enters the cell by active-transport processes that normally mediate the entry of N5-methyl-FH4. At high concentrations, the drug can also diff use into the cell. MTX has an unusually strong affinity for DHFR and effectively inhibits the enzyme. Like tetra hydrofolate itself, MTX becomes polyglutamated within the cell, a process that favors intracellular retention of the compound due to increased negative charge. MTX polyglutamates also potently inhibit DHFR. This inhibition deprives the cell of folate coenzymes and leads to decreased production of compounds that depend on these coen- zymes for their biosynthesis. Although these molecules include the nucleotides adenine, guanine, and thymidine and the amino acids methionine and serine, depletion of thymidine is the most prominent effect. This leads to depressed DNA, RNA, and protein synthesis and, ultimately, to cell death (see Figure 39.7). The inhibition of DHFR can only be reversed by a thousandfold excess of the natural substrate, dihydrofolate (FH2; see Figure 39.7), or by administration of leucovorin, which bypasses the blocked enzyme and replenishes the folate pool. [Note: Leucovorin, or folinic acid, is the N5-formyl group–carrying form of FH4.] MTX is specific for the S phase of the cell cycle.

**2. Resistance**: Nonproliferating cells are resistant to MTX, probably because of a relative lack of DHFR, thymidylate synthase, and/or the glutamylating enzyme. Decreased levels of the MTX polygluta- mate have been reported in resistant cells and may be due to its decreased formation or increased breakdown. Resistance in neo- plastic cells can be due to amplification (production of additional copies) of the gene that codes for DHFR, resulting in increased levels of this enzyme. The enzyme affinity for MTX may also be diminished. Resistance can also occur from a reduced influx of MTX, apparently caused by a change in the carrier-mediated transport responsible for pumping the drug into the cell.

**3. Therapeutic uses**: MTX, usually in combination with other drugs, is effective against acute lymphocytic leukemia, choriocarcinoma, Burkitt lymphoma in children, breast cancer, and head and neck carcinomas. In addition, low-dose MTX is effective as a single agent against certain inflammatory diseases, such as severe psoriasis and rheumatoid arthritis as well as Crohn disease. All patients receiving MTX require close monitoring for possible toxic effects.

**4. Pharmacokinetics**:

**a. Administration and distribution**: MTX is variably absorbed at low doses from the GI tract, but it can also be administered by intramuscular, intravenous (IV), and intrathecal routes (Figure 39.8). [Note: Because MTX does not penetrate the blood-brain barrier, it is administered intrathecally to destroy neoplastic cells that are thriving in the sanctuary of the CNS.] High concentrations of the drug are found in the intestinal epithelium, liver, and kidney as well as in ascites and pleural eff usions. MTX is also distributed to the skin.

**b. Fate:** As previously mentioned, MTX is metabolized to poly- glutamate derivatives. This property is important, because the polyglutamates, which also inhibit DHFR, remain within the cell even in the absence of extracellular drug. This is in contrast to MTX per se, which rapidly leaves the cell as the extracellular drug levels fall. High doses of MTX undergo hydroxylation at the 7 position and become 7-hyroxymethotrexate. This derivative is much less active as an antimetabolite. It is less water soluble than MTX and may lead to crystalluria. Therefore, it is important to keep the urine alkaline and the patient well hydrated to avoid renal toxicity. Excretion of the parent drug and the 7-OH metabolite occurs primarily via urine, although some of the drug and its metabolite appear in feces due to enterohepatic excretion.

**5. Adverse effects**:

**a. Commonly observed toxicities**: In addition to nausea, vomiting, and diarrhea, the most frequent toxicities occur in tissues that are constantly renewing. Thus, MTX causes stomatitis, myelosuppression, erythema, rash, urticaria, and alopecia. Some of these adverse effects can be prevented or reversed by administering leucovorin (see Figure 39.7), which is taken up more readily by normal cells than by tumor cells. Doses of leucovorin must be kept minimal to avoid possible interference with the antitumor action of MTX

 **b. Renal damage**: Although uncommon during conventional therapy, renal damage is a complication of high-dose MTX and its 7-OH metabolite, which can precipitate in the tubules. Alkalinization of the urine and hydration help to prevent this problem.

**c. Hepatic function**: Hepatic function should be monitored. Long- term use of MTX may lead to cirrhosis.

**d. Pulmonary toxicity**: This is a rare complication. Children who are being maintained on MTX may develop cough, dyspnea, fever, and cyanosis. Infiltrates are seen on radiographs. This toxicity is reversible with suspension of the drug.

**e. Neurologic toxicities**: These are associated with intrathecal administration of MTX and include subacute meningeal irritation, stiff neck, headache, and fever. Rarely, seizures, encephalopathy, or paraplegia occur. Long-lasting effects, such as learning disabilities, have been seen in children who received the drug by this route.

**f. Contraindications**: Because MTX is teratogenic in experimental animals and is an abortifacient, it should be avoided in pregnancy. [Note: MTX is used with misoprostol to induce abortion.]

**B. 6-Mercaptopurine**

6-Mercaptopurine [mer-kap-toe-PYOOR-een] (6-MP) is the thiol analog of hypoxanthine. 6-MP and 6-thioguanine were the first purine analogs to prove beneficial for treating neoplastic disease. [Note: Azathioprine, an immunosuppressant, exerts its cytotoxic effects after conversion to 6-MP.] 6-MP is used principally in the maintenance of remission in acute lymphoblastic leukemia. 6-MP and its analog, azathioprine, are also beneficial in the treatment of Crohn disease.

**1. Mechanism of action**:

**a. Nucleotide formation**: To exert its antileukemic effect, 6-MP must penetrate target cells and be converted to the nucleotide analog, 6-MP-ribose phosphate (better known as 6-thioinosinic acid, or TIMP; Figure 39.9). The addition of the ribose phosphate is catalyzed by the salvage pathway enzyme, hypoxanthine- guanine phosphoribosyl transferase (HGPRT).3

**b. Inhibition of purine synthesis**: A number of metabolic processes involving purine biosynthesis and interconversions are affected by the nucleotide analog, TIMP. Like adenosine monophosphate (AMP), guanosine monophosphate (GMP), and inosine mono- phosphate (IMP), TIMP can inhibit the first step of de novo purine-ring biosynthesis (catalyzed by glutamine phosphoribosyl pyrophosphate amidotransferase). TIMP also blocks the formation of AMP and xanthinuric acid from inosinic acid.4

**c. Incorporation into nucleic acids**: TIMP is converted to thioguanine monophosphate (TGMP), which after phosphorylation to di- and triphosphates can be incorporated into RNA. The deoxyribonucleotide analogs that are also formed are incorporated into DNA. This results in nonfunctional RNA and DNA.

**2. Resistance**: Resistance is associated with 1) an inability to biotrans- form 6-MP to the corresponding nucleotide because of decreased levels of HGPRT (for example, in Lesch-Nyhan syndrome, in which patients lack this enzyme), 2) increased dephosphorylation, or 3) increased metabolism of the drug to thiouric acid or other metabolites.

**3. Pharmacokinetics**: Absorption by the oral route is erratic and incomplete. Once it enters the blood circulation, the drug is widely distributed throughout the body, except for the cerebrospinal fluid (CSF; Figure 39.10). The bioavailability of 6-MP can be reduced by the first-pass metabolism in the liver. While undergoing metabolism in the liver, 6-MP is converted to the 6-methylmercaptopurine derivative or to thiouric acid (an inactive metabolite). [Note: The latter reaction is catalyzed by xanthine oxidase.5] Because the xanthine oxidase inhibitor, allopurinol, is frequently used to reduce hyperuricemia in cancer patients receiving chemotherapy, it is important to decrease the dose of 6-MP by 75 percent in these individuals to avoid accumulation of the drug and exacerbation of toxicities (Figure 39.11). The parent drug and its metabolites are excreted by the kidney.

**4. Adverse effects**: Bone marrow depression is the principal toxicity. Side effects also include anorexia, nausea, vomiting, and diarrhea. Occurrence of hepatotoxicity in the form of jaundice has been reported in about one third of adult patients.

**C. 6-Thioguanine**

6-Thioguanine [thye-oh-GWAH-neen] (6-TG), a purine analog, is primarily used in the treatment of acute nonlymphocytic leukemia in combination with daunorubicin and cytarabine. Like 6-MP, 6-TG is con- verted intracellularly to TGMP (also called 6-thioguanylic acid) by the enzyme HGPRT. TGMP is further converted to the di- and triphosphates, thioguanosine diphosphate and thioguanosine triphosphate, which then inhibit the biosynthesis of purines and also the phosphorylation of GMP to guanosine diphosphate. The nucleotide form of 6-TG is incorporated into DNA that leads to cell-cycle arrest.

**1. Pharmacokinetics**: Similar to 6-MP, the absorption of oral 6-TG is also incomplete and erratic. The peak concentration in the plasma is reached in 2 to 4 hours after ingestion. When 6-TG is administered, it is converted to the S-methylation product, 2-amino-6-methylthiopurine by thiopurine methyltransferase (TPMT), which appears in the urine. Patients with low or intermediate TPMT activity accumulate higher concentrations of thioguanine cytotoxic metabo- lites compared to patients with normal TPMT activity. This results in unexpectedly high myelosuppression and has also been associated with the occurrence of secondary malignancies. Approximately 3 percent of whites and blacks express either a homozygous deletion or mutation of the TPMT gene. Because an estimated 10 per- cent of patients may be at increased risk for toxicity because of a heterozygous deletion or mutation of TPMT, TPMT genotyping is recommended before therapy. To a lesser extent, 6-thioxanthine and 6-thiouric acid are also formed by the action of guanase. Because the deamination product 6-thioanthine is an inactive metabolite, 6-TG may be administered along with allopurinol without any dose reduction.

**2. Adverse effects**: Bone marrow depression is the dose-related adverse effect. 6-TG is not recommended for maintenance therapy or continuous long-term treatments due to the risk of liver toxicity.

**D. Fludarabine**

Fludarabine [fl oo-DARE-a-been] is the 5’-phosphate of 2-fl uoroadenine arabinoside, a purine nucleotide analog. It is useful in the treatment of chronic lymphocytic leukemia and may replace chlor ambucil, the cur- rent drug of choice. Fludarabine is also effective against hairy cell leukemia and indolent non-Hodgkin lymphoma. Fludarabine is a prodrug, the phosphate being removed in the plasma to form 2-F-araA, which is taken up into cells and again phosphorylated (initially by deoxycytidine kinase). Although the exact cytotoxic mechanism is uncertain, the triphosphate is incorporated into both DNA and RNA. This decreases their synthesis in the S phase and aff ects their function. Resistance is associated with reduced uptake into cells, lack of deoxycytidine kinase, and decreased affinity for DNA polymerase as well as other mechanisms. Fludarabine is administered IV rather than orally, because intestinal bacteria split off the sugar to yield the very toxic metabolite, fluoro- adenine. Urinary excretion accounts for partial elimination. In addition to nausea, vomiting, and diarrhea, myelosuppression is the dose-limiting toxicity. Fever, edema, and severe neurologic toxicity also occur. At high doses, progressive encephalopathy, blindness, and death have been reported.

**E. Cladribine**

Another purine analog, 2-chlorodeoxyadenosine, or cladribine [KLA-dri- been], undergoes reactions similar to those of fludarabine, and it must be converted to a nucleotide to be cytotoxic. It becomes incorporated at the 3’-terminus of DNA and, thus, hinders elongation. It also affects DNA repair and is a potent inhibitor of ribonucleotide reductase.6 Resistance may be due to mechanisms analogous to those that affect fludarabine, although cross-resistance is not a problem. Cladribine is effective against hairy cell leukemia, chronic lymphocytic leukemia, and non-Hodgkin lymphoma. It also has some activity against multiple sclerosis. The drug is given as a single, continuous infusion. Cladribine distributes throughout the body, including into the CSF. Severe bone marrow suppression is a common adverse effect, as is fever. Peripheral neuropathy has also been reported. The drug is teratogenic.

**F. 5-Fluorouracil**

5-Fluorouracil [fl ure-oh-YOOR-ah-sil] (5-FU), a pyrimidine analog, has a stable fl uorine atom in place of a hydrogen atom at position 5 of the uracil ring. The fluorine interferes with the conversion of deoxyuridylic acid to thymidylic acid, thus depriving the cell of thymidine, one of the essential precursors for DNA synthesis. 5-FU is employed primarily in the treatment of slowly growing solid tumors (for example, colorectal, breast, ovarian, pancreatic, and gastric carcinomas). When applied topically, 5-FU is also effective for the treatment of superficial basal cell carcinomas.

**1. Mechanism of action**: 5-FU per se is devoid of antineoplastic activity. It enters the cell through a carrier-mediated transport system and is converted to the corresponding deoxynucleotide (5-fl uro- deoxyuridine monophosphate [5-FdUMP]; Figure 39.12), which competes with deoxyuridine monophosphate for thymidylate syn- thase.7 5-FdUMP acts as a pseudosubstrate and is trapped with the enzyme and its coenzyme N5,N10-methylene tetrahydrofolic acid (leucovorin), in a ternary complex that cannot proceed to release products. DNA synthesis decreases due to lack of thymidine, lead- ing to imbalanced cell growth and “thymidine-less death” of rapidly dividing cells. [Note: Leucovorin is administered with 5-FU, because the reduced folate coenzyme is required in the thymidylate synthase inhibition. Addition of the coenzyme increases the effectiveness of 5-FU to form a ternary complex and produce an anti pyrimidine eff ect. For example, the standard regimen for advanced colorectal cancer today is irinotecan plus 5-FU/leucovorin.] 5-FU is also incorporated into RNA, and low levels have been detected in DNA. In the latter case, a glycosylase excises the 5-FU, damaging the DNA. 5-FU produces the anticancer effect in the S phase of the cell cycle.

**2. Resistance**: Resistance is encountered when the cells have lost their ability to convert 5-FU into its active form (5-FdUMP) or when they have altered or increased thymidylate synthase levels.

**3. Pharmacokinetics**: Because of its severe toxicity to the GI tract, 5-FU is given IV or, in the case of skin cancer, topically (Figure 39.13). The drug penetrates well into all tissues, including the CNS. 5-FU is rapidly metabolized in the liver, lung, and kidney. It is eventually converted to fluoro-β-alanine, which is removed in the urine, and to CO2, which is exhaled. The dose of 5-FU must be adjusted in the case of impaired hepatic function. Increased rate of 5-FU catabolism through elevated levels of dihydropyrimidine dehydrogenase (DPD) can decrease the bioavailability of 5-FU. The DPD level varies from individual to individual and may differ by as much as sixfold in the general population. Knowledge about an individual’s DPD activity should allow more appropriate dosing of 5-FU .

**4. Adverse effects**: In addition to nausea, vomiting, diarrhea, and alopecia, severe ulceration of the oral and GI mucosa, bone mar- row depression (with bolus injection), and anorexia are frequently encountered. An allopurinol mouthwash has been shown to reduce oral toxicity. A dermopathy (erythematous desquamation of the palms and soles) called the “hand-foot syndrome” is seen after extended infusions.

**G. Capecitabine**

 Capecitabine [cape-SITE-a-been] is a novel, oral fluoropyrimidine carbamate. It is approved for the treatment of metastatic breast cancer that is resistant to first-line drugs (for example, paclitaxel and anthracy- clines) and is currently also used for treatment of colorectal cancer.

**1. Mechanism of action**: After being absorbed, capecitabine, which is itself nontoxic, undergoes a series of enzymatic reactions, the last of which is hydrolysis to 5-FU. This step is catalyzed by thymidine phosphory lase, an enzyme that is concentrated primarily in tumors (Figure 39.14). Thus, the cytotoxic activity of cape citabine is the same as that of 5-FU and is tumor specific. The most important enzyme inhibited by 5-FU (and, thus, cape citabine) is thymidylate synthase.

**2. Pharmacokinetics**: Capecitabine has the advantage of being well absorbed following oral administration. It is extensively metabolized to 5-FU (as described above) and is eventually biotransformed into fluoro-β-alanine and CO2. Metabolites are primarily eliminated in urine or, in the case of CO2, exhaled.

**3. Adverse effects**: These are similar to those with 5-FU, with the toxic- ity occurring primarily in the GI tract. Capecitabine should be used cautiously in patients with hepatic or renal impairment. The drug is contraindicated in individuals who are pregnant or lactating. Patients taking coumarin anticoagulants or phenytoin should be monitored for coagulation parameters and drug levels, respectively.

 **H. Floxuridine**

Floxuridine [floks-YOOR-ih-deen] is an analog (floxuridine is 2’-deoxy- 5-fluorouridine ) of 5-FU. When given by rapid intraarterial injection, floxuridine is rapidly catabolized in the liver to 5-FU and produces anti- metabolite effects. The primary effect is to interfere with the synthesis of DNA and, to a lesser extent, inhibit the formation of RNA. The drug is excreted intact and as fluorouracil, urea, and α-fluoro-β-alanine in the urine. Floxuridine is effective in the palliative management of GI adeno- carcinoma that has metastasized to the liver. The common adverse effects are nausea, vomiting, diarrhea, enteritis, stomatitis, and local- ized erythema.

**I.Cytarabine**

Cytarabine [sye-TARE-ah-been] (cytosine arabinoside, or ara-C) is an ana- log of 2’-deoxycytidine in which the natural ribose residue is replaced by D-arabinose. Ara-C acts as a pyrimidine antagonist. The major clinical use of ara-C is in acute nonlymphocytic (myelogenous) leukemia in combination with 6-TG and daunorubicin.

**1. Mechanism of action**: Ara-C enters the cell by a carrier-mediated process and, like the other purine and pyrimidine antagonists, must be sequentially phosphorylated by deoxycytidine kinase and other nucleotide kinases to the nucleotide form (cytosine arabinoside triphosphate, or ara-CTP ) to be cytotoxic. Ara-CTP is an effective inhibitor of DNA polymerase. The nucleotide is also incorporated into nuclear DNA and can retard chain elongation. It is, therefore, S-phase (and, hence, cell-cycle) specific.

**2. Resistance**: Resistance to ara-C may result from a defect in the trans- port process, a change in phosphorylating enzymes activity (especially deoxycytidine kinase), or an increased pool of the natural dCTP nucleotide. Increased deamination of the drug to uracil arabinoside (ara-U) can also cause resistance.

**3. Pharmacokinetics**: Ara-C is not effective when given orally, because of its deamination to the noncytotoxic ara-U by cytidine deaminase in the intestinal mucosa and liver. Given IV, it distributes throughout the body but does not penetrate the CNS in sufficient amounts to be effective against meningeal leukemia (Figure 39.15). However, it may be injected intrathecally. A new preparation that provides slow release into the CSF is also available. Ara-C undergoes extensive oxidative deamination in the body to ara-U, a pharmacologically inactive metabolite. Both ara-C and ara-U are excreted in urine.

**4. Adverse effects**: Nausea, vomiting, diarrhea, and severe myelosuppression (primarily granulocytopenia) are the major toxicities associated with ara-C. Hepatic dysfunction is also occasionally encountered. At high doses or with intrathecal injection, ara-C may cause leukoencephalopathy or paralysis.

**J. Gemcitabine**

Gemcitabine [jem-SITE-ah-been] is an analog of the nucleoside deoxycytidine. It is used for the first-line treatment of locally advanced or metastatic adenocarcinoma of the pancreas. It also is effective

**1. Mechanism of action**: Gemcitabine is a substrate for deoxycyti- dine kinase, which phosphorylates the drug to 2’,2’-difl uorodeoxy- cytidine triphosphate (Figure 39.16). The latter compound inhibits DNA synthesis by being incorporated into sites in the growing strand that ordinarily would contain cytosine. Evidence suggests that DNA repair does not readily occur. Levels of the natural nucleo- tide, dCTP, are lowered, because gemcitabine competes with the normal nucleoside substrate for deoxycytidine kinase. Gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for the generation of the deoxynucleoside triphosphates required for DNA synthesis.

**2. Resistance**: Resistance to the drug is probably due to its inability to be converted to a nucleotide, caused by an alteration in deoxycytidine kinase. In addition, the tumor cell can produce increased levels of endogenous deoxycytidine that compete for the kinase, thus overcoming the inhibition.

3. **Pharmacokinetics**: Gemcitabine is infused IV. It is deaminated to difluorodeoxyuridine, which is not cytotoxic, and is excreted in urine.

**4. Adverse effects**: Myelosuppression is the dose-limiting toxicity of gemcitabine. Other toxicities include nausea, vomiting, alopecia, rash, and a fl u-like syndrome. Transient elevations of serum transaminases, proteinuria, and hematuria are common.

**IV. ANTIBIOTICS**

The antitumor antibiotics owe their cytotoxic action primarily to their inter- actions with DNA, leading to disruption of DNA function. In addition to intercalation, their abilities to inhibit topoisomerases (I and II) and produce free radicals also play a major role in their cytotoxic eff ect. They are cell- cycle nonspecific.

1. **Dactinomycin**

Dactinomycin [dak-ti-noe-MYE-sin], known to biochemists as actin- omycin D, was the first antibiotic to find therapeutic application in tumor chemotherapy. Dactinomycin is used in combination with sur- gery and vincristine for the treatment of Wilms tumor. In combination with MTX, dactinomycin is effective in the treatment of gestational choriocarcinoma. Some soft-tissue sarcomas also respond.

 **1. Mechanism of action**: The drug intercalates into the minor groove of the double helix between guanine-cytosine base pairs of DNA,8 forming a stable dactinomycin-DNA complex. The complex inter- feres primarily with DNA-dependent RNA polymerase, although at high doses, dactinomycin also hinders DNA synthesis. The drug also causes single-strand breaks, possibly due to action on topoisomerase II or by generation of free radicals.

**2. Resistance**: Resistance is due to an increased efflux of the antibiotic from the cell via P-glycoprotein. DNA repair may also play a role.

**3. Pharmacokinetics**: The drug, administered IV, distributes to many tissues but does not enter the CSF (Figure 39.17). The drug is minimally metabolized in the liver. Most of the parent drug and its metabolites are excreted via bile, and the remainder is excreted via urine.

**4. Adverse effects**: The major dose-limiting toxicity is bone mar- row depression. The drug is immunosuppressive. Other adverse reactions include nausea, vomiting, diarrhea, stomatitis, and alopecia. Extravasation during injection produces serious problems. Dactinomycin sensitizes to radiation, and inflammation at sites of prior radiation therapy may occur.

**B. Doxorubicin and daunorubicin**

Doxorubicin [dox-oh-ROO-bi-sin] and daunorubicin [daw-noe-ROO- bi-sin] are classified as anthracycline antibiotics. Doxorubicin is the hydroxylated analog of daunorubicin. Idarubicin [eye-da-RUE-bi-sin], the 4-demethoxy analog of daunorubicin, and epirubicin [eh-pee-ROO-bih- sin] are also available. Applications for these agents differ despite their structural similarity and their apparently similar mechanisms of action. Doxorubicin is one of the most important and widely used anticancer drugs. It is used in combination with other agents for treatment of sarcomas and a variety of carcinomas, including breast and lung, as well as for treatment of acute lymphocytic leukemia and lymphomas. Daunorubicin and idarubicin are used in the treatment of acute leukemias.

**1. Mechanism of action**: Doxorubicin and other anthracyclines induce cytotoxicity through several different mechanisms. For example, doxorubicin-derived free radicals can induce membrane lipid per- oxidation, DNA strand scission, and direct oxidation of purine or pyrimidine bases, thiols, and amines (Figure 39.18).

**2. Pharmacokinetics**: All these drugs must be administered IV, because they are inactivated in the GI tract. Extravasation is a serious problem that can lead to tissue necrosis. The anthracycline antibiotics bind to plasma proteins as well as to other tissue components, where they are widely distributed. They do not penetrate the blood-brain barrier or the testes. All these drugs undergo extensive hepatic metabolism. Via bile is the major route of excretion, and the drug dose must be modified in patients with impaired hepatic function (Figure 39.19). Some renal excretion also occurs, but the dose generally need not be adjusted in patients with renal failure. Because of the dark red color of the anthracycline drugs, the veins may become visible surrounding the site of infusion, and the drugs also impart a red color to the urine.

**3. Adverse effects**: Irreversible, dose-dependent cardiotoxicity, apparently a result of the generation of free radicals and lipid peroxidation, is the most serious adverse reaction and is more common with daunorubicin and doxorubicin than with idarubicin and epirubicin. Irradiation of the thorax increases the risk of cardiotoxicity. Addition of trastuzumab to protocols with doxorubicin or epirubicin increases congestive heart failure. There has been some success with the iron chelator dexrazone in protecting against the cardiotoxicity of doxorubicin. [Note: A new liposomal-encapsulated doxorubicin has been reported to be less cardiotoxic than the usual formulation.] As with dactinomycin, both doxorubicin and daunorubicin also cause transient bone marrow suppression, stomatitis, and GI tract disturbances. Increased skin pigmentation is also seen. Alopecia is usually severe. Occurrence of multidrug resistance is common, but it is less frequent than with plant alkaloids.

**C. Bleomycin**

Bleomycin [blee-oh-MYE-sin] is a mixture of different copper-chelating glycopeptides that, like the anthracycline antibiotics, cause scission of DNA by an oxidative process. Bleomycin is cell-cycle specifi c and causes cells to accumulate in the G2 phase. It is primarily used in the treat- ment of testicular cancers in combination with vinblastine or etoposide. Response rates are close to 100 percent if cisplatin is added to the regimen. Bleomycin is also effective, although not curative, for squamous cell carcinomas and lymphomas.

**1. Mechanism of action**: A DNA-bleomycin-Fe2+ complex appears to undergo oxidation to bleomycin-Fe3+. The liberated electrons react with oxygen to form superoxide or hydroxyl radicals, which, in turn, attack the phosphodiester bonds of DNA, resulting in strand break- age and chromosomal aberrations (Figure 39.20).

**2. Resistance**: Although the mechanisms of resistance have not been elucidated, experimental systems have implicated increased levels of bleomycin hydrolase (or deamidase), glutathione-S-transferase, and possibly, increased efflux of the drug. DNA repair also may contribute.

**3. Pharmacokinetics:** Bleomycin is administered by a number of routes, including subcutaneous, intramuscular, IV, and intracavitary. The bleomycin-inactivating enzyme (a hydrolase) is high in a number of tissues (for example, liver and spleen) but is low in lung and is absent in skin (accounting for the drug’s toxicity in those tissues). Most of the parent drug is excreted unchanged into the urine by glomerular filtration, necessitating dose adjustment in patients with renal failure.

**4. Adverse effects**: Pulmonary toxicity is the most serious adverse effect, progressing from rales, cough, and infiltrate to potentially fatal fibrosis. The pulmonary fibrosis that is caused by bleomycin is often referred as “bleomycin lung.” Mucocutaneous reactions and alopecia are common. Hypertrophic skin changes and hyper- pigmentation of the hands are prevalent. There is a high incidence of fever and chills and a low incidence of serious anaphylactoid reactions. Bleomycin is unusual in that myelosuppression is rare.

**V. ALKYLATING AGENTS**

Alkylating agents exert their cytotoxic effects by covalently binding to nucleophilic groups on various cell constituents. Alkylation of DNA is probably the crucial cytotoxic reaction that is lethal to the tumor cells. Alkylating agents do not discriminate between cycling and resting cells, but they are most toxic for rapidly dividing cells. They are used in combination with other agents to treat a wide variety of lymphatic and solid cancers. In addition to being cytotoxic, all are mutagenic and carcinogenic and can lead to secondary malignancies such as acute leukemia.

1. **Mechlorethamine**

Mechlorethamine [mek-lor-ETH-ah-meen] was developed as a vesicant (nitrogen mustard) during World War I. Its ability to cause lympho- cytopenia led to its use in lymphatic cancers. Because it can covalently attach to two separate nucleotides, such as guanine on the DNA molecules, it is called a “bifunctional agent.” Mechlorethamine was used primarily in the treatment of Hodgkin disease and may find use in the treatment of some solid tumors.

**1. Mechanism of action**: Mechlorethamine is transported into the cell, where the drug forms a reactive intermediate that alkylates the N7 nitrogen of a guanine residue in one or both strands of a DNA molecule (Figure 39.21). This alkylation leads to cross-linkages between guanine residues in the DNA chains and/or depurination, thus facilitating DNA strand breakage. Alkylation can also cause miscoding mutations. Although alkylation can occur in both cycling and resting cells (and, therefore, is cell-cycle nonspecific), proliferat- ing cells are more sensitive to the drug, especially those in the G1 and S phases.

**2. Resistance**: Resistance has been ascribed to decreased permeability of the drug, increased conjugation with thiols such as glutathione, and, possibly, increased DNA repair.

**3. Pharmacokinetics**: Mechlorethamine is very unstable, and solutions must be made up just prior to administration. Mechlorethamine is also a powerful vesicant (blistering agent) and is only administered IV. Because of its reactivity, scarcely any drug is excreted.

**4. Adverse effects**: The adverse effects caused by mechlorethamine include severe nausea and vomiting (centrally mediated). [Note: These eff ects can be diminished by pretreatment with ondansetron, granisetron, or palonosetron with dexamethasone.] Severe bone mar- row depression limits extensive use. Latent viral infections (for example, herpes zoster) may appear because of immunosuppression. Extravasation is a serious problem. If it occurs, the area should be infiltrated with isotonic sodium thiosulfi te to inactivate the drug.

**B. Cyclophosphamide and ifosfamide**

These drugs are very closely related mustard agents that share most of the same primary mechanisms and toxicities. They are unique in that they can be taken orally and are cytotoxic only after generation of their alkylating species, which are produced through hydroxylation by cytochrome P450 (CYP450). These agents have a broad clinical spectrum, being used either singly or as part of a regimen in the treatment of a wide variety of neoplastic diseases, such as Burkitt lymphoma and breast cancer. Nonneoplastic disease entities, such as nephrotic syn- drome and intractable rheumatoid arthritis, are also eff ectively treated with low doses of cyclophosphamide.

**1. Mechanism of action**: Cyclophosphamide [sye-kloe-FOSS-fah-mide] is the most commonly used alkylating agent. Both cyclophosph- amide and ifosfamide [eye-FOSS-fah-mide] are fi rst biotransformed to hydroxylated intermediates primarily in the liver by the CYP450 system (Figure 39.22). The hydroxylated intermediates then undergo breakdown to form the active compounds, phosphoramide mustard and acrolein. Reaction of the phosphoramide mustard with DNA is considered to be the cytotoxic step.

**2. Resistance**: Resistance results from increased DNA repair, decreased drug permeability, and reaction of the drug with thiols (for example, glutathione). Cross-resistance does not always occur.

**3. Pharmacokinetics**: Unlike most of the alkylating agents, cyclo- phosphamide and ifosfamide can be administered by the oral route (Figure 39.23). After oral administration, minimal amounts of the parent drug are excreted into the feces (after biliary transport) or into the urine by glomerular fi ltration.

**4. Adverse effects**: The most prominent toxicities of both drugs (after alopecia, nausea, vomiting, and diarrhea) are bone marrow depression, especially leukocytosis, and hemorrhagic cystitis, which can lead to fibrosis of the bladder. The latter toxicity has been attributed to acrolein in the urine in the case of cyclophosphamide and to toxic metabolites of ifosfamide. [Note: Adequate hydration as well as IV injection of MESNA (sodium 2-mercaptoethane sulfonate), which neutralizes the toxic metabolites, minimizes this problem.] Other toxicities include eff ects on the germ cells, resulting in amenorrhea, testicular atrophy, aspermia, and sterility. Veno-occlusive disease of the liver is seen in about 25 percent of the patients. A fairly high inci- dence of neurotoxicity has been reported in patients on high-dose ifosfamide, probably due to the metabolite, chloroacetaldehyde. Secondary malignancies may appear years after therapy.