55 The Rational Basis for Cancer Chemotherapy

Branimir I. Sikic

Modern cancer chemotherapy originated in the 1940s with the demonstration that nitrogen mustard possessed antitumor activity against human lymphomas and leukemias. Approximately 10 types of human cancer have 40 to 80% "cure" rates using chemotherapy alone or chemotherapy plus surgery or radiation (Table 55.1). For this purpose cure is defined as the disappearance of any evidence of tumor for several years and a high actuarial probability of a normal life span.

Patients with other types of unresectable cancer also may benefit from chemotherapy, as evidenced by prolongation of life, shrinkage of tumor, and improvement in symptoms. Notable among these are ovarian epithelial and breast carcinomas, oat cell (small cell undifferentiated) carcinoma of the lung, and acute myelocytic leukemia. Cancers that are for the most part resistant to today's agents include melanoma, colorectal and renal carcinomas, and non–oat cell cancers of the lung.

CONCEPTS IN TUMOR CELL BIOLOGY

The Normal Cell Cycle

The *normal cell cycle* consists of a definable sequence of events that characterize the growth and division of cells and can be observed by morphological and biochemical means. The cell cycle is depicted in Fig. 55.1. Two of the four phases of the cell cycle can be studied directly: the *M-phase,* or mitosis, is easily visible using light microscopy because of chromosomal condensation, spindle formation, and cell division. The *S-phase* is the period of DNA synthesis and is observed by measuring the incorporation of tritiated thymidine into cell nuclei.

The *mitotic index* is the fraction or percentage of cells in mitosis within a given cell population. The *thymidine labeling index* is the fraction of cells incorporating radioactive thymidine. They represent cells in M-phase and S-phase and define the proliferative characteristics of normal and tumor cells.

The Tumor Cell Cycle

The duration of the S-phase in human tumors is 10 to 20 hours. This period is followed by the *G_2-phase,* or period of preparation for mitosis, in which cells contain a tetraploid number of chromosomes. The G_2-phase lasts only 1 to 3 hours for most cell types, with mitosis itself lasting approximately 1 hour. The two daughter cells then enter the *G_1-phase,* whose duration varies from several hours to days. The G_1-phase also can give rise to a resting state, termed G_0, in which cells are relatively inactive metabolically and are resistant to most chemotherapeutic drugs.

The *generation time,* or T_c, is the time required to complete one cycle of cell growth and division. The T_c will vary with the duration of the G_1-phase. The factors that influence daughter cells to enter the G_0, or resting stage, are not well understood. The ability to cause such resting cells to reenter the cell cycle would be quite useful, since *proliferating cells generally are more sensitive to chemotherapy than are resting cells.*

DRUGS AND THE CELL CYCLE

Various classification schemes have been proposed to describe the effects of drugs on the cell cycle. One such

TABLE 55.1 Cancers with 40 to 80 Percent Cure Rates

Age	Type of Cancer
Childhood	Acute lymphocytic leukemia
	Burkitt's sarcoma
	Ewing's sarcoma
	Retinoblastoma
	Rhabdomyosarcoma
	Wilms' tumor
Adult	Hodgkin's disease
	Non-Hodgkin's disease
	Trophoblastic choriocarcinoma
	Testicular and ovarian germ cell cancers

classification divides the anticancer drugs into three categories:

1. *Class 1 agents* (e.g., radiation, mechlorethamine, and carmustine) exert their cytotoxicity in a *nonspecific* (i.e., non–proliferation dependent) manner. They kill both normal and malignant cells to the same extent.
2. *Class 2 agents* are phase specific and reach a plateau in cell kill with increasing dosages. Only a certain *proportion* of cells are sensitive to the toxic effects of these drugs. For example, hydroxyurea and cytarabine kill only cells in the S-phase. Similarly, bleomycin is most toxic to cells in G_2- and early M-phases. Because they affect only a small fraction of the cell population at any one time, it has been suggested that these drugs should be given either by continuous infusion or in frequent small doses. Such a dosage regimen would increase the number of tumor cells exposed to the drug during the sensitive phase of their cell cycle.
3. *Class 3 agents* kill *proliferating* cells in preference to resting cells. It has been recommended that these proliferation-dependent but non–phase-specific agents be administered in single large doses to take advantage of their sparing effect on normal cells that may be in G_0.

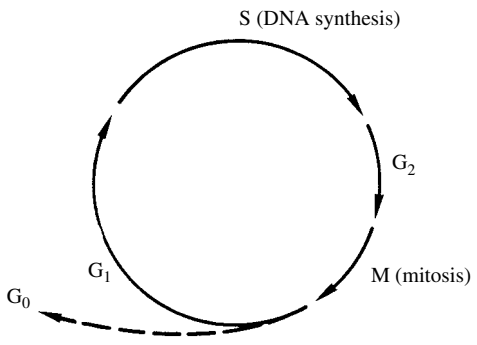

FIGURE 55.1
The cell cycle. S, G_1, G_2, and G_0 are phases of the cell cycle.

Unfortunately, many human cancers have a large proportion of cells in the resting phase, and these cells are also resistant to the class 3 agents, which include cyclophosphamide, dactinomycin, and fluorouracil.

This classification of anticancer drugs has inherent limitations. For instance, it may be difficult to generalize about the phase specificity of a particular drug, since this may vary among cell types. Several techniques are available to synchronize cell populations in such a way that most cells will be in the same phase of the cell cycle. After synchronization, one can treat cells in each phase and determine their relative sensitivity to drugs throughout the cell cycle.

Some drugs that exert their maximum cytotoxicity during the S-phase of the cycle also prevent cells from progressing through the cell cycle to the S-phase; this is accomplished by sublethal inhibition of RNA and protein synthesis. The antimetabolites methotrexate, fluorouracil, and mercaptopurine all can inhibit RNA synthesis in G_1- and G_2-phases and inhibit DNA synthesis during S-phase. This inhibition of cell cycle progression actually may result in reduced cytotoxicity, and such agents have been termed *S-phase-specific but self-limited.*

TUMOR GROWTH AND GROWTH FRACTION

The rate of growth of human and experimental cancers is initially quite rapid (exponential) and then slows until a plateau is reached. The decrease in growth rate with increasing tumor size is related both to a decrease in the proportion of cancer cells actively proliferating (termed the *growth fraction*) and to an increase in the rate of cell loss due to hypoxic necrosis, poor nutrient supply, immunological defense mechanisms, and other processes.

The rate of spontaneous cell death for some human tumors is thought to be a significant factor in limiting growth. However, the growth fraction, or percentage of cells in the cell cycle, is the most important determinant of overall tumor enlargement. The doubling times of human tumors have been estimated by direct measurement of chest radiographs of lesions or palpable masses to be 1 to 6 months.

The *growth fraction* indicates dividing cells that are potentially sensitive to chemotherapy; thus, it is not surprising that tumors with high growth fractions are the ones most easily curable by drugs. Among human tumors, only Burkitt's lymphoma and trophoblastic choriocarcinoma are readily curable by single-agent chemotherapy; both of these tumors have growth fractions close to 100%.

As tumors grow larger, the growth fraction within the tumor decreases, and the greater the distance of cells from nutrient blood vessels, the more likely they are to be in the G_0-, or resting, phase. The growth fraction is less than 10% for slow-growing cancers of the colon or lung.

A number of factors must be considered before chemotherapy is instituted for a human cancer that has a low growth fraction. For instance, the larger the tumor, the more cells will be present in the nonproliferating, relatively resistant state. Therefore, the earlier chemotherapy is instituted, the greater the chance of a favorable response. Debulking of tumors by surgery or radiation therapy may be a means of stimulating the remaining cells into active proliferation. Small metastases may respond to drugs more dramatically than will large primary tumors or a larger metastasis in the same patient.

Several cycles of treatment may be necessary to achieve a substantial reduction in tumor size. The chemotherapeutic regimen, especially when one is dealing with large, solid tumors, probably should include agents that have cytotoxic activity against resting cells.

THE LOG CELL KILL HYPOTHESIS

Cytotoxic drugs act by *first-order kinetics;* that is, at a given dose, they kill a *constant fraction* of the tumor cells rather than a fixed number of cells. For example, a drug dose that would result in a three-log cell kill (i.e., 99.9% cytotoxicity) would reduce the tumor burden of an animal that has 10^8 leukemic cells to 10^5 cells. This killing of a fraction of cells rather than an absolute number per dose is called the *log cell kill hypothesis.*

The earliest detectable human cancers usually have a volume of at least 1 cc and contain 10^9 (1 billion) cells. This number reflects the result of at least 30 cycles of cell division, or cell doublings, and represents a kinetically advanced stage in the tumor's growth. Most patients actually have tumor burdens that are greater than 10^9. Since the major limiting factor in chemotherapy is cytotoxicity to normal tissues, only a limited log cell kill can be expected with each individual treatment.

Even in the absence of tumor regrowth, several cycles of therapy would be required for eradication of the tumor, assuming it was sensitive to the drugs employed. When a tumor has decreased in size to approximately 10^8 cells, it is generally no longer detectable clinically and is considered a clinically complete remission. Regrowth of residual cells is the obvious cause of relapse in patients who have achieved clinically complete remissions.

DRUG RESISTANCE

Many patients undergoing chemotherapy fail to respond to treatment from the outset; their cancers are resistant to the available agents. Other patients respond initially, only to relapse.

Cancers can be regarded as populations of cells undergoing spontaneous mutations. The population becomes increasingly heterogeneous as the tumor grows and increasing numbers of mutations occur. Tumors of the same type and size will vary in their responsiveness to therapy because of the chance occurrences of drug-resistant mutations during tumor growth.

Assuming the same initial drug sensitivity, smaller tumors are generally more curable than larger tumors because of the increased probability of drug-resistant mutations in the larger tumors. Therefore, therapy *earlier* in the course of tumor growth should increase the chance for cure. *Combination chemotherapy* is often more effective than treatment with single drugs. Tumors that are resistant to drugs from the outset will always have a largely drug-resistant population and will be refractory to treatment.

Many kinds of biochemical resistance to anticancer drugs have been described. The biochemical and genetic mechanisms of resistance to *methotrexate* are now known in some detail. Three major resistance pathways have been described: (1) decreased drug transport into cells; (2) an alteration in the structure of the target enzyme dihydrofolate reductase (DHFR), resulting in reduced drug affinity; and (3) an increase in DHFR content of tumor cells. The increase in DHFR content occurs through a process of *gene amplification,* that is, a reduplication or increase in the number of copies per cell of the gene coding for DHFR. Amplification of various genes may be a relatively frequent event in tumor cell populations and an important genetic mechanism for generating resistance to drugs.

Tumor cells may become generally resistant to a variety of cytotoxic drugs on the basis of decreased uptake or retention of the drugs. This form of resistance is termed *pleiotropic,* or *multidrug, resistance,* and it is the major form of resistance to anthracyclines, vinca alkaloids, etoposide, paclitaxel, and dactinomycin. The gene that confers multidrug resistance (termed *mdr I*) encodes a high-molecular-weight membrane protein called *P-glycoprotein,* which acts as a drug efflux pump in many tumors and normal tissues.

Possible biochemical mechanisms of resistance to *alkylating agents* include changes in cell DNA repair capability, increases in cell thiol content (which in turn can serve as alternative and benign targets of alkylation), decreases in cell permeability, and increased activity of glutathione transferases. Increased metallothionein content has been associated with tumor cell resistance to cisplatin.

Drugs that require metabolic activation for antitumor activity, such as the *antimetabolites* 5-fluorouracil and 6-mercaptopurine, may be ineffective if a tumor is deficient in the required activating enzymes. Alter-

natively, a drug may be metabolically inactivated by resistant tumors, which is the case with cytarabine (pyrimidine nucleoside deaminase) and bleomycin (bleomycin hydrolase). Leukemias have been shown to develop resistance to L-asparaginase because of a drug-related induction of the enzyme asparagine synthetase.

Major mechanisms of cellular resistance to anticancer drugs are depicted in Fig. 55.2.

CANCER THERAPY AND THE IMMUNE SYSTEM

Although manipulation of the host immune response in animal tumor models has at times yielded impressive therapeutic results, attempts to extend these results to human cancers generally have been disappointing.

Several proteins that stimulate subsets of lymphocytes involved in various aspects of the immune response are now produced by recombinant DNA techniques. The pharmacology of these "lymphokines" as potential anticancer agents is being investigated. *Interleukin (IL) 2,* originally described as a T-cell growth factor, induces the production of cytotoxic lymphocytes (lymphokine-activated killer cells, or LAK cells). IL-2 produces remissions in 10 to 20% of patients with melanoma or renal cell carcinoma when infused at high doses either alone or with lymphocytes that were previously harvested from the patient and incubated with IL-2 in vitro.

The ability of certain anticancer agents to suppress both humoral and cellular immunity has been exploited in the field of organ transplantation and in diseases thought to be caused by an abnormal or heightened immune response. In particular, the alkylating agents cyclophosphamide and chlorambucil have been used in this context, as have several of the antimetabolites, including methotrexate, mercaptopurine, azathioprine, and thioguanine. Daily treatment with these agents rather than high-dose intermittent therapy is the preferred schedule for immune suppression.

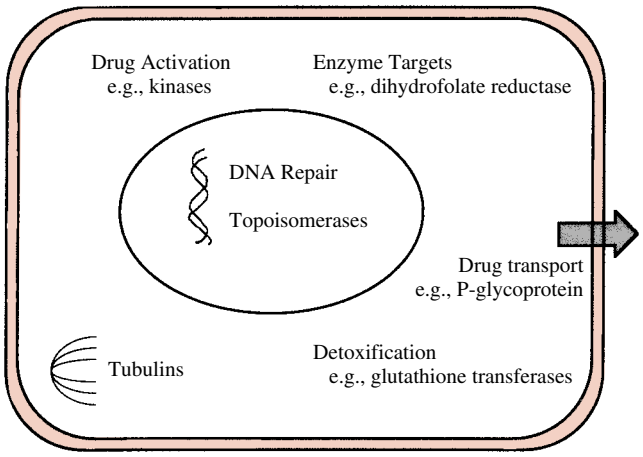

FIGURE 55.2
Mechanisms of cellular resistance to anticancer drugs.

GENERAL TOXICOLOGICAL PROPERTIES OF ANTICANCER DRUGS

Most of the drugs used in cancer treatment have a therapeutic index that approaches unity, exerting toxic effects on both normal and tumor tissues even at optimal dosages. This *lack of selective toxicity* is the major limiting factor in the chemotherapy of cancer. Rapidly proliferating normal tissues, such as bone marrow, gastrointestinal tract, and hair follicles, are the major sites of acute toxicity of these agents. In addition, chronic and cumulative toxicities may occur. The most commonly encountered toxicities of antineoplastic agents are described in the following section; more detailed information on individual agents is presented in Chapter 56.

Bone Marrow Toxicity

Chemotherapy may result in the destruction of actively proliferating hematopoietic precursor cells. White blood cell and platelet counts may in turn be decreased, resulting in an increased incidence of life-threatening infections and hemorrhage. Maximum toxicity usually is observed 10 to 14 days after initiation of drug treatment, with recovery by 21 to 28 days. In contrast, the nitrosourea drugs exhibit hematological toxicity that is delayed until 4 to 6 weeks after beginning treatment.

The risk of serious infections has been shown to increase greatly when the peripheral blood granulocyte count falls below 1000 cells/mm^3. A chronic bone marrow toxicity or hypoplastic state may develop after long-term treatment with nitrosoureas, other alkylating agents, and mitomycin C. Thus, patients frequently will require a progressive reduction in the dosages of *myelosuppressive* drugs when they are undergoing long-term therapy, since such treatment may result in chronic pancytopenia.

Gastrointestinal Tract Toxicity

The nausea and vomiting frequently observed after anticancer drug administration are actually thought to be caused by a stimulation of the vomiting center or chemoreceptor trigger zone in the central nervous system (CNS) rather than by a direct gastrointestinal effect. These symptoms are ameliorated by treatment with phenothiazines and other centrally acting antiemetics. Commonly, nausea begins 4 to 6 hours after treatment and lasts 1 or 2 days. Although this symptom is distressing to patients, it is rarely severe enough to require cessation of therapy. Anorexia and alterations in taste perception also may be associated with chemotherapy.

The serotonin antagonist ondansetron (*Zofran*) has proved effective in the prevention of nausea and vomiting due to chemotherapy.

Damage to the normally proliferating mucosa of the gastrointestinal tract may produce stomatitis, dysphagia, and diarrhea several days after treatment. Oral ulcerations, esophagitis, and proctitis may cause pain and bleeding.

Hair Follicle Toxicity

Most anticancer drugs damage hair follicles and produce partial or complete alopecia. Patients should be warned of this reaction, especially if paclitaxel, cyclophosphamide, doxorubicin, vincristine, methotrexate, or dactinomycin is used. Hair usually regrows normally after completion of chemotherapy.

PHARMACOKINETIC CONSIDERATIONS IN CANCER CHEMOTHERAPY

Pharmacokinetic Sanctuaries

The existence of the blood-brain barrier is an important consideration in the chemotherapy of neoplastic diseases of the brain or meninges. Poor drug penetration into the CNS has been a major cause of treatment failure in acute lymphocytic leukemia in children. Treatment programs for this disease now routinely employ craniospinal irradiation and intrathecally administered methotrexate as prophylactic measures for the prevention of relapses. The testes also are organs in which inadequate antitumor drug distribution can be a cause of relapse of an otherwise responsive tumor.

The multidrug transporter P-glycoprotein is expressed in the endothelial lining of the brain and testis but not in other organs and is thought to be a major component of the blood-brain and blood-testis drug barriers.

Schedules of Administration

Although the effects of various schedules are not always predictable, drugs that are rapidly metabolized, excreted, or both, especially if they are phase specific and thus act on only one portion of the cell cycle (e.g., cytarabine), appear to be more effective when administered by continuous infusion or frequent dose fractionation than by high-dose intermittent therapy. On the other hand, intermittent high-dose treatment of Burkitt's lymphoma with cyclophosphamide is more effective than fractionated treatment, since cyclophosphamide acts on all phases of the cell cycle and almost all of the tumor cells in that disease are actively proliferating.

The classic example of *schedule dependency* is cytarabine, a drug that specifically inhibits DNA synthesis and is cytotoxic only to cells in S-phase. Continuous infusion or frequent administration of cytarabine hydrochloride is superior to intermittent injection of the drug. Bleomycin is another drug for which continuous infusion may increase therapeutic efficacy.

Administration of some anticancer drugs by *continuous infusion* has been shown to improve their therapeutic index through selective reduction of toxicity with retained or enhanced antitumor efficacy.

Routes of Administration

In addition to the usual intravenous or oral routes, some anticancer agents have been administered by regional intraarterial perfusion to increase drug delivery to the tumor itself and at the same time diminish systemic toxicity. Thus, patients with metastatic carcinomas of the liver and little or no disease elsewhere (a common occurrence in colorectal cancer) can be treated with a continuous infusion of fluorouracil or floxuridine through a catheter implanted in the hepatic artery.

Intracavitary administration of various agents has been used for patients with malignant pleural or peritoneal effusions. *Intraperitoneal instillations* of cisplatin, etoposide, bleomycin, 5-fluorouracil, and interferon are well tolerated and are being evaluated in patients with ovarian carcinomas, in whom the tumor is frequently restricted to the peritoneal cavity.

Other routes of administration can be employed in certain situations. Methotrexate and cytarabine are given *intrathecally* or *intraventricularly* to prevent relapses in the meninges in acute lymphocytic leukemia and to treat carcinomatous meningitis. Thiotepa and bleomycin have been administered by intravesical instillation to treat early bladder cancers. Fluorouracil can be applied topically for certain skin cancers.

Drug Interactions

Antineoplastic drugs may participate in several types of drug interactions. Methotrexate, for example, is highly bound to serum albumin and can be displaced by salicylates, sulfonamides, phenothiazines, phenytoin, and other organic acids. The induction of hepatic drug-metabolizing enzymes by phenobarbital may alter the metabolism of cyclophosphamide to both active and inactive metabolites. Mercaptopurine metabolism is blocked by allopurinol, an occurrence that may result in lethal toxicity if the dosage of mercaptopurine is not reduced to one-fourth of the usual dosage. Methotrexate is secreted actively by the renal tubules, and its renal clearance may be delayed by salicylates.

Procarbazine exhibits an interesting interaction with ethanol, resulting in headaches, diaphoresis, and facial

erythema; patients taking this drug should be forewarned to abstain from alcohol. Procarbazine is also a monoamine oxidase (MAO) inhibitor and may potentiate the effects of drugs that are substrates for this enzyme.

The biliary and renal excretion of some drugs (e.g., anthracyclines, vinca alkaloids, dactinomycin, etoposide) by the P-glycoprotein multidrug transporter can be inhibited by other drugs that are also transported by P-glycoprotein.

COMBINATION CHEMOTHERAPY

The value of combination chemotherapy has been proved in humans. The combined use of two or more drugs often is superior to single-agent treatment in many cancers, and certain principles have been used in designing such treatments:

1. Each drug used in the combination regimen should have some *individual therapeutic activity* against the particular tumor being treated. A drug that is not active against a tumor when used as a single agent is likely to increase toxicity without increasing the therapeutic efficacy of a combined drug regimen.
2. Drugs that *act by different mechanisms* may have additive or synergistic therapeutic effects. Tumors may contain heterogeneous clones of cells that differ in their susceptibility to drugs. Combination therapy will thus increase log cell kill and diminish the probability of emergence of resistant clones of tumor cells.
3. Drugs with *different dose-limiting toxicities* should be used to avoid cumulative damage to a single organ.
4. Intensive *intermittent schedules* of drug treatment should allow time for recovery from the acute toxic effects of antineoplastic agents, primarily bone marrow toxicity. The use of nonmyelosuppressive agents can be considered during the recovery period, especially for treatment of fast-growing cancers.
5. Several *cycles of treatment* should be given, since one or two cycles of therapy are rarely sufficient to eradicate a tumor. *Most curable tumors require at least six to eight cycles of therapy.*

The chemotherapy of advanced Hodgkin's disease is one of the best examples of successful combination chemotherapy. Combination therapy with the MOPP regimen (mechlorethamine, *Oncovin* [vincristine sulfate], procarbazine, prednisone), alternating with ABVD (*Adriamycin* [doxorubicin hydrochloride], bleomycin, vinblastine, dacarbazine), has resulted in cure rates of 50 to 60%.

The treatment of Hodgkin's disease also illustrates the use of combined modalities, that is, radiation plus chemotherapy. The combined modality approach to several childhood tumors (e.g., Ewing's sarcoma, Wilms' tumor, and rhabdomyosarcoma) has dramatically increased the cure rates for these diseases.

Adjuvant chemotherapy involves the use of antineoplastic drugs when surgery or radiation therapy has eradicated the primary tumor but historical experience with similar patients indicates a high risk of relapse due to micrometastases. Adjuvant chemotherapy should employ drugs that are known to be effective in the treatment of advanced stages of the particular tumor being treated. Adjuvant chemotherapy has played a major role in the cure of several types of childhood cancers as well as breast cancer, colorectal cancer, and osteosarcoma in adults.

Study Questions

1. A patient of yours has been receiving 5-fluorouracil as palliative therapy for adenocarcinoma of the pancreas. You suspect that the patient has become resistant to the treatment. You want to understand the most likely cause of the resistance before you select another agent. Which of the following is the most likely cause?
   (A) Drug transport into cells is decreased.
   (B) P-glycoprotein is increased.
   (C) The tumor can no longer activate the drug.
   (D) The tumor is detoxifying the drug more rapidly.
   (E) The tumor has developed an increase in metallothionein content.
2. Neurotoxicity is rarely dose limiting in cancer chemotherapy. The only antineoplastic agent that has a dose-limiting neurotoxicity is
   (A) Bleomycin
   (B) Cisplatin
   (C) Vincristine
   (D) Doxorubicin
   (E) Methotrexate
3. You are asked to devise therapy for a patient with rapidly dividing cancer. You have no additional

information on the nature of the tumor, but you decide that you want to begin by choosing a drug that will kill the tumor cells but spare normal cells. You have the following agents to choose among. Which is your first choice?
(A) Hydroxyurea
(B) Cytarabine
(C) Bleomycin
(D) Mechlorethamine
(E) Dactinomycin

4. To optimize drug therapy, it is necessary to know in what phase of the cell cycle antineoplastic agents are effective. Which one of the following agents is cytotoxic only to cells in the S-phase of the cycle?
(A) Hydroxyurea
(B) Mechlormethamine
(C) Bleomycin
(D) Carmustine
(E) Fluorouracil

5. Combination chemotherapy is frequently used and is often superior to single-agent treatment. All of the following principles have been used in designing combinations EXCEPT which of the following?
(A) Each drug in the combination regimen should have some therapeutic activity individually.
(B) Drugs with different dose-limiting toxicities should be used to avoid damage to a single organ.
(C) Several cycles of treatment should be given.
(D) Intensive intermittent schedules of drug treatment.
(E) Drugs with similar dose-limiting toxicities should be used as initial combination therapy.

ANSWERS

1. **C.** The most likely reason for resistance to 5-fluorouracil or other agents that require activation is that tumors can no longer activate the drug. There is no evidence that 5-fluorouracil becomes unable to penetrate tumor cells. There may be an increase in P-glycoprotein, but this is not usually associated with 5-fluorouracil. There may be an induction in the drug metabolism for some antineoplastic drugs, but this does not appear to be the case for 5-fluorouracil. Increased metallothionein content has been associated with resistance in the case of cisplatin but not 5-fluorouracil.
2. **C.** The dose-limiting toxicity of bleomycin is pulmonary toxicity and that of cisplatin is renal. Doxorubicin produces cardiotoxicity; hematoxicity is dose limiting for methotrexate.
3. **E.** Dactinomycin is a class 3 agent, that is, an agent that kills proliferating cells in preference to resting cells. Hydroxyurea and cytarabine are class 2 agents that specifically kill cells in S-phase. Bleomycin is a class 2 agent that is specific for cells in G_2 and early M-phase. Mechlorethamine (class 1) appears to kills normal and malignant cells to about the same extent.
4. **A.** Carmustine and mechlormethamine kill both normal and malignant cells to the same extent. Hydroxyurea and bleomycin kill cells preferentially in specific phases of the cell cycle. Hydroxyurea is specific for S-phase, while bleomycin is most toxic to cells in G_2- and early M-phase. Flurouracil is cytotoxic in G_1 and G_2 phases.
5. **E.** Intensive intermittent schedules allow time for recovery from the acute toxic effects of the antineoplastic agents. If a drug has no activity by itself, it is not likely to be beneficial in a combination. It is important not to include two drugs with the same dose-limiting toxicity. Most curable tumors require at least six to eight cycles of therapy.

SUPPLEMENTAL READING

Bernal SD (ed.). Drug Resistance in Oncology. New York: Marcel Dekker, 1997.
Brigden M and McKenzie M. Treating cancer patients. Practical monitoring and management of therapy-related complications. Can Fam Physician 2000;46:2258–2268.
Burns EA and Leventhal EA. Aging, immunity, and cancer. Cancer Control 2000;7:513–522.
DeVita VT, Hellman S, and Rosenberg SA (eds.). Cancer: Principles and Practice of Oncology (6th ed.). Philadelphia: Lippincott, 2000.
Lipp HP (ed.). Anticancer Drug Toxicity. Marcel Dekker: New York, 1999.
Roninson IB (ed.). Molecular and Cellular Biology of Multidrug Resistance in Tumor Cells. New York: Plenum, 1990.
Xu XC. COX-2 inhibitors in cancer treatment and prevention, a recent development. Anticancer Drugs 2002;13:127–137.

CASE Study Treatment of Nausea

You are filling in for a colleague who is on vacation when one of her patients makes an appointment to talk with you about his complaint. The patient is a 50-year-old man being treated for Hodgkin's disease using the MOPP regimen. The patient indicates that he was doing quite well until 2 days ago, when he began having nausea and vomiting that were "almost unbearable." The patient indicates that he is ready to terminate his treatment, since the side effects are quite severe, but he wants your opinion first.

You indicate that his regimen is the best available treatment and that the cure rate is excellent, but only if the treatment is continued. You suggest that other agents may help his nausea and vomiting. You prescribe ondansetron. After 2 days, the patient comes back and indicates that the drug decreased the nausea and vomiting but that he was developing severe dermatitis that he attributed to the new agent. You believe he is correct and prescribe chlorpromazine. He calls you the next week to tell you that the new drug worked and he will continue with his chemotherapy.