**Chapter 39 part 2**

**C. Nitrosoureas**

Carmustine [KAR-mus-teen] and lomustine [LOE-mus-teen] are closely related nitrosoureas. Because of their ability to penetrate the CNS, the nitrosoureas are primarily employed in the treatment of brain tumors. They fi nd limited use in the treatment of other cancers. [Note: Streptozocin (STREP-toe-zoe-sin) is another nitrosourea that is specifically toxic to the β cells of the islets of Langerhans, hence its use in the treatment of insulinomas.]

**1. Mechanism of action**: The nitrosoureas exert cytotoxic effects by an alkylation that inhibits replication and, eventually, RNA and protein synthesis. Although they alkylate DNA in resting cells, cytotoxicity is expressed primarily on cells that are actively dividing. Therefore, nondividing cells can escape death if DNA repair occurs. Nitrosoureas also inhibit several key enzymatic processes by car- bamoylation of amino acids in proteins in the targeted cells.

**2. Resistance:** Although the true nature of resistance to nitrosoureas is unknown, it probably results from DNA repair and reaction of the drugs with thiols.

**3. Pharmacokinetics**: In spite of the similarities in their structures, carmustine is administered IV, whereas lomustine is given orally. Because of their lipophilicity, they distribute widely in the body to many tissues, but their most striking property is their ability to read- ily penetrate the CNS. The drugs undergo extensive metabolism. Lomustine is metabolized to active products. The kidney is the major excretory route for the nitrosoureas (Figure 39.24).

**4. Adverse effects**: These include delayed hematopoietic depression, which may be due to metabolic products. An aplastic mar- row may develop on prolonged use. Renal toxicity and pulmonary fibrosis related to duration of therapy is also encountered. [Note: Streptozotocin is also diabetogenic.]

**D. Dacarbazine**

Dacarbazine [dah-KAR-bah-zeen], an agent that has found use in the treatment of melanoma, is an alkylating agent that must undergo biotransformation to an active metabolite, methyltriazenoimidazole carboxamide (MTIC). This metabolite is responsible for the drug’s activity as an alkylating agent by forming methylcarbonium ions that can attack the nucleophilic groups in the DNA molecule. Thus, similar to other alkylating agents, the cytotoxic action of dacarbazine has been attributed to the ability of its metabolite to methylate DNA on the O6 position of guanine. Dacarbazine is administered IV. Its major adverse effects are nausea and vomiting. Myelosuppression (thrombocytopenia and neutropenia) occur later in the treatment cycle. Hepatotoxicity with hepatic vascular occlusion may also occur in long-term treatments.

**E. Temozolomide**

The treatment of tumors in the brain is particularly difficult. Recently, temozolomide [te-moe-ZOE-loe-mide], a triazene agent, has been approved for use against treatment-resistant gliomas and anaplastic astrocytomas. Temozolomide is related to dacarbazine, because both must undergo biotransformation to an active metabolite, MTIC, which probably is responsible for the methylation of DNA on the 6 position of guanine. Unlike dacarbazine, temozolomide does not require the CYP450 system for metabolic transformation, and it undergoes chemi- cal transformation under normal physiological pH. Temozolomide also has the property of inhibiting the repair enzyme, O6-guanine- DNA-alkyltransferase. A property that distinguishes temozolomide from dacarbazine is the former’s ability to cross the blood-brain bar- rier. Temozolomide is taken orally and has excellent oral bioavailability. The parent drug and metabolites are excreted in urine (Figure 39.25). Temozolomide is taken for 5 consecutive days and repeated every 28 days. Similar to dacarbazine, its major initial toxicities are nausea and vomiting. Myelosuppression (thrombocytopenia and neutropenia) occur later in the treatment cycle.

**F. Other alkylating agents**

Melphalan [MEL-fah-lan], a phenylalanine derivative of nitrogen mus- tard, is used in the treatment of multiple myeloma. This is a bifunctional alkylating agent that can be given orally. Although melphalan can be given orally, the plasma concentration diff ers from patient to patient due to variation in intestinal absorption and metabolism. The dose of melphalan is carefully adjusted by monitoring the platelet and white blood cell counts. Chlorambucil [clor-AM-byoo-sil] is another bifunctional alky- lating agent that is used in the treatment of chronic lymphocytic leu- kemia. Both melphalan and chlorambucil have moderate hematologic toxicities and upset the GI tract. Busulfan [byoo-SUL-fan] is another oral agent that is effective against chronic granulocytic leukemia. Busulfan is also a bifunctional alkylating agent that can cause myelosuppression. In aged patients, busulfan can cause pulmonary fibrosis. Like other alkylating agents, all of these agents are leukemognic.

**VI. MICROTUBULE INHIBITORS**

The mitotic spindle is part of a larger, intracellular skeleton (cytoskeleton) that is essential for the movements of structures occurring in the cytoplasm of all eukaryotic cells. The mitotic spindle consists of chromatin plus a sys- tem of microtubules composed of the protein tubulin. The mitotic spindle is essential for the equal partitioning of DNA into the two daughter cells that are formed when a eukaryotic cell divides. Several plant-derived substances used as anticancer drugs disrupt this process by affecting the equilibrium between the polymerized and depolymerized forms of the microtubules, thereby causing cytotoxicity.

**A.Vincristine and vinblastine**

Vincristine [vin-KRIS-teen] (VX) and vinblastine [vin-BLAS-teen] (VBL) are structurally related compounds derived from the periwinkle plant, Vinca rosea. They are, therefore, referred to as the vinca alkaloids. A new (and less toxic) agent is vinorelbine [vye-NOR-el-been] (VRB). Although the vinca alkaloids are structurally very similar to each other, their therapeutic indications are different. They are generally administered in combination with other drugs. VX is used in the treatment of acute lymphoblastic leukemia in children, Wilms tumor, Ewing soft-tissue sarcoma, and Hodgkin and non-Hodgkin lymphomas as well as some other rapidly proliferating neoplasms. [Note: VX (trade name, ONCOVIN) is the “O” in the POMP regimen for leukemia and the MOPP regimen for Hodgkin lymphoma. Due to relatively milder bone-suppressing ability, VX is used in a number of other protocols.] VBL is administered with bleomycin and cisplatin for the treatment of metastatic testicular carcinoma. It is also used in the treatment of systemic Hodgkin and non- Hodgkin lymphomas. VRB is beneficial in the treatment of advanced non–small cell lung cancer, either as a single agent or with cisplatin.

1. **Mechanism of action:** VX and VBL are both cell-cycle specific and phase specific, because they block mitosis in metaphase (M phase). Their binding to the microtubular protein, tubulin, is GTP dependent and blocks the ability of tubulin to polymerize to form microtubules. Instead, paracrystalline aggregates consisting of tubulin dimers and the alkaloid drug are formed. The resulting dysfunctional spindle apparatus, frozen in metaphase, prevents chromosomal segregation and cell proliferation (Figure 39.26).

**2. Resistance**: Resistant cells have been shown to have an enhanced efflux of VX, VBL, and VRB via P-glycoprotein in the cell membrane. Alterations in tubulin structure may also affect binding of the vinca alkaloids.

**3. Pharmacokinetics**: IV injection of these agents leads to rapid cytotoxic effects and cell destruction. This, in turn, can cause hyperuricemia due to the oxidation of purines that are released from frag- menting DNA molecules, producing uric acid. The hyperuricemia is ameliorated by administration of the xanthine oxidase–inhibitor allopurinol. The vinca alkaloids are concentrated and metabolized in the liver by the CYP 450 pathway. They are excreted in bile and feces. Doses must be modified in patients with impaired hepatic function or biliary obstruction.

**4. Adverse effects**: Both VX and VBL have certain toxicities in com- mon. These include phlebitis or cellulitis, if the drugs extravasate during injection, as well as nausea, vomiting, diarrhea, and alopecia. However, the adverse effects of VX and VBL are not identical. VBL is a more potent myelosuppressant than VX, whereas peripheral neuropathy (paresthesias, loss of reflexes, foot drop, and ataxia) is associated with VX. Constipation is more frequently encountered with VX, which can also cause inappropriate antidiuretic hormone secretion. The anticonvulsants phenytoin, phenobarbital, and carbamazepine can accelerate the metabolism of VX, whereas the azole antifungal drugs can slow its metabolism. Granulocytopenia is dose limiting for VRB.

**B. Paclitaxel and docetaxel**

Better known as Taxol, paclitaxel [PAK-li-tax-el] is the first member of the taxane family to be used in cancer chemotherapy. A semisynthetic paclitaxel is now available through chemical modification of a precursor found in the needles of Pacific yew species. Substitution of a side chain has resulted in docetaxel [doe-see-TAX-el], which is the more potent of the two drugs. Paclitaxel has shown good activity against advanced ovarian cancer and metastatic breast cancer. Favorable results have been obtained in non–small cell lung cancer when administered with cisplatin. Docetaxel is showing impressive benefits, with fewer side effects, in these conditions.

**1. Mechanism of action**: Both drugs are active in the G2/M phase of the cell cycle. They bind reversibly to the β-tubulin subunit, but unlike the vinca alkaloids, they promote polymerization and stabili- zation of the polymer rather than disassembly (Figure 39.27). Thus, they shift the depolymerization-polymerization process to accumulation of microtubules. The overly stable microtubules formed are nonfunctional, and chromosome desegregation does not occur. This results in death of the cell.

**2. Resistance**: Like the vincaalkaloids, resistance has been associated with the presence of amplified P-glycoprotein or a mutation in the tubulin structure.

**3. Pharmacokinetics:** These agents are infused and have similar pharmacokinetics. Both have a large volume of distribution, but neither enters the CNS. Hepatic metabolism by the CYP450 system and biliary excretion are responsible for their elimination in stool. Thus, dose modification is not required in patients with renal impairment, but doses should be reduced in patients with hepatic dysfunction.

**4. Adverse effects:** The dose-limiting toxicity of paclitaxel and docetaxel is neutropenia. [Note: Patients with fewer than 1500 neutrophils/mm3 should not be given these agents.] Treatment with granulocyte colony–stimulating factor (filgrastim) can help to reverse neutropenia and prevent the problems associated with this condition. Peripheral neuropathy can develop with either of these drugs. A transient, asymptomatic bradycardia is sometimes observed with paclitaxel, and fluid retention is seen with docetaxel. The latter drug is contraindicated in patients with cardiac disease. Alopecia occurs, but vomiting and diarrhea are uncommon. [Note: Because of serious hypersensitivity reactions (including dyspnea, urticaria, and hypotension), a patient who is to be treated with paclitaxel is premedicated with dexamethasone and diphenhydramine as well as with an H2 blocker.]

**VII. STEROID HORMONES AND THEIR ANTAGONISTS**

Tumors that are steroid hormone–sensitive may be either 1) hormone responsive, in which the tumor regresses following treatment with a specific hormone; 2) hormone dependent, in which removal of a hormonal stimu- lus causes tumor regression; or 3) both. Hormone treatment of responsive tumors usually is only palliative, except in the case of the cytotoxic effect of glucocorticoids at higher doses (for example, prednisone) on lympho- mas. Removal of hormonal stimuli from hormone-dependent tumors can be accomplished by surgery (for example, in the case of orchiectomy— surgical removal of one or both testes— for patients with advanced prostate cancer) or by drugs (for example, in breast cancer, for which treatment with the antiestrogen tamoxifen is used to prevent estrogen stimulation of breast cancer cells). For a steroid hormone to influence a cell, that cell must have intracellular (cytosolic) receptors that are specific for that hormone (Figure 39.28A).

**A.Prednisone**

Prednisone [PRED-ni-sone] is a potent, synthetic, anti-inflammatory corticosteroid with less mineralocorticoid activity than cortisol. The use of this compound in the treatment of lymphomas arose when it was observed that patients with Cushing syndrome, which is associated with hypersecretion of cortisol, have lymphocytopenia and decreased lymphoid mass. [Note: At high doses, cortisol is also lymphocytolytic and leads to hyperuricemia due to the breakdown of lymphocytes.] Prednisone is primarily employed to induce remission in patients with acute lymphocytic leukemia and in the treatment of both Hodgkin and non-Hodgkin lymphomas.

**1. Mechanism of action**: Prednisone itself is inactive and must first be reduced to prednisolone by 11-β-hydroxysteroid dehydrogenase. This steroid then binds to a receptor that triggers the production of specific proteins (see Figure 39.28A).

**2. Resistance:** Resistance is associated with an absence of the receptor protein or a mutation that lowers receptor affinity for the hormone. However, in some resistant cells, a receptor-hormone complex is formed, although a stage of gene expression is apparently affected.

**3. Pharmacokinetics:** Prednisone is readily absorbed orally. Like other glucocorticoids, it is bound to plasma albumin and transcortin. It undergoes 11-β-hydroxylation to prednisolone in the liver. Prednisolone is the active drug. The latter is glucuronidated and excreted in urine along with the parent compound.

**4. Adverse effects:** Prednisone has many of the adverse eff ectsassociated with glucocorticoids. It can predispose to infection (due to its immunosuppressant action) and to ulcers and pancreatitis. Other effects include hyperglycemia, cataract formation, glaucoma, osteoporosis, and change in mood (euphoria or psychosis).

**B. Tamoxifen**

Tamoxifen [tah-MOX-ih-fen] is an estrogen antagonist. It is structurally related to the synthetic estrogen diethylstilbestrol and is used for first- line therapy in the treatment of estrogen receptor–positive breast can- cer. Tamoxifen has weak estrogenic activity, and it is classifi ed as a selective estrogen-receptor modulator (SERM). Another SERM that has been approved for advanced breast cancer in postmenopausal women is toremifene [tore-EM-ih-feen]. It also finds use prophylactically in reducing breast cancer occurrence in women who are at high risk. However, because of possible effects stimulating premalignant lesions due to its estrogenic properties, tamoxifen is currently approved only for 5 years of use.

**1. Mechanism of action:** Tamoxifen binds to the estrogen receptor, but the complex is transcriptionally not productive. That is, the complex fails to induce estrogen-responsive genes, and RNA synthesis does not ensue (Figure 39.28B). The result is a depletion (down-reg- ulation) of estrogen receptors, and the growth-promoting effects of the natural hormone and other growth factors are suppressed. [Note: Estrogen competes with tamoxifen. Therefore, in premeno- pausal women, the drug is used with a gonadotropin-releasing hor- mone (GnRH) analog such as leuprolide, which lowers estrogen lev- els.] The action of tamoxifen is not related to any specifi c phase of the cell cycle.

**2. Resistance**: Resistance is associated with a decreased affinity for the receptor or the presence of a dysfunctional receptor.

**3. Pharmacokinetics:** Tamoxifen is effective on oral administration. It is partially metabolized by the liver. Some metabolites possess antagonist activity, whereas others have agonist activity. Unchanged drug and its metabolites are excreted predominantly through the bile into the feces (Figure 39.29).

**4. Adverse effects:** Side effects caused by tamoxifen are similar to the effects of natural estrogen, including hot flashes, nausea, vomiting, skin rash, vaginal bleeding, and discharge (due to some slight estrogenic activity of the drug and some of its metabolites). Hypercalcemia requiring cessation of the drug may occur. Tamoxifen can also lead to increased pain if the tumor has metastasized to bone. Tamoxifen has the potential to cause endometrial cancer. Other toxicities include thromboembolism and effects on vision. [Note: Because of a more favorable adverse effect profile, aromatase inhibitors are making an impact in the treatment of breast cancer.]

**C. Aromatase inhibitors**

The aromatase reaction is responsible for the extra-adrenal synthesis of estrogen from androstenedione, which takes place in liver, fat, muscle, skin, and breast tissue, including breast malignancies. Peripheral aromatization is an important source of estrogen in postmenopausal women. Aromatase inhibitors decrease the production of estrogen in these women.

**1. Aminoglutethimide**: Aminoglutethimide [ah-mee-noe-glue-TETH- ih-mide] was the first aromatase inhibitor to be identifi ed for the treatment of metastatic breast cancer in postmenopausal women. Aminoglutethimide was shown to inhibit both the adrenal synthesis of pregnenolone (a precursor of estrogen) from cholesterol as well as the extra-adrenal synthesis. Because the drug also inhibits hydro- cortisone synthesis, which evokes a compensatory rise in adrenocor- ticotropic hormone secretion sufficient to overwhelm the blockade of the adrenal gland, the drug is usually taken with hydrocortisone. Due to its nonselective properties and unfavorable side effects, as well as the need to concomitantly administer hydrocortisone (cortisol), newer aromatase inhibitors (described below) have been developed.

**2. Anastrozole and letrozole**: The imidazole aromatase inhibitors, such as anastrozole [an-AS-troe-zole] and letrozole [LE-troe-zole], are nonsteroidal. They have gained favor in the treatment of breast cancer because 1) they are more potent (they inhibit aromatization by greater than 96 percent, compared to less than 90 percent with aminoglutethimide), 2) they are more selective than aminoglute- thimide, 3) they do not need to be supplemented with hydrocorti- sone, 4) they do not predispose to endometrial cancer, and 5) they are devoid of the androgenic side effects that occur with the steoidal aromatase inhibitors. Although anastrozole and letrozole are considered to be second-line therapy after tamoxifen for hormone- dependent breast cancer in the United States, they have become fi rst-line drugs in other countries for the treatment of breast cancer in postmenopausal women. They are orally active and cause almost a total suppression of estrogen synthesis. They are cleared primarily by liver metabolism.

**3. Exemestane**: A steroidal, irreversible inhibitor of aromatase, exemestane [ex-uh-MES-tane], is orally well absorbed and widely distributed. Hepatic metabolism is by the CYP3A4 isozyme, but, to date, no interactions have been reported. Because the metabolites are excreted in urine, doses of the drug must be adjusted in patients with renal failure. Its major toxicities are nausea, fatigue, and hot flashes. Acne and hair changes also occur.

**D. Progestins**

Megestrol [me-JESS-trole] acetate was formerly the progestin used most widely in treating metastatic hormone-responsive breast and endome- trial neoplasms. It is orally effective. Other agents are usually compared to it in clinical trials. However, the aromatase inhibitors are replacing it in therapy.

**E. Leuprolide and goserelin**

GnRH is normally secreted by the hypothalamus and stimulates the anterior pituitary to secrete the gonadotropic hormones; luteinizing hormone (LH), the primary stimulus for the secretion of testosterone by the testes; and follicle-stimulating hormone (FSH), which stimulates the secretion of estrogen. The synthetic nonapeptides, leuprolide [loo- PROE-lide] and goserelin [GOE-se-rel-in], are analogs of GnRH. As GnRH agonists, they occupy the GnRH receptor in the pituitary, which leads to its desensitization and, consequently, inhibition of release of FSH and LH. Thus, both androgen and estrogen syntheses are reduced (Figure 39.30). Response to leuprolide in prostatic cancer is equivalent to that of orchiectomy with regression of tumor and relief of bone pain. These drugs have some benefit in premenopausal women with advanced breast cancer and have largely replaced estrogens in therapy for pros- tate cancer. Leuprolide is available 1) as a sustained-release preparation, 2) subcutaneous, or 3) as a depot intramuscular injection to treat meta- static carcinoma of the prostate. Goserelin acetate is implanted intra- muscularly. Levels of androgen may initially rise but then fall to castra- tion levels. The adverse effects of these drugs, including impotence, hot flashes, and tumor flare, are minimal compared to those experienced with estrogen treatment.

**F. Estrogens**

Estrogens, such as ethinyl estradiol or diethylstilbestrol, had been used in the treatment of prostatic cancer. However, they have been large- ly replaced by the GnRH analogs because of fewer adverse effects. Estrogens inhibit the growth of prostatic tissue by blocking the produc- tion of LH, thereby decreasing the synthesis of androgens in the testis. Thus, tumors that are dependent on androgens are affected. Estrogen treatment can cause serious complications, such as thromboemboli, myocardial infarction, strokes, and hypercalcemia. Men who are taking estrogens may experience gynecomastia and impotence.

**G. Flutamide, nilutamide, and bicalutamide Flutamide**

[FLOO-tah-mide], nilutamide [nye-LOO-ta-mide], and bicalut- amide [bye-ka-LOO-ta-mide] are synthetic, nonsteroidal antiandrogens used in the treatment of prostate cancer. They compete with the natu- ral hormone for binding to the androgen receptor and prevent its trans- location into the nucleus (see Figure 39.30). Flutamide is metabolized to an active hydroxy derivative that binds to the androgen receptor. Flutamide blocks the inhibitory effects of testosterone on gonadotro- pin secretion, causing an increase in serum LH and testosterone levels. Therefore, flutamide is always administered in combination with leupro- lide or goserelin, which can desensitize the hypothalamus-pituitary axis. These antiandrogens are taken orally. [Note: Flutamide requires dosing three times a day and the others once a day.] These agents are cleared through the kidney. Side effects include gynecomastia and GI distress, and, in the case of flutamide, liver failure could occur. Nilutamide can cause visual problems.

**VIII. MONOCLONAL ANTIBODIES**

Monoclonal antibodies have become an active area of drug development for anticancer therapy and other nonneoplastic diseases, because they are directed at specific targets and often have fewer adverse effects. They are created from B lymphocytes (from immunized mice or hamsters) fused with “immortal” B-lymphocyte tumor cells. The resulting hybrid cells can be individually cloned, and each clone will produce antibodies directed against a single antigen type. Recombinant technology has led to the creation of “humanized” antibodies that overcome the immunologic problems pre- viously observed following administration of mouse (murine) antibodies. Currently, several monoclonal antibodies are available in the United States for the treatment of cancer. Trastuzumab, rituximab, bevacizumab, and cetuximab are described below. Others include gemtuzumab ozogamicin, which is a monoclonal antibody conjugated with a plant toxin that binds to CD33 (a cell-surface receptor that is present on the leukemia cells of 80 percent of patients with acute myelocytic leukemia); alemtuzumab, which is effective in treatment of B-cell chronic lymphocytic leukemia that no longer responds to other agents; and I131-tositumomab, which is used in relapsed non-Hodgkin lymphoma.

**A.Trastuzumab**

In patients with metastatic breast cancer, overexpression of transmem- brane human epidermal growth factor–receptor protein 2 (HER2) is seen in 25 to 30 percent of patients. Trastuzumab [tra-STEW-zoo-mab], a recombinant DNA–produced, humanized monoclonal antibody, specifically targets the extracellular domain of the HER2 growth receptor that has intrinsic tyrosine kinase activity. The drug, usually administered with paclitaxel, can cause regression of breast cancer and metastases in a small percentage of these individuals. [Note: At least 50 tyrosine kinases mediate cell growth or division by phosphorylating signaling proteins. They have been implicated in the development of many neo- plasms by an unknown mechanism.] Trastuzumab binds to HER2 sites in breast cancer tissue and inhibits the proliferation of cells that over- express the HER2 protein, thereby decreasing the number of cells in the S phase.

**1. Mechanism of action**: How the antibody causes its anticancer effect remains to be elucidated. Several mechanisms have been proposed: for example, down-regulation of HER2-receptor expression, an induction of antibody-dependent cytotoxicity, or a decrease in angiogenesis due to an effect on vascular endothelial growth fac- tor. Efforts are being directed toward identifying those patients with tumors that are sensitive to the drug.

**2. Pharmacokinetics**: Trastuzumab is administered IV. Trastuzumab does not penetrate the blood-brain barrier.

**3. Adverse effects**: The most serious toxicity associated with the use of trastuzumab is congestive heart failure. The toxicity is worsened if given in combination with anthracycline. Extreme caution should be exercised when giving the drugs to patients with preexisting cardiac dysfunction. Other adverse effects include infusion-related fever and chills, headache, dizziness, nausea, vomiting, abdominal pain, and back pain, but these effects are well tolerated. Cautious use of the drug is recommended in patients who are hypersensitive to the Chinese hamster ovary cell components of the proteins or to ben- zyl alcohol (in which case sterile water can be used in place of the bacteriostatic solution provided for preparation of the injection).

**B. Rituximab**

Rituximab (ri-TUCKS-ih-mab) was the first monoclonal antibody to be approved for the treatment of cancer. It is a genetically engineered, chi- meric monoclonal antibody directed against the CD20 antigen that is found on the surfaces of normal and malignant B lymphocytes. CD20 plays a role in the activation process for cell-cycle initiation and dif- ferentiation. The CD20 antigen is expressed on nearly all B-cell non- Hodgkin lymphomas but not in other bone marrow cells. Rituximab has proven to be effective in the treatment of posttransplant lymphoma and in chronic lymphocytic leukemia.

**1. Mechanism of action**: The Fab domain of rituximab binds to the CD20 antigen on the B lymphocytes, and its Fc domain recruits immune effector functions, inducing complement and antibody- dependent, cell-mediated cytotoxicity of the B cells. The antibody is commonly used with other combinations of anticancer agents, such as cyclophosphamide, doxorubicin, vincristine (Oncovin ), and predni- sone (CHOP).

**2. Pharmacokinetics**: Rituximab is infused IV and causes a rapid deple- tion of B cells (both normal and malignant). The fate of the antibody has not been described.

**3. Adverse effects**: Severe adverse reactions have been fatal. It is important to infuse rituximab slowly. Hypotension, bronchospasm, and angioedema may occur. Chills and fever commonly accompany the first infusion, especially in patients with high circulating levels of neoplastic cells, because of rapid activation of complement, which results in the release of tumor necrosis factor α and interleukins. Pretreatment with diphenhydramine, acetaminophen, and broncho- dilators can ameliorate these problems. Cardiac arrhythmias can also occur. Tumor lysis syndrome has been reported within 24 hours of the first dose of rituximab. This syndrome consists of acute renal failure that may require dialysis, hyperkalemia, hypocalcemia, hyper- uricemia, and hyperphosphatasemia (an abnormally high content of alkaline phosphatase in the blood). Leukopenia, thrombocyto- penia, and neutropenia have been reported in less than 10 percent of patients.

**C. Bevacizumab**

The monoclonal antibody bevacizumab [be-vah-SEE-zoo-mab] is the first in a new class of anticancer drugs called antiangiogenesis agents. Bevacizumab is approved for use as a first-line drug against meta- static colorectal cancer and is given with 5-FU-based chemotherapy. Bevacizumab is infused IV. It attaches to and stops vascular endothe- lial growth factor from stimulating the formation of new blood ves- sels. Without new blood vessels, tumors do not receive the oxygen and essential nutrients necessary for growth and proliferation. The most common adverse effects of this treatment are hypertension, stomatitis, and diarrhea. Less common are bleeding in the intestines, protein in the urine, and heart failure. Among the rare serious side effects are bowel perforation, opening of healed wounds, and stroke.

**D. Cetuximab**

Cetuximab [see-TUX-i-mab] is another chimeric monoclonal antibody that has recently been approved to treat colorectal cancer. It is believed to exert its antineoplastic effect by targeting the epidermal growth fac- tor receptor on the surface of cancer cells and interfering with their growth. It is usually combined with irinotecan during treatment. Like other antibodies, it is administered IV. Cetuximab has caused difficulty breathing and low blood pressure during the first treatment, and inter- stitial lung disease has been reported. Other side effects include rash, fever, constipation, and abdominal pain.

**IX. OTHER CHEMOTHERAPEUTIC AGENTS**

**A. Platinum coordination complexes**

Cisplatin [SIS-pla-tin] was the first member of the platinum coordina- tion complex class of anticancer drugs, but because of its severe toxicity, carboplatin [KAR-boe-pla-tin] was developed. The mechanisms of action of the two drugs are similar, but their potency, pharmacokinetics, patterns of distribution, and dose-limiting toxicities differ sig- nificantly. Cisplatin has synergistic cytotoxicity with radiation and other chemotherapeutic agents. Oxaliplatin [ox-AL-ih-pla-tin], a new member of this class of drugs, is a closely related analog of carboplatin. Cisplatin has found wide application in the treatment of solid tumors, such as metastatic testicular carcinoma in combination with VBL and bleomycin, ovarian carcinoma in combination with cyclophosphamide, or alone for bladder carcinoma. Carboplatin is used when patients cannot be vigorously hydrated, as is required for cisplatin treatment, or if they suffer from kidney dysfunction or are prone to neuro- or ototoxicity. Oxaliplatin is showing excellent activity against advanced colorectal cancer.

**1. Mechanism of action**: The mechanism of action for this class of drugs is similar to that of the alkylating agents. In the high-chloride milieu of the plasma, cisplatin persists as the neutral species, which enters the cell and loses its chlorides in the low-chloride milieu. It then binds to the N7 of guanine in DNA, forming inter- and intra- strand cross-links. The resulting cytotoxic lesion inhibits both DNA replication and RNA synthesis. Similarly, the chemical moieties that replace the chlorides in the carboplatin structure are removed hydrolytically to form the active drug. Cytotoxicity can occur at any stage of the cell cycle, but cells are most vulnerable to the actions of these drugs in the G1 and S phases. Both drugs can also bind proteins and other compounds containing thiol (–SH) groups.

**2. Resistance:** Sensitivity to these agents is decreased if cells have elevated glutathione levels or increased DNA repair, or if metallothionein (a protein rich in –SH groups) is induced. Decreased cel- lular uptake has also been implicated. Cross-resistance between cis- platin and carboplatin is not invariable. However, there is none with oxaliplatin.

**3. Pharmacokinetics:** These agents are administered IV in saline solu- tion. They can also be given intraperitoneally for ovarian cancer and intraarterially to perfuse other organs. More than 90 percent of cis- platin is covalently bound to plasma proteins, but the binding of carboplatin to plasma proteins is very low. The highest concentra- tions of the drugs are found in the liver, kidney, and intestinal, tes- ticular, and ovarian cells, but little penetrates into the CSF. The renal route is the main avenue for excretion (Figure 39.31).

**4. Adverse eff ects**: Severe, persistent vomiting occurs for at least 1 hour after administration of cisplatin and may continue for as long as 5 days. Premedication with antiemetic agents is usually helpful. The major limiting toxicity is dose-related nephrotoxicity, involving the distal convoluted tubule and collecting ducts. This can be ame- liorated by aggressive hydration and diuresis. Hypomagnesemia and hypocalcemia usually occur concurrently. [Note: It is impor- tant to correct calcium levels before correcting magnesium levels.] Other toxicities include ototoxicity with high-frequency hearing loss and tinnitus, mild bone marrow suppression, some neurotox- icity characterized by paresthesia and loss of proprioception, and hypersensitivity reactions ranging from skin rashes to anaphylaxis. Patients concomitantly receiving aminoglycosides are at greater risk for nephrotoxicity and ototoxicity. Unlike cisplatin, carboplatin causes only mild nausea and vomiting, and it is not nephro-, neuro-, or ototoxic. Its dose-limiting toxicity is myelosuppression.

**B. Irinotecan and topotecan**

Irinotecan [eye-rin-oh-TEE-kan] and topotecan [toe-poe-TEE-kan] are semisynthetic derivatives of an earlier, more toxic drug, camptothecin [camp-toe-THEE-sin]. They have a complicated multiring structure con- taining a lactone ring that is essential for activity. Topotecan is used in metastatic ovarian cancer when primary therapy has failed and also in the treatment of small cell lung cancer. Irinotecan is used as a fi rst-line drug together with 5-FU and leucovorin for the treatment of colon or rectal carcinoma.

**1. Mechanism of action**: These drugs are S-phase specifi c. They inhibit topoisomerase I, which is essential for the replication of DNA in human cells (Figure 39.32). Unlike etoposide, which inhibits the related enzyme topoisomerase II (see below), topotecan was the fi rst clinically useful topoisomerase I inhibitor. SN-38 (the active metab- olite of irinotecan) is formed from irinotecan by carboxylesterase- mediated cleavage of the carbamate bond between the camptoth- ecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I. The topoisomerases relieve torsional strain in DNA by causing revers- ible, single-strand breaks. By binding to the enzyme-DNA complex, topotecan or SN-38 prevents religation of the single-strand breaks.

**2. Resistance:** Several mechanisms may explain resistance. Among them are the ability to transport the drugs out of the cell, decreased ability to convert irinotecan to the active SN-38 metabolite, or a down-regulation or mutation in topoisomerase I.

**3. Pharmacokinetics**: Topotecan and irinotecan are infused IV. Hydrolysis of the lactone ring destroys the activity of these drugs. Both the drugs and their metabolites are eliminated in urine. Therefore, the dose may have to be modified in patients with impaired kidney function.

**4. Adverse effects**: Bone marrow suppression, particularly neutropenia, is the dose-limiting toxicity for topotecan. Frequent peripheral blood counts should be performed on patients taking this drug. [Note: Topotecan should not be used in patients with a baseline neutrophil count of less than 1500 cells/mm3. Doing so could result in infection and death.] Other hematologic complications, including thrombocytopenia and anemia, may also occur. Nonhematologic effects include diarrhea, nausea, vomiting, alopecia, and headache. Myelosuppression is also seen with irinotecan, and delayed diarrhea may be severe and require treatment with loperamide.

**C. Etoposide**

Etoposide [e-toe-POE-side] and its analog, teniposide [ten-i-POE-side], are semisynthetic derivatives of the plant alkaloid, podophyllotoxin. They block cells in the late S to G2 phase of the cell cycle. Their major target is topoisomerase II. Binding of the drugs to the enzyme-DNA complex results in persistence of the transient, cleavable form of the complex and, thus, renders it susceptible to irreversible double-strand breaks (Figure 39.33). Resistance to topoisomerase inhibitors is conferred either by presence of the multidrug-resistant P-glycoprotein or by mutation of the enzyme. Etoposide finds its major clinical use in the treatment of oat cell carcinoma of the lung and in combination with bleomycin and cis- platin for testicular carcinoma. Teniposide is used as a second-line agent in the treatment of acute lymphocytic leukemia. Etoposide may be administered either IV or orally, whereas teniposide is only administered IV. They are highly bound to plasma proteins and distribute through- out the body, but they enter the CSF poorly. Despite this, teniposide has shown effectiveness against gliomas and neuroblastomas. Metabolites are converted to glucuronide and sulfate conjugates and are excreted in urine. Drugs that induce the CYP450 system lead to an acceleration of teniposide metabolism. Dose-limiting myelosuppression (primarily leu- kopenia) is the major toxicity for both drugs. Leukemia may develop in patients who were treated with etoposide. Other toxicities are alopecia, anaphylactic reactions, nausea, and vomiting.

**D. Imatinib**

Imatinib [i-MAT-in-ib] mesylate is used for the treatment of chronic myel- oid leukemia in blast crisis as well as GI stromal tumor. It acts as a signal transduction inhibitor, used specifically to inhibit tumor tyrosine kinase activity. A deregulated BCR-ABL kinase is present in the leukemia cells of almost every patient with chronic myeloid leukemia. In the case of GI stromal tumor, an unregulated expression of tyrosine kinase is associ- ated with a growth factor. The ability of imatinib to occupy the “kinase pocket” prevents the phosphorylation of tyrosine on the substrate mol- ecule and, hence, inhibits subsequent steps that lead to cell prolifera- tion. Imatinib has the advantage over interferon-α in that it can be given orally. It also has a more rapid hematologic response than interferon-α plus cytarabine. Studies of cell lines indicate that resistance may occur by amplifi cation of the BCR-ABL gene and/or by increased effl ux due to increased multidrug-resistance protein. The drug is very well absorbed orally. It undergoes metabolism by the CYP450 system to several com- pounds, of which the N-demethyl derivative is active. Excretion is pre- dominantly through feces. Adverse eff ects include fl uid retention and edema, hepatotoxicity, and thrombocytopenia or neutropenia as well as nausea and vomiting.

**E. Gefitinib**

Gefitinib [ge-FI-tih-nib] targets the epidermal growth factor receptor. It is approved for the treatment of non–small cell lung cancer that has failed to respond to other therapy, and it is eff ective in 10 to 20 per- cent of patients with this cancer. Gefi tinib is usually used as a single agent. Gefi tinib is absorbed after oral administration and undergoes extensive metabolism in the liver by the CYP450 enzyme CYP3A4. At least fi ve metabolites have been identifi ed, only one of which has sig- nifi cant antitumor activity. The major route of excretion of the drug and its metabolites is the feces. The most common adverse eff ects are diarrhea, nausea, and acne-like skin rashes. A rare but potentially fatal adverse eff ect is interstitial lung disease, which presents as acute dys- pnea with cough.

**F. Procarbazine**

Procarbazine [proe-KAR-ba-zeen] is used in the treatment of Hodgkin disease and other cancers. Procarbazine rapidly equilibrates between the plasma and the CSF after oral or parenteral administration. It must undergo a series of oxidative reactions to exert its cytotoxic action that causes inhibition of DNA, RNA, and protein synthesis. Metabolites and the parent drug are excreted via the kidney. Bone marrow depression is the major toxicity, and nausea, vomiting, and diarrhea are common. The drug is also neurotoxic, causing symptoms ranging from drowsi- ness to hallucinations to paresthesias. Because it inhibits monoamine oxidase, patients should be warned against ingesting foods that con- tain tyramine (for example, aged cheeses, beer, and wine). Ingestion of alcohol leads to a disulfi ram-type reaction). Procarbazine is both muta- genic and teratogenic. Nonlymphocytic leukemia has developed in patients treated with the drug.

**G. L-Asparaginase**

L-Asparaginase [ah-SPAR-a-gi-nase] catalyzes the deamination of aspar- agine to aspartic acid and ammonia. The form of the enzyme used che- motherapeutically is derived from bacteria. L-Asparaginase is used to treat childhood acute lymphocytic leukemia in combination with VX and prednisone. Its mechanism of action is based on the fact that some neoplastic cells require an external source of asparagine because of their limited capacity to synthesize suffi cient amounts of that amino acid to support growth and function. L-Asparaginase hydrolyzes blood asparagine and, thus, deprives the tumor cells of this amino acid, which is needed for protein synthesis (Figure 39.34). Resistance to the drug is due to increased capacity of tumor cells to synthesize asparagine. The enzyme must be administered either IV or intramuscularly, because it is destroyed by gastric enzymes. Toxicities include a range of hyper- sensitivity reactions (because it is a foreign protein), a decrease in clot- ting factors, liver abnormalities, pancreatitis, seizures, and coma due to ammonia toxicity.

**H. Interferons**

Human interferons have been classified into the three types α, β, and γ on the basis of their antigenicity. The α interferons are primarily leukocytic, whereas the β and γ interferons are produced by connective tissue fibroblasts and T lymphocytes, respectively. Recombinant DNA techniques in bacteria have made it possible to produce large quanti- ties of pure interferons, including two species designated interferon-α- 2a and -2b that are employed in treating neoplastic diseases. Interferon- α-2a is currently approved for the management of hairy cell leukemia, chronic myeloid leukemia, and acquired immunodeficiency syndrome (AIDS)–related Kaposi sarcoma. Interferon-α-2b is approved for the treatment of hairy cell leukemia, melanoma, AIDS-related Kaposi sar- coma, and follicular lymphoma.

**1. Mechanism of action**: Interferons secreted from producing cells interact with surface receptors on other cells, at which site they exert their effects. Bound interferons are neither internalized nor degraded. The α and β interferons compete with each other for binding and, therefore, presumably bind at the same receptor or in close proximity. The γ interferons bind at different receptors. As a consequence of the binding of interferon, a series of complex intra- cellular reactions take place. These include synthesis of enzymes, suppression of cell proliferation, activation of macrophages, and increased cytotoxicity of lymphocytes. However, the exact mecha- nism by which the interferons are cytotoxic is unknown.

**2. Pharmacokinetics**: Interferons are well absorbed after intramus- cular or subcutaneous injections. An IV form of interferon-α-2b is also available. Interferons undergo glomerular filtration and are degraded during reabsorption, but liver metabol ism is minimal.