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; or
  - 2) hormone dependent, in which removal of a hormonal stimulus causes tumor regression; or
  - 3) both.

- 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

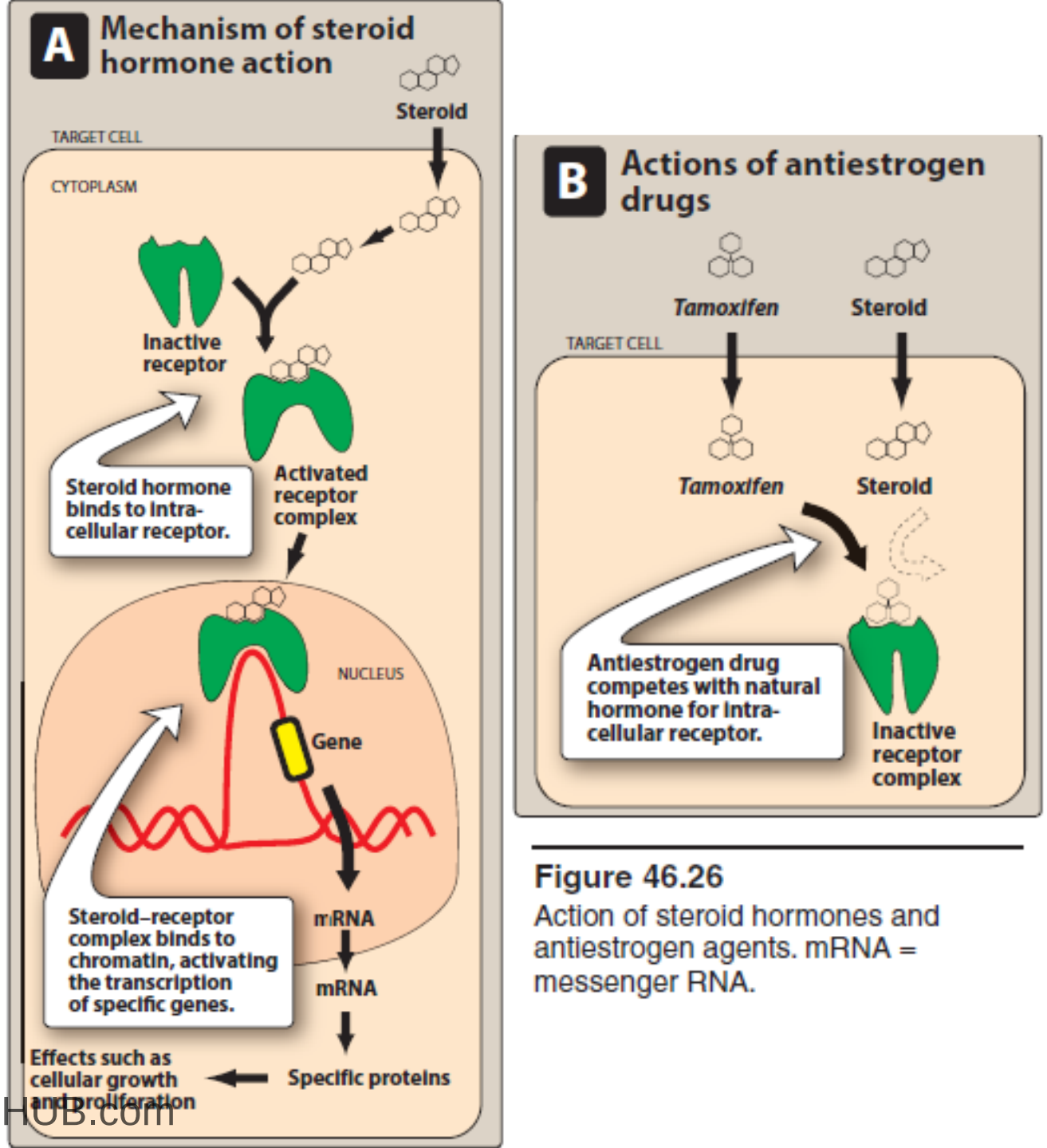


Figure 46.26
Action of steroid hormones and antiestrogen agents. mRNA = messenger RNA.

A. Prednisone

- *Prednisone* [PRED-ni-sone] is a potent, synthetic, anti-inflammatory corticosteroid with less mineralocorticoid activity than *cortisol*.
- [Note: At high doses, *cortisol* is 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.
- *Prednisone* itself is inactive and must first undergo 11-β-hydroxylation to *prednisolone* in the liver.
- *Prednisolone* is the active drug.

B. Tamoxifen

- *Tamoxifen* is an estrogen antagonist with some estrogenic activity, and it is classified as a selective estrogen receptor modulator (SERM).
- It is used for first-line therapy in the treatment of estrogen receptor–positive breast cancer.
- It also finds use prophylactically in reducing breast cancer occurrence in women who are at high risk.
- However, because of possible stimulation of premalignant lesions due to its estrogenic properties, patients should be closely monitored during therapy.

1. Mechanism of action:

- *Tamoxifen* binds to estrogen receptors in the breast tissue, but the complex is unable to translocate into the nucleus for its action of initiating transcriptions.

- That is, the complex fails to induce estrogen-responsive genes, and RNA synthesis does not ensue (Figure 46.26B).

- The result is a depletion (down-regulation) 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 premenopausal women, the drug is used with a gonadotropin releasing hormone (GnRH) analog such as *leuprolide,* which lowers estrogen levels.]

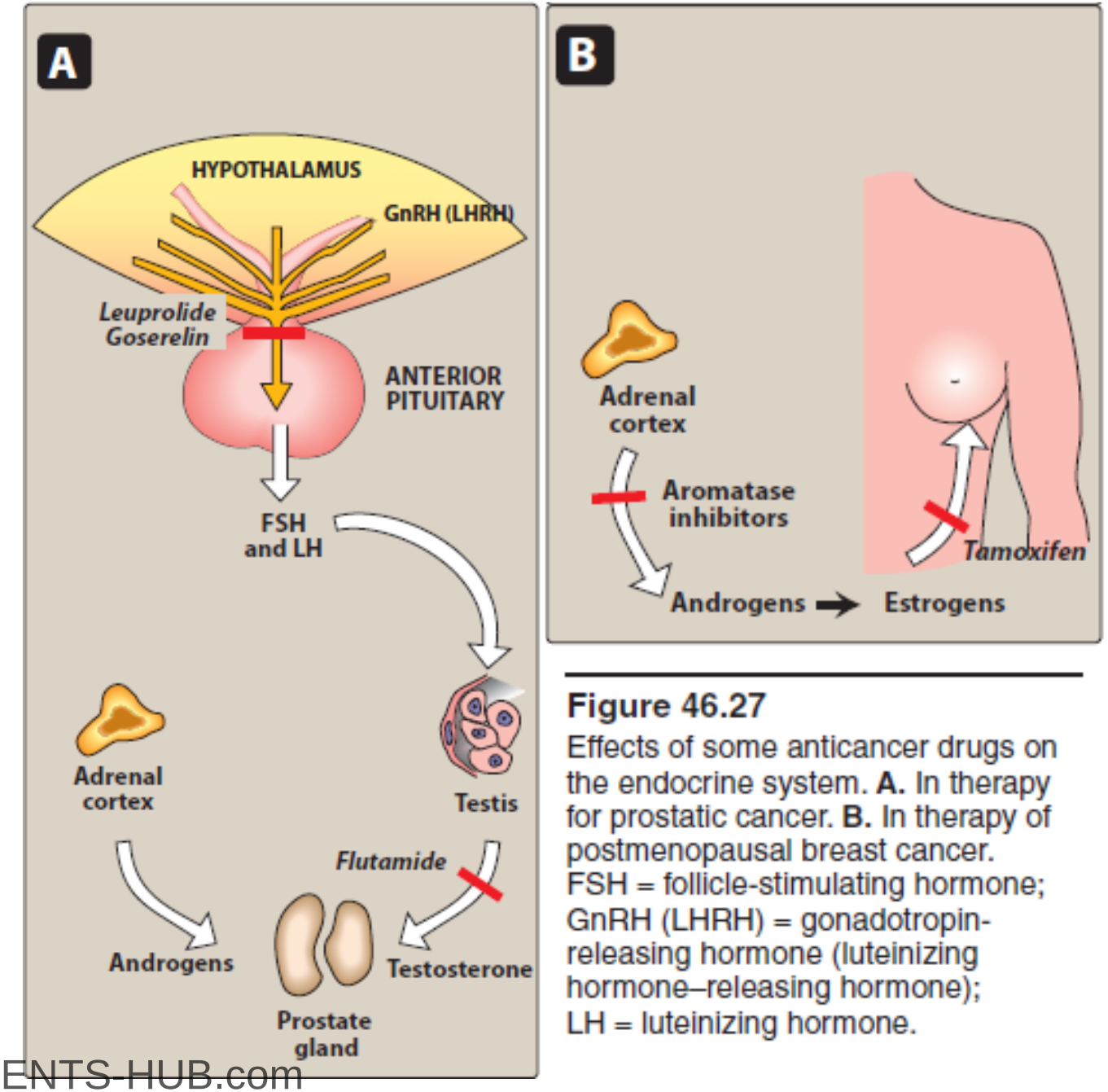


Figure 46.27

Effects of some anticancer drugs on the endocrine system. **A.** In therapy for prostatic cancer. **B.** In therapy of postmenopausal breast cancer. FSH = follicle-stimulating hormone; GnRH (LHRH) = gonadotropin-releasing hormone (luteinizing hormone–releasing hormone); LH = luteinizing hormone.

2. Pharmacokinetics:

- *Tamoxifen* is effective after oral administration.
- It is partially metabolized by the liver.
- Some metabolites possess antagonist activity, whereas others have agonist activity.
- Unchanged drug and metabolites are excreted predominantly through the bile into the feces.
- *Tamoxifen* is an inhibitor of CYP3A4 and P-glycoprotein.

3. Adverse effects:

- Side effects caused by *tamoxifen* include hot flashes, nausea, vomiting, skin rash, and vaginal bleeding and discharge (due to estrogenic activity of the drug and some of its metabolites).

- Hypercalcemia may occur, requiring cessation of the drug.

- *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.]

D. 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 tissues, 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. Anastrozole and letrozole:

- nonsteroidal aromatase inhibitors.
- They do not predispose patients to endometrial cancer
- Although *anastrozole* and *letrozole* are considered second-line therapy after *tamoxifen* for hormone dependent breast cancer in the United States, they have become first-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.
- Both drugs are extensively metabolized in the liver, and metabolites and parent drug are excreted primarily in the urine.

2. Exemestane:

- A steroidal, irreversible inhibitor of aromatase, *exemestane* is orally well absorbed and widely distributed.
- Hepatic metabolism is by the CYP3A4 isoenzyme.
- 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. Alopecia and dermatitis have also been noted.

E. Progestins

- *Megestrol acetate is a progestin that was widely used* in treating metastatic hormone-responsive breast and endometrial neoplasms.

- It is orally effective.

- Other agents are usually compared to it in clinical trials; however, the aromatase inhibitors are replacing it in therapy.

F. Leuprolide, goserelin, and triptorelin

- GnRH is normally secreted by the hypothalamus and stimulates the anterior pituitary to secrete the gonadotropic hormones:
  - 1) luteinizing hormone (LH), the primary stimulus for the secretion of testosterone by the testes, and
  - 2) follicle-stimulating hormone (FSH), which stimulates the secretion of estrogen

- *Leuprolide ,goserelin*, and *triptorelin are synthetic analogs of* GnRH.

- 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.

- 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 prostate cancer.

- *Leuprolide is available as*
  - *1) a* sustained-release intradermal implant,
  - 2) a subcutaneous depot injection, or
  - 3) an intramuscular depot injection to treat metastatic carcinoma of the prostate.

- *Goserelin acetate is a subcutaneous implant,* and *triptorelin pamoate is injected intramuscularly.*

- *Levels of androgen* may initially rise but then fall to castration levels.

- The adverse effects of these drugs, including impotence, hot flashes, and tumor flare, are minimal compared to those experienced with estrogen treatment.

G. Estrogens

- Estrogens, such as *ethinyl estradiol, had been used in the treatment* of prostatic cancer.
- However, they have been largely replaced by the GnRH analogs because of fewer adverse effects.
- Estrogens inhibit the growth of prostatic tissue by blocking the production 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.

H. Flutamide, nilutamide, and bicalutamide

- *They are synthetic, nonsteroidal* antiandrogens used in the treatment of prostate cancer.
- They compete with the natural hormone for binding to the androgen receptor and prevent its translocation into the nucleus.
- These antiandrogens are taken orally and are cleared through the kidney.
- Side effects include gynecomastia and GI distress. Rarely, liver failure has
- occurred with *flutamide. 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 previously observed following administration of mouse (murine) antibodies.

- The use of the monoclonal antibodies
  - *trastuzumab,*
  - *rituximab,*
  - *bevacizumab, and*
  - *cetuximab in the* treatment of cancer is described below.

- Many other monoclonal antibody treatments are available, examples of which include
- *alemtuzumab, which* is used in the treatment of refractory B-cell chronic lymphocytic leukemia,
- *panitumumab, which is effective in metastatic colorectal tumors, and*
- *I131- tositumomab, which is used in relapsed non-Hodgkin lymphoma.*

- *[Note:* Monoclonal antibodies also find application in a number of other disorders, such as inflammatory bowel disease, psoriasis, and rheumatoid arthritis.]

A. Trastuzumab

- In patients with metastatic breast cancer, overexpression of transmembrane human epidermal growth factor receptor protein 2 (HER2) is seen in 25% to 30% of patients.
- HER2 overexpression is also noted in gastric and gastroesophageal cancers.
- *Trastuzumab*, a humanized monoclonal antibody, specifically targets the extracellular domain of the HER2 growth receptor that has intrinsic tyrosine kinase activity.
- [Note: At least 50 tyrosine kinases mediate cell growth or division by phosphorylating signaling proteins. They have been implicated in the development of many neoplasms by an unknown mechanism.]

1. Mechanism of action:

- *Trastuzumab* binds to HER2 sites in breast cancer, gastric cancer, and gastroesophageal tissues and inhibits the proliferation of cells that overexpress the HER2 protein, thereby decreasing the number of cells in the S-phase.

- By binding to HER2, it blocks downstream signaling pathways, induces antibody-dependent cytotoxicity, and prevents the release of HER2.

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 anthracyclines.
- Extreme caution should be exercised when giving the drug to patients with preexisting cardiac dysfunction.

B. Rituximab

- *Rituximab* was the first monoclonal antibody to be approved for the treatment of cancer.

- It is a genetically engineered, chimeric 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 differentiation.

- *Rituximab* is effective in the treatment of lymphomas, chronic lymphocytic leukemia, and rheumatoid arthritis.

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 *prednisone* (CHOP).

2. 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 corticosteroids can ameliorate these problems.
- Tumor lysis syndrome has been reported within 24 hours of the first dose of *rituximab*.
- This syndrome consists of hyperkalemia, hypocalcemia, hyperuricemia, hyperphosphatasemia (an abnormally high content of alkaline phosphatase in the blood), and acute renal failure that may require dialysis.

C. Bevacizumab

- The monoclonal antibody *bevacizumab* is an IV antiangiogenesis agent.
- *Bevacizumab* is approved for use as a first-line drug against metastatic colorectal cancer and is given with *5-FU*–based chemotherapy.
- It attaches to and stops vascular endothelial growth factor from stimulating the formation of new blood vessels (neovascularization).
- Without new blood vessels, tumors do not
- receive the oxygen and essential nutrients necessary for growth and
- proliferation.

D. Cetuximab and panitumumab

- *Cetuximab* is another chimeric monoclonal antibody infused intravenously and approved to treat metastatic colorectal cancer and head and neck cancers.

- It exerts its antineoplastic effect by targeting the epidermal growth factor receptor (EGFR) on the surface of cancer cells and interfering with their growth.

- *Cetuximab, panitumumab* [pan-i-TUE-moo-mab], and
- other agents that target this receptor cause a distinct acneiform-type rash. The appearance of this rash has been associated with a positive response to therapy.

IX. PLATINUM COORDINATION COMPLEXES

- **Cisplatin,**
- **carboplatin, and**
- **oxaliplatin**

- *Cisplatin* was the first member of the platinum coordination complex class of anticancer drugs, but because of its severe toxicity, *carboplatin* was developed.

- The mechanisms of action of the two drugs are similar, but their potency, pharmacokinetics, patterns of distribution, and dose-limiting toxicities differ significantly (Figure 46.29).

- *Cisplatin* has synergistic cytotoxicity with radiation and other chemotherapeutic agents.

DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Cisplatin	IV, IP, IA	Neurotoxicity, myelosuppression, ototoxicity, N, V, electrolyte wasting, infusion reaction, nephrotoxicity	Anticonvulsants	CBC, CMP, electrolytes, hearing	Aggressive pre- and posthydration required, high incidence of nausea and vomiting
Carboplatin	IV, IP, IA	Myelosuppression, N, V, infusion reaction	Aminoglycosides	CBC	Dose calculated using AUC
Oxaliplatin	IV	Neurotoxicity, N, V, infusion reaction, hepatotoxicity, myelosuppression	*Warfarin*	CBC, neurologic function, hepatic function	Cold-related and cumulative peripheral neuropathy

- It 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 a closely related analog of *carboplatin* used in the setting of colorectal cancer.

1. Mechanism of action:

- The mechanism of action for this class of drugs is similar to that of the alkylating agents.

- It binds to guanine in DNA, forming inter- and intrastrand crosslinks.

- The resulting cytotoxic lesion inhibits both polymerases for DNA replication and RNA synthesis. 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.

3. Adverse effects:

- 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 required.
- The major limiting toxicity is dose-related nephrotoxicity, involving the distal convoluted tubule and collecting ducts.
- This can be prevented by aggressive hydration. Other toxicities include ototoxicity
- with high-frequency hearing loss and tinnitus.

- Unlike *cisplatin, carboplatin* causes only mild nausea and vomiting, and it is rarely nephro-, neuro-, or ototoxic.

- Its dose-limiting toxicity is myelosuppression.

- *Oxaliplatin* has a distinct side effect of cold-induced peripheral neuropathy that usually resolves within 72 hours of administration.

- It also causes myelosuppression and cumulative peripheral neuropathy. Hepatotoxicity has also been reported. These agents may cause hypersensitivity reactions ranging from skin rashes to anaphylaxis.

X. TOPOISOMERASE INHIBITORS

- inhibition of topoisomerase enzymes, a class of enzymes that reduce supercoiling of DNA

A. Camptothecins

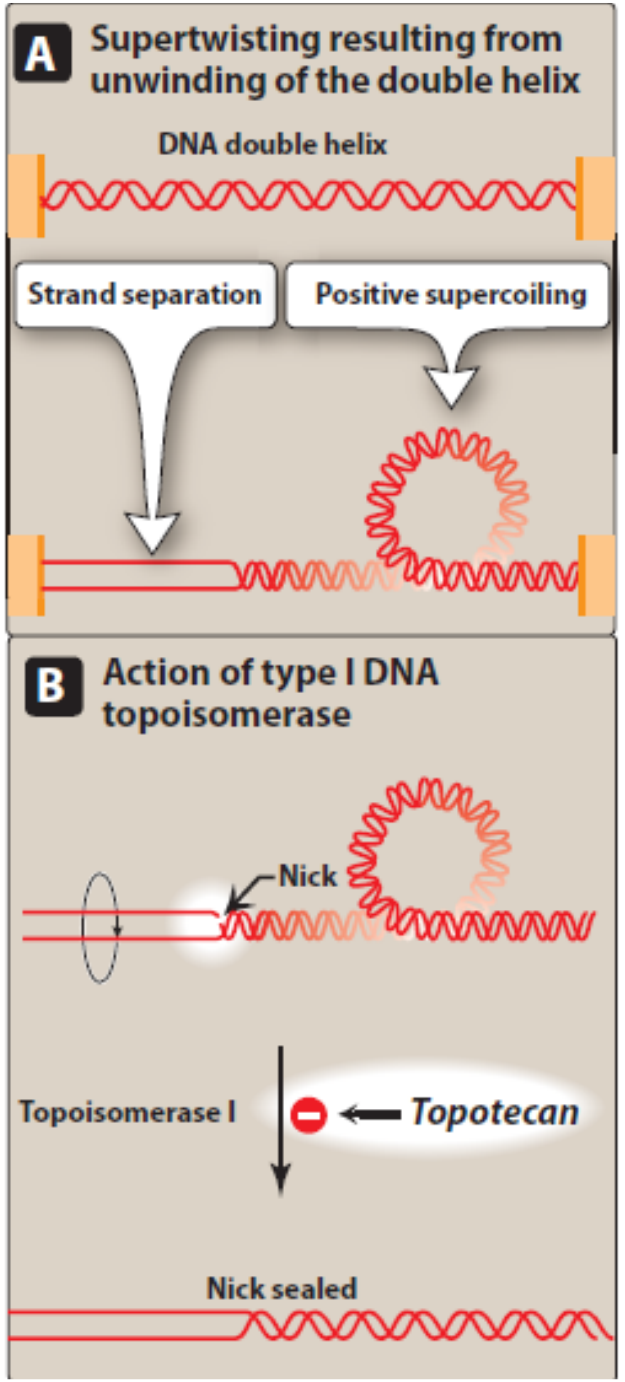
- Camptothecins are plant alkaloids.
- *Irinotecan* and *topotecan* are semisynthetic derivatives of *camptothecin*.
- *Topotecan* is used in metastatic ovarian cancer when primary therapy has failed and also in the treatment of small cell lung cancer
- *Irinotecan* is used with *5-FU* and *leucovorin* for the treatment of colorectal carcinoma.

1. Mechanism of action:

- inhibit topoisomerase I, which is essential for the replication of DNA in human cells.

- SN-38 (the active metabolite of *irinotecan*) is approximately 1000 times as potent as *irinotecan* as an inhibitor of topoisomerase I.

- The topoisomerases relieve torsional strain in DNA by causing reversible, single-strand breaks.



2. Adverse effects:

- Bone marrow suppression, particularly neutropenia, is the dose-limiting toxicity for *topotecan*.

- Myelosuppression is also seen with *irinotecan*.

- Acute and delayed diarrhea may be severe and require treatment with *atropine* during the infusion or high doses of *loperamide* in the days following the infusion.

B. Etoposide

- *Etoposide* is a semisynthetic derivative of the plant alkaloid, podophyllotoxin.
- Its major target is topoisomerase II.
- *Etoposide* finds its major clinical use in the treatment of lung cancer and in combination with *bleomycin* and *cisplatin* for testicular carcinoma. *Etoposide* may be administered either IV or orally.
- Dose-limiting myelosuppression (primarily leukopenia) is the major toxicity.

XI. TYROSINE KINASE INHIBITORS

- The tyrosine kinases are a family of enzymes that are involved in several important processes within a cell, including signal transduction and cell division.

- Many tyrosine kinase inhibitors are available, and these agents have a wide variety of applications in the treatment of cancer

- Some of the more common agents are discussed below.

A. Imatinib, dasatinib, and nilotinib

- *Imatinib mesylate* is used for the treatment of chronic myelogenous leukemia (CML) as well as GI stromal tumors.
- 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 CML.
- In the case of GI stromal tumors, an unregulated expression of tyrosine kinase is associated with a growth factor.

- The ability of *imatinib* to occupy the “kinase pocket” prevents the phosphorylation of tyrosine on the substrate molecule and, hence, inhibits subsequent steps that lead to cell proliferation.

- *Nilotinib* and *dasatinib* are also first-line options for CML.

- These agents are all available in oral formulations, and they are associated with notable toxicities, such as fluid retention and QT prolongation).

B. Erlotinib

- *Erlotinib* is an inhibitor of the epidermal growth factor receptor tyrosine kinase.
- It is an oral agent approved for the treatment of NCSLC and pancreatic cancer.
- *Erlotinib* is absorbed after oral administration and undergoes extensive metabolism in the liver by the CYP3A4 isoenzyme.
- The most common adverse effects are diarrhea, nausea, acne-like skin rashes, and ocular disorders.
- A rare but potentially fatal adverse effect is interstitial lung disease, which presents as acute dyspnea with cough.

C. Sorafenib and sunitinib

- *Sorafenib* and *sunitinib* are oral serine/threonine and tyrosine kinase inhibitors used mainly in renal cell carcinoma.
- *Sorafenib* is also part of the treatment strategy for hepatocellular carcinoma, and *sunitinib* is used in GI stromal tumors and pancreatic neuroendocrine tumors.
- These agents target cell surface kinases thus slowing tumor growth.
- Adverse effects include diarrhea, fatigue, hand and foot syndrome, and hypertension.

XII. MISCELLANEOUS AGENTS

- **A. Procarbazine**
- **B. Asparaginase and pegaspargase**
- **C. Interferons**

A. Procarbazine

- *Procarbazine* is used in the treatment of Hodgkin disease and other cancers.
- *Procarbazine* rapidly equilibrates between the plasma and the CSF after oral 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 drowsiness to hallucinations to paresthesias.
- Because it inhibits monoamine oxidase, patients should be warned against ingesting foods that contain high levels of tyramine (for example, aged cheeses, beer, and wine) as this could cause a hypertensive crisis.
- Ingestion of alcohol leads to a disulfiram-like reaction.
- *Procarbazine* is both mutagenic and teratogenic.
- Nonlymphocytic leukemia has developed in patients treated with the drug.

B. Asparaginase and pegaspargase

- *l-Asparaginase* and the pegylated formulation *pegaspargase* catalyze the deamination of asparagine to aspartic acid and ammonia, thus depriving the tumor cells of this amino acid, which is needed for protein synthesis.

- The form of the enzyme used chemotherapeutically is derived from bacteria.

- *l-Asparaginase* is used to treat childhood acute lymphocytic leukemia in combination with *VX* and *prednisone*.

- The enzyme must be administered either IV or intramuscularly, because it is destroyed by gastric enzymes.

- Toxicities include a range of hypersensitivity reactions (because it is a foreign protein), a decrease in clotting factors, liver abnormalities, pancreatitis, seizures, and coma due to ammonia toxicity.

C. Interferons

- Human interferons are biological response modifiers and 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 quantities 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,
  - CML, and
  - (AIDS)-related Kaposi sarcoma.

- *Interferon-α-2b* is approved for the treatment of
  - hairy cell leukemia,
  - melanoma,
  - AIDS-related Kaposi sarcoma, and
  - follicular lymphoma

- Interferons interact with surface receptors on other cells, at which site they exert their effects.

- As a consequence of the binding of interferon, a series of complex intracellular reactions take place.
- These include synthesis of enzymes, suppression of cell proliferation, activation of macrophages, and increased cytotoxicity of lymphocytes.

- However, the exact mechanism by which the interferons are cytotoxic is unknown.

Interferons are well absorbed after intramuscular or subcutaneous injections.

An IV form of *interferon-α-2b* is also available.

- Flu-like symptoms and GI upset are common with these agents. Suicidal ideation and seizures have been reported.

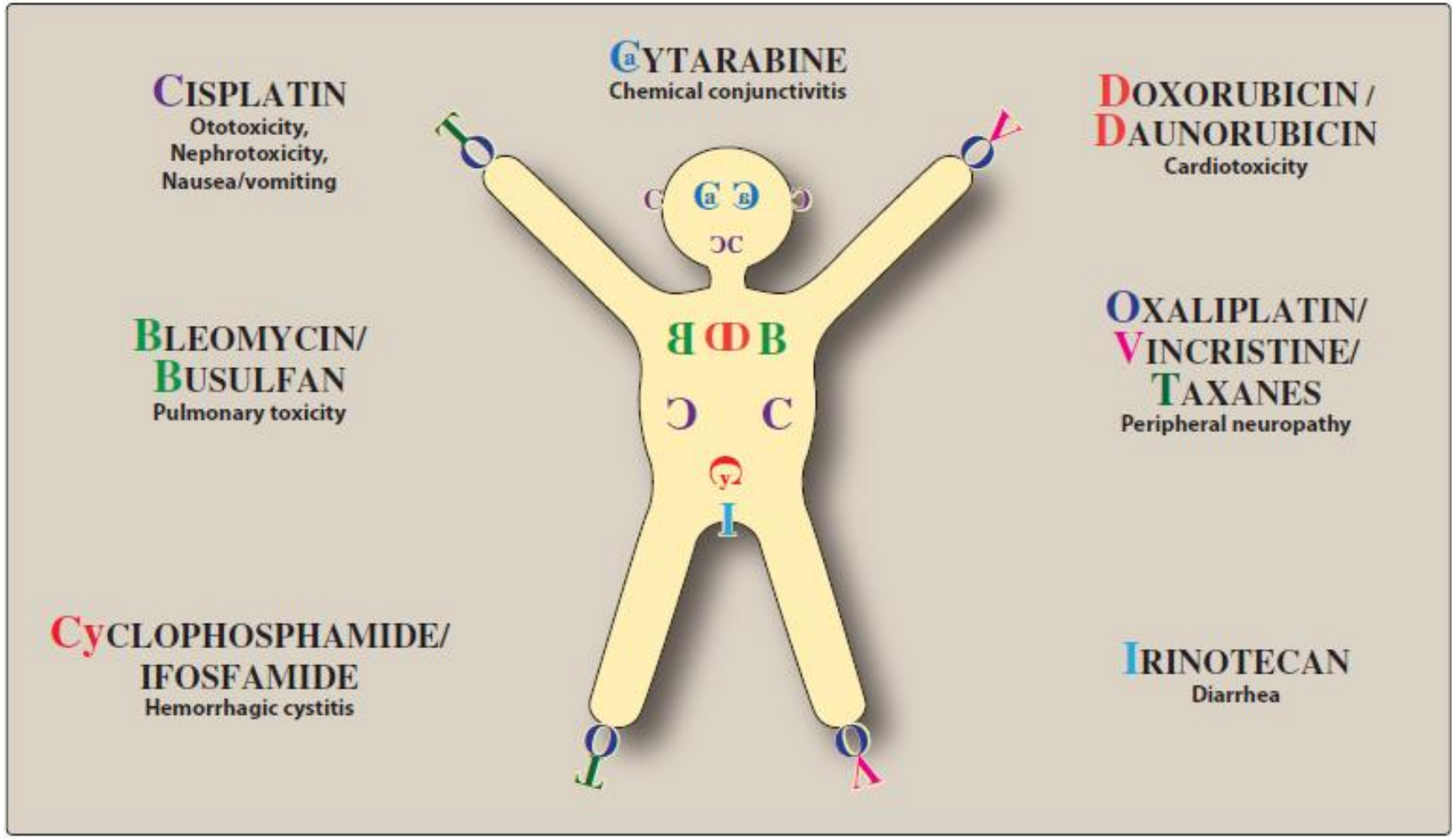


Figure 46.35
Chemo Man—a summary of toxicity of chemotherapeutic agents.