

PRINCIPLES OF CANCER CHEMOTHERAPY

• **PRINCIPLES OF CANCER CHEMOTHERAPY**

- Cancer chemotherapy **strives to cause a lethal cytotoxic event in the cancer cell that can arrest a tumor's progression.**
- The attack is generally **directed against metabolic sites essential to cell replication—for example, the availability of purines and pyrimidines that are the building blocks for DNA or RNA synthesis**
- Ideally, **anti-cancer drugs should interfere only with cellular processes that are unique to malignant cells.**
- **Unfortunately, most anti-cancer** drugs do not specifically recognize neoplastic cells but, rather, **affect all proliferating cells—both normal and abnormal.**

- **PRINCIPLES AND DEFINITIONS**
- Log-kill hypothesis
- Cytotoxic actions of anticancer drugs **follow first-order kinetics.**
- When we say that destruction of cancer cells by chemotherapeutic agents follows first-order kinetics; we mean that **a given dose of drug destroys a constant fraction or proportion of a cell population rather than a constant number of cells.**
- They kill a **fixed percentage** of tumor cells, **not a fixed number.**

- The term "log kill" is used to describe this phenomenon.
- The log-kill hypothesis **also proposes that the magnitude of tumor cell kill by anticancer drugs is a logarithmic function.**
- This leads to one rationale for drug combinations.

- **For example, a 3-log-kill dose of an effective drug will reduce a cancer cell population of 10^{12} cells to 10^9 (a total kill of 999×10^9 cells); the same dose would reduce a starting population of 10^{10} cells to 10^3 cells (a kill of 999×10^3 cells). In both cases, the dose reduces the numbers of cells by 3 orders of magnitude, or "3 logs."**
- **For another example, a diagnosis of leukemia is generally made when there are about 10^9 (total) leukemic cells.**

- **Consequently, if treatment leads to a 99.999-percent kill, then 0.001 percent of 10^9 cells (or 10^4 cells) would remain.**
- **This is defined as a five-log kill. At this point, the patient appears asymptomatic; that is, the patient is in remission.**
- **For most bacterial infections, a five-log (100,000-fold) reduction in the number of microorganisms results in a cure, because the host's immune system can destroy the remaining bacterial cells.**
- **However, in treating cancer, because tumor cells are not as readily eliminated, additional treatment is required to totally eradicate the leukemic cell population.**

- **For this reason, most cancer treatment begins with debulking by surgery and/or radiation in order to initially reduce the neoplastic cell burden before chemotherapy, immunotherapy, or a combination of these treatment modalities is begun.**
- **Because tumor cells are similar to normal cells, it has been difficult to develop anticancer agents which selectively kill tumor cells without harming normal tissues.**

- **Growth fraction**
- **Cytotoxic drugs are more effective against tumors that have a high growth fraction (i.e a large percentage actively dividing).**
- **Normal cells with high growth fraction (e.g., bone marrow) are also more sensitive to anticancer drugs.**

- **Cell-cycle specificity**
- **Some anticancer drugs act specifically on tumor cells undergoing cycling.**
- **Drugs that act specifically on phases of the cell cycle are called cell-cycle specific (CCS) and are more effective in tumors with high-growth fraction (leukemias, lymphomas).**

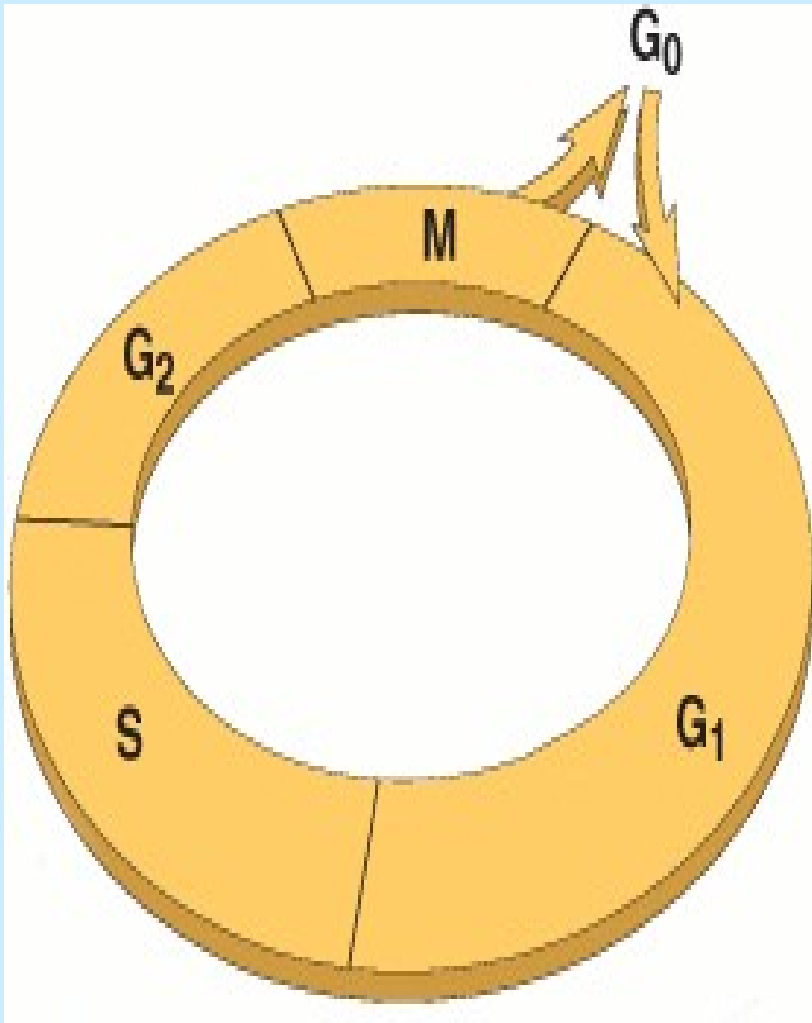
- **Chemotherapeutic agents that are effective only against replicating cells —that is those cells that are cycling— are said to be cell-cycle specific.**
- **Such agents are called cell cycle-specific agents [CCS] because they exert their actions during distinct phases of the cell cycle.**

- Drugs that are **cell-cycle nonspecific [CCNS]** (many bind to and damage DNA) can be used in **BOTH** tumors with **low-growth fraction**, as well as tumors with **high-growth fraction**.

- Lets expand on this a bit....

- **Tumor susceptibility and the growth (cell) cycle:**
- **Cancer cell population kinetics and the cancer cell cycle are important determinants of the actions and clinical uses of anticancer drugs.**
- **Tumor cells are remarkably similar to noncancerous human cells. Thus, there are relatively few drug strategies for destroying tumor cells while sparing non neoplastic cells.**
- **Both normal cells and tumor cells go through growth cycles (next slide).**

Cell cycle



- Multi-step process
- Regulated by environment and genes
- **G₀- Cells resting**
- **G₁- In the first phase (G₁) the cell grows (increases in size).**
- **S- When it has reached a certain size it enters the phase of DNA-synthesis (the S phase) where the chromosomes are duplicated. [DNA is copied (2 copies present in cell)]**
- **G₂- During the next phase (G₂) the cell prepares itself for division.**
- **M- During mitosis (M) the chromosomes are separated and segregated to the daughter cells, which thereby get exactly the same chromosome set up.**
- The cells are then back in G₁ and the cell cycle is completed.

- **Both normal cells and tumor cells go through growth cycles**
- **But normal and cancer cells differ primarily with regard to the number of cells that are in the various stages of the cycle, and the number of cells undergoing cell division.**
- **The fraction of tumor cells that are in the replicative cycle ("growth fraction") influences their susceptibility to most cancer chemotherapeutic agents.**

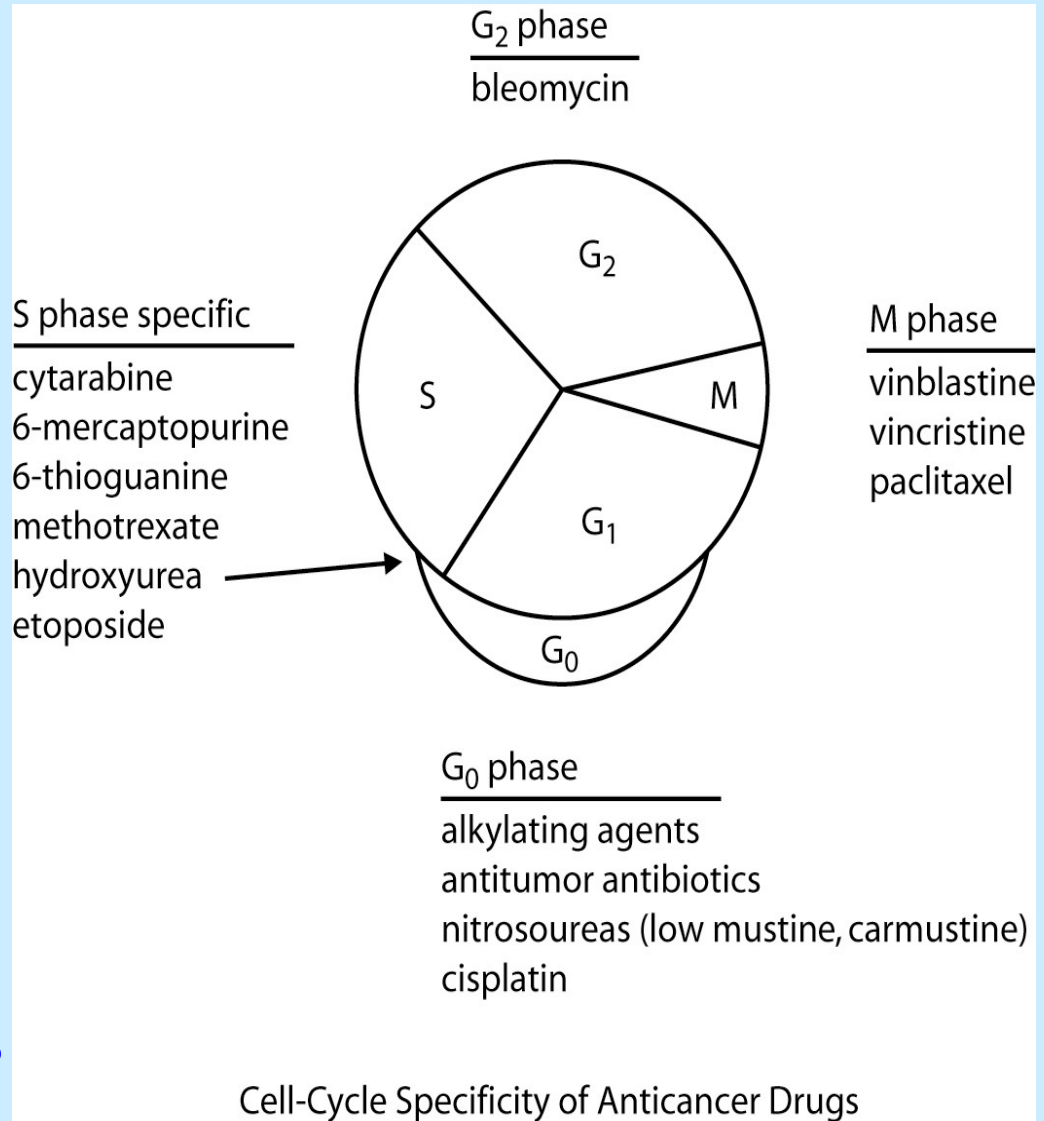
- **Cell cycle specific (CCS) drugs are usually most active in a specific phase of the cell cycle.**
- **CCS drugs are particularly effective when a large proportion of the tumor cells are proliferating (ie, when the growth fraction is high).**

- **Rapidly dividing cells are generally more sensitive to anticancer drugs, whereas nonproliferating cells (those in the G0 or resting phase;) usually survive the toxic effects of many of these agents.**
- **Most anticancer drugs act by killing cells that are dividing**

- **In general, agents that interfere with DNA synthesis are S-phase specific;**
- **Those that interfere with microtubules disrupt mitosis and are called M-phase specific.**
- **The drugs accomplish this by interfering with DNA, RNA, or protein synthesis or by inhibiting the formation of microtubules in mitosis.**

- **Other cancer drugs kill tumor cells in both cycling and resting phases of the cell cycle..... those in the G0 or resting phase**
- **DNA alkylating agents damage tumor cells regardless of whether the cell is actively dividing.**
- **Because of this property, these agents are called “cell cycle- nonspecific” [CCNS] drugs.**
- **The nonspecific drugs, although having generally more toxicity in cycling cells, are also useful against tumors that have a low percentage of replicating cells**
- **Newer agents selectively target cancer cells by using monoclonal antibody technology.**

- **S phase specific**
- **Antimetabolites**
- **G2 phase**
- **bleomycin**
- **M phase specific**
- **Vinca alkaloids**
- **Paclitaxel**
- **G0 phase**
- **Alkylating agents**
- **Cisplatin**
- **Antitumor antibiotics**
- **nitrosoureas**



- **Summary (see end of chapter in your notes)**
- The "log-kill" hypothesis states that cytotoxic anticancer agents kill **a certain percentage, not a fixed number**, of cells.
- Cytotoxic drugs are most effective **against rapidly dividing cells**.
- **Drugs that act on proliferating cells are cell-cycle specific and are usually also cycle-phase specific.**
- **Drugs that act on nonproliferating cells are dose dependent and cell-cycle independent.**

- Rationales for combination drug usage are that **each drug will independently kill a fixed percentage** and that one drug will still kill a cancer cell that has developed resistance to a different drug in the cocktail.
- **Rapidly proliferating normal cells are more sensitive to cytotoxic drugs.**
- **Bone marrow suppression often determines the upper limit of tolerable chemotherapy.**

DRUGS

Table IX-1-1. Characteristics of Important Anticancer Drugs

Drug	Mechanism	Uses	Side Effects
Cyclophosphamide	Alkylating agent—attacks guanine N7—dysfunctional DNA	Non-Hodgkin, ovarian, breast cancer, neuroblastoma	BMS, mucositis, hemorrhagic cystitis (mesna , traps acrolein and is protective), hepatotoxicity (high dose)
Cisplatin	Alkylating agent—cross-links DNA strands	Testicular, ovarian, bladder, lung cancer	Nausea, vomiting (use ondansetron); nephrotoxicity (use amifostine); neurotoxicity (deafness)
Procarbazine	Alkylating agent	Hodgkin	BMS, pulmonary toxicity, hemolysis, neurotoxicity, leukemogenic
Doxorubicin	Intercalator, forms free radicals, inhibits topoisomerase	Hodgkin, breast, endometrial, lung, and ovarian cancers	BMS—delayed CHF (dexrazoxane is an iron-chelating agent preventing the formation of free radicals; it is not a free radical “trapper”), alopecia, vesicant, radiation “recall”
Methotrexate (CCS)	Antimetabolite—inhibits DHF reductase (S phase)	Leukemias, lymphomas, breast cancer; rheumatoid arthritis, psoriasis	BMS, mucositis, crystalluria; leucovorin (folinic acid) rescue
5-Fluorouracil (CCS)	Pyrimidine antimetabolite (S phase) bioactivated to inhibit thymidylate synthetase	Breast, ovarian, head, and neck cancer—topical for basal cell cancer and keratoses	BMS, GI irritation, alopecia
6-Mercaptopurine (CCS)	Purine antimetabolite (S phase) bioactivated by HGPR transferase	Acute lymphocytic leukemia; immunosuppression	BMS, hepatotoxicity (jaundice, necrosis), GI distress
Bleomycin (CCS)	Complexes with Fe and O ₂ → DNA strand scission (G ₂ phase)	Hodgkin, testicular, head, neck, skin cancer	Pneumonitis, pulmonary fibrosis, mucocutaneous reactions (blisters), alopecia, hypersensitivity
Vincristine Vinblastine (CCS)	↓ Microtubular polymerization—spindle poisons (M phase)	Vinblastine—Hodgkin, testicular cancer, Kaposi Vincristine—Hodgkin, leukemias, Wilms	BMS, GI, alopecia Neurotoxicity

Definition of abbreviations: BMS, bone marrow suppression; CCS, cell-cycle specific; CHF, congestive heart failure; GI, gastrointestinal.

- Table IX-1-1 lists **mechanisms of action, selected clinical uses, and side effects of major anticancer drugs.**
- ***We cant get away from memorizing this table. ITS HIGH YIELD!***
- **Note that:**
- Step 1 questions related to antineoplastic agents are most likely going to ask you about **mechanism of action, cell cycle specificity, or side effects.**

- I have prepared a table to facilitate the memorization of the **selected clinical uses**

CANCER TREATMENT TABLES

Ovarian

Cyclo-phosphamide
Cisplatin
Doxorubicin
5-Fluoro-uracil

Non-Hodgkin

Cyclo-phosphamide

Breast cancer

Cyclo-phosphamide
Doxorubicin
Methotrexate
5-Fluoro-uracil

Neuroblastoma

Cyclo-phosphamide

Testicular

Cisplatin
Bleomycin
Vinblastin

Bladder

Cisplatin

Lung cancer

Cisplatin
Doxorubicin

Hodgkin

Procarbazine
Vincristine
Vinblastine
Doxorubicin:
Bleomycin

Endometrial

Doxorubicin

Leukemias,

Methotrexate
Vincristine

Lymphomas

Methotrexate

Head and neck cancer

5-Fluoro-uracil
Bleomycin

Basal cell cancer

5-Fluoro-uracil
Bleomycin

Wilms

Vincristine

Acute lymphocytic leukemia

6-Mercapto-purine

Immuno-suppression

6-Mercapto-purine

Kaposi

Vinblastine

Cancer Side effects table

Cyclophosphamide	BMS, mucositis, hemorrhagic cystitis, hepatotoxicity (high dose)
Cisplatin	Nausea, vomiting (use ondansetron); nephrotoxicity (use amifostine); neurotoxicity (deafness)
Procarbazine	BMS, pulmonary toxicity, hemolysis, neurotoxicity, leukemogenic
Doxorubicin	BMS—delayed CHF (dexrazoxane is an iron-chelating agent preventing the formation of free radicals; it is not a free radical “trapper”), alopecia, vesicant, radiation “recall”
Methotrexate	BMS, mucositis, crystalluria; leucovorin (folinic acid) rescue
5-Fluoro-uracil	BMS, GI irritation, alopecia
6-Mercapto-purine	BMS, hepatotoxicity (jaundice, necrosis), GI distress
Vincristine	Neurotoxicity
Vinblastine	BMS, GI, alopecia

- **Cancer Side effects**
- **NOTE that**
- **Cisplatin IS NOT associated with BMS**
- **Methotrexate is associated with crystalluria and leucovorin (folinic acid) rescue**
- **6-Mercaptopurine & Cyclophosphamide are both associated with hepatotoxicity; but cyclophosphamide is distinguished for causing hemorrhagic cystitis**
- **Cisplatin is associated with both nephrotoxicity and neurotoxicity**
- **ViNcristine is associated with Neurotoxicity**
- ***Pick out these things as you work through this table, and you will pick off ALL the questions in this section of the course.***

Drugs

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TOXICITY OF ANTICANCER DRUGS

- Table IX-1-2 shows the dose-limiting and distinctive toxicities of anticancer drugs.
- **NOTE that** Though bone marrow suppression, nausea, vomiting, ulcers, alopecia are common side effects; however, **you are probably more likely to be asked about the unique side effects of certain drugs.**

- **Unfortunately, therapy aimed at killing rapidly dividing cells also affects normal cells undergoing rapid proliferation.**
- **This contributes to the toxic manifestations of chemotherapy.**

- **Rapidly proliferating cells, such as the bone marrow, gastrointestinal tract mucosa, hair follicles, and gonads, are the most sensitive to cytotoxic drugs.**
- **These cells are all replaced at a much greater rate than most other noncancerous cells in the normal human.**
- **Most often, bone marrow suppression (BMS) is dose limiting.**

- **Because of the rapid growth rate of these cells, they are susceptible to damage by anticancer drugs, and are the most sensitive to cytotoxic drugs.**
- **However, many drugs cause toxicity that is unrelated to cell growth rate**

- Anticancer drug dosage is usually carefully titrated to avoid **excessive neutropenia** (granulocytes $<500/\text{mm}^3$) and **thrombocytopenia** (platelets $<20,000/\text{mm}^3$).
- Colony stimulating factors, erythropoietin, and thrombopoietin can be supportive \rightarrow \downarrow infections and need for antibiotics.

- **Severe vomiting, stomatitis, and alopecia occur to a lesser or greater extent during therapy with all antineoplastic agents.**
- Vomiting is often controlled by administration of antiemetic drugs.
- Some toxicities, such as myelosuppression that predisposes to **infection**, are common to many chemotherapeutic agents, whereas other adverse reactions are confined to specific agents, for example, **cardiotoxicity with doxorubicin** and **pulmonary fibrosis with bleomycin**.
- **The duration of the side effects varies widely. For example, alopecia is transient, but the cardiac, pulmonary, and bladder toxicities are irreversible.**

Toxicity of Anticancer Drugs

Toxicity	Drug(s)
Renal	Cisplatin, methotrexate
Hepatic	6-MP, busulfan, cyclophosphamide
Pulmonary	Bleomycin, busulfan, procarbazine
Cardiac	Doxorubicin, daunorubicin
Neurologic	Vincristine, cisplatin, paclitaxel
Immunosuppressive	Cyclophosphamide, methotrexate
Other	Cyclophosphamide (hemorrhagic cystitis); procarbazine (leukemia); asparaginase (pancreatitis)

- END
- The slides above and those below are selected quickly from my database
- Hope you can extract the juice from them.

- Tumor cells are derived from normal cells in which proliferation is poorly controlled. Because tumor cells are similar to normal cells, it has been difficult to develop anticancer agents which selectively kill tumor cells without harming normal tissues.
- Most anticancer agents act by inhibiting cell proliferation. Generally this is achieved by either damaging DNA or preventing DNA repair. Essentially, there are four ways in which most anticancer drugs inhibit proliferation:
 - Crosslinking DNA. Prevents separation of DNA strands.
 - Linking alkyl groups to DNA bases. Inhibits repair of DNA.
 - Mimicking DNA bases, resulting in 1) incorporation of drug into DNA or RNA, where it prevents repair or terminates the chain or 2) negative feedback on enzymes that synthesize or recycle purines.
 - Intercalating between base pairs of DNA, disrupting the triplicate codons or producing oxygen free radicals which damage DNA.
- Hormonal anticancer drugs antagonize receptors, preventing endogenous growth-promoting hormones from binding. Other hormonal agents are agonists at receptors that, when activated, inhibit tumor growth.
- In caring for patients on chemotherapy, it is essential to evaluate the patient for dose-limiting side effects (some, such as permanent cardiomyopathy from Adriamycin, are initially asymptomatic), to know how to treat neutropenic fever, and to effectively manage nausea and vomiting.

- **The cell cycle**
- **Tumor cells are remarkably similar to noncancerous human cells. Thus, there are relatively few drug strategies for destroying tumor cells while sparing non neoplastic cells. Newer agents selectively target cancer cells by using monoclonal antibody technology.**
- **Neoplastic and normal cells differ primarily with regard to the number of cells undergoing cell division, and most anticancer drugs act by killing cells that are dividing. The drugs accomplish this by interfering with DNA, RNA, or protein synthesis or by inhibiting the formation of microtubules in mitosis.**
- **Such agents are called cell cycle-specific agents because they exert their actions during distinct phases of the cell cycle (Fig. 8.1). In general, agents that interfere with DNA synthesis are S-phase specific; those that interfere with microtubules disrupt mitosis and are called M-phase specific.**
- **DNA alkylating agents damage tumor cells regardless of whether the cell is actively dividing. Because of this property, these agents are called “cell cycle- nonspecific” drugs.**

- • Resistance and Recurrence
- **If a tumor cell is to be killed by an anticancer drug,**
- **1) the drug must reach the tumor cell,**
- **2) the tumor cell must enter the phase of the cell cycle that is targeted by the drug, and**
- **3) the cell must not be resistant to the drug.**
- **Cancer cells become resistant to anticancer agents through a variety of mechanisms including**
- **1) reduced uptake of drug into cell,**
- **2) enhanced production of enzymes that repair damaged DNA,**
- **3) production of chemically altered enzymes which are no longer recognized by drugs that inhibit unaltered enzymes,**
- **4) reduced transformation of prodrugs (inactive precursors) into cytotoxic agents and 5) enhanced transformation of toxic agents into inactive metabolites.**

- **Some tumors become resistant to several classes of antitumor agents, even if they have never been exposed to some of these agents. This is called multidrug resistance.**
- **Affected drugs include antibiotics, colchicine, the vinca alkaloids (vincristine & vinblastine) and epidophyllotoxins (VP-16). Cross-resistance among these agents is striking because they do not share a common mechanism of action.**
- **Multidrug resistance is due to increased expression of an energy-dependent membrane glycoprotein ‘pump’ which lowers the intracellular concentration of chemotherapeutic agents.**
- **The multidrug resistance gene is likely one of multiple genes that are induced to protect cells from toxic insults.**

- Anticancer chemotherapy: drug resistance
 - **Types of resistance:**
 - **Primary -- resistance is present prior to first drug exposure**
 - Examples:
 - » colon cancer
 - » non-small cell lung cancer
 - **Acquired -- resistance develops to single drug after treatment;**
 - usually associated with an increased expression of tumor cell genes
 - may be a multidrug-resistant phenotype
 - » often due to increased expression of MDRI gene (coding for a cell surface glycoprotein involve been drug transport {efflux})
 - Overexpression of the multidrug resistance-associated protein (NPR) may cause resistance-examples: Anthracyclines, Vinca alkaloids, epipodophyllotoxins
 - Changes in topoisomerase II {repairs DNA damage caused by antitumor drugs}
 - **Drug-resistant tumor cells may be selected by exposure to single agent, low-dose chemotherapy:**
 - **Examples of mutations leading to drug resistance:**
 - single agent: deletion of activating enzyme -- deoxycytidine kinase for cytosine arabinoside
 - multiple agents: Overexpression of drug efflux pump.
 - genetic change: loss of p53 suppressor oncogene -- may lead to resistance
 - genetic change: mutation of p53 or overexpression of bcl-2 gene (translocated in nodular non-Hodgkin's lymphoma) inactivates apoptosis {programmed cell death}

- **Toxicity of Anticancer Drugs**
- **Erythropoietic and leukopoietic cells, cells lining the gastrointestinal tract, and hair follicle cells are replaced at a much greater rate than most other noncancerous cells in the normal human.**
- Because of the rapid growth rate of these cells, they are susceptible to damage by anticancer drugs. **Bone marrow suppression, mucositis, and alopecia are predictable side effects of most anti cancer agents.** In addition, **many drugs cause toxicity that is unrelated to cell growth rate** (Fig. 8.3).

- Anticancer drugs: selective toxicity
 - Cancers that are rapidly dividing are most vulnerable to chemotherapeutic agents
 - These neoplasms have a high percentage of dividing cells -- large growth fraction
 - Normal tissues that divide rapidly are also damaged by the chemotherapeutic agents: side effects associated with chemotherapy are often do to effects of drugs on such normal tissues:
 - toxicity: bone marrow suppression (marrow cells are rapidly dividing)
 - toxicity: alopecia (hair follicle cells are rapidly dividing)
 - toxicity: GI disturbances-- nausea and vomiting (gastric mucosal cells are rapidly dividing)
 - Some of these toxicities, such as bone marrow suppression, may be dose limiting.
 - Some cancers are slowly dividing (examples: colon and lung carcinoma) -- a characteristic that makes successful chemotherapy difficult.

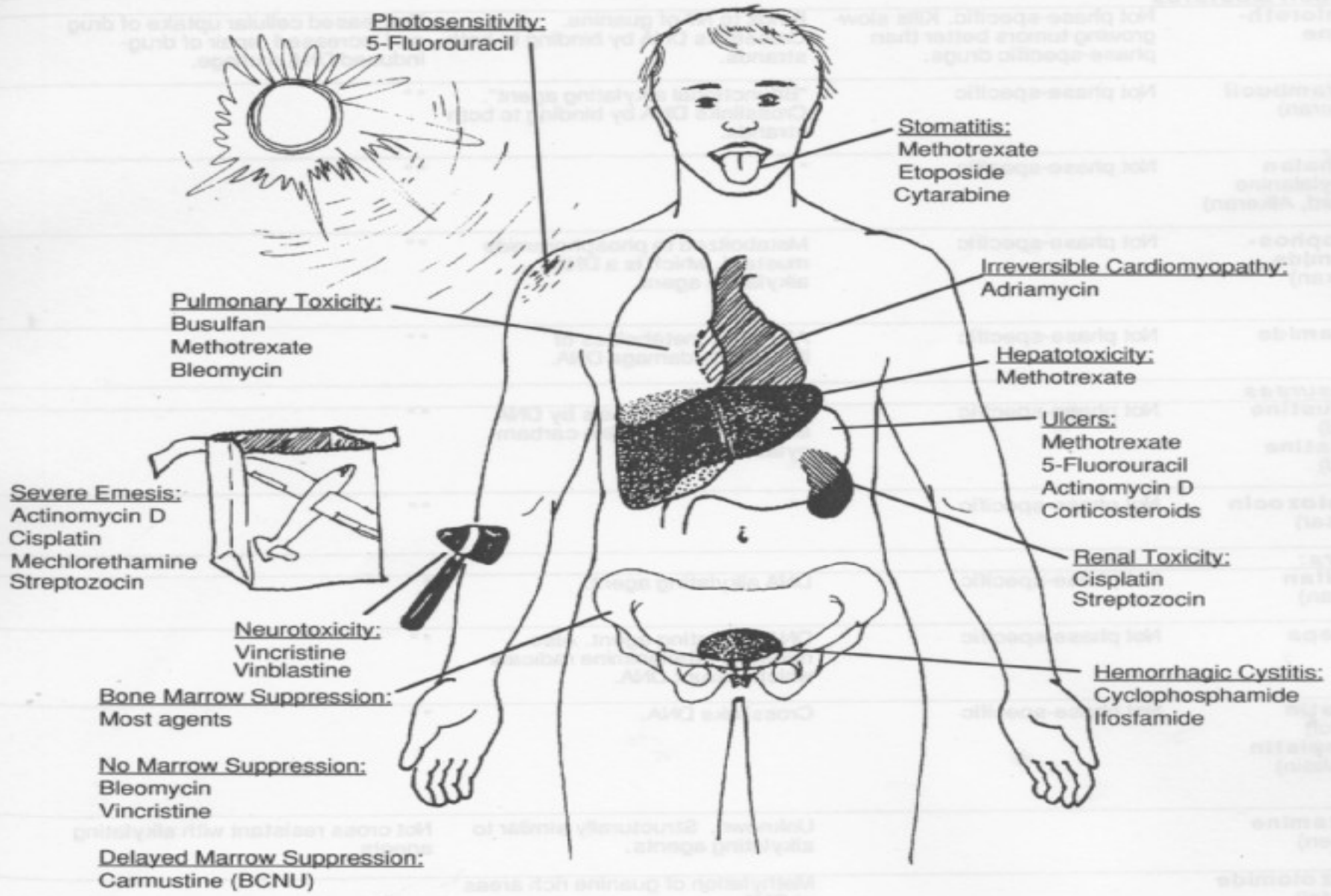


Figure 8.3 Notable side effects of chemotherapeutic agents.

- **Cancer Cell Burden: - a big challenge**
 - **Widespread cancer may correspond to a cell burden of 10^{12} .**
 - **Clinical remission and symptomatic improvement may require killing 99.9% of tumor cells.**
 - **Even with 99.9% cell kill, 10^9 cells remain (nine "logs" remaining)**
 - **Some of these remaining cells may be resistant or may not be accessible to chemotherapeutic agents (central nervous system)**
 - **Successful chemotherapy must ultimately target (tumor stem cells).**
 - **By comparison, a three "log" kill may be curative for bacterial infections, since host resistance factors can eliminate residual disease, unlike the situation in treating cancer.**
 - **To achieve the objective of total cancer cell kill, several approaches are used:**
 - **Combination therapy**
 - » **drugs with differing toxicity profiles**
 - » **drugs with differing mechanisms**
 - » **drugs with synergistic action**
 - » **Chemotherapy in combination with surgical and radiation intervention.**
 - **Combination Chemotherapy Curative:**
 - » **Testicular cancer**
 - » **Lymphoma**
 - **Combination Chemotherapy -- palliative treatment for many other tumors.**

- **Combination therapy**
- **Chemotherapeutic regimens often consist of several agents which have different mechanisms of action and minimize overlapping toxic effects.**
- **This affords multiple points of attack on the tumor cell while sparing normal organs from the toxicity produced by higher doses of a single drug.**
- **Most anticancer drugs cause bone marrow suppression. Bone marrow- sparing drugs (e.g., vincristine) are frequently included in combination regimens, if the tumor is sensitive.**
- **Combination Therapy: Combination chemotherapeutic protocols and principles**
 - **Each drug: independent activity against the specific tumor**
 - **Each drug: different mechanism of action {targeting different steps along a pathway}**
 - **No cross-resistance among the drugs in the protocol {rationale: Tumor cell subpopulation resistant to one drug, would not be resistant to another drug in the combination protocol}**
 - **Each drug: different dose limiting toxicity**

- **Following high-dose chemotherapy or chemotherapy with radiation therapy, severe myelosuppression may occur:**
 - **Bone marrow transplantation may be used**
 - **If bone marrow transplantation is part of the protocol, the most favorable relationship between cell kill and drug dose has been observed with:**
 - alkylating agents (busulfan; cyclophosphamide)
 - Use of alkylating agents as part of the myeloablative protocol results in higher tumor cell kill.
 - **Autologous bone marrow transplant: patient's bone marrow or peripheral blood stem cells:**
 - isolated
 - cryopreserved
 - infused back into patients following high-dose chemotherapy
 - **Allogenic bone marrow transplant: Bone marrow from an appropriate donor re-constitutes the patient's immune system**
 - Following allogenic transplantation, immune mechanisms contribute to control of malignant disease {graft-vs.-tumor effect}
 - **Bone marrow transplantation -- Most Effective:**
 - when tumors are initially responsive to chemotherapeutic agents
 - Acute leukemia
 - Hodgkin's disease
 - non-Hodgkin's lymphoma
 - testicular carcinoma
 - **Bone marrow transplantation -- Least Effective:**
 - Epithelial-derived cancer
 - » non-small cell lung carcinoma
 - » colorectal cancer

- **Cellular Considerations**
- **Transformed cells proliferate abnormally, forming local tumors.**
 - Tumors may contain a sub population of cells (tumor stem cells) that only divide repeatedly but also metastasize to remote sites.
- **Cancer treatment may involve surgery, radiation, and/or chemotherapy.**
- **In 1998, about half of patients with cancer can be cured with drug treatment contributing in about 17% of cases**
- Cancer chemotherapy can be curative even in metastatic disease. For example:
 - Testicular cancer
 - Diffuse large cell lymphoma
 - Hodgkin's disease
 - Choriocarcinoma
 - Certain childhood tumors:
 - acute lymphoblastic leukemia
 - Burkett's lymphoma
 - Wilms' tumor
 - Embryonal rhabdomyosarcoma
- **Certain cancers are more resistant to current treatment (current drug treatment may be effectively palliative)--Examples::**
 - lung cancer
 - colon cancer

• Dosing Principles

- **Drugs: more effective in combination (may be synergistic)**
- **More effective if drugs do not share common mechanisms of resistance.**
- **More beneficial if drugs do not overlap in major toxicities.**
- **Drugs should be administered near their maximum individual doses**
- **Drugs should be administered as frequently as possible -- to maximize dose intensity {dose per unit time} limiting tumor regrowth.**
- **Desirable: maximum cell kill with each treatment cycle, using the highest those possible, repeating doses as frequently as tolerable.**