Anticancer Drugs
Part 1

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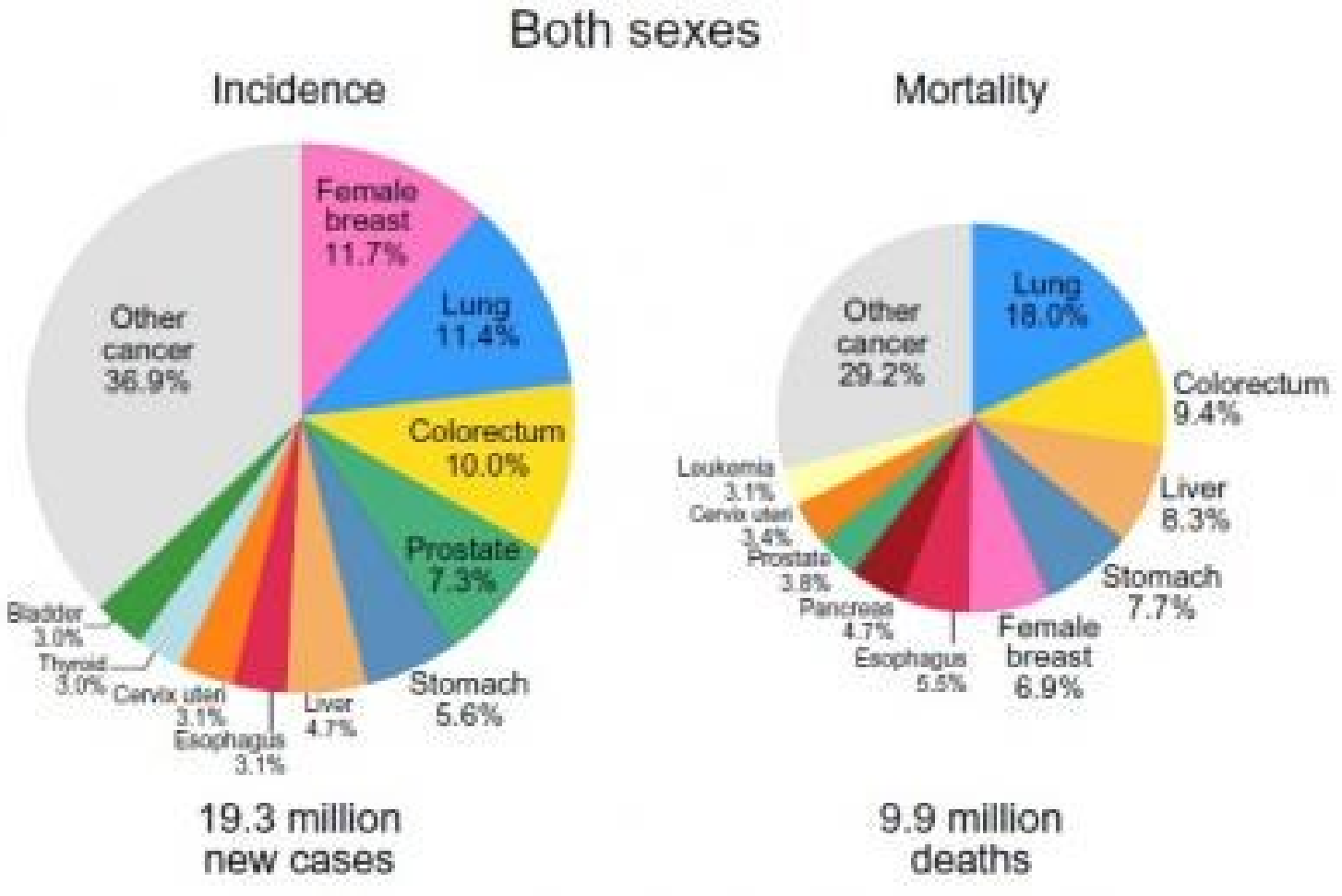
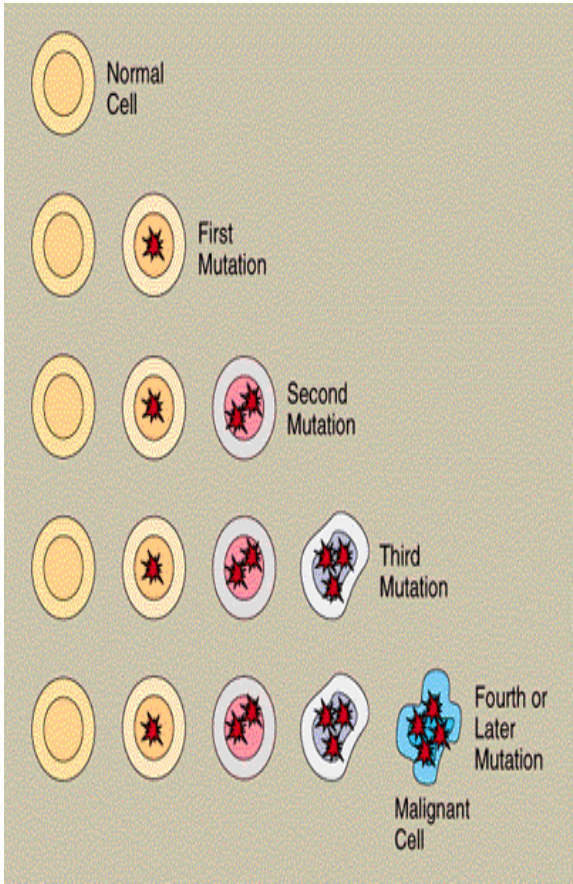
Pharmacology 3

The problem

- Cancer is a leading cause of death worldwide, accounting for 9.9 million deaths in 2020.



- Cancer arises from one single cell. The transformation from a normal cell into a tumor cell is **a multistage process**.
- Cancer cells are altered host cells:
  - shorter cell cycle (accelerated)
  - excessive proliferation
  - higher activity of nucleic acid and protein synthesis
  - altered cell-cell communication
  - invasive (disrupt normal healthy tissues)
  - migration to distant sites - metastasis



Treatment

- A correct cancer diagnosis is essential for adequate and effective treatment because every cancer type requires a specific treatment regimen.
- Treatment encompasses one or more modalities such as surgery, and/or radiotherapy, and/or chemotherapy.
- The primary goal is to cure cancer and improving the patient's quality of life.

PRINCIPLES OF CANCER CHEMOTHERAPY

- Cause a lethal cytotoxic event or apoptosis in the cancer.
- Generally directed toward DNA or against metabolic sites essential to cell replication
  - for example, the availability of purines and pyrimidines.

- Ideally, these anticancer drugs should interfere only with cellular processes that are unique to malignant cells.
- Unfortunately, most anticancer drugs do not specifically recognize neoplastic cells but, rather, affect both normal and abnormal cells.

Treatment strategies

- **1. Goals of treatment:**
  - The ultimate goal of chemotherapy is a cure (long-term, disease-free survival).
  - A true cure requires the eradication of every neoplastic cell.
  - If a cure is not attainable, then the goal becomes control of the disease (stop the cancer from enlarging and spreading) to extend survival and maintain the best quality of life (palliative therapy).

Treatment strategies

2. Chemotherapy is indicated when:

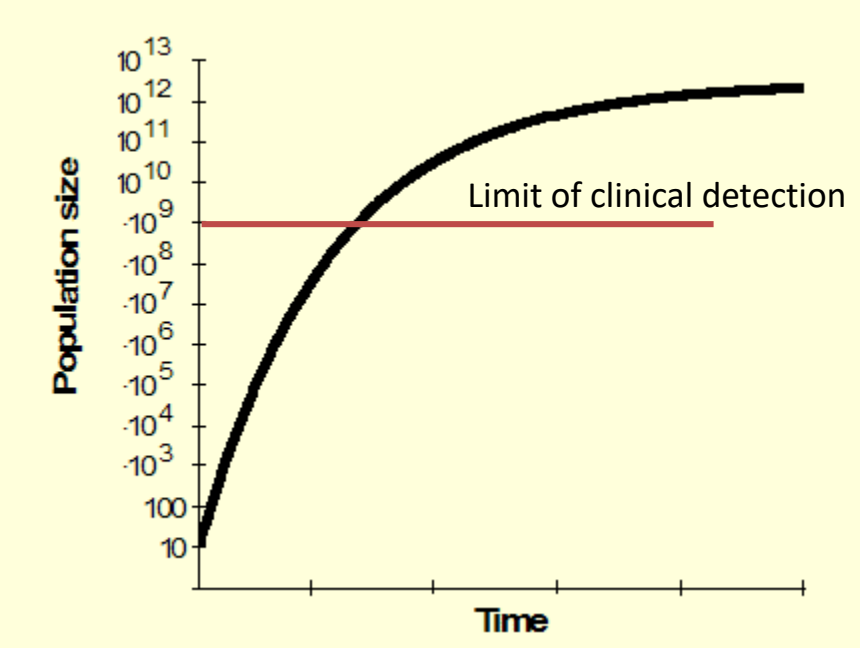
- Neoplasms are disseminated and are not amenable to surgery.
- Also used as a supplemental treatment to attack micrometastases following surgery and radiation treatment, (adjuvant chemotherapy).
- Prior to the surgical procedure in an attempt to shrink the cancer (neoadjuvant chemotherapy)
- Also given in low doses to assist in prolonging a remission (maintenance chemotherapy).

Cell growth kinetics

- **Cell growth fraction** is the proportion of cells in the tumor dividing or preparing to divide.

  As the tumor enlarge, the cell growth fraction decreases because a large proportion of cells may not be able to obtain adequate nutrients and blood supply for replication.

- **Tumor doubling time** is the time for the tumor to double in size. As the tumor gets larger, its doubling time gets longer.



Gompertzian Growth Curve

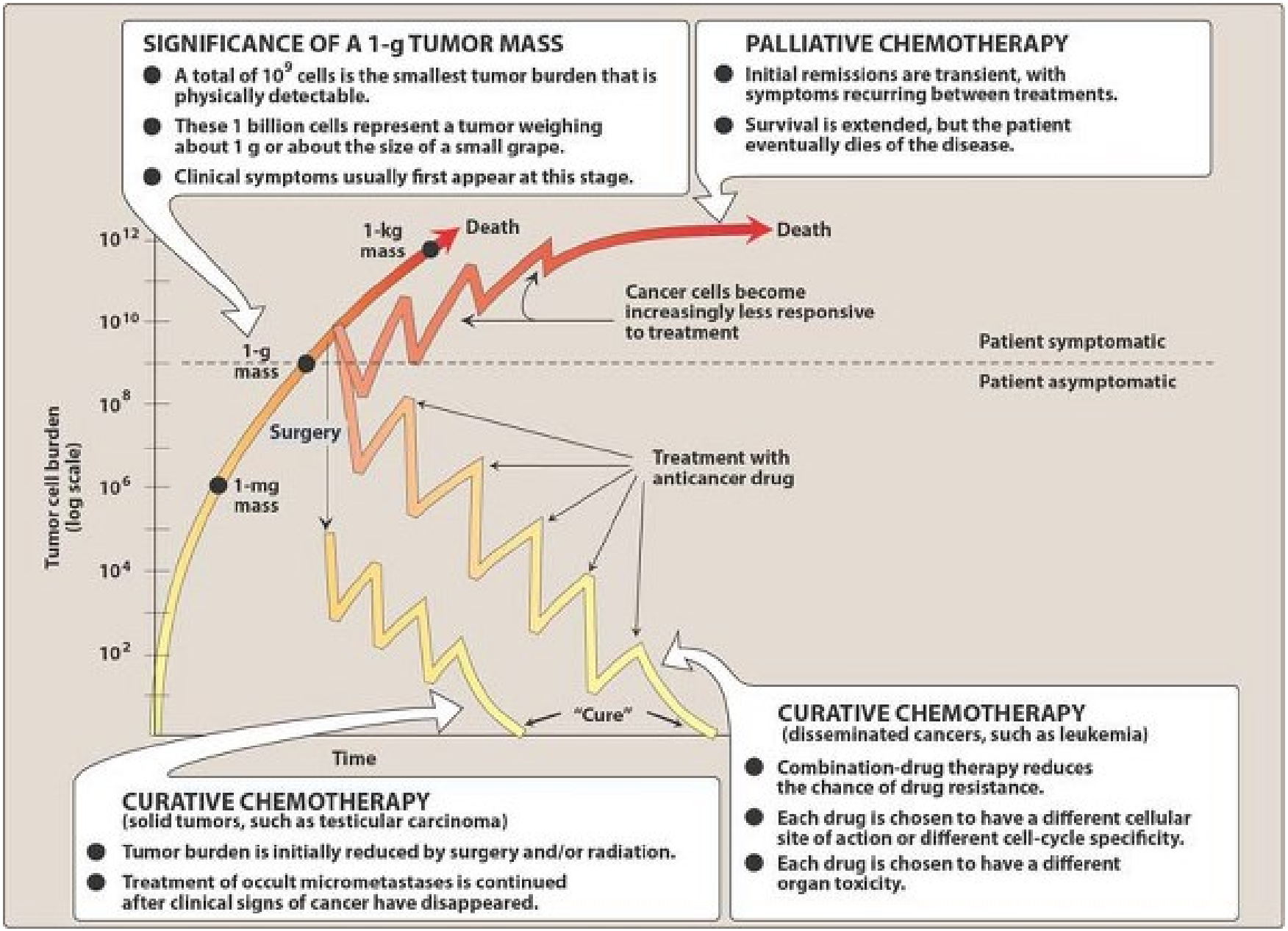
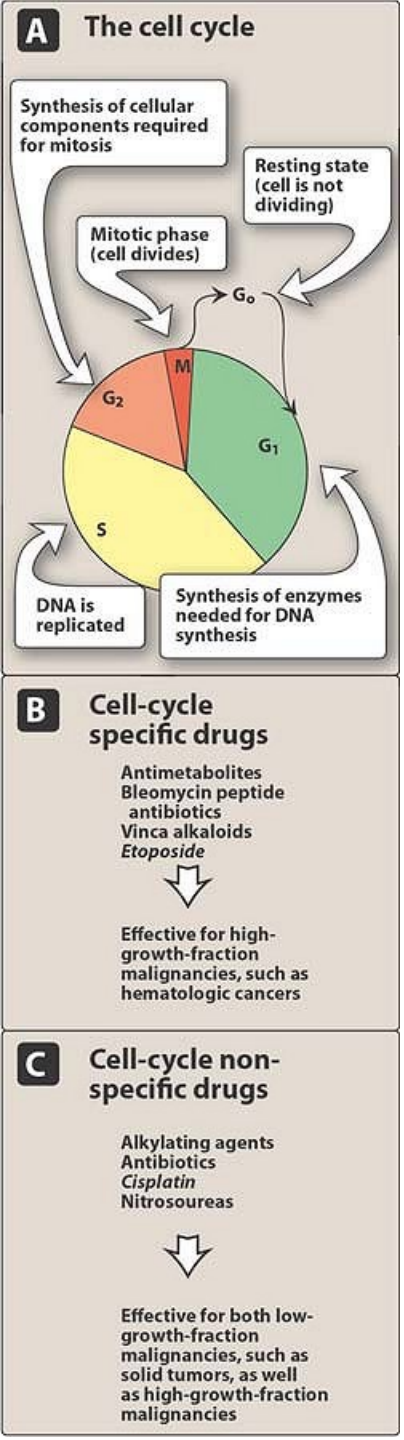


Figure 39.3 Effects of various treatments on the cancer cell burden in a hypothetical patient.

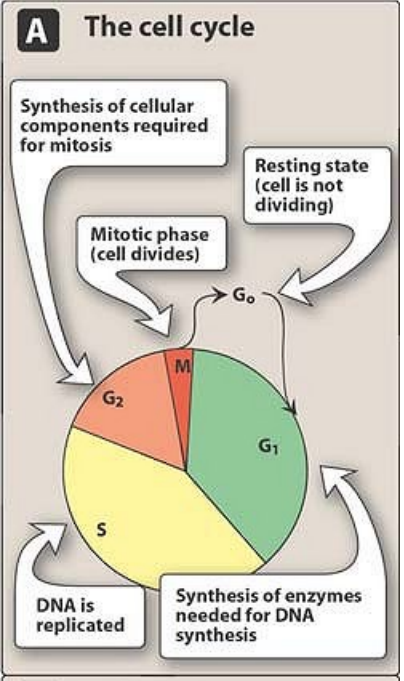
Treatment strategies

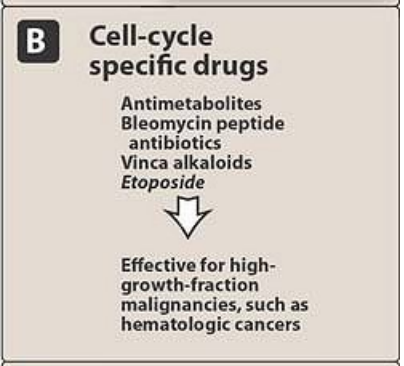


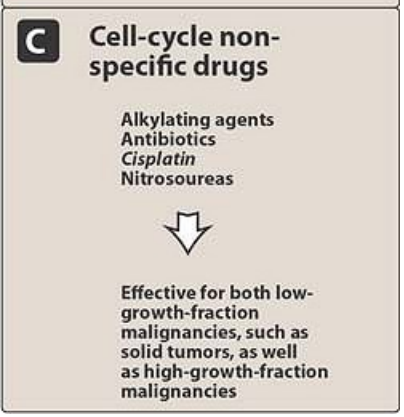
3. Tumor susceptibility and the growth cycle:

- The fraction of tumor cells that are in the replicative cycle ("cell growth fraction") influences their susceptibility to anticancer agents.
- Rapidly dividing cells are generally more sensitive to anticancer drugs, whereas slowly proliferating cells are less sensitive to chemotherapy. In general, nonproliferating cells (those in the G0 phase) usually survive the toxic effects of many of these agents.

Treatment strategies







3. Tumor susceptibility and the growth cycle:

- Chemotherapeutic agents may be classified according to their reliance on cell cycle kinetics for their cytotoxic effect:

a. Cell-cycle specific drugs: are effective only against replicating cells (that is, those cells that are cycling).

b. **Cell-cycle <u>non-specific</u> drugs:** used for replicating and non-replicating cells

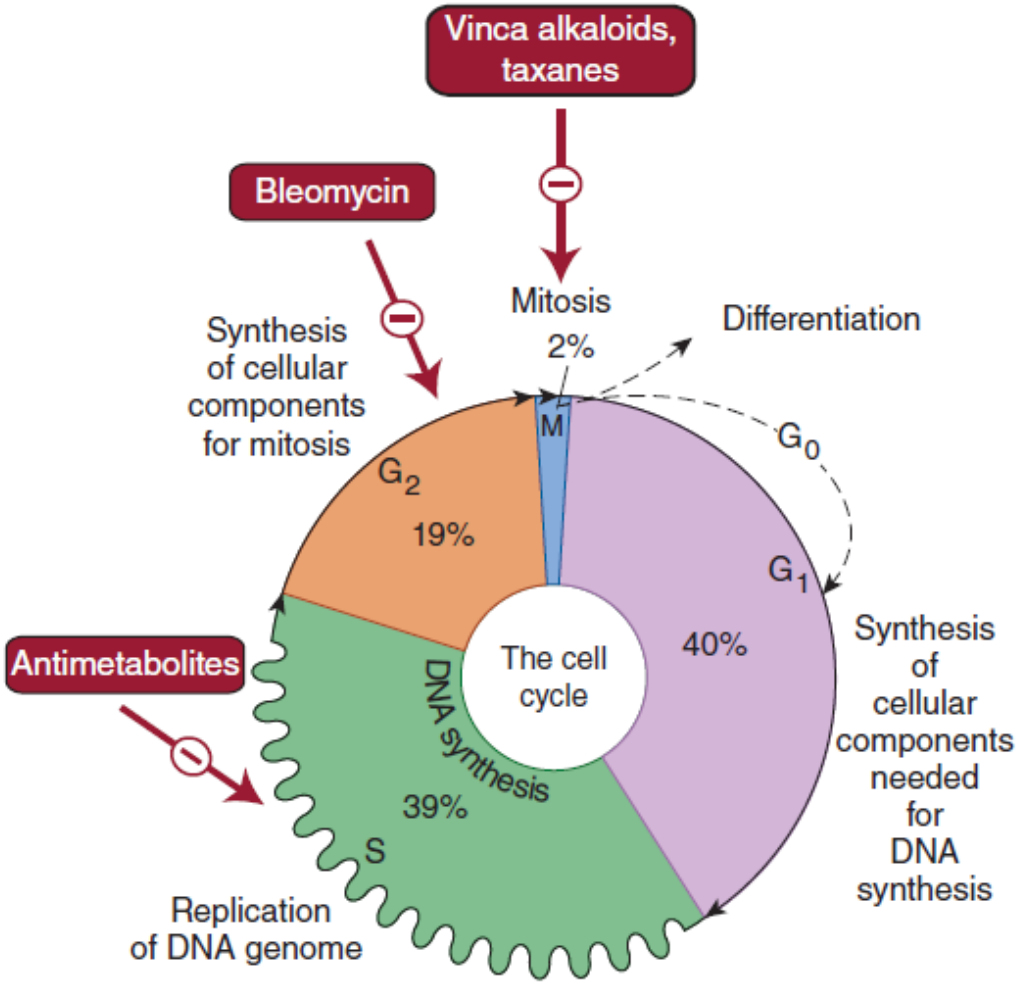


FIGURE 54–1 Phases of the cell cycle that are susceptible to the actions of cell cycle-specific (CCS) drugs. All dividing cells—normal and neoplastic—must traverse these cell cycle phases before and during cell division. Tumor cells are usually most responsive to specific drugs (or drug groups) in the phases indicated. Cell cycle-nonspecific (CCNS) drugs act on tumor cells while they are actively cycling and while they are in the resting phase (G_0). (Reproduced and modified, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 12th ed. McGraw-Hill, 2012: Fig. 54–2.)

Treatment regimens and scheduling

- **The Log-Kill Hypothesis**
- In cancer chemotherapy, destruction of cancer cells follows first-order kinetics (a given dose of drug for a defined time period destroys a constant fraction of cells regardless the absolute number of cells, this is called LOG KILL or fraction kill).

- A key principle that stems from this finding and that is applicable to hematologic malignancies is an inverse relationship between tumor cell number and curability.

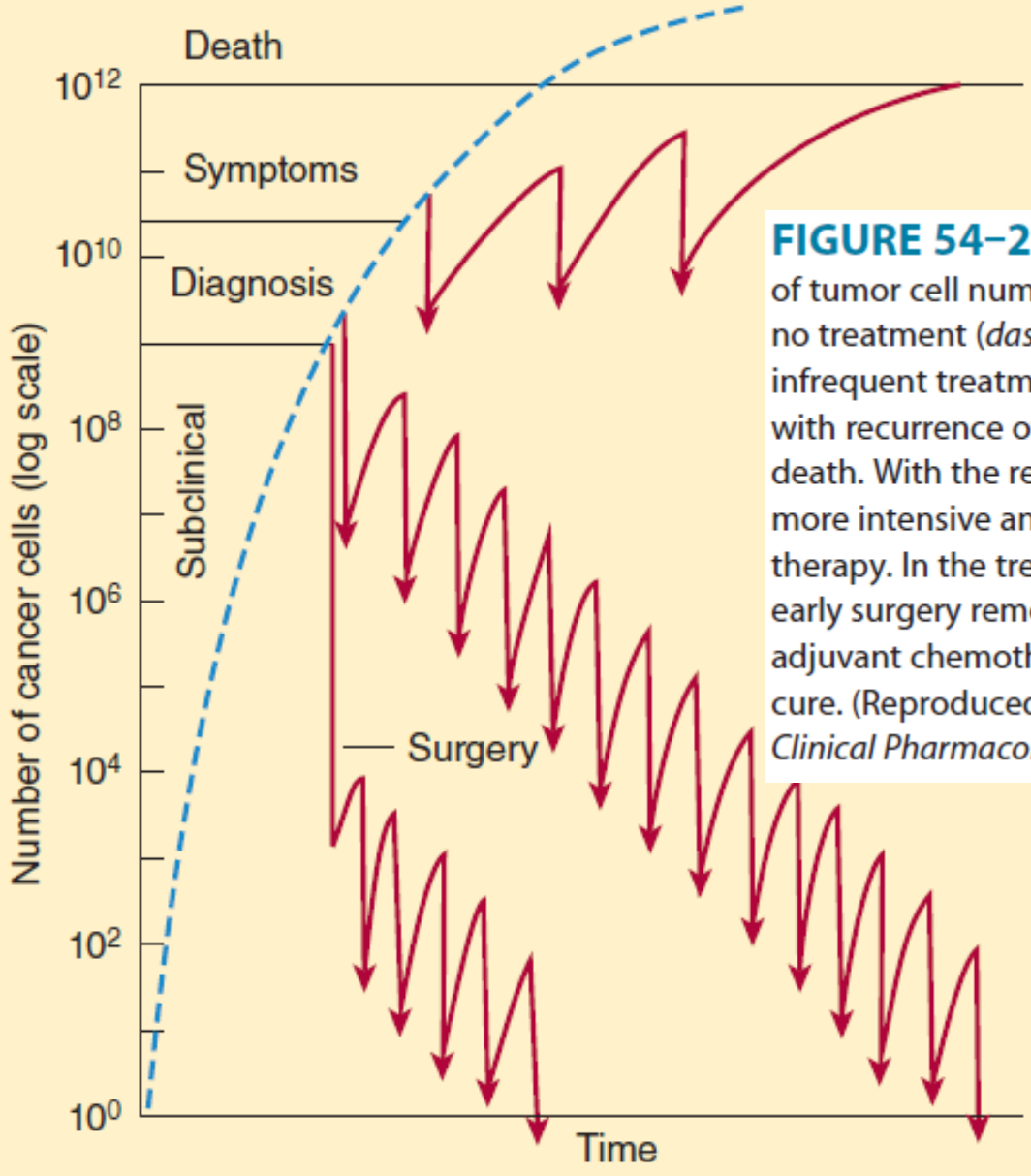


FIGURE 54–2 Relationship, based on the log-kill hypothesis, of tumor cell number to 3 approaches to drug treatment and to no treatment (*dashed line*). In the protocol diagrammed at the top, infrequent treatment (indicated by *arrows*) prolongs survival but with recurrence of symptoms between treatments and eventual death. With the regimen diagrammed in the middle section that is more intensive and begun earlier, cure results after many cycles of therapy. In the treatment diagrammed near the bottom of the graph, early surgery removes much of the tumor burden, and intensive adjuvant chemotherapy has been used long enough to produce a cure. (Reproduced with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 12th ed. McGraw-Hill, 2012: Fig. 54–1.)

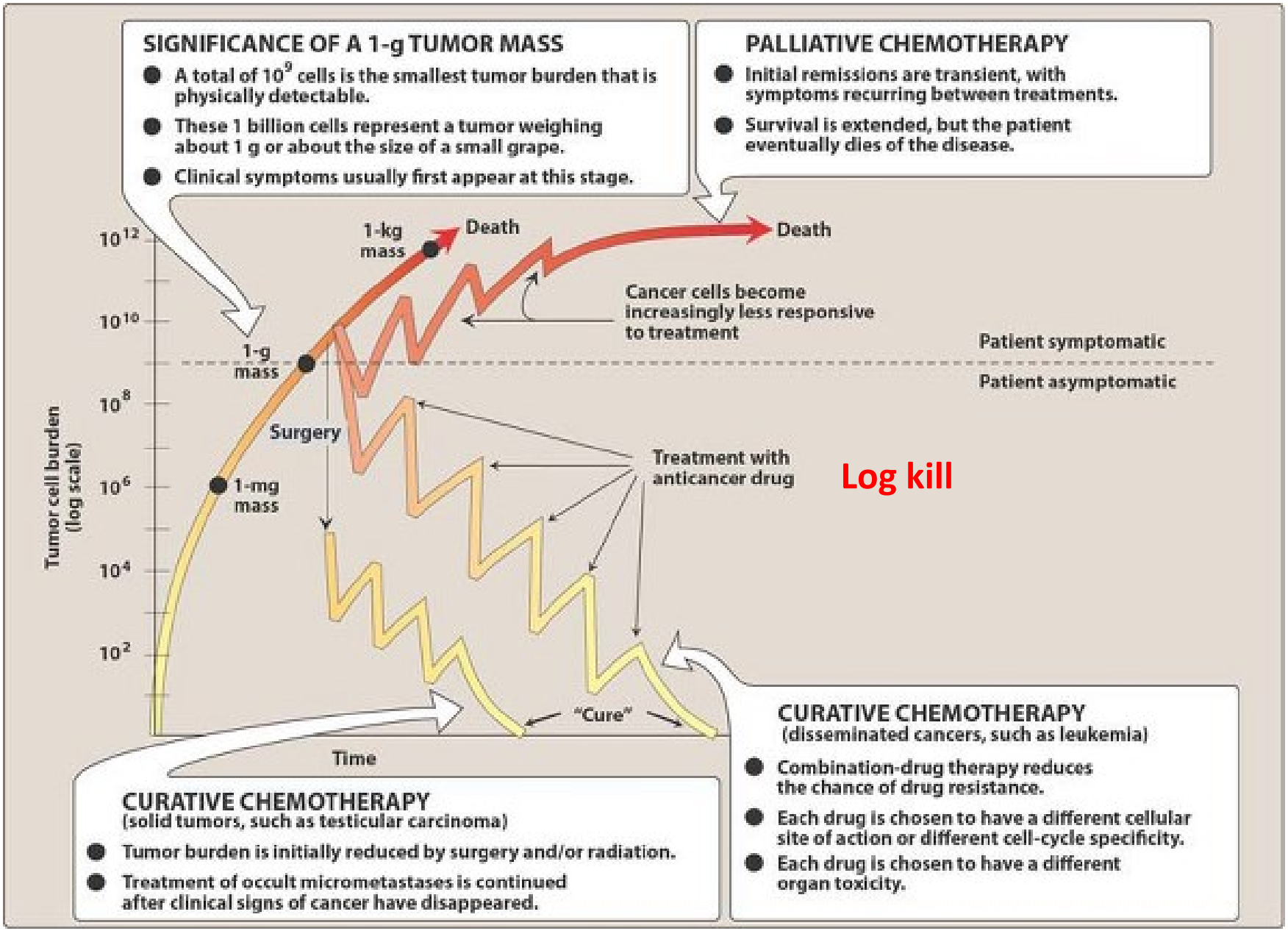


Figure 39.3 Effects of various treatments on the cancer cell burden in a hypothetical patient.

Treatment regimens and scheduling

- Chemotherapy dosing may be based on **body weight**, body surface area **(BSA)** or area under the concentration versus time curve **(AUC),** with an effort being made to tailor the medications to each patient.

- BSA is most frequently used because it provides an accurate comparison of activity and toxicity across species. In addition, BSA correlates with cardiac output, which determine renal and hepatic blood flow and thus affects drug elimination.

- **Dosing adjustments** may be required for kidney and liver dysfunction to prevent toxicity.

Treatment protocols

- **Drug combination** is more successful than single drug treatment in most cancers.
- The following principles are important for selecting appropriate drugs to use in combination chemotherapy:

(1) Each drug should be active when used alone against the particular cancer.

(2) The drugs should have different mechanisms of action.

(3) Cross-resistance between drugs should be minimal.

(4) The drugs should have different toxic effects

Treatment protocols

- The advantages of combinations:
  - Provide maximal cell killing within the range of tolerated toxicity
  - Effective against a broader range of cell lines in the heterogeneous tumor population
  - May delay or prevent the development of resistant cell lines.
- Many cancer treatment protocols have been developed, and each one is applicable to a particular neoplastic state

Drug Regimen

Course 1: Hyper-CVAD (Cycles 1, 3, 5, & 7)

Days	Drug	Dose	Route	Comments
1-3	Cyclophosphamide	300mg/m²	IV over 2hrs, 12hrly total of 6 doses.	Mesna see below
4-5	Doxorubicin	50mg/m²	IV continuously over 48hrs	
4 & 11	Vincristine	1.4mg/m²	Intravenous infusion in 50ml sodium chloride 0.9% over 10 minutes, as per national guidance. Nurse to remain with patient throughout infusion	Maximum 2mg
1-4 11-14	Dexamethasone	40mg	Oral, daily	

Course 2: MTX/ARA-C (Cycles 2, 4, 6, & 8)

Days	Drug	Dose	Route	Comments
1-2	Methotrexate	1g/m²	IV for 24hrs continuously	200mg/m² for 2hrs then 800mg/m² for 22hrs
2-3	Cytarabine	3g/m²	IV over 2hrs, 12hrly total of 4 doses	

Cycle Frequency

Every 21 days up to 8 cycles

TABLE 54–1 Selected examples of cancer chemotherapy. (*Do not attempt to memorize type of treatment for each cancer. In this chapter focus on the drugs' mechanism of action, dose-limiting adverse effects and general mechanisms of resistance*).

Diagnosis	Examples of Commonly-Used Anticancer Drugs
Acute lymphocytic leukemia in children	Prednisone, vincristine, and asparaginase or an anthracycline, plus intrathecal methotrexate
Acute myelogenous leukemia in adults	Cytarabine and idarubicin or daunorubicin
Breast carcinoma	Cytotoxic agents, hormonal therapy with tamoxifen or an aromatase inhibitor (eg, anastrozole), trastuzumab
Chronic myelogenous leukemia	Imatinib, newer tyrosine kinase inhibitors, interferon
Colon carcinoma	Fluorouracil plus leucovorin plus oxaliplatin
Hodgkin's lymphoma	ABVD regimen: doxorubicin (Adriamycin), bleomycin, vincristine, dacarbazine, and prednisone
Non-Hodgkin's lymphoma	CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus rituximab
Ovarian carcinoma	Paclitaxel and carboplatin
Pancreatic carcinoma	Gemcitabine and erlotinib
Prostate carcinoma	GnRH agonist (eg, leuprolide) or antagonist (eg, abarelix) and androgen receptor antagonist
Lung carcinoma	Carboplatin, paclitaxel, and bevacizumab
Testicular carcinoma	PEB regimen: cisplatin (Platinol), etoposide, and bleomycin

GnRH, gonadotropin-releasing hormone.

Acronyms often are used to designate chemotherapy regimen

Problems associated with chemotherapy

A. Resistance:

- Drug resistance is a major problem in cancer chemotherapy.
- Mechanisms of resistance include the following:

1. **Increased DNA repair—** ex: alkylating agents and cisplatin.

2. Formation of trapping agents—production of thiol trapping agents (eg, glutathione). This mechanism of resistance is seen with alkylating agents.

3. Changes in target enzymes—Changes in the drug sensitivity of a target enzyme, dihydrofolate reductase, and increased synthesis of the enzyme are mechanisms of resistance of tumor cells to methotrexate.

Problems associated with chemotherapy

4. Decreased activation of prodrugs—a decrease in the activity of the tumor cell enzymes needed to convert prodrugs to their cytotoxic metabolites, ex: 5-fluorouracil.

5. Inactivation of anticancer drugs—most of the purine and pyrimidine antimetabolites.

6. Decreased drug accumulation

This form of multidrug resistance involves the increased expression of a normal gene (MDR1) for a cell surface glycoprotein (P-glycoprotein).

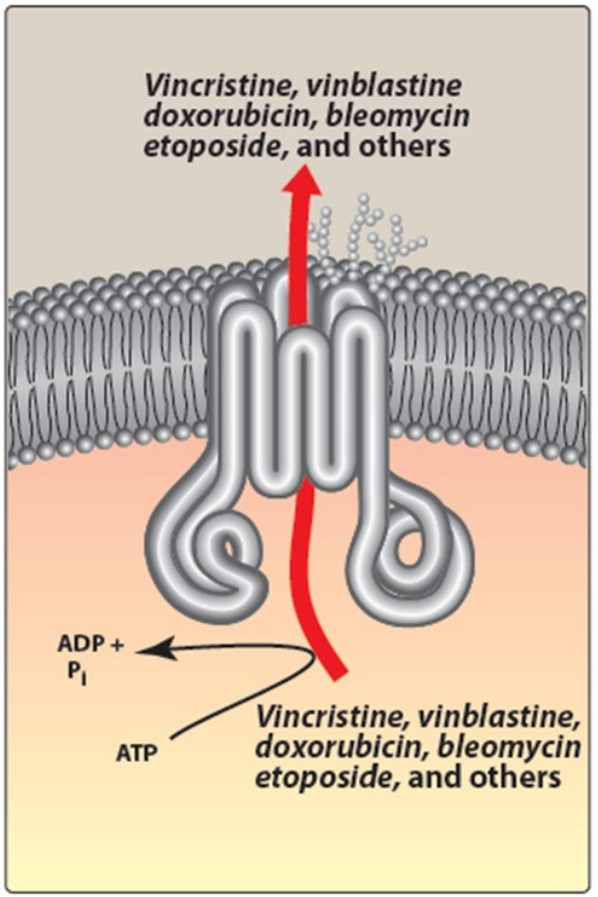


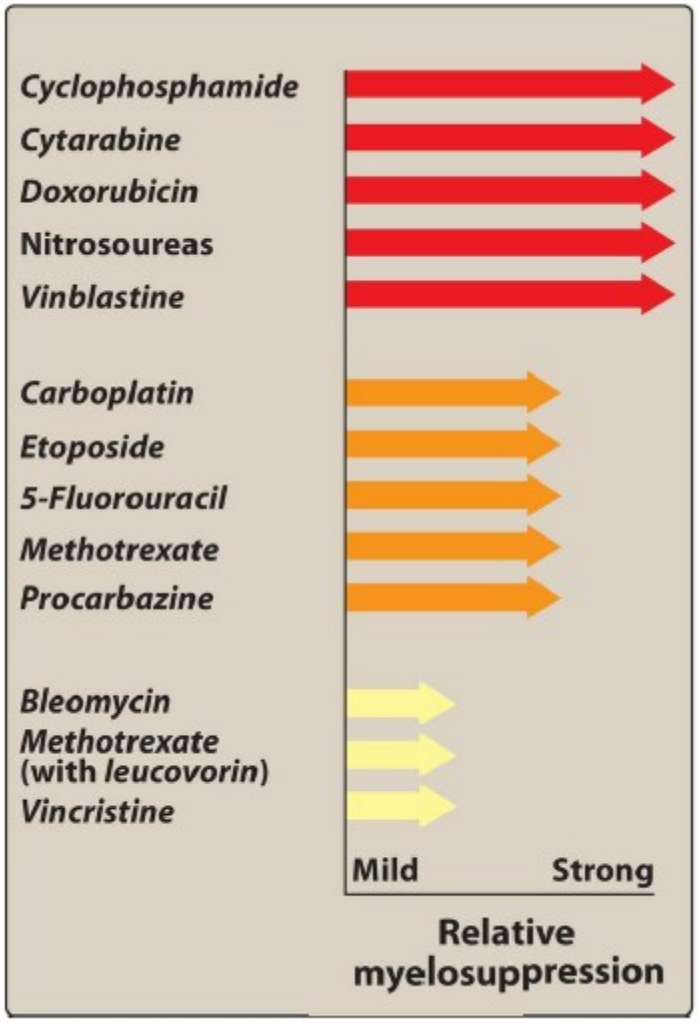
Figure 39.5
The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.

Problems associated with chemotherapy

B. Toxicity:

Common adverse effects

- Therapy also affects normal cells undergoing rapid proliferation (buccal mucosa, bone marrow, gastrointestinal (GI) mucosa, and hair).
  1. Severe vomiting (use antiemetic)
  2. Stomatitis
  3. Bone marrow suppression
  4. Alopecia
  - occur to a lesser or greater extent during therapy with all antineoplastic agents.



Questions?