Al-Mustaqbal University College
Department of Pharmacy
4th stage
Pharmacology III
Lecture: 1

ANTICANCER DRUGS

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OVERVIEW

Cancer is a term for diseases in which **abnormal cells divide without control** and can **invade** nearby tissues and other parts of the body through the blood and lymph systems (**metastasis**).

Carcinoma: It begins in the **skin or the tissue that covers** the surface of internal organs and **glands** such as prostate cancer, breast cancer, lung cancer, and colorectal cancer.

Sarcomas: It begins in the tissues that **support and connect** the body. A sarcoma can develop in fat, muscles, nerves, tendons, joints, blood vessels, lymph vessels, cartilage, or bone.

Leukemias: It is a cancer of the **blood,** the 4 main types of leukemia are ALL, CLL, AML, & CML.

Lymphomas: It is cancer that begins in the **lymphatic system**. There are 2 main types of lymphomas: Hodgkin lymphoma and non-Hodgkin lymphoma.

PRINCIPLES OF CANCER CHEMOTHERAPY

Cancer chemotherapy strives to cause a **lethal cytotoxic** event or **apoptosis** in the cancer cells that can **arrest a tumor's progression**.

The **attack** is generally directed toward **DNA or against metabolic sites essential to cell replication**, for example, the availability of **purines** and **pyrimidines**, which are the building blocks for DNA or RNA synthesis.

Ideally, these anticancer drugs should **interfere only** with cellular processes that are unique to **malignant** cells.

Unfortunately, most currently available anticancer drugs do **not specifically** recognize neoplastic cells but, rather, affect all kinds of proliferating cells, **both normal and abnormal**.

Therefore, almost all antitumor agents have a **steep dose-response curve** for both **therapeutic** and **toxic** effects.

Treatment strategies

Goals of treatment:

- The **ultimate goal** of chemotherapy is a **cure** (that is, long-term, disease-free survival), which requires the **eradication of every neoplastic cell**.
- If a cure is **not attainable**, then the goal becomes **control of the disease** to **extend survival** and **maintain the best quality of life**.
- In **advanced stages** of cancer, the likelihood of controlling the cancer is **far from reality** and the **goal is palliation** (relieving symptoms, which may not extend survival).

Treatment strategies

Indications for treatment:

Chemotherapy is sometimes used when neoplasms are **disseminated** and are **not amenable** to **surgery**.

Adjuvant chemotherapy: when chemotherapy is used to **attack** micrometastases **following surgery and radiation.**

Neoadjuvant chemotherapy: Chemotherapy given **prior to the surgical** procedure in an attempt to **shrink cancer.**

Maintenance chemotherapy: chemotherapy given in **lower doses** to assist in **prolonging remission**.

Treatment strategies

Tumor susceptibility and the growth cycle:

Rapidly dividing cells are generally **more sensitive** to chemotherapy, whereas **slowly proliferating** cells are **less sensitive** to chemotherapy.

A. Cell cycle specificity of drugs

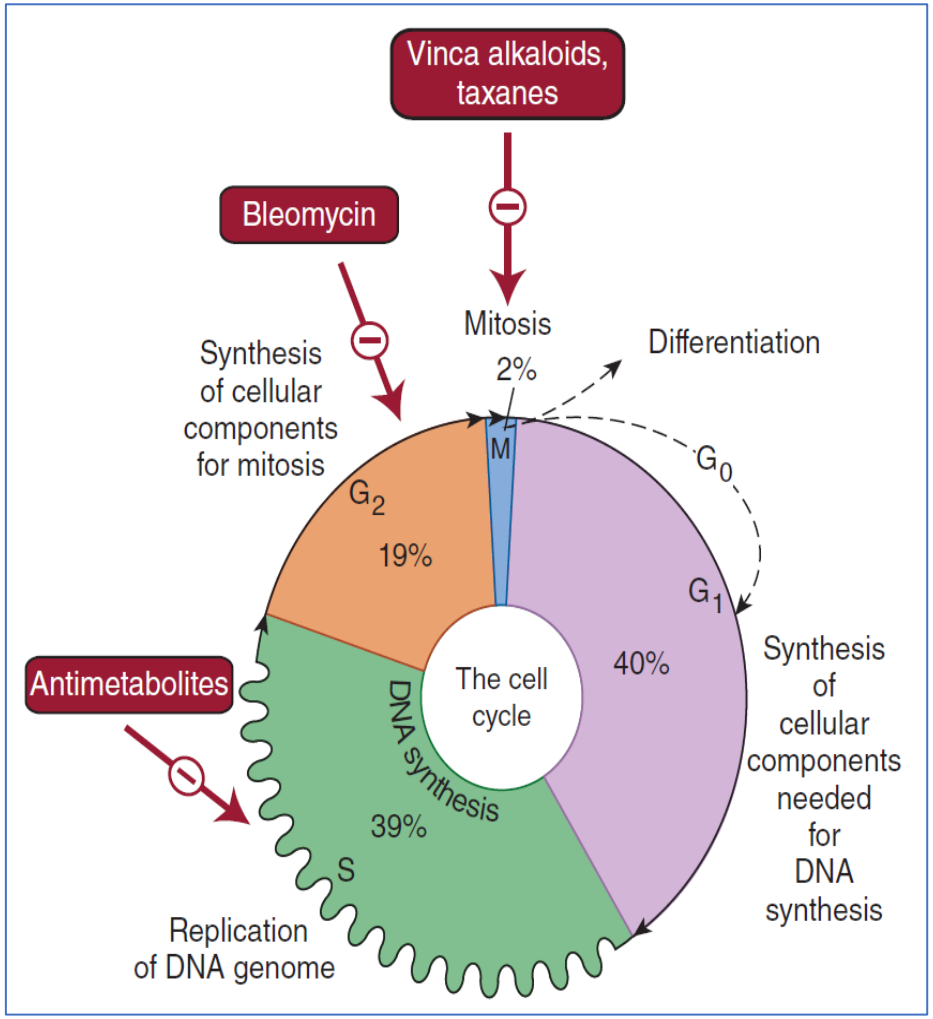
B. Tumor growth rate

Treatment strategies

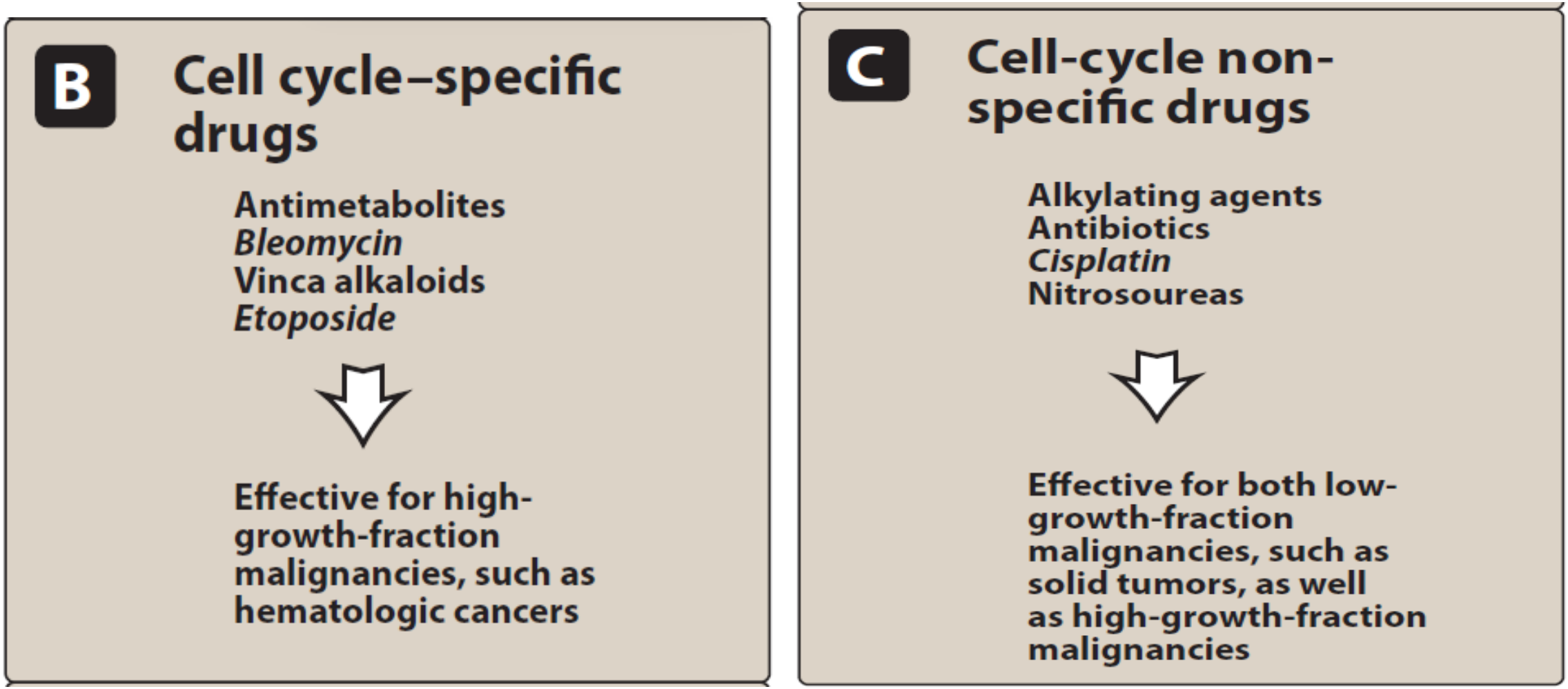
A. Cell cycle specificity of drugs:

Chemotherapeutic agents that are **effective only against replicating cells** are said to **be cell cycle specific**, whereas other agents are said to be **cell cycle nonspecific**.

The **nonspecific drugs**, although having generally **more toxicity** in cycling cells, are also **useful** against tumors that have a **low percentage of replicating cells**.



Treatment strategies



Treatment strategies

B. Tumor growth rate:

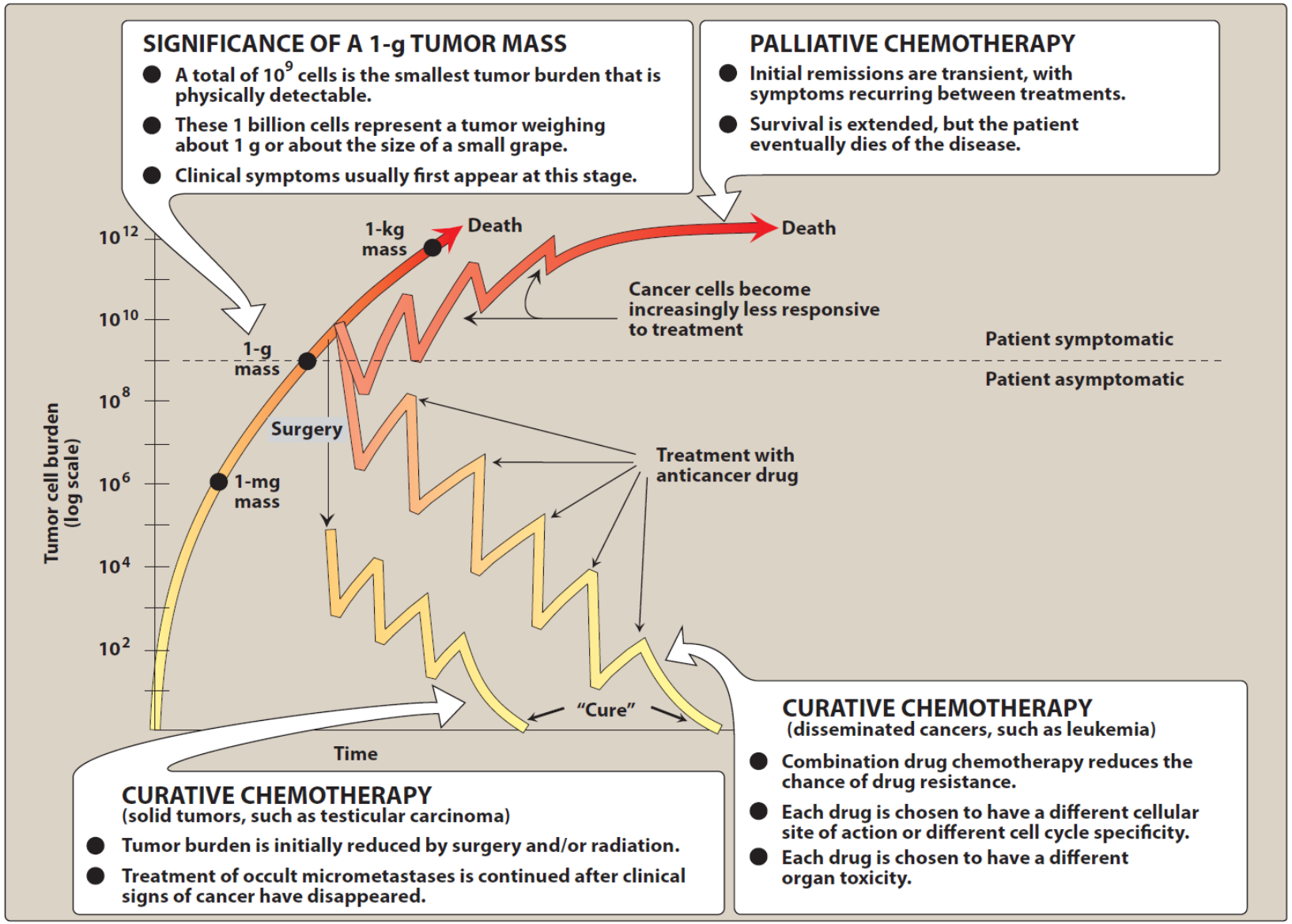
The growth rate of most **solid tumors** in vivo is **initially rapid**, but the growth rate usually **decreases** as the **tumor size increases**.

This is due to the **unavailability** of nutrients and oxygen caused by **inadequate** vascularization and **lack** of blood circulation.

Tumor burden can be **reduced** through **surgery, radiation**, or by **using cell cycle-nonspecific** drugs to **increase** their **susceptibility** to cell **cycle-specific** chemotherapeutic agents.

Treatment strategies

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



Treatment regimens and scheduling

Drug dosages are usually calculated on the basis of **body surface area**, in an effort to tailor the medications to each patient.

1. Log kill phenomenon:

Destruction of cancer cells by chemotherapeutic agents follows **first-order kinetics** (that is, a given **dose of drug** destroys a **constant fraction** of cells).

For 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% of 10^9 cells** (or 10^4 cells) would **remain**.

This is defined as **a 5-log kill** (reduction of **10^5 cells**), at this point, the patient will become **asymptomatic**, and the **patient is in remission**.

Treatment regimens and scheduling

2. Pharmacologic sanctuaries:

Leukemic or other tumor cells **find sanctuary** in tissues such as the CNS, where transport constraints **prevent** certain **chemotherapeutic** agents from **entering**.

Therefore, a patient may require **irradiation** of the craniospinal axis or **intrathecal administration** of drugs to eliminate the leukemic cells at that site.

Similarly, drugs may be unable to penetrate certain areas of **solid tumors**.

Treatment regimens and scheduling

3. Treatment protocols:

Combination-drug chemotherapy is **more successful** than **single-drug** treatment in most of the cancers for which chemotherapy is **effective**.

- Combination of drugs
- Advantages of drug combinations
- Treatment protocol

Treatment regimens and scheduling

A. Combinations of drugs:

Cytotoxic agents with qualitatively **different toxicities**, and with **different molecular sites** and **mechanisms of action**, are usually **combined at full doses**.

This results in **higher response rates**, due to additive and/or potentiated cytotoxic effects, and nonoverlapping host toxicities.

In **contrast**, agents with **similar** dose-limiting toxicities, such as myelosuppression, nephrotoxicity, or cardiotoxicity, can be **combined safely only by reducing the doses of each**.

Treatment regimens and scheduling

B. Advantages of drug 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**

Treatment regimens and scheduling

c. Treatment protocols:

Many cancer treatment **protocols** have been developed, and **each one is applicable** to a **particular neoplastic state**, and they are usually identified by an **acronym**.

For example, a common regimen called **R-CHOP**, used for the treatment of **non-Hodgkin lymphoma**, consists of **r**ituximab, **c**yclophosphamide, **h**ydroxydaunorubicin (doxorubicin), **O**ncovin (vincristine), and **p**rednisone or prednisolone.

Therapy is scheduled **intermittently** (approximately 21 days apart) to **allow recovery** or **rescue of the patient's immune system**, which is also affected by the chemotherapeutic agents, thus reducing the risk of **serious infection**.

Problems associated with chemotherapy

1. Resistance:

Some neoplastic cells (for example, melanoma) are **inherently resistant** to most anticancer drugs.

Other tumor types may **acquire resistance** to the cytotoxic effects of a medication by **mutating**, particularly after **prolonged administration of suboptimal drug doses**.

The development of drug resistance is **minimized** by **short-term**, **intensive**, **intermittent** therapy with **combinations** of drugs.

Drug **combinations** are also effective against a **broader range of resistant cells** in the tumor population.

Problems associated with chemotherapy

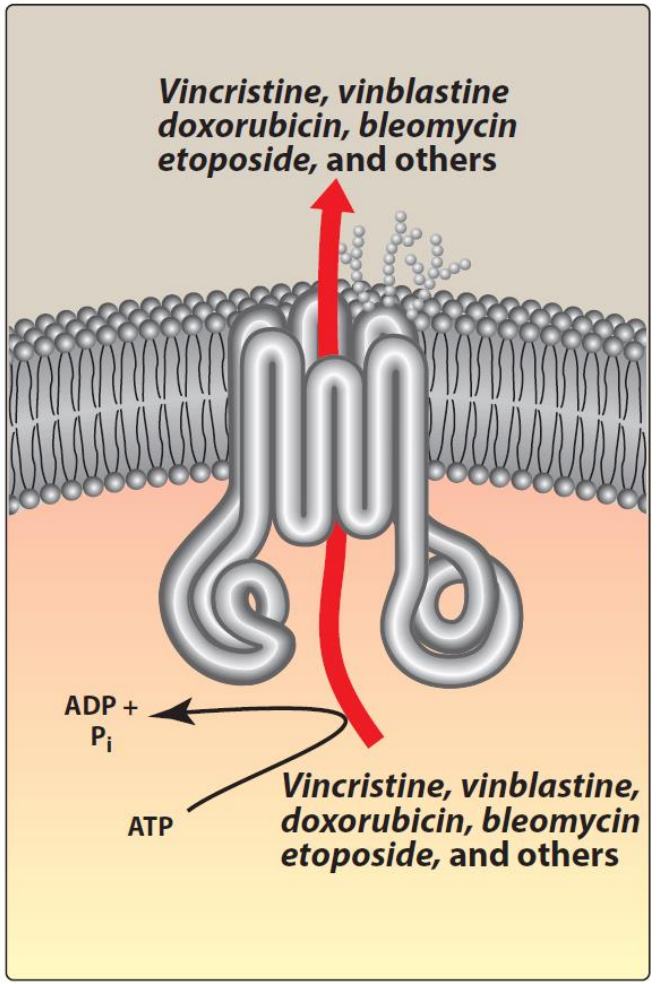
2. Multidrug resistance:

This resistance is due to **ATP-dependent pumping** of drugs out of the cell in the presence of transmembrane **P-glycoprotein** (P for "permeability).

Cross-resistance following the use of **structurally unrelated** agents also occurs.

For example, cells that are resistant to the cytotoxic effects of the **Vinca alkaloids** are also resistant to **dactinomycin** and to the **anthracycline** antibiotics, as well as to **colchicine**, and vice versa.

These drugs are all **naturally** occurring substances, each of which has a **hydrophobic aromatic ring** and a **positive charge** at neutral pH.



Problems associated with chemotherapy

2. Multidrug resistance:

Note: P-glycoprotein is normally expressed at **low levels in most cell types**, but **higher levels** are found in the **kidney**, **liver**, **pancreas**, **small intestine, colon,** and **adrenal gland**.

It has been suggested that the **presence of P-glycoprotein** may account for the **intrinsic resistance** to chemotherapy observed with **adenocarcinomas**.

Certain drugs at **high concentrations** (for example, verapamil) can **inhibit the pump** and, thus, **interfere** with the **efflux** of the anticancer agent.

However, these drugs are **undesirable** because of **adverse** pharmacological actions of their own.

Pharmacologically inert pump blockers are being sought

Problems associated with chemotherapy

3. Toxicity: A. Common adverse effects:

Severe vomiting, stomatitis, bone marrow suppression, and alopecia occur to a lesser or greater extent during therapy with **all antineoplastic agents**.

Vomiting is often controlled by the administration of **antiemetic** drugs.

Some toxicities, such as **myelosuppression** that predisposes to infection, are common to **many chemotherapeutic** agents.

Whereas bladder toxicity with cyclophosphamide, 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 can be irreversible.

Problems associated with chemotherapy

3. Toxicity: B. Minimizing adverse effects:

1)The use of **cytoprotectant** drugs, 2) perfusing the **tumor locally** (for example, sarcoma of the arm), 3) **removing** some of the patient's **marrow** prior to intensive treatment and then **reimplanting** it, 4) or promoting intensive **diuresis** to prevent **bladder toxicities**.

5) The **megaloblastic anemia** that occurs with methotrexate can be effectively counteracted by administering **folinic acid** (leucovorin).

6) With the availability of human granulocyte colony-stimulating factor (**filgrastim**), the **neutropenia** associated with the treatment of cancer by many drugs can be partially reversed.

Problems associated with chemotherapy

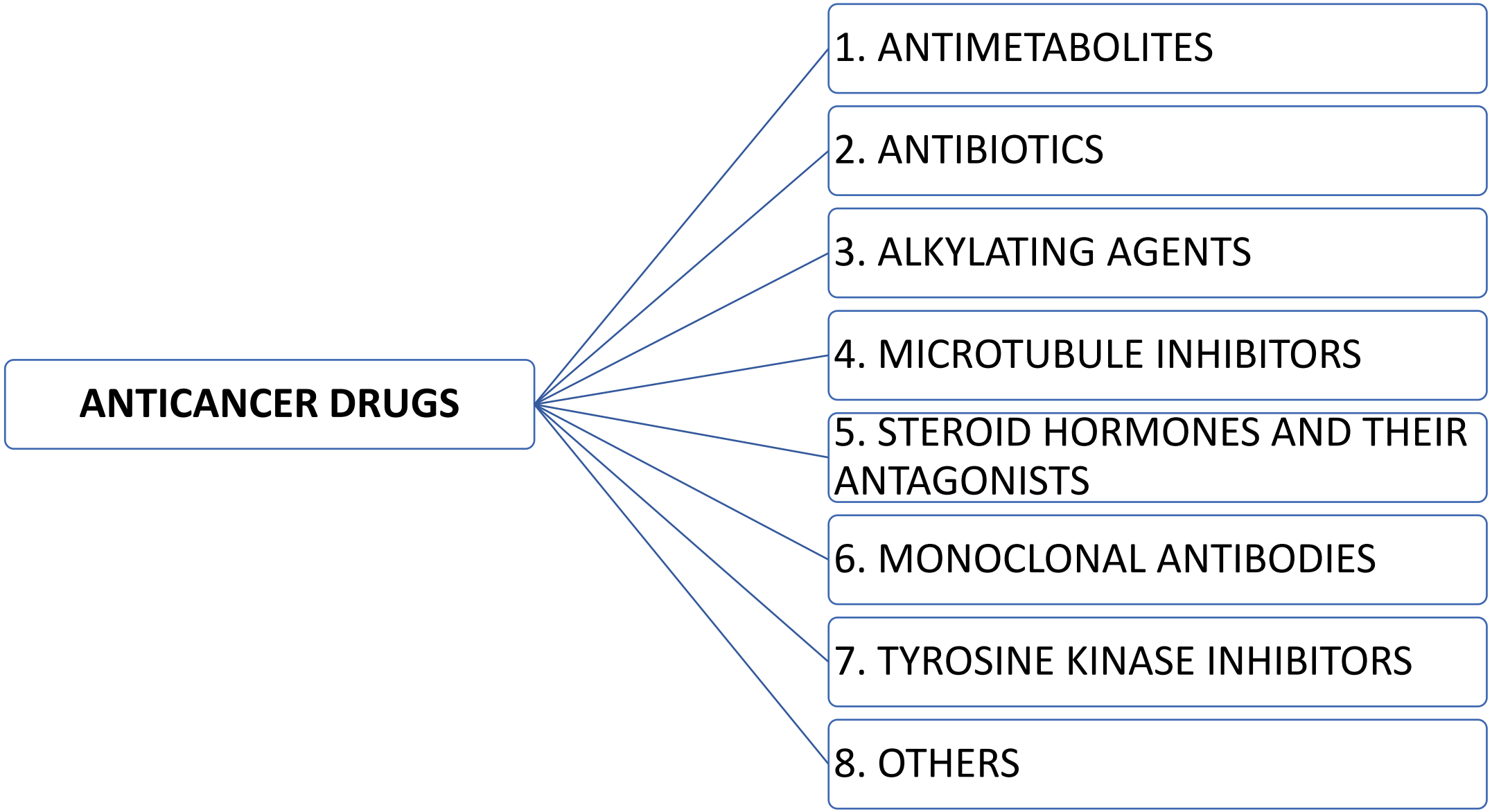
4. Treatment-induced tumors:

Because most **antineoplastic** agents are **mutagens**, neoplasms (for example, acute nonlymphocytic leukemia) may arise **10 or more years** after the original cancer was cured.

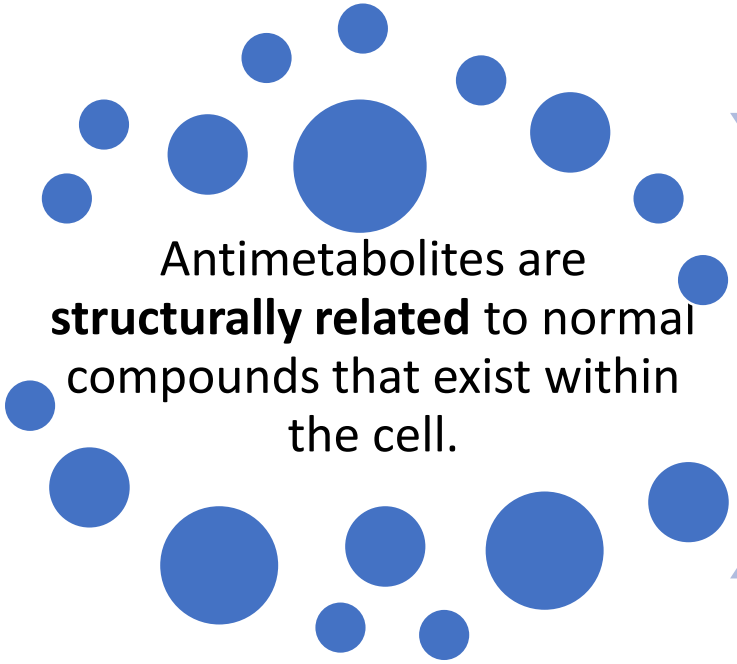
Treatment-induced neoplasms are especially a problem after therapy with **alkylating agents**.

Most tumors that develop from cancer chemotherapeutic agents **respond well to treatment strategies**.

ANTICANCER DRUGS



ANTIMETABOLITES



Antimetabolites are **structurally related** to normal compounds that exist within the cell.

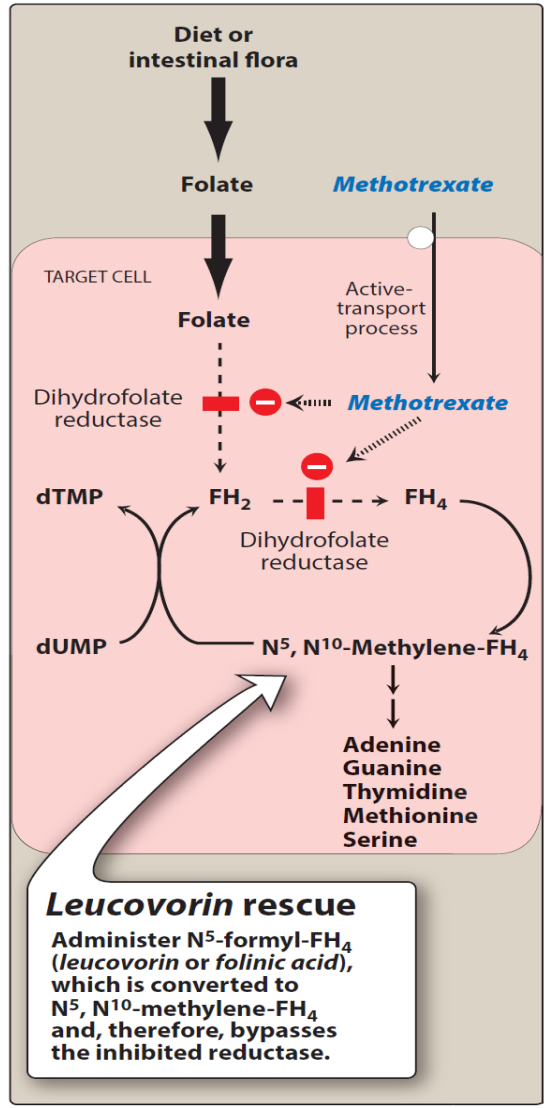
They generally **interfere** with the **availability of normal purine or pyrimidine** nucleotide precursors, either by **inhibiting their synthesis** or by **competing with them in DNA or RNA** synthesis.

Their maximal cytotoxic effects are in **S-phase** and are, therefore, **cell cycle specific**.

ANTIMETABOLITES/A. Methotrexate, pemetrexed, and pralatrexate

1. Mechanism of action:

- **MTX** is **structurally** related to **folic acid** and acts by **inhibiting dihydrofolate reductase (DHFR)**, the enzyme that converts folic acid to its active, coenzyme form, tetrahydrofolic acid (FH4).
- The inhibition of DHFR can only be **reversed** by a **1000-fold excess** of the natural substrate, **dihydrofolate** (FH2), **or** by administration of **leucovorin** (folinic acid), which bypasses the blocked enzyme and replenishes the folate pool.
- MTX is **specific** for the **S-phase** of the cell cycle.
- **Pemetrexed** in addition to **inhibiting DHFR**, also **inhibits thymidylate synthase** and **other enzymes** involved in folate metabolism and DNA synthesis.
- **Pralatrexate** is a **newer** antimetabolite that also **inhibits DHFR**.



ANTIMETABOLITES/A. Methotrexate, pemetrexed, and pralatrexate

2. Therapeutic uses:

- MTX, usually in **combination** with other drugs, is effective against acute lymphocytic leukemia, Burkitt lymphoma in children, breast cancer, bladder cancer, and head and neck carcinomas.
- In addition, **low-dose MTX** is effective as a **single agent** against certain **inflammatory diseases**, such as severe psoriasis and rheumatoid arthritis, as well as Crohn disease.
- All patients receiving MTX require **close monitoring** for possible toxic effects.
- **Pemetrexed** is primarily used in **non–small cell lung cancer**.
- **Pralatrexate** is used in **relapsed** or **refractory T-cell lymphoma**.

3. Resistance:

Nonproliferating cells are resistant to MTX, probably **because** of a **relative lack** of DHFR, thymidylate synthase, and/ or the glutamylating enzyme.

Decreased levels of the **MTX polyglutamate** have been reported in resistant cells and may be due to its decreased formation or increased breakdown.

Resistance in neoplastic cells can be due to the **amplification** of the **gene** that codes for **DHFR**, resulting in increased levels of this enzyme.

The enzyme **affinity** for MTX may also be diminished. Resistance can also occur from a reduced **influx of MTX.**

ANTIMETABOLITES/A. Methotrexate, pemetrexed, and pralatrexate

4. Pharmacokinetics:

MTX is **variably absorbed** at low doses from the **GIT**, but it can also be administered by **IM**, **IV**, and **intrathecal** routes.

Because MTX does not **easily penetrate the BBB**, it can be administered **intrathecally** to destroy neoplastic cells that are thriving in the **sanctuary of the CNS**.

High doses of MTX undergo **hydroxylation** at the 7 positions and become 7-hydroxy methotrexate, Which is much **less active** and **less water** soluble than MTX and may lead to **crystalluria**.

Excretion of the parent drug and the 7-OH metabolite occurs primarily **via urine**, although some of the drug and its metabolite appear in **feces** due to **enterohepatic excretion**.

ANTIMETABOLITES/A. Methotrexate, pemetrexed, and pralatrexate

5. Adverse effects:

MTX adverse effects include N/V/D, stomatitis, rash, alopecia, myelosuppression, renal damage (in high-dose), and neurologic toxicities (in intrathecal route)

Pemetrexed should be given with **folic acid and vitamin B12** supplements to **reduce** hematologic and GI toxicities.

It is also recommended to **pretreat** with **corticosteroids** to **prevent** cutaneous reactions.

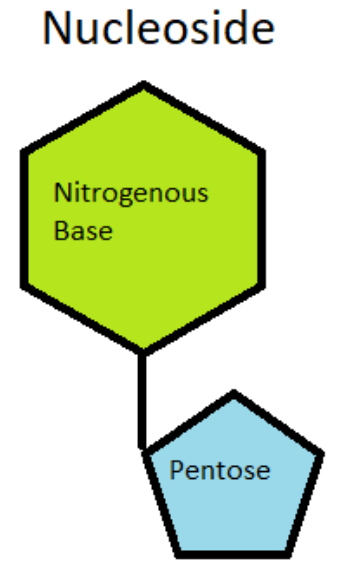
One of the more common side effects of **pralatrexate** is **mucositis**. Doses must be **adjusted** or withheld based on the severity of mucositis.

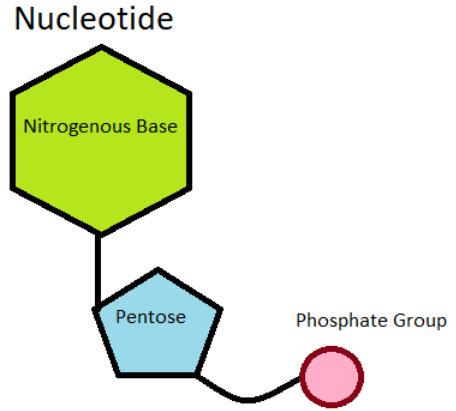
Pralatrexate also requires supplementation with **folic acid and vitamin B12**.

ANTIMETABOLITES

OTHER ANTIMETABOLITES:

- **Azacitidine** (pyrimidine nucleoside analog of cytidine)
- **Capecitabine** (fluoropyrimidine carbamate)
- **5-Fluorouracil** (pyrimidine analog)
- **Cytarabine** (pyrimidine antagonist)
- **Gemcitabine** (analog of the nucleoside deoxycytidine)
- **Cladribine** (purine nucleotide analog)
- **Fludarabine** (purine nucleotide analog)
- **6-Mercaptopurine** (purine analogs)





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