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

ANTICANCER DRUGS 1

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OVERVIEW

Cancer is a complex and diverse group of diseases characterized by the **uncontrolled growth** and **spread** of abnormal cells (**metastasis**).

Carcinoma: cancer occurs in the **epithelial tissues** and **glands** such as prostate cancer, breast cancer, lung cancer, and colorectal cancer.

Sarcomas: cancer occurs in the **connective tissues** such as fat, muscles, nerves, tendons, joints, blood vessels, lymph vessels, cartilage, or bone.

Leukemias: cancer occurs in **bone marrow** and **blood-forming cells,** the 4 main types of leukemia are ALL, CLL, AML, & CML.

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

PRINCIPLES OF CANCER CHEMOTHERAPY

- Cancer **chemotherapy aims** to **cause** a **lethal cytotoxic event or apoptosis in the cancer cells** that can **arrest** the progression of tumor growth.
- 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**, anticancer drugs should **interfere only** with cellular processes that are unique to **malignant** cells.
- **Unfortunately**, most traditional anticancer drugs **do not specifically** recognize neoplastic cells but, rather, **affect all kinds** of proliferating cells, **both** normal and abnormal.

PRINCIPLES OF CANCER CHEMOTHERAPY

- Therefore, almost **all antitumor** agents have a **steep dose-response curve** for **both** therapeutic and toxic effects.
- **Newer agents** are being developed that take a **different approach** to cancer treatment by **blocking checkpoints** and **allowing** the patient's **own immune system** to attack cancer cells.
- Chemotherapeutic agents are also used in **non-cancer diseases**, e.g. **methotrexate** in rheumatoid arthritis and psoriasis, **azathioprine** in organ transplantation, and **hydroxyurea** in sickle cell anemia.
- **Principles** of cancer chemotherapy include:

A. Treatment **strategies**

B. Treatment **regimens** and **scheduling**

C. Resistance with chemotherapy

D. **Toxicity** with chemotherapy

A. Treatment Strategies

1. Goals of treatment:

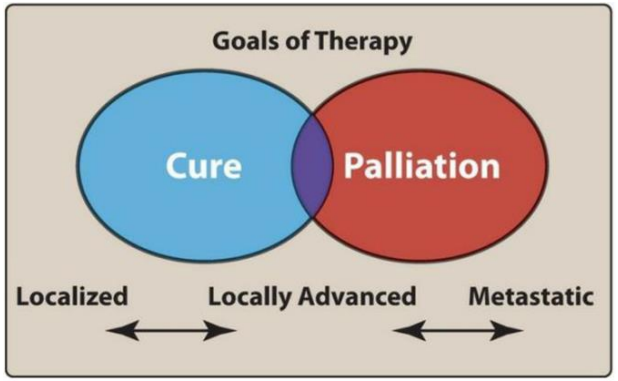
- Chemotherapy **reduces neoplastic cell burden** to maintain the "normal" existence of the disease with the patient as a chronic disease.
- Accordingly, **three goals** are intended **depending** upon complicated factors mainly the **type and stage of cancer**:

- **The first fundamental goal** of cancer chemotherapy is to **cure the disease**.
- Cure **means** long-term **disease-free survival**.
- **True cure** requires the **eradication** of every neoplastic cell.

A. Treatment Strategies

1. Goals of treatment:

- **The second goal** becomes **control** of the disease by **stopping** the cancer from **enlarging** and **spreading** to extend survival and maintain the "**best quality**" of life.
- In **advanced** stages of cancer, controlling the disease is **not possible**.



- **The third goal** is **palliation**.
- Palliation means **alleviation of symptoms** and **avoidance of life-threatening toxicity**.
- This means that chemotherapeutic drugs may be used to **relieve symptoms** caused by the cancer and **improve the quality** of life, even though the drugs **may not extend survival**.
- The **goal** of treatment should always be **kept in mind**, as it often **influences treatment** decisions.

A. Treatment Strategies

2. Indications for treatment:

Chemotherapy is **indicated** in the following cases:

A. Initial Chemotherapy:

- chemotherapy is **indicated** when neoplasms are **disseminated** and are **not amenable** to **surgery**, e.g. esophageal, head and neck cancers, and leukemia.

B. **Adjuvant chemotherapy:**

- chemotherapy is **indicated** as a **supplemental** treatment to **attack micrometastases following surgery** and **radiation** treatment.

C. Neoadjuvant chemotherapy:

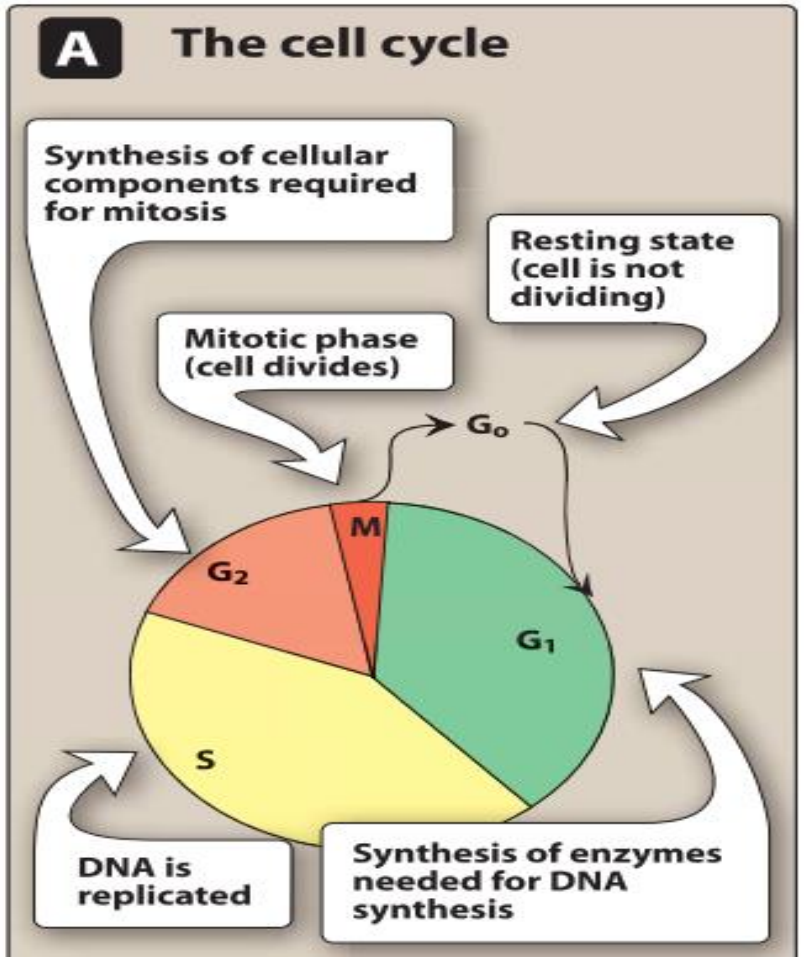
- chemotherapy is given **before** the **surgical** procedure in an attempt to **shrink the cancer**.

D. Maintenance chemotherapy:

- Chemotherapy is given in **lower doses** to assist in **prolonging remission**.

A. Treatment Strategies

3. Tumor susceptibility and the growth cycle:



B

Cell cycle–specific drugs

Antimetabolites
Bleomycin
Etoposide
Vinca alkaloids

Effective for high-growth-fraction malignancies such as hematologic cancers

C

Cell cycle non-specific drugs

Alkylating agents
Antibiotics
Cisplatin
Nitrosoureas

Effective for both low-growth-fraction malignancies, such as solid tumors, as well as high-growth-fraction malignancies

B. Treatment regimens and scheduling

- **Drug dosages** are usually **calculated** based on **body surface area**, to **tailor** the dosage to **each patient**.

$$\text{BSA } (m^2) = \sqrt{\frac{\text{Height (cm) x Weight (Kg)}}{3{,}600}}$$

- **Destruction** of cancer cells by chemotherapeutic agents follows **first-order kinetics** (that is, a given dose of drug destroys a constant fraction of cells), this is termed as **"log kill".**
- **Combination** chemotherapy is **more successful** than **single-drug** treatment in most cancers for which chemotherapy is **effective**.
- **Cytotoxic** agents with **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**.

B. Treatment regimens and scheduling

- 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**.
- The **advantages** of combination chemotherapy are that it:

1. provides **maximal cell killing** within the range of tolerated toxicity
2. It is effective against a **broader range of cell lines** in the heterogeneous tumor population
3. It may **delay or prevent** the development of **resistant cell lines**.

B. Treatment regimens and scheduling

Treatment protocols

- **Many** cancer treatment **protocols** have been developed, and each is applicable to a **particular neoplastic state**, 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.
- Therapy is **scheduled intermittently** to **allow recovery or rescue of the immune system**, which is also **affected** by the **chemotherapeutic** agents, thus **reducing** the risk of **serious infection**.

C. Resistance with chemotherapy

- **Resistance** one of the **major difficulties** in cancer therapy is the development of resistance to cancer chemotherapy. Resistance could be **categorized** into **two forms**:

1 Inherited or primary resistance:

- Some types of neoplasms are **inherently resistant** to **some anticancer** drugs (e.g. **melanoma**) **even** when the chemotherapy treatment is **used for the first time**.

2. Acquired resistance:

- The previously sensitive tumor cells will **develop resistance** during treatment with chemotherapy.
- This type of resistance is **developed by modulations** made by the **tumor cells** to overcome the **lethal effect** of the drug.

C. Resistance with chemotherapy

2. Acquired resistance:

- These **modulations may** include:

1. **Decreased accumulation** of drug (e.g. P glycoprotein)
2. **Insufficient activation** of the drug (e.g. 5-FU, mercaptopurine)
3. **Decreased taking up** the drug (e.g. methotrexate)
4. **Increased the concentration of the target enzyme** (e.g. methotrexate)
5. **Utilization of the alternative metabolic pathway** (e.g. antimetabolites)
6. **Increased repair** of drug-induced lesions (e.g. alkylating agents)
7. **Mutations** in various genes that gave rise to the resistant target site (e.g. overexpression of antiapoptotic genes).

C. Resistance with chemotherapy

- **Resistance** to chemotherapy commonly **developed with**:

1. Long term regimens
2. Continuous regimens
3. Suboptimal dose regimens
4. Single-drug regimens

- Therefore, to **minimize resistance**, it is advised to use **short-term, intermittent, and intensive drug combination regimens**.

D. Toxicity with chemotherapy

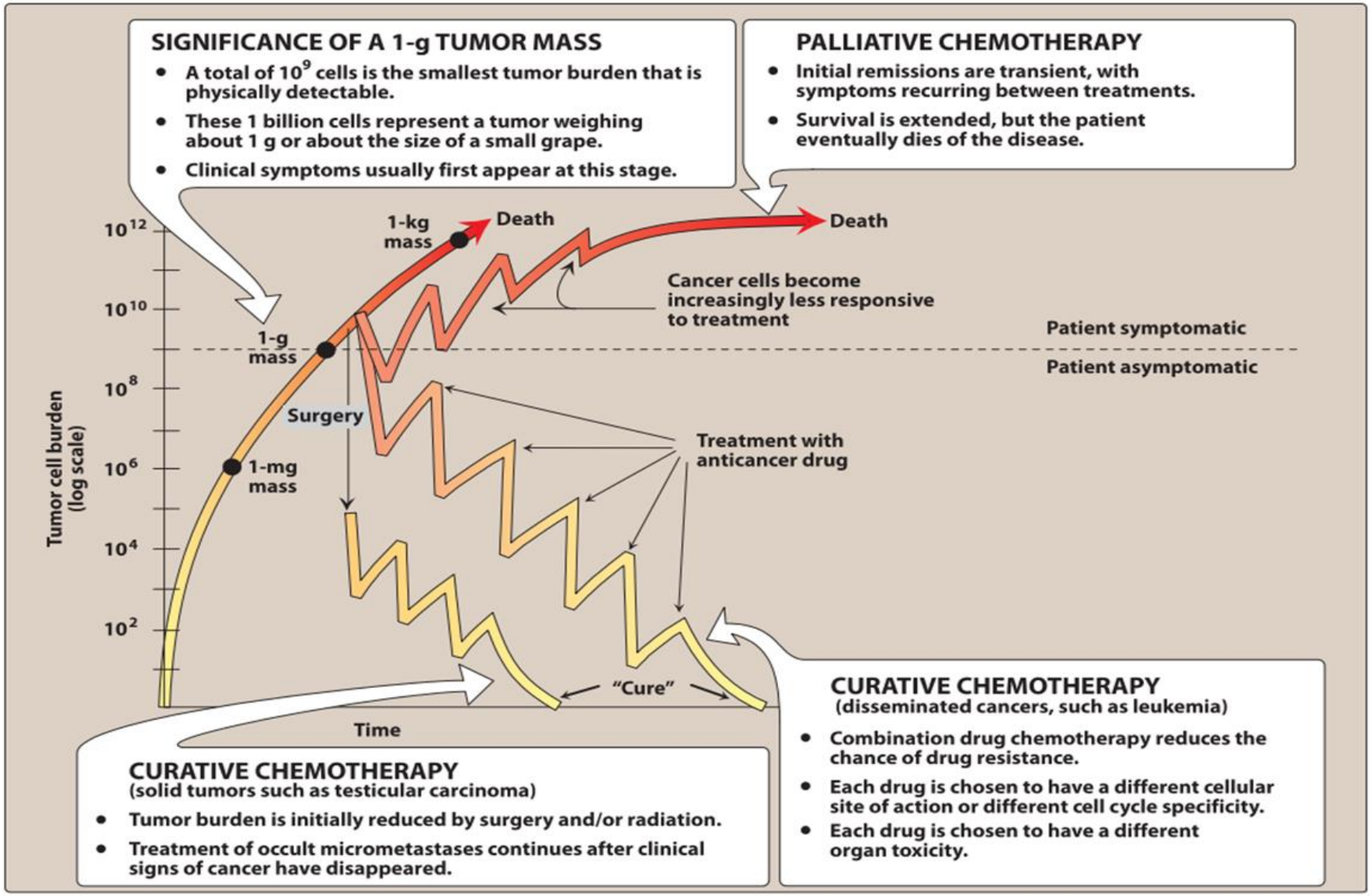
- Therapy aimed at **killing** rapidly dividing **cancer** cells also affects **normal cells undergoing rapid proliferation**
- For example, cells of the buccal mucosa, bone marrow, GI mucosa, and hair follicles)
- **Contributing** to the **toxic manifestations** of chemotherapy.

D. Toxicity with chemotherapy

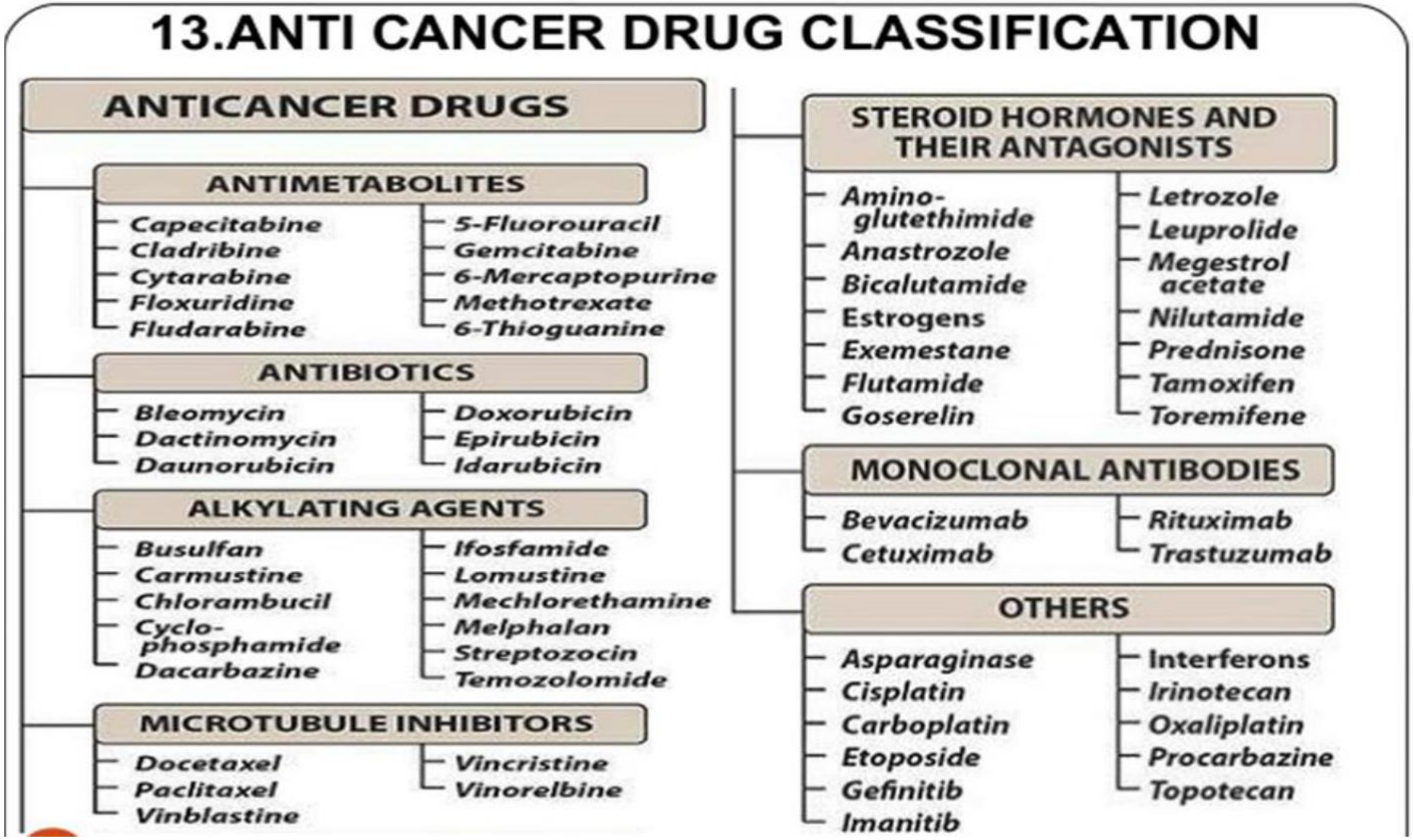
Common adverse effects

- Most chemotherapeutic agents have a **narrow therapeutic index**.
- **Severe vomiting, stomatitis, bone marrow suppression, and alopecia** occur to varying extents during therapy with **most 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.
- **Other** adverse reactions are confined to **specific** agents, such as **bladder toxicity with cyclophosphamide**, **cardiotoxicity with doxorubicin**, and **pulmonary fibrosis with bleomycin**.
- The **duration** of the adverse effects **varies** widely, for example, **alopecia is transient**, but the **cardiac, pulmonary, and bladder toxicities** can be **irreversible**.

Cancer cell burden with/without treatment



Classification of anticancer drugs



II. ANTIBIOTICS

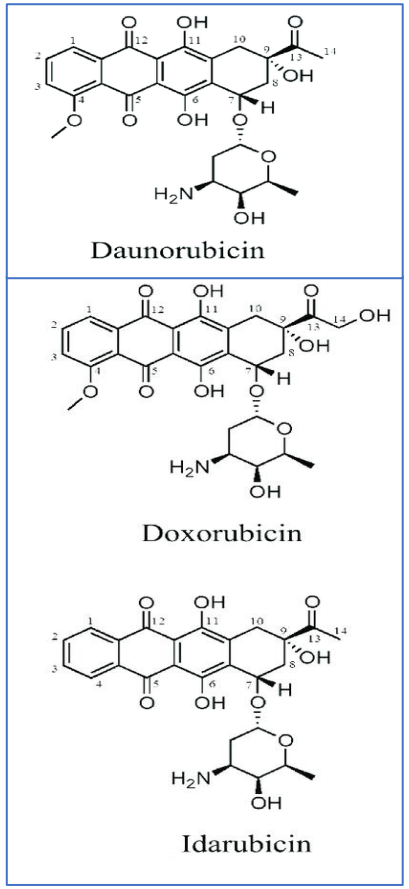
- The antitumor antibiotics owe their **cytotoxic action** primarily to their **interactions with DNA**, leading to **disruption of DNA function**.
- In addition to **intercalation**, their abilities to **inhibit topoisomerases (I and II)** and **produce free radicals** also play a major role in their cytotoxic effect.
- **They** are cell cycle **nonspecific**, with **bleomycin** as an **exception**.
- They include:

A. Anthracyclines (Doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone)

B. Bleomycin

A. Anthracyclines

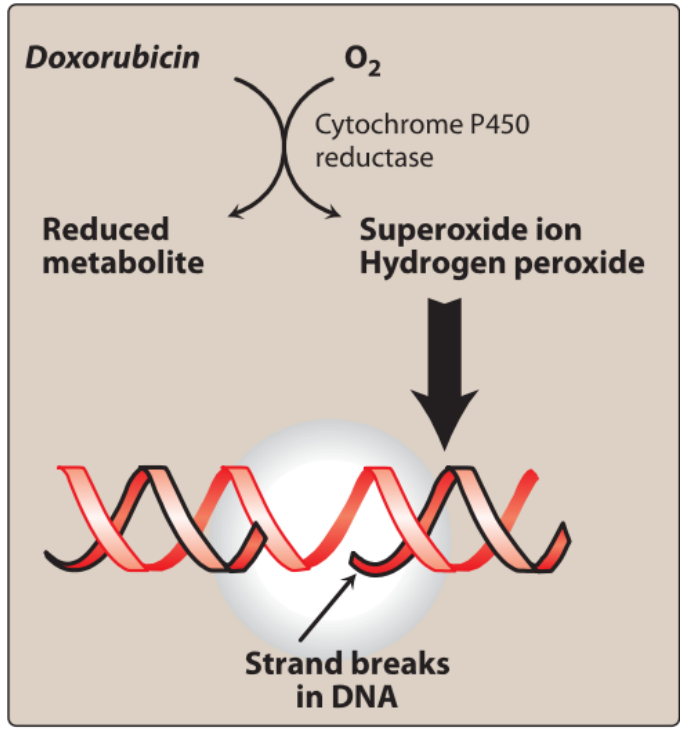
- **Doxorubicin** is the **hydroxylated analog** of **daunorubicin, while, Idarubicin**, is the **4-demethoxy** analog of **daunorubicin.**
- Therapeutic **uses** for these agents **differ** despite their **structural similarity** and **similar mechanisms of action**.
- **Doxorubicin** is one of the most important and **widely** used anticancer drugs.
- It is used in **combination** with other agents for treatment of **sarcomas** and a variety of **carcinomas**, including **breast cancer**, as well as for treatment of **ALL** and **lymphomas**.
- **Daunorubicin** and **idarubicin** are used in the treatment of **acute leukemias.**
- **Mitoxantrone** is used in **prostate cancer**.



A. Anthracyclines

1. Mechanism of action:

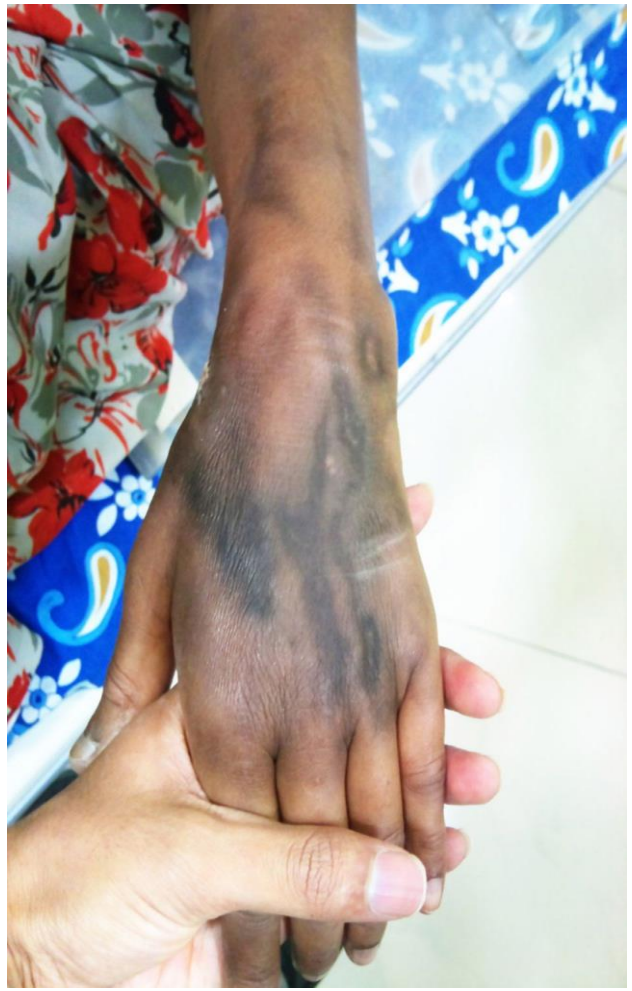
- Doxorubicin and other anthracyclines induce **cytotoxicity** through **several** different **mechanisms**.
- For example, doxorubicin-derived **free radicals** can induce membrane **lipid peroxidation**, **DNA strand scission**, and **direct oxidation** of purine or pyrimidine bases, thiols, and amines.



A. Anthracyclines

2. Pharmacokinetics:

- These agents **must** be administered **IV**, because they are **inactivated in the GIT**.
- **Extravasation** is a serious problem that can lead to tissue **necrosis**.
- They **bind to plasma proteins** as well as to **other tissue components**, where they are **widely** distributed.
- They do **not penetrate** the **BBB** or the **testes**.
- These agents **undergo extensive hepatic metabolism**, and **dosage adjustments** are needed in patients with **impaired hepatic function**.
- **Biliary** excretion is the **major route** of **elimination**.
- Because of the **dark red color** of the anthracycline drugs, the **veins** may become **visible surrounding the site of infusion**, and **red discoloration of urine** may occur.



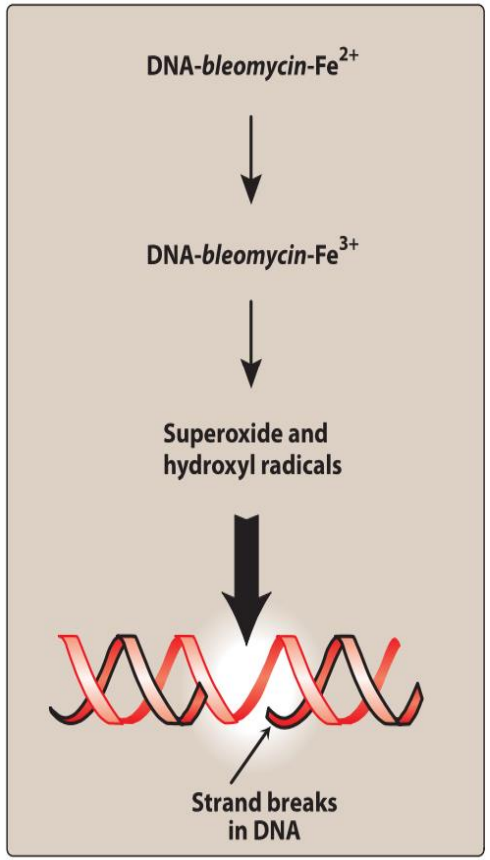
A. Anthracyclines

3. Adverse effects:

- **Irreversible**, **dose-dependent cardiotoxicity** is the most serious adverse reaction and is more common with **daunorubicin** and **doxorubicin** than with **idarubicin and epirubicin**.
- There has been some success with the iron chelator **dexrazoxane** in **protecting** against the **cardiotoxicity** of doxorubicin.
- The **liposomal-encapsulated doxorubicin** is reported to be **less cardiotoxic** than the **standard formulation**.

B. Bleomycin

- **Bleomycin** is a **mixture** of different **copper-chelating glycopeptides** that, like the anthracycline antibiotics, cause **scission of DNA** by an **oxidative process**.
- Bleomycin is **cell cycle-specific** and causes cells to accumulate in the **G2 phase**.
- It is primarily used in the treatment of **testicular cancers and Hodgkin lymphoma**.



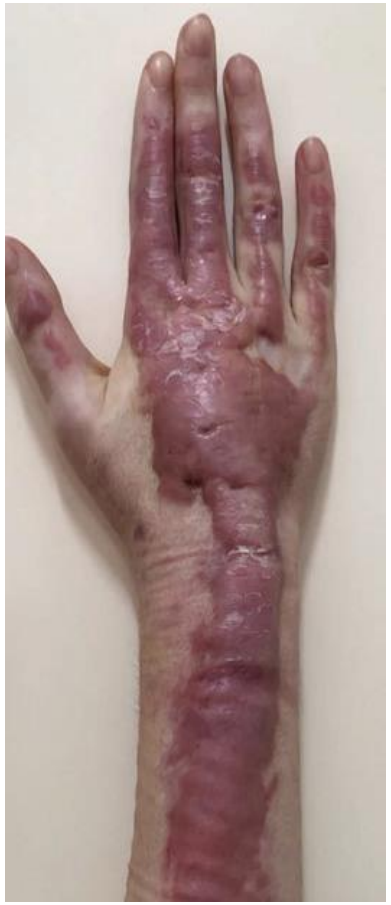
1. Mechanism of action:

- A **DNA-bleomycin-Fe^{2+} complex** appears to undergo **oxidation** to **bleomycin-Fe^{3+}**.
- The **liberated electrons** react with **oxygen** to form **superoxide** or **hydroxyl radicals**, which, in turn, **attack** the **phosphodiester bonds of DNA**, resulting in **strand breakage** and **chromosomal aberrations**.

B. Bleomycin

2. Pharmacokinetics:

- Bleomycin is administered by several **routes**.
- The bleomycin-inactivating enzyme (a **hydrolase**) is **high in** several tissues (for example, **liver** and **spleen**) but is **low** in the **lung** and **absent** in the **skin**, accounting for **toxicity** in those tissues.
- Most of the **parent drug** is excreted **unchanged** in the **urine**, necessitating **dose adjustment** in patients with **renal failure**.



3. Adverse effects:

- **Pulmonary toxicity** is the most serious adverse effect, **progressing** from rales, cough, and infiltrate to potentially fatal fibrosis.
- The pulmonary fibrosis that is caused by bleomycin is often referred to as "**bleomycin lung".**
- **Hypertrophic skin changes** and **hyperpigmentation** of the **hands** are prevalent.
- Bleomycin is unusual in that **myelosuppression** is **rare**.

THANK YOU FOR YOUR ATTENTION