Al-Mustaqbal University College
Department of Pharmacy
4th stage
Pharmacology III
Lecture: 2

ANTICANCER DRUGS

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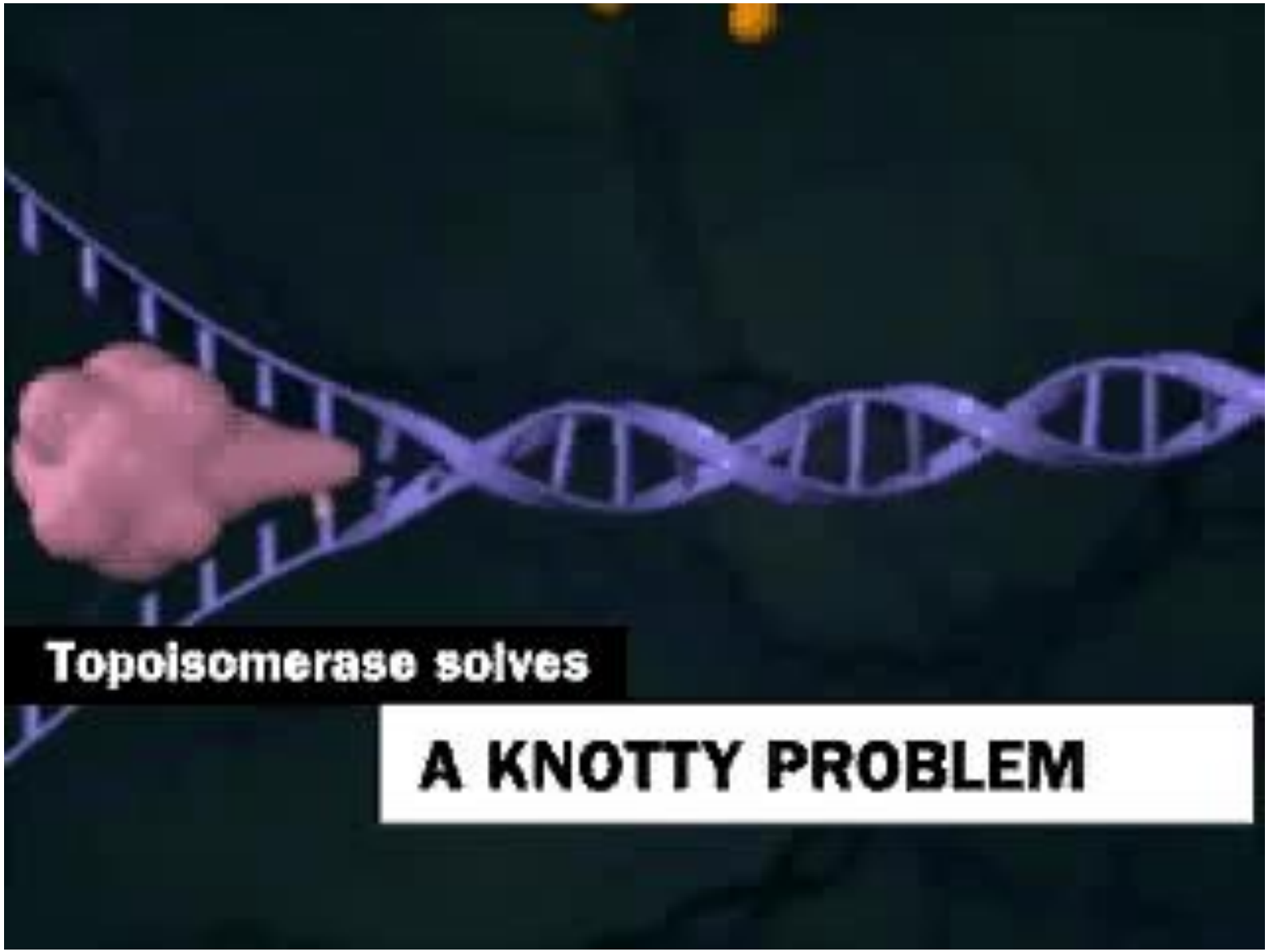
2. ANTITUMOR ANTIBIOTICS

- 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.
- With the exception of bleomycin they are cell **cycle nonspecific** and include:
  - ✓**Anthracyclines**: Doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone
  - ✓**Bleomycin**
  - ✓**Mitomycin**

2. ANTITUMOR ANTIBIOTICS



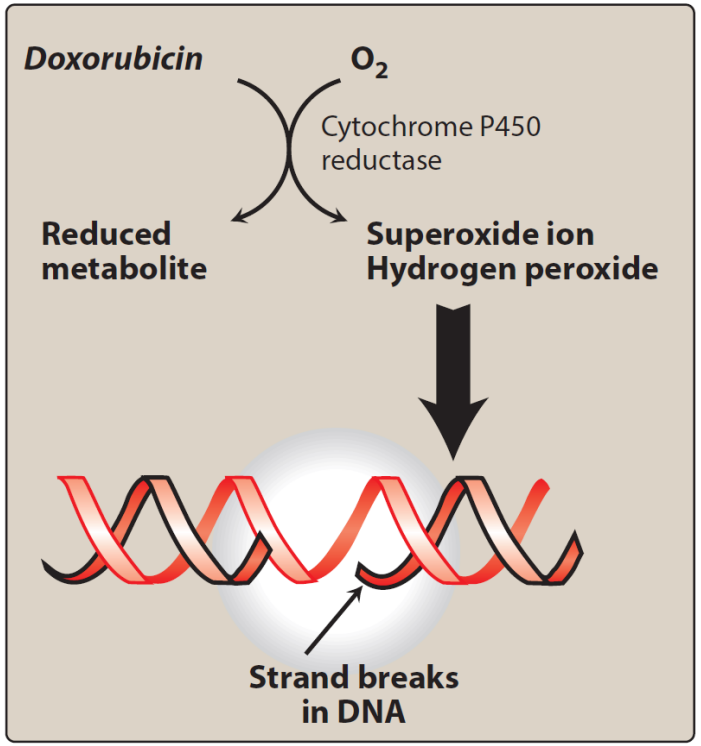
A. Anthracyclines

- They include **Doxorubicin** (hydroxylated analog of daunorubicin)and **daunorubicin**, **Idarubicin** (4-demethoxy analog of daunorubicin), **epirubicin**, and **mitoxantrone**.
- **Applications** for these agents **differ** despite their structural similarity and their apparently 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 the treatment of sarcomas and a variety of carcinomas, including breast and lung, as well as for the treatment of ALL and lymphomas.
- **Daunorubicin** and **idarubicin** are used in the treatment of acute leukemias, and **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 the **direct oxidation** of purine or pyrimidine bases, thiols, and amines.



A. Anthracyclines

2. Pharmacokinetics:

- All these drugs must be administered **IV because** they are inactivated in the GI tract.
- **Extravasation** is a serious problem that can lead to tissue **necrosis**.
- The anthracycline antibiotics **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.
- Some **renal excretion** also occurs, but dosage adjustments are generally **not needed** in renal dysfunction.
- 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.

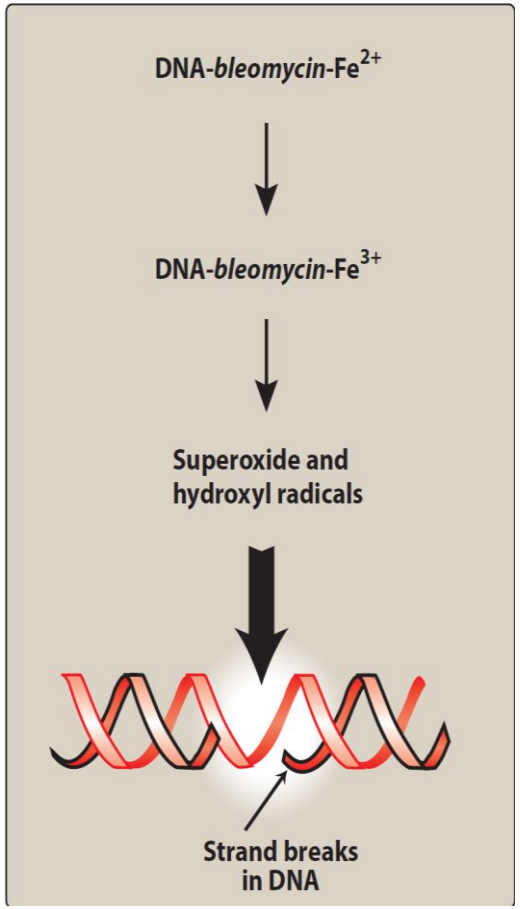
A. Anthracyclines

3. Adverse effects:

- Irreversible, dose-dependent **cardiotoxicity**, apparently a result of the generation of free radicals and lipid peroxidation, is the most serious adverse reaction and is more common with daunorubicin and doxorubicin than with idarubicin and epirubicin.
- Addition of **trastuzumab** (Herceptin®) to protocols with doxorubicin or epirubicin **increases** congestive heart failure.
- 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 usual formulation.

B. Bleomycin

- **Bleomycin** is a mixture of different **copper-chelating glycopeptides**, that cause the **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–Fe2+** complex appears to undergo oxidation to **bleomycin–Fe3+.**
- 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. Resistance:

- **Increased levels** of bleomycin hydrolase (or deaminase), glutathione S-transferase, **increased efflux** of the drug have been implicated, and **DNA repair** also may contribute.

3. Pharmacokinetics:

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

B. Bleomycin

4. Adverse effects:

- **Mucocutaneous reactions** such as (rash, erythema, hyperpigmentation, & urticaria) and **alopecia** are common.
- **Hypertrophic skin changes** and **hyperpigmentation** of the hands are prevalent.
- There is a **high incidence** of fever and chills and a **low incidence** of serious anaphylactoid reactions.
- **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**."
- Bleomycin is unusual in that **myelosuppression** is rare.

3. ALKYLATING AGENTS

- Alkylating agents exert their cytotoxic effects by **covalently binding to nucleophilic (electron-rich) groups** on various cell constituents.
- **Alkylation of DNA** is probably the crucial cytotoxic reaction that is **lethal to the tumor cells**.
- Agents do **not discriminate** between cycling and resting cells, even though they are **more toxic** for rapidly dividing cells.
- They are used in **combination** with other agents to treat a wide variety of **lymphatic** and **solid** cancers.
- In addition to being cytotoxic, all are **mutagenic** and **carcinogenic** and can lead to **secondary malignancies** such as acute leukemia.

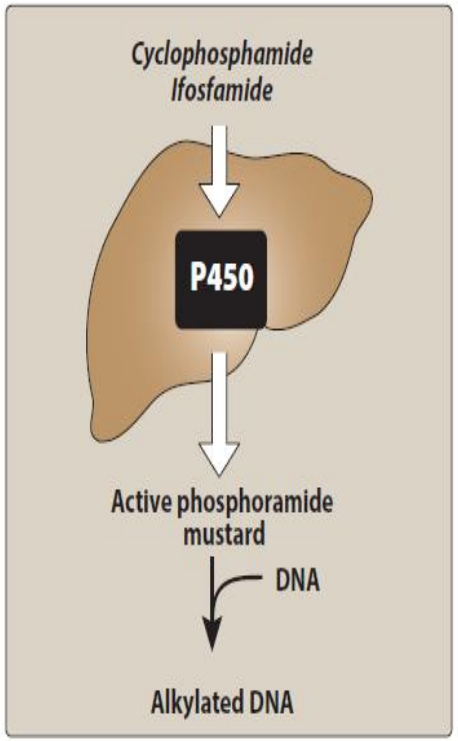
A. Cyclophosphamide and ifosfamide

- These drugs are very closely **related mustard** agents that share most of the same primary mechanisms and toxicities.
- They are **cytotoxic only** after the generation of their **alkylating species**, which are produced through **hydroxylation by cytochrome P450** (CYP450).
- These agents have a **broad clinical spectrum**, being used either **singly** or as **part** of a regimen in the treatment of a wide variety of neoplastic diseases, such as non-Hodgkin lymphoma, sarcoma, and breast cancer.

A. Cyclophosphamide and ifosfamide

1. Mechanism of action:

- **Cyclophosphamide** is the most commonly used alkylating agent.
- **Both** cyclophosphamide and ifosfamide are **first** biotransformed to **hydroxylated intermediates** primarily in the **liver** by the CYP450 system.
- **Then** hydroxylated intermediates then **undergo breakdown** to form the **active compounds**, phosphoramide mustard, and acrolein.
- **Reaction** of the phosphoramide mustard **with DNA** is considered to be the **cytotoxic step**.
- The parent drug and its metabolites are primarily **excreted in the urine**.



A. Cyclophosphamide and ifosfamide

2. Pharmacokinetics:

- Cyclophosphamide is available in **oral** or **IV** preparations, whereas ifosfamide is **IV only**.
- Cyclophosphamide is **metabolized** in the liver to **active** and **inactive** metabolites, and minimal amounts are excreted in the urine as an **unchanged** drug.
- Ifosfamide (prodrug) is **metabolized** primarily by CYP450 3A4 and 2B6 isoenzymes, it is mainly **renally excreted**.

3. Resistance:

- Resistance results from **increased DNA repair, decreased drug permeability**, and the **reaction of the drug with thiols** (for example, glutathione).
- **Cross-resistance** does **not** always occur.

A. Cyclophosphamide and ifosfamide

4. Adverse effects:

- A **unique** toxicity of both drugs is **hemorrhagic cystitis**, which can lead to fibrosis of the bladder.
- **Bladder toxicity** has been attributed to **acrolein** in the urine in the case of cyclophosphamide and to **toxic metabolites** of ifosfamide.
- **Adequate hydration** as well as IV injection of **MESNA** (sodium 2-mercaptoethane sulfonate), which neutralizes the toxic metabolites, can minimize this problem.
- A fairly high incidence of **neurotoxicity** has been reported in patients on **high-dose ifosfamide**, probably due to the metabolite chloroacetaldehyde.

B. Nitrosoureas

- **Carmustine** and **lomustine** are closely related **nitrosoureas**.
- Because of their ability to **penetrate the CNS**, nitrosoureas are **primarily** employed in the treatment of **brain tumors**.

1. Mechanism of action:

- The nitrosoureas exert cytotoxic effects by an **alkylation that inhibits replication** and, eventually, RNA and protein synthesis.
- **Although** they alkylate DNA in **resting cells**, cytotoxicity is expressed primarily on cells that are **actively dividing**.
- Therefore, **nondividing** cells can escape death if DNA repair occurs.
- Nitrosoureas also **inhibit several key enzymatic processes** by carbamoylation of amino acids in proteins in the targeted cells.

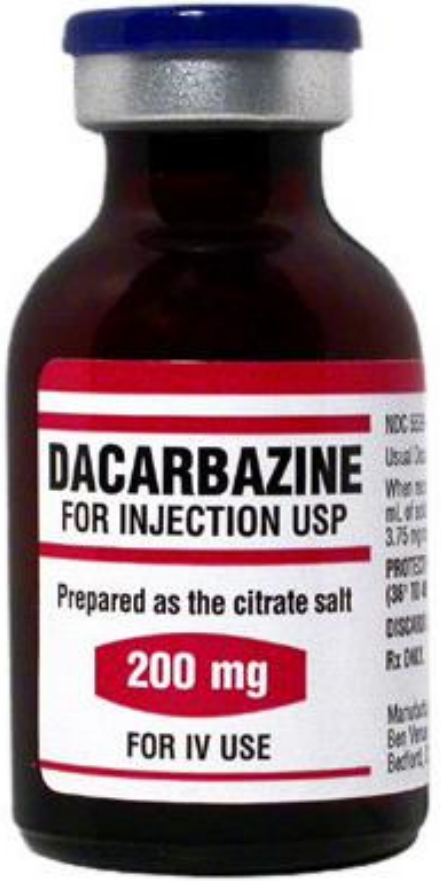
B. Nitrosoureas

2. Pharmacokinetics:

- In spite of the similarities in their structures, **carmustine** is administered **IV** and as chemotherapy **wafer implants**, whereas **lomustine** is given **orally**.
- Because of their **lipophilicity**, they **distribute widely** in the body, but their most striking property is their ability to **readily penetrate the CNS**.
- The drugs undergo **extensive metabolism**.
- **Lomustine** is metabolized to active products.
- The **kidney** is the major excretory route for the nitrosoureas.

C. Dacarbazine

- Dacarbazine is an **alkylating agent** that must undergo biotransformation to an **active metabolite**, methyltriazenoimidazole carboxamide (**MTIC**).
- This **metabolite** is responsible for the **drug's activity** as an alkylating agent by **forming methylcarbonium ions** that can **attack** the nucleophilic groups in the DNA molecule.
- The **cytotoxic action** of dacarbazine has been attributed to the ability of its **metabolite** to **methylate DNA on the O6 position of guanine**.
- Dacarbazine has found use in the **treatment** of **melanoma and Hodgkin lymphoma**.



D. Temozolomide

- **Temozolomide**, a **triazene** agent, has been approved for use against **glioblastomas, anaplastic astrocytomas, and metastatic melanoma**.
- Temozolomide also undergoes biotransformation to an **active metabolite, MTIC**, which probably is responsible for the **methylation of DNA on the 6 position of guanine**.
- Temozolomide also has the **property of inhibiting the repair enzyme**, O6-guanine-DNA alkyl transferase.
- Temozolomide differs from dacarbazine in that **it crosses the BBB**.
- Temozolomide is administered **intravenously** or **orally** and has excellent bioavailability after oral administration.
- The parent drug and metabolites are **excreted in urine**.

OTHER ALKYLATING AGENTS

Melphalan:

- **Melphalan** a phenylalanine derivative of nitrogen mustard, is used in the treatment of **multiple myeloma**.
- This is a **bifunctional** alkylating agent that can be given **orally**.
- **Although** melphalan can be given **orally**, the **plasma concentration** differs from patient to patient due to variations in **intestinal absorption and metabolism**.
- The **dose of melphalan** is carefully adjusted by monitoring the **platelet and white blood cell counts**.

OTHER ALKYLATING AGENTS

- **Mechlorethamine:**
- It was developed as **a vesicant** (nitrogen mustard) during **World War I**. Its ability to cause lymphocytopenia led to its use in lymphatic cancers.

- **Chlorambucil:**
- It is another **bifunctional alkylating agent** that is used in the treatment of **chronic lymphocytic leukemia**.
- **Both** melphalan and chlorambucil have moderate **hematologic toxicities and GIT upset.**

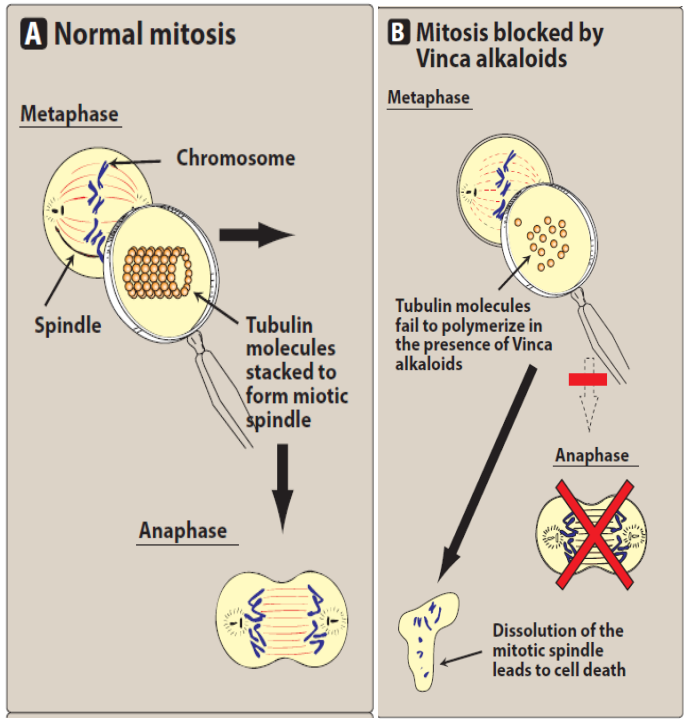
- **Busulfan:**
- It is another oral agent that is effective against **chronic granulocytic leukemia**.

4. MICROTUBULE INHIBITORS

- The **mitotic spindle** is part of a larger, intracellular skeleton (cytoskeleton) that is **essential** for the **movements of structures** occurring in the **cytoplasm** of all eukaryotic cells.
- The mitotic spindle **consists** of **chromatin** plus a system of **microtubules** composed of the protein **tubulin**.
- The mitotic spindle is **essential** for the **equal partitioning of DNA into the two daughter cells** that are formed when a eukaryotic cell divides.
- Several plant-derived substances used as anticancer drugs disrupt this process by affecting the **equilibrium** between the **polymerized and depolymerized** forms of the microtubules, thereby causing **cytotoxicity**.

A. Vincristine, vinblastine, and vinorelbine

- **Vincristine (VX) and vinblastine (VBL)** are **structurally related** compounds derived from the **periwinkle plant**, ***Vinca rosea,*** therefore, referred to as the **Vinca alkaloids**.
- A **less neurotoxic** agent is **vinorelbine (VRB)**.
- Although the Vinca alkaloids are **structurally similar** to one another, their therapeutic **indications are different**.
- They are generally administered in **combination** with other drugs.



A. Vincristine, vinblastine, and vinorelbine

- **VX** is used in the treatment of acute lymphoblastic leukemia in children, Wilms tumor, Ewing soft tissue sarcoma, and Hodgkin and non-Hodgkin lymphomas, as well as some other rapidly proliferating neoplasms.
- Due to relatively **mild myelosuppressive** activity, **VX** is used in a number of other protocols.
- **VBL** is administered with bleomycin and cisplatin for the treatment of metastatic testicular carcinoma.
- It is also used in the treatment of systemic Hodgkin and non-Hodgkin lymphomas.
- **VRB** is beneficial in the treatment of advanced non–small cell lung cancer, either as a single agent or with cisplatin.

A. Vincristine, vinblastine, and vinorelbine

1. Mechanism of action:

- VX, VRB, and VBL are all **cell cycle-specific and phase-specific** because they block mitosis in metaphase **(M-phase**).
- Their binding to the microtubular protein, **tubulin**, **blocks the ability of tubulin to polymerize to form microtubules**.
- Instead, **paracrystalline aggregates** consisting of tubulin dimers and the alkaloid drug are formed.
- The resulting **dysfunctional spindle apparatus**, **frozen in metaphase**, **prevents** chromosomal segregation and cell proliferation.

A. Vincristine, vinblastine, and vinorelbine

2. Pharmacokinetics:

- **IV** injection of these agents leads to **rapid cytotoxic** effects and **cell destruction**.
- This, in turn, can cause **hyperuricemia** due to the oxidation of purines that are released from fragmenting DNA molecules.
- The Vinca alkaloids are concentrated and metabolized in the **liver** by the CYP450 pathway and eliminated in **bile and feces**.
- **Doses** must be **modified** in patients with impaired hepatic function or biliary obstruction.

A. Vincristine, vinblastine, and vinorelbine

3. Adverse effects:

- **VX and VBL** have certain toxicities in common, these include **phlebitis or cellulitis**, if the drugs **extravasate** during injection, as well as **N/V/D and alopecia**.
- However, the adverse effects of VX and VBL are not identical.
- **VBL** is a more **potent myelosuppressant** than **VX**, whereas **peripheral neuropathy** (paresthesias, loss of reflexes, foot drop, and ataxia) is associated with **VX**.
- **Constipation** is more frequently encountered with **VX**.
- These agents **should not** be administered **intrathecally,** this potential drug **error** can result in **death**, and special precautions should be in place for administration.

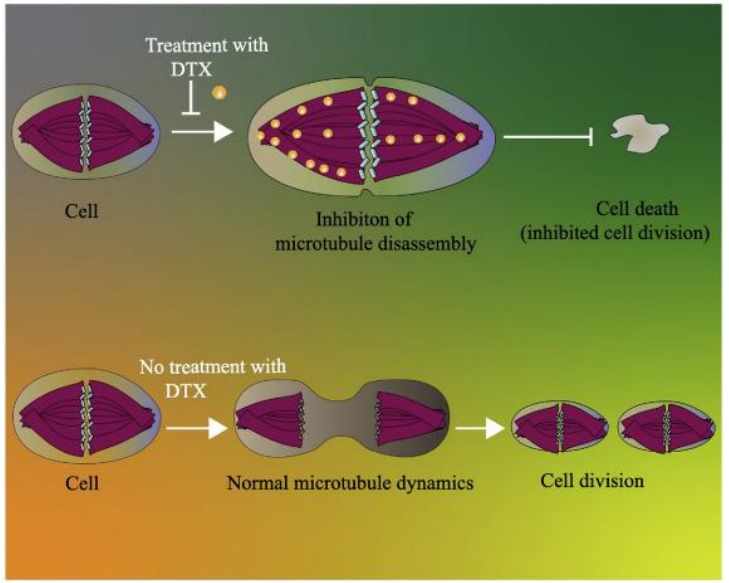
B. Paclitaxel and docetaxel

- **Paclitaxel** was the **first** member of the **taxane family** to be used in cancer chemotherapy.
- A **semisynthetic paclitaxel** is now available through chemical modification of a precursor found in the needles of **Pacific yew species**.
- An **albumin-bound** form is also available.
- Substitution of a side chain has resulted in **docetaxel**, which is the **more potent** of the two drugs.
- **Paclitaxel** has shown good activity against **advanced ovarian cancer** and **metastatic breast cancer**.
- Favorable results have been obtained in **non–small cell lung cancer** when **administered with cisplatin.**
- **Docetaxel** is commonly used in **prostate, breast, GI, and non–small cell lung cancers**.

B. Paclitaxel and docetaxel

1. Mechanism of action:

- Both drugs are active in the **G2/M-phase** of the cell cycle, but **unlike the Vinca alkaloids**, they **promote polymerization and stabilization** of the polymer rather than disassembly, leading to the **accumulation of microtubules**.
- The **overly stable** microtubules formed are **nonfunctional**, and **chromosome desegregation** does **not occur,** this results in **death of the cell**.



B. Paclitaxel and docetaxel

2. Pharmacokinetics:

- These agents undergo **hepatic metabolism** by the CYP450 system and are **excreted** via the **biliary system**.
- **Dose modification** is not required in patients with renal impairment, **but** doses should be **reduced** in patients with hepatic dysfunction.

3. Adverse effects:

- The dose-limiting toxicities of paclitaxel and docetaxel are **neutropenia** and **leukopenia**.
- **Alopecia** occurs, but vomiting and diarrhea are **uncommon**.
- **Note:** Because of **serious hypersensitivity** reactions (including dyspnea, urticaria, and hypotension), patients who are treated with **paclitaxel** should be **premedicated** with dexamethasone and diphenhydramine, as well as with an H2 blocker.

THANK YOU FOR YOUR ATTENTION