Al-Mustaqbal University
College of Pharmacy
4th stage
Pharmacology III
Lecture: 6

ANTICANCER DRUGS III

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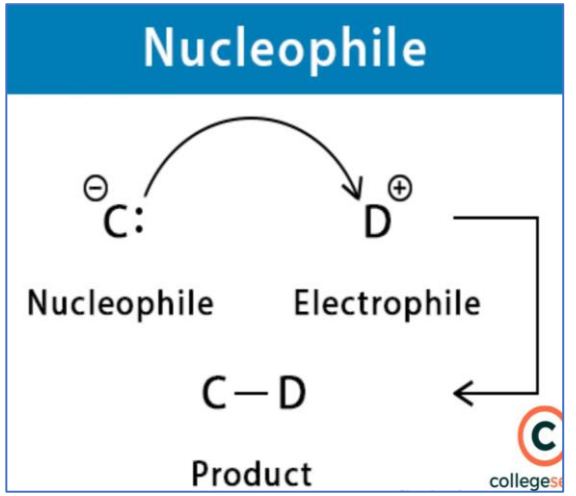
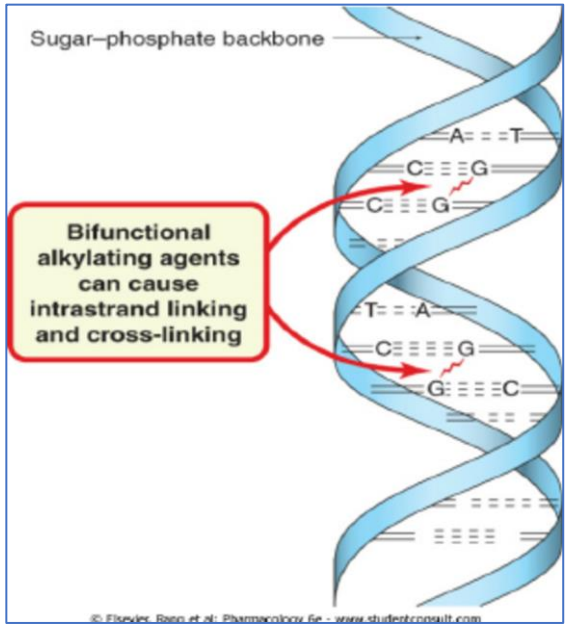
III. Alkylating AGENTS

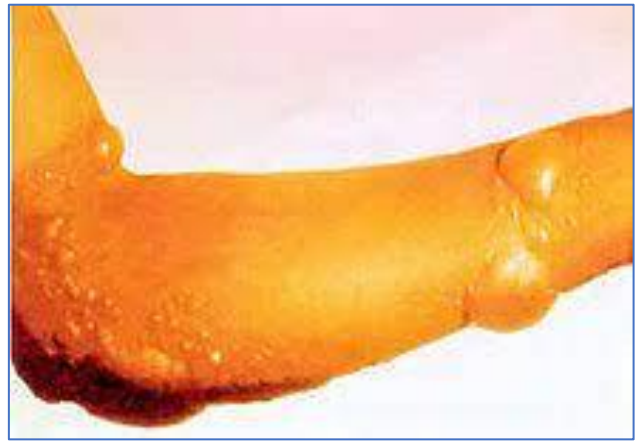
- Alkylating agents exert their **cytotoxic effects** by **covalently binding to nucleophilic groups** on various **cell constituents**.
- **Alkylation of DNA** is probably the **crucial** cytotoxic reaction that is **lethal to the tumor cells**.
- Alkylating agents **do not discriminate** between **cycling** and **resting** cells, even though they are **most 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

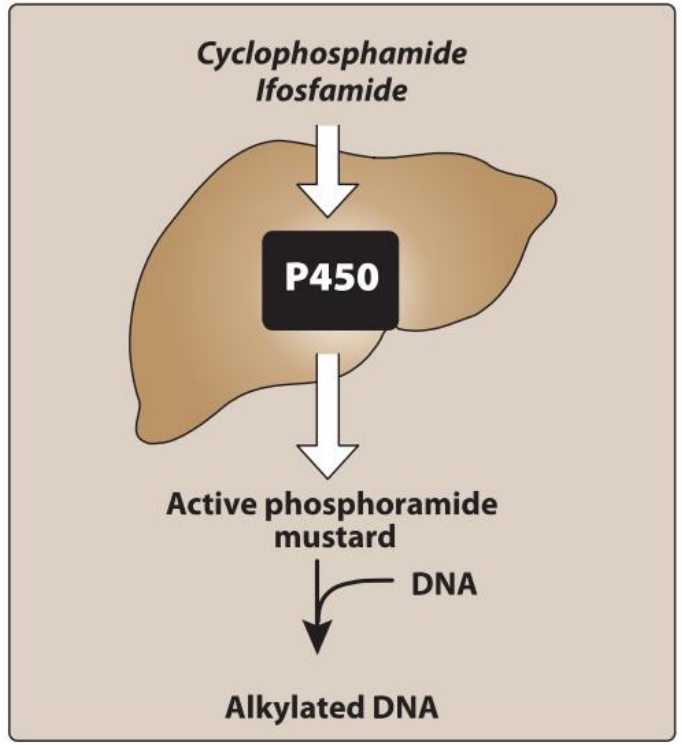
- These drugs are very closely related **mustard agents** that share most of the **same** primary **mechanisms and toxicities**.
- These agents have a **broad clinical spectrum** and are used as **single** agents or in **combinations** in the treatment of a **wide variety** of neoplastic diseases, such 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.
- The hydroxylated intermediates then **undergo metabolism** to form the **active compounds**, **phosphoramide mustard** and **acrolein**.
- **Reaction** of the phosphoramide mustard **with DNA** is considered to be the **cytotoxic step**.



A. Cyclophosphamide and ifosfamide

2. Pharmacokinetics:

- **Cyclophosphamide** is available in **oral** and **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** is metabolized primarily by **CYP450 3A4** and **2B6** isoenzymes.
- It is **mainly renally excreted**.

A. Cyclophosphamide and ifosfamide

3. Adverse effects:

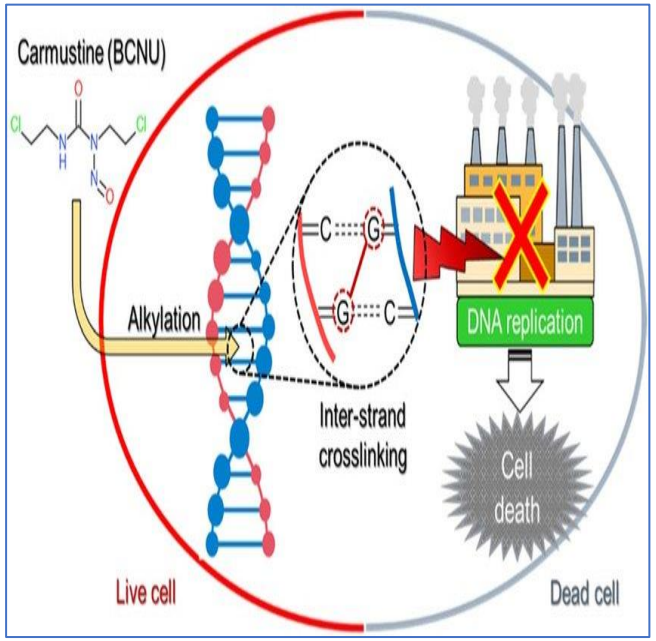
- A **unique** toxicity of both drugs is **hemorrhagic cystitis**, which can lead to **fibrosis of the bladder**.
- Bladder toxicity has been **attributed** to **acrolein in the urine** in the case of **cyclophosphamide** and to **toxic metabolites** of **ifosfamide**.
- **Adequate hydration** as well as **IV injection of MESNA** (2-**m**ercapto**e**thane **s**ulfonate Na), which **neutralizes** the toxic metabolites, can **minimize this problem**.
- **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**, the nitrosoureas are primarily employed in the **treatment of brain tumors**.

1. Mechanism of action:

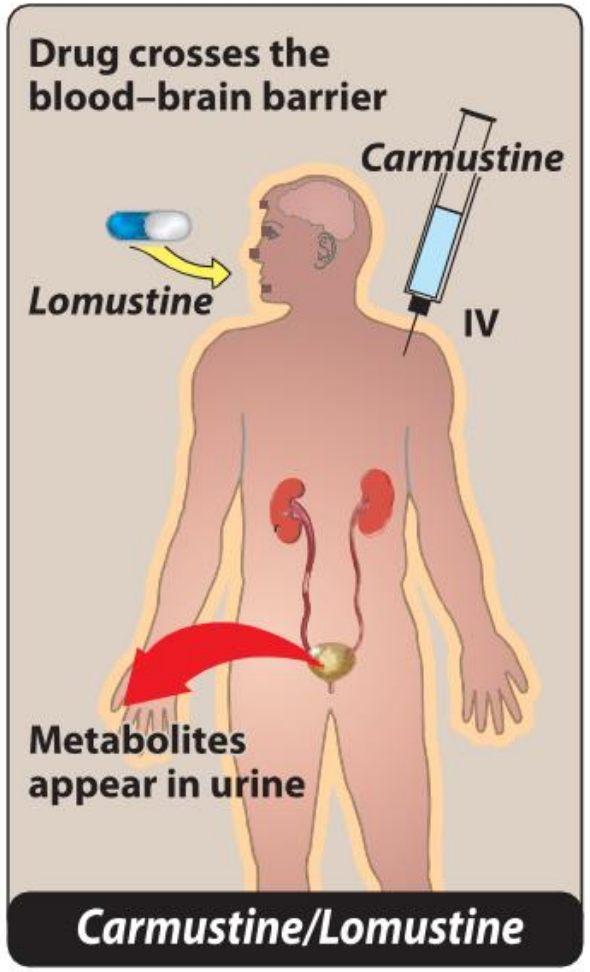
- They exert **cytotoxic** effects by an **alkylation** that **inhibits replication** and, eventually, **RNA and protein synthesis**.
- Although they alkylate DNA in **resting cells**, cytotoxicity is **expressed primarily** in cells that are **actively dividing**.
- Therefore, **nondividing** cells 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

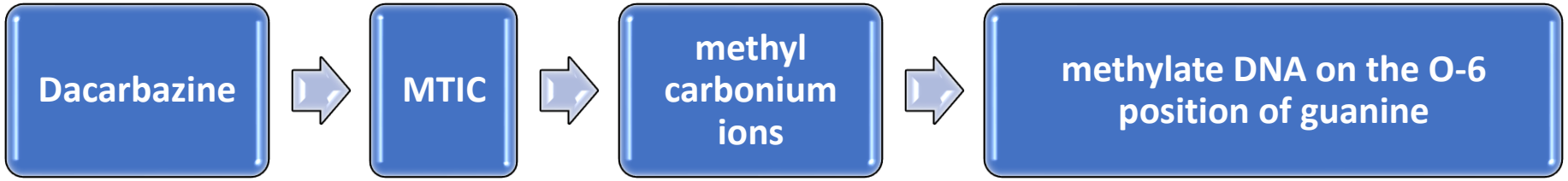
2. Pharmacokinetics:

- **Carmustine** is administered **IV** and as **chemotherapy wafer implants**, whereas **lomustine** is given **orally**.
- Because of their **lipophilicity**, these agents **distribute widely** in the body and readily **penetrate the CNS**.
- These drugs undergo **extensive metabolism, Lomustine** is metabolized to **active products**.
- The **kidney** is the major **excretory route** for the **nitrosoureas**.



C. Dacarbazine and temozolomide

- **Dacarbazine** is an **alkylating** agent that must undergo **biotransformation** to an **active** metabolite, **m**ethyl**t**riazeno**i**midazole **c**arboxamide (**MTIC**).
- **MTIC** is responsible for the **alkylating activity** of this agent by **forming methyl carbonium ions** that **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 O-6 position of guanine**.
- Dacarbazine has found use in the treatment of **melanoma and Hodgkin lymphoma**.



C. Dacarbazine and temozolomide

- **Temozolomide** is **related to dacarbazine** because **both** must undergo biotransformation to an active metabolite, **MTIC**, which is likely **responsible** for the **methylation** of DNA on the O-6 and N-7 position of guanine.
- **Unlike** dacarbazine, **temozolomide** does **not require** the **CYP450** system for metabolic transformation, and it undergoes chemical transformation at **normal physiological pH**.
- **Temozolomide** also **inhibits the repair enzyme**, **O-6-guanine DNA alkyl transferase**.
- Temozolomide **differs** from dacarbazine in that it **crosses the BBB** and, therefore, is used in the treatment of **brain tumors** such as **glioblastomas** and **astrocytomas**.
- It is also used in **metastatic melanoma**.
- Temozolomide is **administered IV** or **orally** and has **excellent bioavailability** after oral administration.
- The parent drug and metabolites are **excreted in urine**.
-

D. Other alkylating agents

1. 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**.

2. Chlorambucil:

- It is another **bifunctional alkylating** agent that is used in the treatment of **CLL**.

3. Busulfan:

- It is an alkylating agent that is effective against **CML**.
- This agent can cause **pulmonary fibrosis** ("busulfan lung").

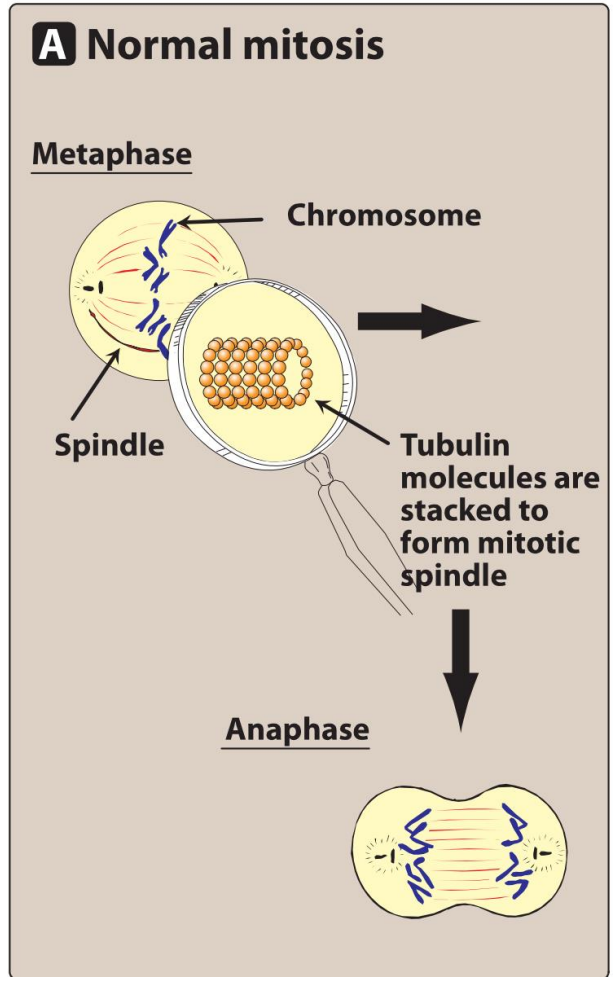
D. Other alkylating agents

4. Melphalan:

- **It is** 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 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.
- Like other alkylating agents, all of these agents are **leukemogenic**.

IV. 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**.

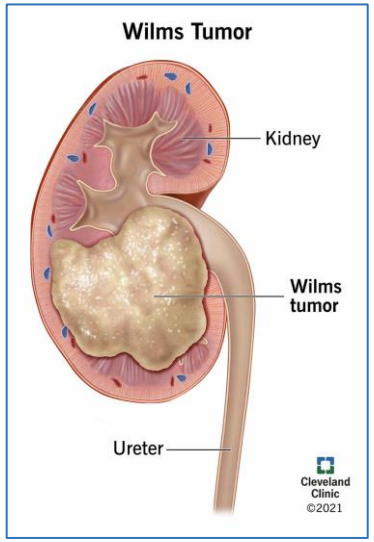


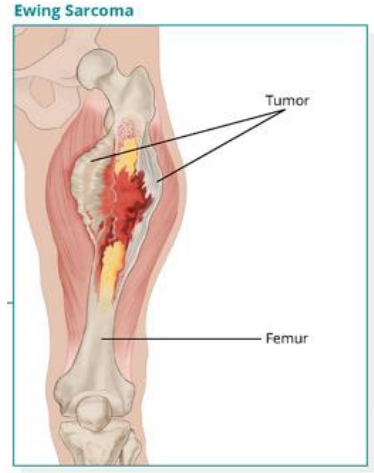
A. Vinca Alkaloids (Vincristine and vinblastine)

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

A. Vinca Alkaloids (Vincristine and vinblastine)

- **VX (Oncovin®)**is used in the **treatment** of ALL 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 **several** 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**.

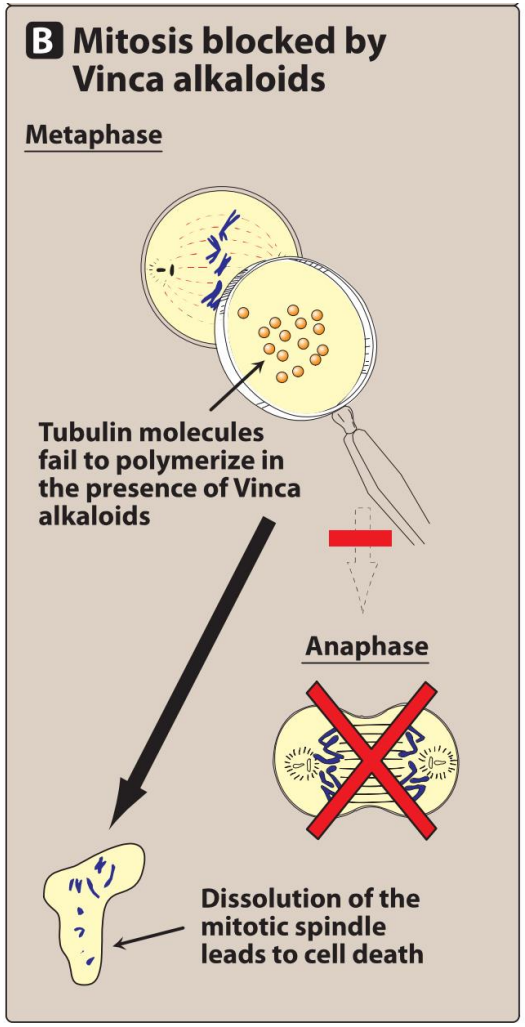




A. Vinca Alkaloids (Vincristine and vinblastine)

1. Mechanism of action:

- These agents are 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. Vinca Alkaloids (Vincristine and vinblastine)

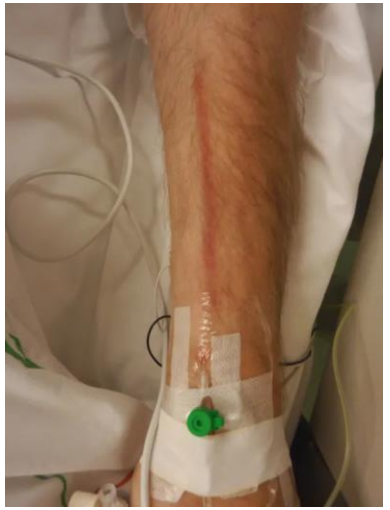
2. Pharmacokinetics:

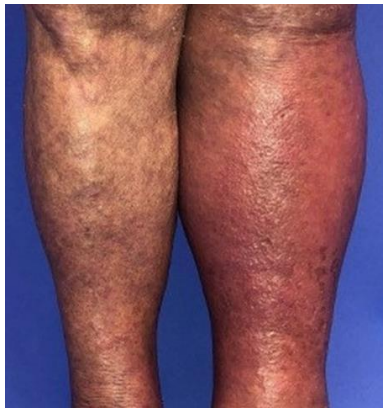
- **IV** injection of these agents leads to **rapid cytotoxic effects and cell destruction**.
- This, in turn, can cause **hyperuricemia** due to the oxidation of purines that are released from fragmenting DNA molecules.
- The Vinca alkaloids are **concentrated** and **metabolized** in the **liver**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

A. Vinca Alkaloids (Vincristine and vinblastine)

3. Adverse effects:

- **VX** and **VBL** are both associated with **phlebitis** or **cellulitis** if **extravasation** occurs during injection, as well as nausea, vomiting, diarrhea, and **alopecia**.
- **VBL** is a **potent myelosuppressant.**
- Whereas **peripheral neuropathy** (paresthesias, loss of reflexes, foot drop, and ataxia) and **constipation** are **more common** 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.





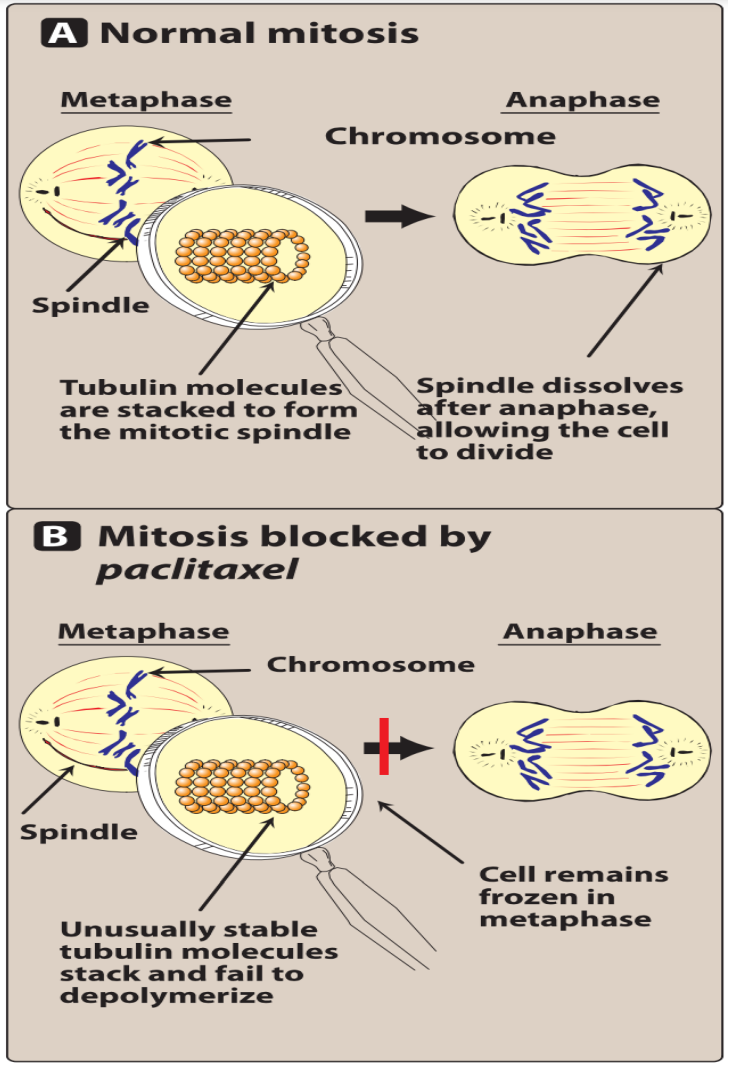
B. Taxane Family (Paclitaxel and docetaxel)

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

B. Taxane Family (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 microtubules formed are **overly stable** and **nonfunctional**, and **chromosome desegregation** does **not occur,** which results in **cell death**.



B. Taxane Family (Paclitaxel and docetaxel)

2. Pharmacokinetics:

- These agents undergo **hepatic metabolism** by the CYP450 system and are **excreted** via the **biliary system**.
- **Dosages** should be **reduced** in patients with **hepatic dysfunction**.

- **3. Adverse effects:**
- The **dose-limiting** toxicities of paclitaxel and docetaxel are **neutropenia and leukopenia**.
- **Peripheral neuropathy** is also a common adverse effect of the taxanes.
- **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 receptor antagonist**.

V. STEROID HORMONES AND THEIR ANTAGONISTS

- **Tumors** that are **sensitive** to steroid hormones may be:

1)**Hormone-responsive**, in which the tumor regresses following treatment with a specific hormone.

2)**Hormone-dependent**, in which removal of a hormonal stimulus causes tumor regression.

3)**Both**

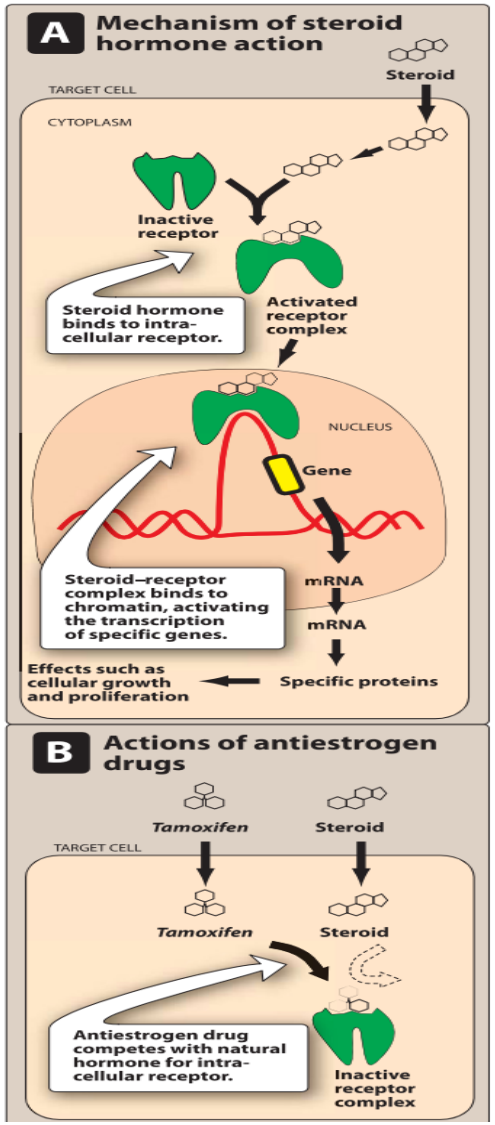
- **Removal** of **hormonal stimuli** from hormone-dependent tumors can be **accomplished** by:

1) Surgery (for example, in the case of **orchiectomy** for patients with advanced prostate cancer)
2) **Drugs** (for example, in **breast cancer** treatment with the **antiestrogen tamoxifen** prevents estrogen stimulation of breast cancer cells.

- For a **steroid hormone** to influence a cell, that cell must have **intracellular** (cytosolic) receptors that are specific for that hormone.

A. Tamoxifen

- **Tamoxifen** is a selective estrogen receptor modulator (**SERM**).
- It is an estrogen **antagonist** in **breast tissue** and an **agonist** in other tissues, such as **bone** and the **endometrium**.
- Tamoxifen is used for **first-line therapy** in the treatment of **estrogen receptor-positive breast cancer**.
- It is also used for the **prevention** of breast cancer in high-risk women.



1. Mechanism of action:

- Tamoxifen **competes** with **estrogen** for binding to **estrogen receptor**s in the **breast** tissue and **inhibits** estrogen-induced growth of breast cancer.
- The result is a depletion (**down-regulation**) of **estrogen receptors**, and the **growth-promoting effects** of the natural hormone and other growth factors are **suppressed**.

A. Tamoxifen

2. Pharmacokinetics:

- Tamoxifen is effective after **oral** administration.
- It is **partially metabolized** by the liver.
- Some **metabolites** possess estrogen **antagonist activity**, whereas others have **agonist** activity.
- Unchanged drug and metabolites are **excreted** predominantly through the **bile into the feces**.
- Tamoxifen is an **inhibitor** of **CYP3A4** and **P-glycoprotein**.

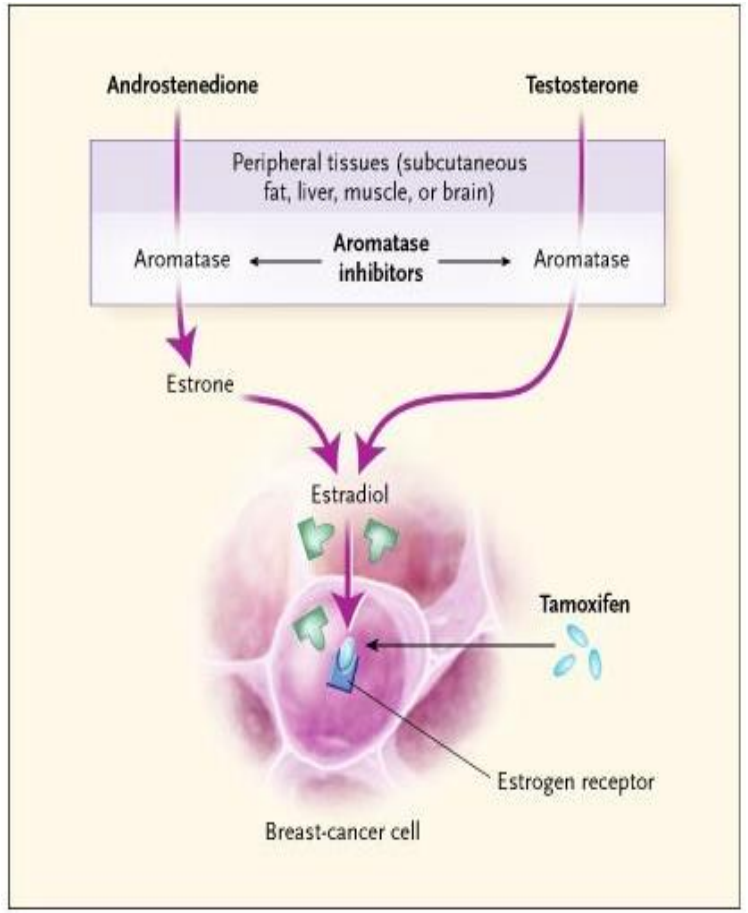
- **3. Adverse effects:**
- Hot flashes, nausea, vomiting, skin rash, and vaginal bleeding and discharge (due to **estrogenic** activity of the drug and some of its **metabolites** in the endometrial tissue).
- Tamoxifen has the **potential** to cause **endometrial cancer**.
- Other toxicities include **thromboembolism** and effects on **vision**.

B. Fulvestrant and raloxifene

- **Fulvestrant** is an estrogen receptor **antagonist** that is given via **intramuscular** injection to patients with **hormone receptor-positive metastatic breast cancer**.
- This agent binds to and causes **estrogen receptor down-regulation** on tumors and other targets.
- **Raloxifene** is an **oral SERM** that **blocks** estrogen effects in the **uterine and breast tissues** while **promoting** effects in the **bone** to inhibit resorption.
- This agent **reduces** the risk of estrogen receptor-positive **invasive breast cancer** in **postmenopausal** women.
- **Both** drugs are known to cause **hot flashes, arthralgias, and myalgias**.

C. Aromatase inhibitors

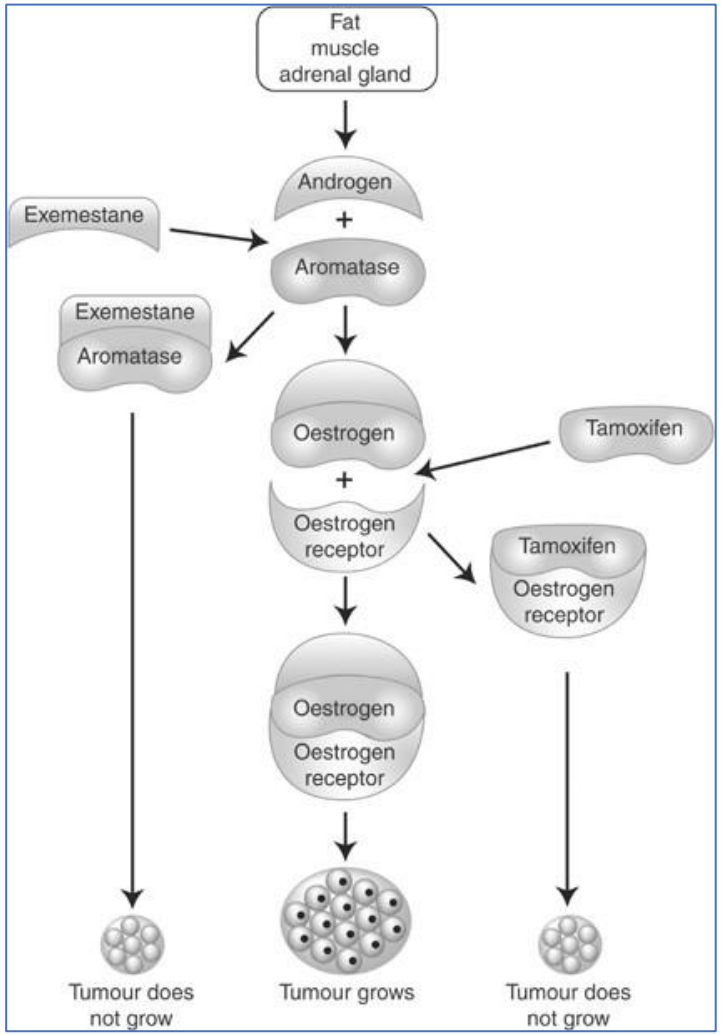
- The **aromatase reaction** is responsible for the **extra-adrenal synthesis of estrogen** from **androstenedione.**
- This process takes place in the **liver, fat, muscle, skin, and breast tissues**, including breast malignancies.
- Peripheral aromatization is an important source of estrogen in **postmenopausal** women.
- Aromatase inhibitors **decrease** the production of **estrogen** in these women.



C. Aromatase inhibitors

1. Anastrozole and letrozole:

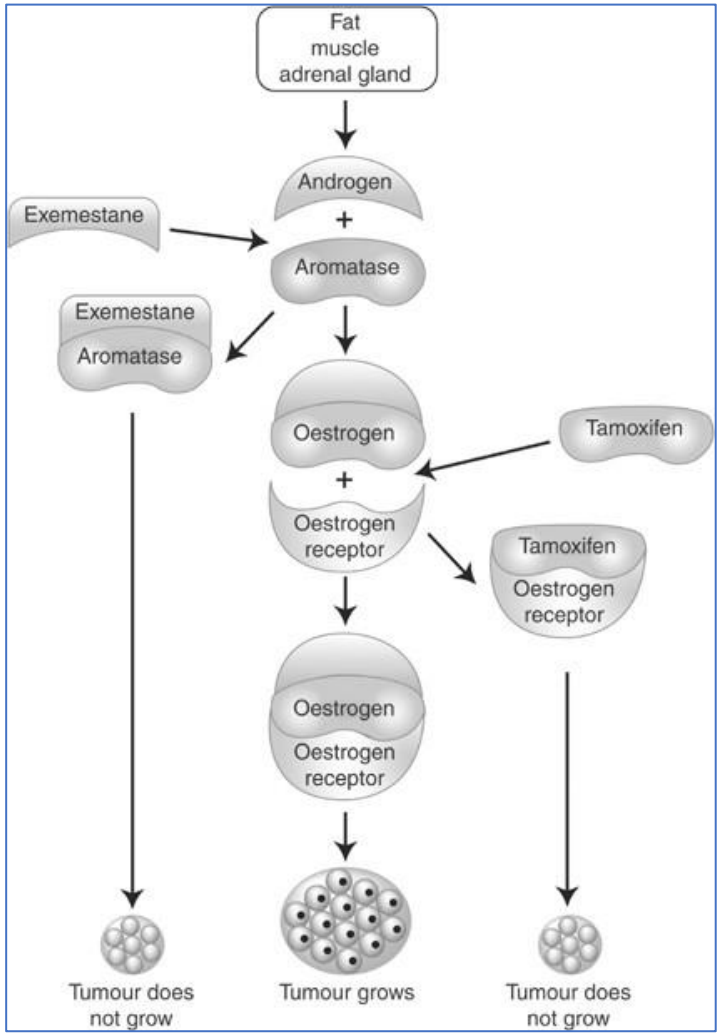
- Anastrozole an letrozole are **nonsteroidal aromatase inhibitors.**
- These agents are considered **first-line** drugs for the treatment of **breast cancer** in **postmenopausal** women.
- They are **orally** active and cause almost a **total suppression** of estrogen synthesis.
- Anastrozole and letrozole **do not predispose** patients to **endometrial cancer**.
- **Both** drugs are extensively **metabolized** in the **liver** and metabolites and parent drug are **excreted** primarily in the **urine**.



C. Aromatase inhibitors

2. Exemestane:

- A **steroidal, irreversible inhibitor** of aromatase, exemestane, is well absorbed after **oral** administration and **widely distributed**.
- **Hepatic metabolism** occurs via the CYP3A4 isoenzyme.
- Because the metabolites are **excreted** in **urine**, **doses** of the drug must be **adjusted** in patients with **renal failure**.
- Major toxicities are <u>nausea, fatigue, and hot flashes</u>.
- **Alopecia** and **dermatitis** have also been noted

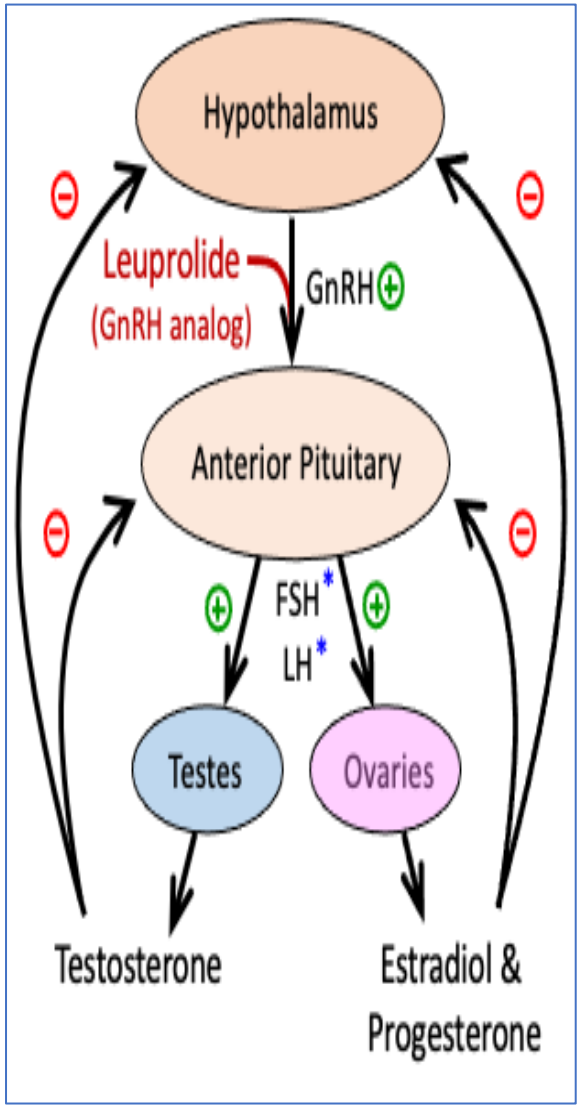


D. Leuprolide, goserelin, and triptorelin

- Gonadotropin-releasing hormone (**GnRH**) is normally **secreted** by the **hypothalamus**.
- GnRH **stimulates** the **anterior pituitary** to secrete the following **gonadotropic hormones**:

1. **LH** which **stimulates** the secretion of **testosterone** by the testes.
2. **FSH** which **stimulates** the secretion of **estrogen**.

- **Leuprolide, goserelin, and triptorelin** are **synthetic analogs of GnRH**.
- As GnRH analogs, they **occupy the GnRH receptor** in the **pituitary**, which leads to its **desensitization** and, consequently, **inhibition** of the **release of FSH and LH**.
- Thus, **both androgen** and **estrogen** synthesis are **reduced**.

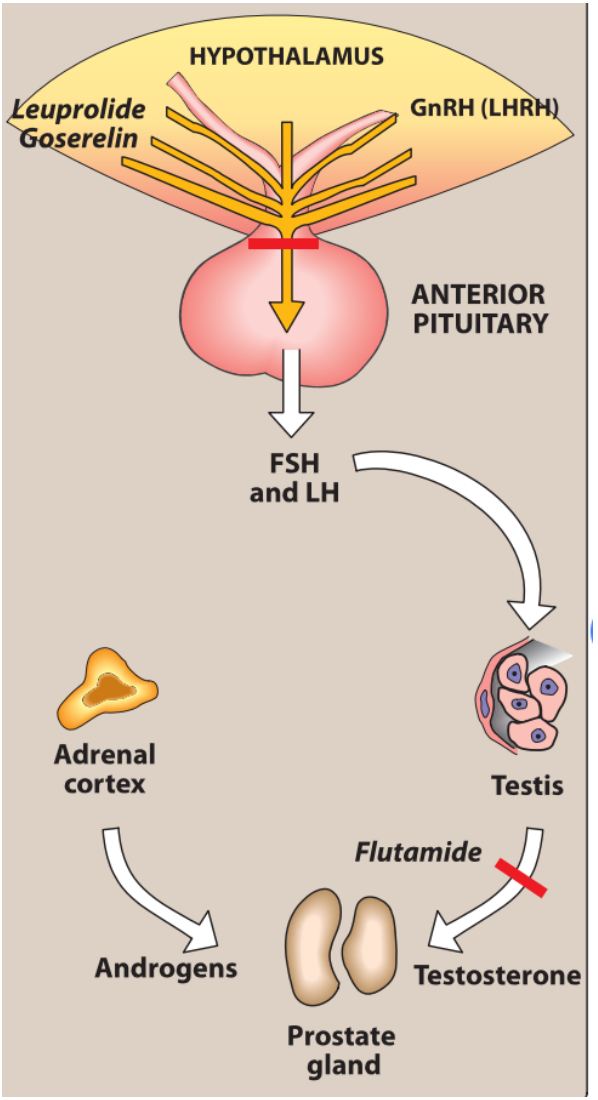


D. Leuprolide, goserelin, and triptorelin

- **Response** to **leuprolide** in **prostatic cancer** is **equivalent** to that of **orchiectomy** with regression of tumor and relief of bone pain.
- These drugs have **some benefit in premenopausal women** with advanced **breast cancer** and have largely **replaced estrogens** in therapy for **prostate cancer**.
- **Leuprolide** is available **as SC daily injection, SC depot injection, and IM depot injection** to treat **metastatic carcinoma of the prostate**.
- **Goserelin acetate** is **SC implant**, and **triptorelin pamoate** is injected **IM**.
- **Levels of androgen in prostate cancer** patients may **initially rise** but **then fall** to castration levels.
- The **adverse effects** of these drugs, including **impotence, hot flashes**, and **tumor flare**, are **minimal** compared to those experienced with estrogen treatment.

E. Antiandrogens

- **Flutamide, nilutamide, bicalutamide, and enzalutamide** are **oral** antiandrogens used in the treatment of **prostate cancer**.
- They **compete** with the natural hormone for **binding to the androgen receptor** and **prevent** its action in the prostate.
- Adverse effects include **gynecomastia, constipation, nausea, and abdominal pain**.
- **Rarely**, **liver failure** has occurred with **flutamide**.
- **Nilutamide** can cause **visual problems**.



THANK YOU FOR YOUR ATTENTION