Al-Mustaqbal University College
Department of Pharmacy
4th stage
Pharmacology III
Lecture: 3

ANTICANCER DRUGS

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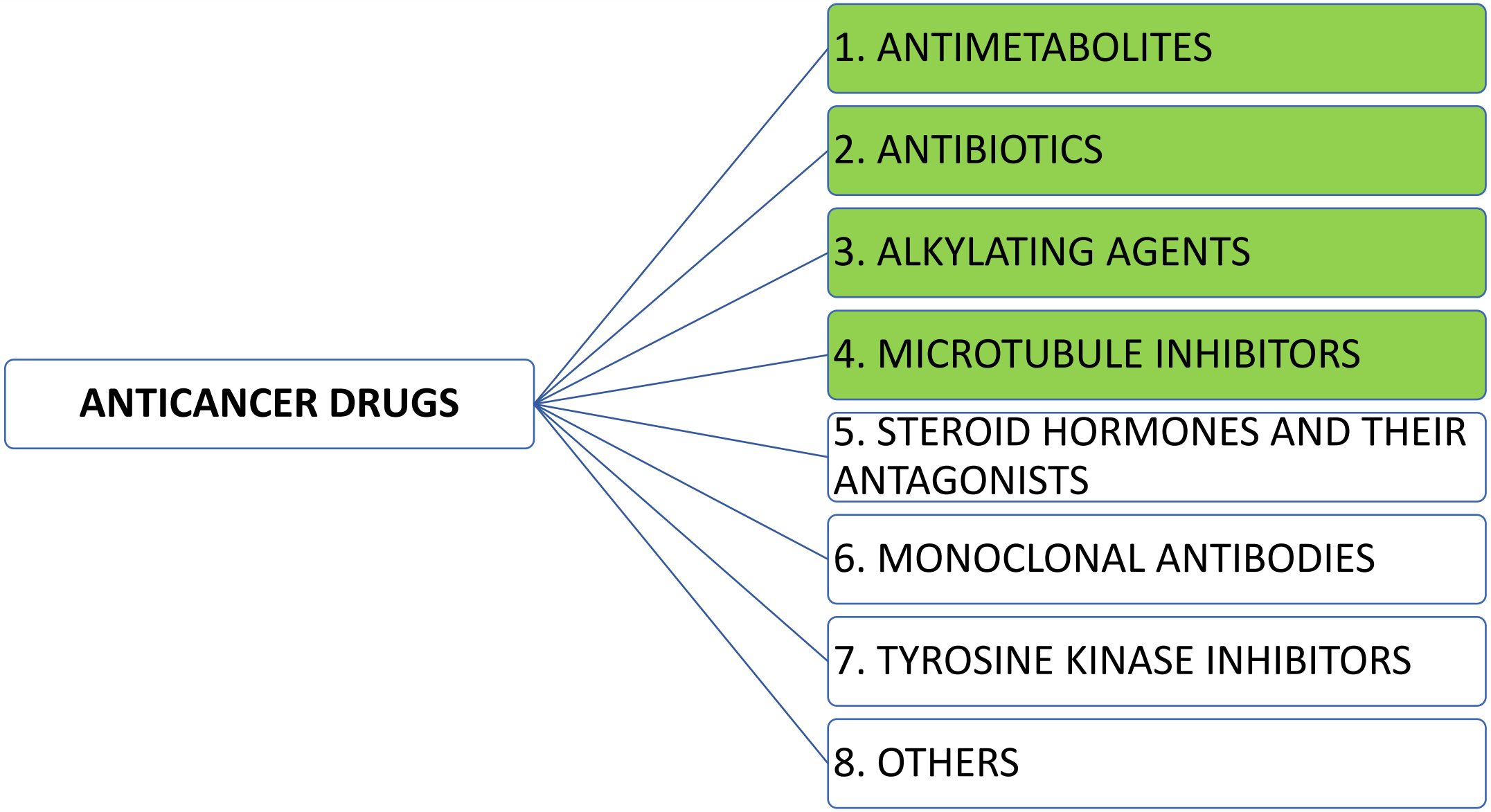
ANTICANCER DRUGS

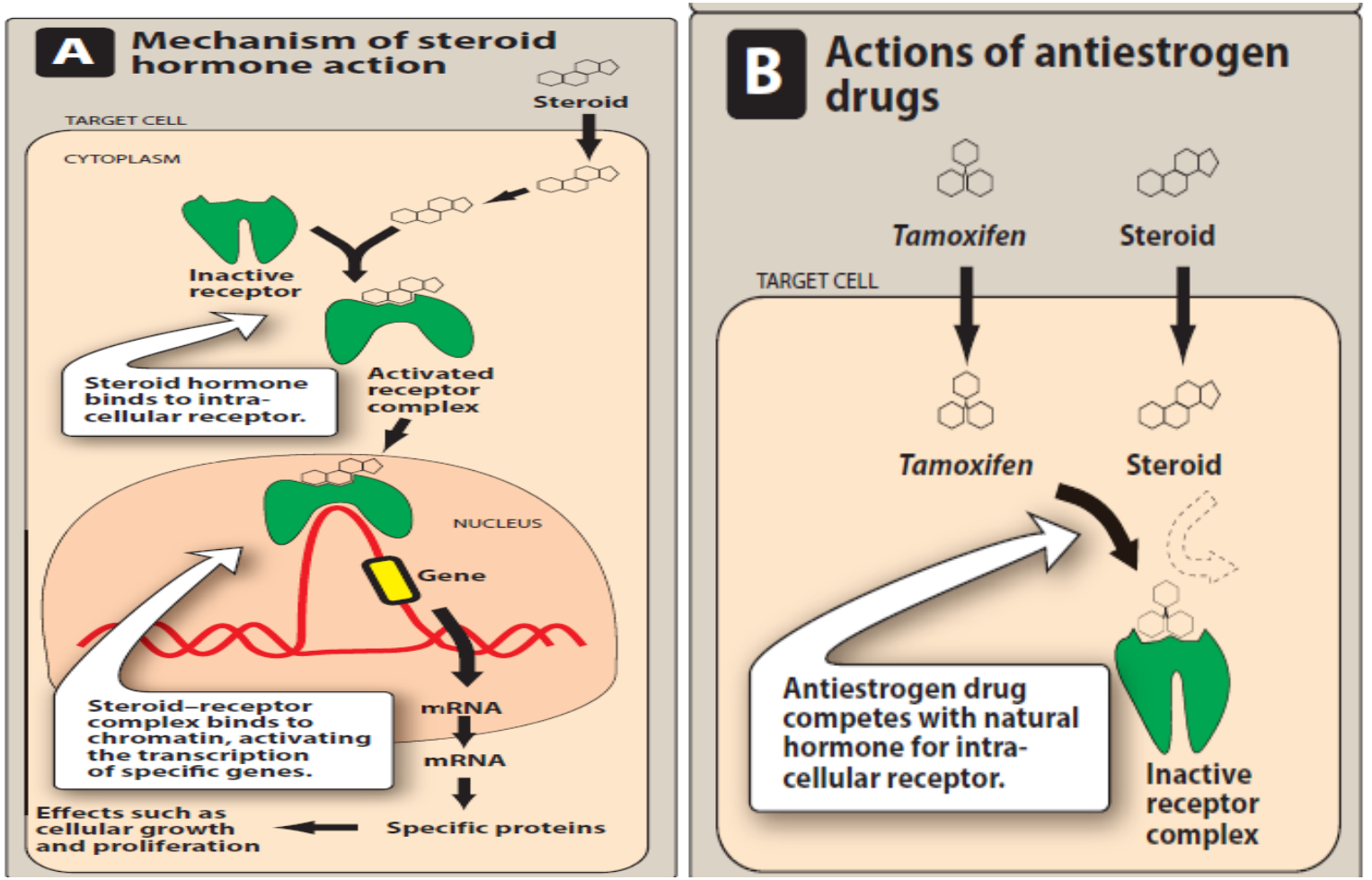


5. STEROID HORMONES AND THEIR ANTAGONISTS

- Tumors that are **steroid hormone-sensitive** may be:
  1. Either **hormone-responsive**, in which the tumor regresses following treatment with a specific hormone.
  2. Or **hormone-dependent**, in which removal of a hormonal stimulus causes tumor regression.
  3. or **both**.
- **Removal of hormonal stimuli** from hormone-dependent tumors can be accomplished:
  1. either by **surgery** (for example, in the case of **orchiectomy**—surgical removal of one or both testes—for patients with advanced prostate cancer)
  2. or by **drugs** (for example, in breast cancer, for which treatment with the antiestrogen **tamoxifen** is used to prevent estrogen stimulation of breast cancer cells.

5. STEROID HORMONES AND THEIR ANTAGONISTS

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

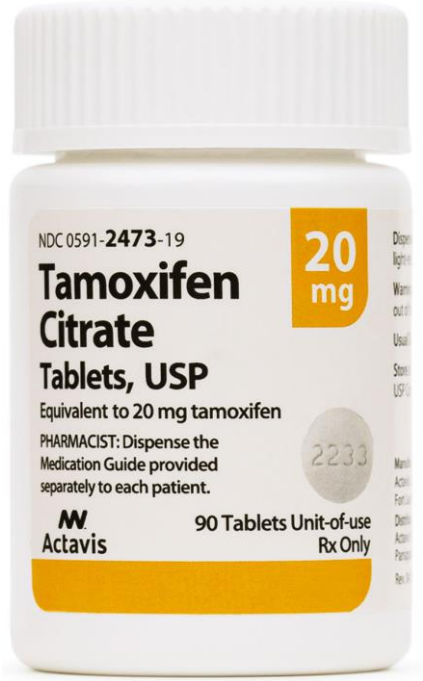


A. Prednisone

- It is a **potent, synthetic, anti-inflammatory** corticosteroid with **less mineralocorticoid** activity than cortisol.
- **Prednisone** is primarily employed to **induce remission** in patients with **ALL** and in the treatment of **both Hodgkin and non-Hodgkin lymphomas**.
- Prednisone is readily absorbed **orally,** also it is bound to plasma **albumin** and **transcortin**.
- Prednisone itself is **inactive** and must first undergo **11-β-hydroxylation** to **prednisolone** in the liver.
- **Prednisolone** is the active drug, that **binds to a receptor** that triggers the production of specific proteins.
- The latter is **glucuronidated** and **excreted in urine** along with the parent compound.

B. Tamoxifen

- Tamoxifen is an **estrogen antagonist** with some **estrogenic activity**, and it is classified as a selective estrogen receptor modulator (**SERM**).
- It is used for **first-line therapy** in the treatment of **estrogen receptor-positive breast cancer**.
- It also finds use **prophylactically** in reducing breast cancer occurrence in women who are at high risk.
- However, because of **possible stimulation of premalignant lesions** due to its estrogenic properties, patients should be closely **monitored** during therapy



B. Tamoxifen

1. Mechanism of action:

- Tamoxifen **binds to estrogen receptors** in the breast tissue, but the **complex is unable to translocate** into the **nucleus** for its action of initiating transcriptions.
- That is, the complex **fails to induce** estrogen-responsive genes, and RNA synthesis does not ensue.
- 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**.

- **2. Pharmacokinetics:**
- Tamoxifen is effective after **oral administration**, **partially metabolized** by the liver.
- Some metabolites possess **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.

B. Tamoxifen

3. Adverse effects:

- Side effects caused by tamoxifen include hot flashes, nausea, vomiting, skin rash, and vaginal bleeding and discharge (estrogenic activity).
- **Hypercalcemia** may occur, requiring cessation of the drug.
- Tamoxifen can also lead to **increased pain** if the tumor has metastasized to bone.
- Tamoxifen has the potential to cause **endometrial cancer**.
- Other toxicities include **thromboembolism** and effects on **vision**.

C. Fulvestrant and raloxifene

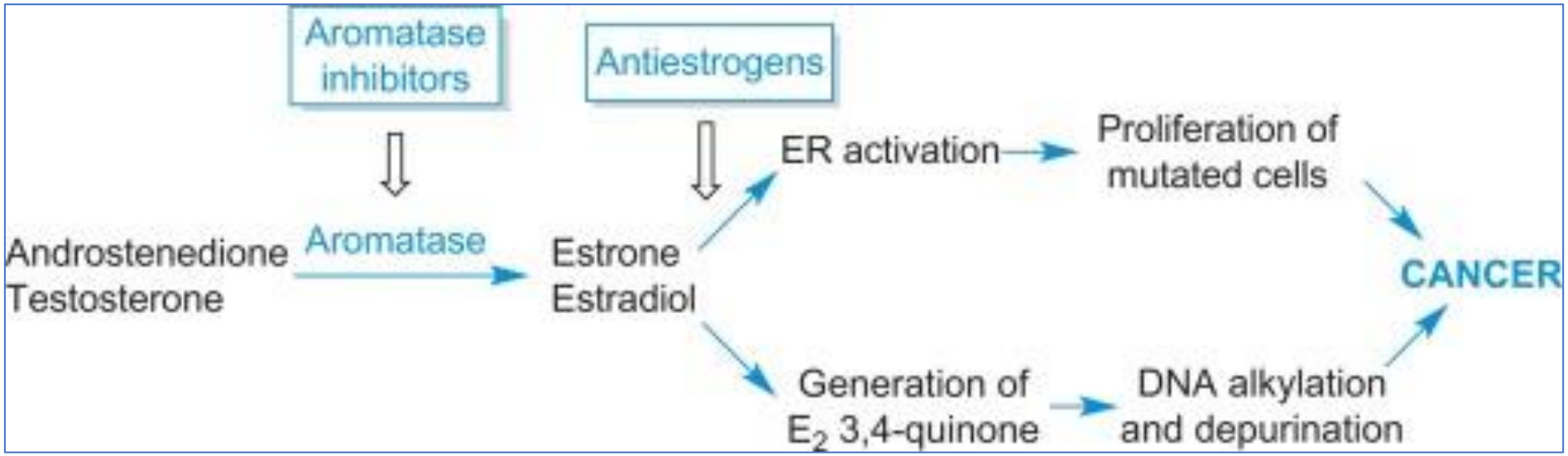
- **Fulvestrant:**
- It is an estrogen receptor antagonist that is given via **IM** injection to patients with hormone receptor-positive metastatic breast cancer.
- This agent binds to and causes estrogen **receptor down-regulation** on tumors and other targets.

- **Raloxifene:**
- It is a **SERM** given **orally** that acts to **block** estrogen effects in the **uterine and breast tissues** while **promoting** effects in the **bone to inhibit resorption**.
- This agent has been shown to **reduce the risk** of estrogen receptor–positive invasive breast cancer in **postmenopausal** women.

- Both agents are known to cause **hot flashes, arthralgias,** and **myalgias**.

D. Aromatase inhibitors

- The aromatase reaction is **responsible for the extra-adrenal synthesis of estrogen from androstenedione**, which 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.



D. Aromatase inhibitors

1. Anastrozole and letrozole:

- They are imidazole or nonsteroidal aromatase inhibitors.
- They do **not predispose** patients to **endometrial cancer** and are devoid of the **androgenic side effects** that occur with steroidal aromatase inhibitors such as **aminoglutethimide**.
- They are considered **second-line** therapy after tamoxifen for hormone-dependent breast cancer in the United States.
- Also they become **first-line** drugs in other countries for the treatment of breast cancer in postmenopausal women.
- They are **orally** active and cause almost a **total suppression** of estrogen synthesis.
- **Both** drugs are extensively **metabolized** in the **liver**, and metabolites and parent drug are **excreted** primarily in the **urine**.

D. Aromatase inhibitors

2. Exemestane:

- A **steroidal, irreversible inhibitor** of aromatase.
- Exemestane is **orally** well-absorbed and **widely** distributed.
- **Hepatic** metabolism is by the CYP3A4 isoenzyme.
- **Because** the metabolites are excreted in the **urine**, doses of the drug must be **adjusted** in patients with **renal failure**.
- Its major toxicities are **nausea, fatigue, and hot flashes**.
- **Alopecia** and **dermatitis** have also been noted.

E. Progestins

- **Megestrol acetate** is a progestin that was widely used in treating metastatic hormone-responsive breast and endometrial neoplasms.
- It is **orally** effective.
- Other agents are usually **compared** to it in clinical trials; however, **aromatase inhibitors** are replacing it in therapy.

F. Leuprolide, goserelin, and triptorelin

- **GnRH** is normally secreted by the hypothalamus and stimulates the anterior pituitary to secrete the gonadotropic hormones:
- 1) **luteinizing hormone (LH),** the primary stimulus for the secretion of testosterone by the testes.
- 2) **follicle-stimulating hormone (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**.
- Response to **leuprolide in prostatic cancer** is **equivalent** to that of **orchiectomy** with regression of tumor and relief of bone pain.

F. Leuprolide, goserelin, and triptorelin

- **Leuprolide** is available as:
- 1) a sustained-release intradermal implant.
- 2) a subcutaneous depot injection.
- 3) an intramuscular depot injection to treat metastatic carcinoma of the prostate.

- **Goserelin acetate** is a subcutaneous implant, and **triptorelin pamoate** is injected intramuscularly.
- Levels of androgen 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.

6. MONOCLONAL ANTIBODIES

- Monoclonal antibodies have become an **active area** of drug development because they are **directed at specific targets** and often have **fewer adverse effects.**
- They are created from **B lymphocytes** (from immunized mice or hamsters) **fused** with **"immortal" B-lymphocyte tumor cells**.
- The resulting **hybrid cells** can be individually **cloned**, and each clone will produce **antibodies** directed against a **single antigen type**.
- **Recombinant** technology has led to the creation of **"humanized"** antibodies that overcome the **immunologic problems** previously observed following the administration of mouse (murine) antibodies.
- Many other monoclonal antibody therapies such as **trastuzumab**, **rituximab**, **bevacizumab**, and **cetuximab** in the treatment of cancer.

A. Trastuzumab

- In patients with **metastatic breast cancer**, overexpression of **transmembrane** human epidermal growth factor receptor protein 2 (**HER2**) is seen in 25% to 30% of patients.
- HER2 overexpression is **also noted** in **gastric** and **gastroesophageal cancers**.
- Trastuzumab, a **humanized monoclonal antibody**, specifically targets the **extracellular domain** of the **HER2** growth receptor that has **intrinsic tyrosine kinase activity**.

- [Note: At least **50 tyrosine kinases** mediate cell growth or division by phosphorylating signaling proteins.
- They have been implicated in the **development** of many **neoplasms** by an unknown mechanism.]

A. Trastuzumab

1. Mechanism of action:

- Trastuzumab **binds to HER2** sites in breast cancer, gastric cancer, and gastroesophageal tissues and **inhibits the proliferation** of cells that overexpress the HER2 protein, thereby **decreasing** the number of cells in **the S-phase**.
- By binding to HER2, it **blocks downstream signaling pathways**, induces antibody-dependent **cytotoxicity**, and prevents the **release of HER2**.

2. Adverse effects:

- The most serious toxicity associated with the use of trastuzumab is **congestive heart failure**.
- The toxicity is worsened if given in combination with **anthracyclines**.
- **Extreme caution** should be exercised when giving the drug to patients with **preexisting cardiac dysfunction**.

B. Rituximab

- Rituximab was the **first monoclonal antibody** to be approved for the treatment of cancer.
- It is a genetically **engineered, chimeric** monoclonal antibody directed against the **CD20 antigen** that is found on the **surfaces** of normal and malignant **B lymphocytes**.
- **CD20** plays a role in the activation process for **cell cycle initiation** and **differentiation**.
- The CD20 antigen is expressed on **nearly all B-cell** non-Hodgkin **lymphomas** but **not in** other **bone marrow cells**.
- Rituximab is **effective** in the treatment of **lymphomas**, **CLL**, and **rheumatoid arthritis**.
- **Fatal** severe adverse reactions may occur and It is important to **infuse** rituximab **slowly**.
- Hypotension, bronchospasm, and angioedema may occur. Chills and fever commonly accompany the **first infusion.**

7. PLATINUM COORDINATION COMPLEXES

- **Cisplatin** was the **first** member of the platinum coordination complex class of anticancer drugs, but because of its severe toxicity, carboplatin was developed.
- **Cisplatin** has **synergistic** cytotoxicity with **radiation** and **other** chemotherapeutic agents.
- It has found **wide application** in the treatment of **solid tumors**, such as metastatic testicular carcinoma in combination with VBL and bleomycin, ovarian carcinoma in combination with cyclophosphamide, or alone for bladder carcinoma.

- **Carboplatin** is used when patients **cannot** be vigorously hydrated, **as is required for cisplatin** treatment, or if they suffer from **kidney dysfunction** or are prone to **neuro- or ototoxicity**.
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- **Oxaliplatin** is a closely related **analog of carboplatin** used in the setting of **colorectal cancer**.

7. PLATINUM COORDINATION COMPLEXES

1. Mechanism of action:

- The mechanism of action for this class of drugs is **similar** to that of the **alkylating agents**.
- In the **high-chloride** milieu of the plasma, cisplatin persists as the **neutral species**, which **enters** the cell and **loses** its chlorides in the **low-chloride** milieu.
- It then **binds to guanine** in DNA, forming **inter-** and **intrastrand** crosslinks.
- The resulting cytotoxic lesion **inhibits both** polymerases for DNA replication and RNA synthesis.
- Cytotoxicity can occur at **any stage** of the cell cycle, but cells are most **vulnerable** to the actions of these drugs in the **G1 and S-phases**.

7. PLATINUM COORDINATION COMPLEXES

2. Pharmacokinetics:

- These agents are administered via **IV infusion,** Cisplatin, and carboplatin can also be given **intraperitoneally** for ovarian cancer and **intra-arterially** to perfuse other organs.
- The **highest concentrations** of the drugs are found in the liver, kidney, intestinal, testicular, and ovarian cells, but **little** penetrates into the **CSF**.
- **The renal route** is the main avenue for **excretion**.

7. PLATINUM COORDINATION COMPLEXES

3. Adverse effects:

- **Severe, persistent vomiting** occurs for at least **1 hour after** administration of cisplatin and may continue for **as long as 5 days**. Premedication with **antiemetic** agents is required.
- The major limiting toxicity is dose-related **nephrotoxicity**, involving the distal convoluted tubule and collecting ducts. This can be prevented by **aggressive hydration**.
- Other toxicities include **ototoxicity** with high-frequency **hearing loss and tinnitus**.
- Unlike cisplatin, **carboplatin** causes only **mild nausea and vomiting** and it is **rarely nephro-, neuro-, or ototoxic**. Its dose-limiting toxicity is **myelosuppression**.
- **Oxaliplatin** has a distinct side effect of **cold-induced peripheral neuropathy** that usually resolves within **72 hours** of administration.
- It also causes **myelosuppression** and cumulative peripheral **neuropathy**. **Hepatotoxicity** has also been reported.
- These agents may cause **hypersensitivity** reactions ranging from **skin rashes to anaphylaxis**.

8. TOPOISOMERASE INHIBITORS

A. Camptothecins

- Camptothecins **are plant alkaloids** originally isolated from the Chinese tree **Camptotheca**.
- **Irinotecan** and **topotecan** are **semisynthetic** derivatives of camptothecin.
- **Topotecan** is used in **metastatic ovarian cancer** when primary therapy has failed and also in the treatment of **small-cell lung cancer**.
- **Irinotecan** is used **with 5-FU and leucovorin** for the treatment of **colorectal carcinoma**.

8. TOPOISOMERASE INHIBITORS

1. Mechanism of action:

- These drugs are **S-phase specific** and **inhibit topoisomerase I**, which is **essential for the replication of DNA in human cells**.
- **SN-38** (the active metabolite of irinotecan) is **approximately 1000** times as potent as irinotecan as an inhibitor of topoisomerase I.
- The **topoisomerases** relieve **torsional strain** in DNA by causing **reversible, single-strand breaks**.

2. Adverse effects:

- **Bone marrow suppression**, particularly **neutropenia**, is the dose-limiting toxicity for topotecan.
- Frequent blood counts should be performed on patients taking this drug.
- **Myelosuppression** is also seen with **irinotecan**.
- **Acute and delayed diarrhea** may be severe and require treatment with atropine during the infusion or high doses of loperamide in the days following the infusion.

8. TOPOISOMERASE INHIBITORS

B. Etoposide

- Etoposide is a **semisynthetic** derivative of the plant alkaloid, **podophyllotoxin**.
- It blocks cells in the **late S- to G2 phase** of the cell cycle.
- Its major target is **topoisomerase II**.
- Etoposide finds its major clinical use in the treatment of **lung cancer** and in **combination** with **bleomycin** and **cisplatin for testicular carcinoma**.
- Etoposide may be administered either **IV or orally**.
- Dose-limiting **myelosuppression** (primarily **leukopenia**) is the major toxicity.

9. TYROSINE KINASE INHIBITORS

A. Imatinib, dasatinib, and nilotinib:

- **Imatinib mesylate** is used for the treatment of **CML** as well as **GI stromal tumors**.
- It acts as a signal **transduction inhibitor**, used specifically to **inhibit tumor tyrosine kinase** activity.
- The ability of imatinib to **occupy the "kinase pocket"** prevents the **phosphorylation** of tyrosine on the substrate molecule and, hence, **inhibits subsequent** steps that lead to cell **proliferation**.
- **Nilotinib** and **dasatinib** are also **first-line** options for **CML**.
- These agents are all available in **oral formulations**, and they are associated with notable **toxicities**, such as **fluid retention and QT prolongation**.

9. TYROSINE KINASE INHIBITORS

B. Erlotinib:

- **Erlotinib** is an **inhibitor** of the **epidermal growth factor receptor tyrosine kinase**.
- It is an **oral agent** approved for the treatment **of non–small cell lung cancer** and **pancreatic cancer**.
- Erlotinib is **absorbed** after oral administration and undergoes **extensive metabolism** in the liver by the CYP3A4 isoenzyme.
- The most **common adverse effects** are diarrhea, nausea, acne-like skin rashes, and ocular disorders.
- A **rare but potentially fatal** adverse effect is an **interstitial lung disease**, which presents as acute dyspnea with cough.

THANK YOU FOR YOUR ATTENTION