Al-Mustaqbal University
College of Pharmacy
4th stage
Pharmacology III
Lecture: 8

ANTICANCER DRUGS IV

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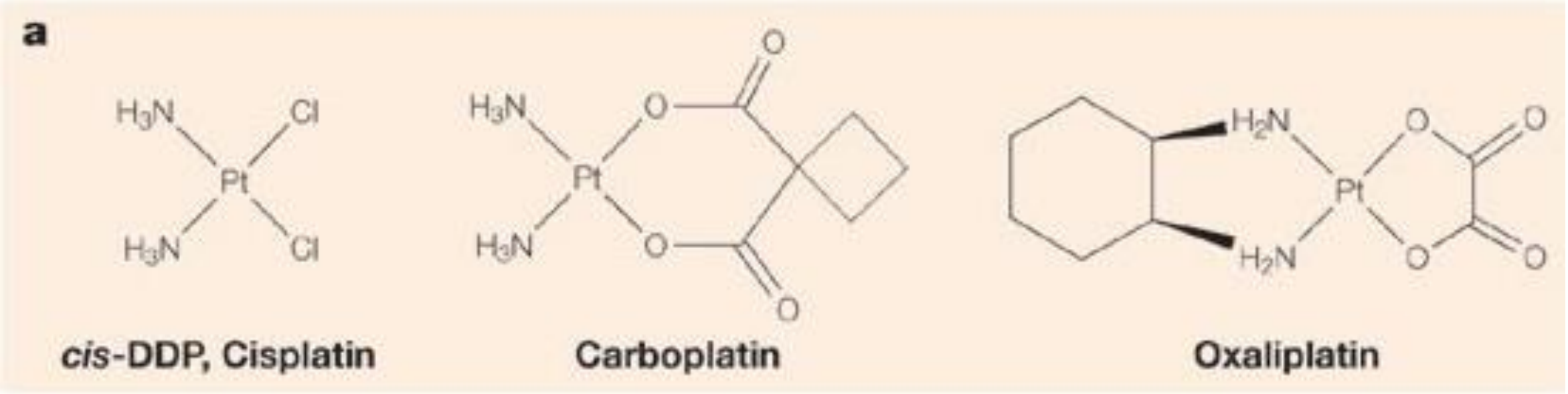
VI. PLATINUM COORDINATION COMPLEXES

- Platinum coordination complexes are a **class of chemical compounds** that **contain platinum as a central metal ion surrounded** by a **coordinated group of ligands**.
- These include **cisplatin, carboplatin, and oxaliplatin**.
- These compounds exhibit **similar mechanisms** of action, **but with different** chemical properties and side effect profiles.



cis-DDP, Cisplatin Carboplatin Oxaliplatin

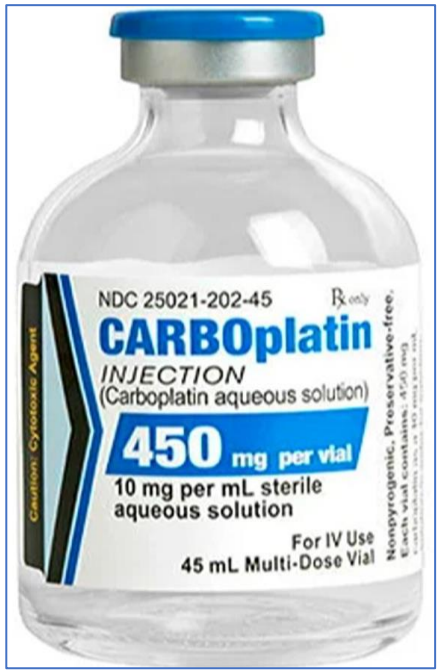
VI. PLATINUM COORDINATION COMPLEXES

- **Cisplatin** was the **first** member of the platinum coordination complex class of anticancer drugs, but because of **severe toxicity**, **carboplatin** was developed.
- **Cisplatin** has **synergistic cytotoxicity** with **radiation** and other **chemotherapeutic agents**.
- It has found **wide application** in the treatment of:

1. **Solid tumor**, such as **metastatic testicular carcinoma** in **combination** with **VBL and bleomycin.**
2. **Ovarian carcinoma** in **combination** with **cyclophosphamide.**
3. **Alone** for **bladder carcinoma**.

VI. PLATINUM COORDINATION COMPLEXES

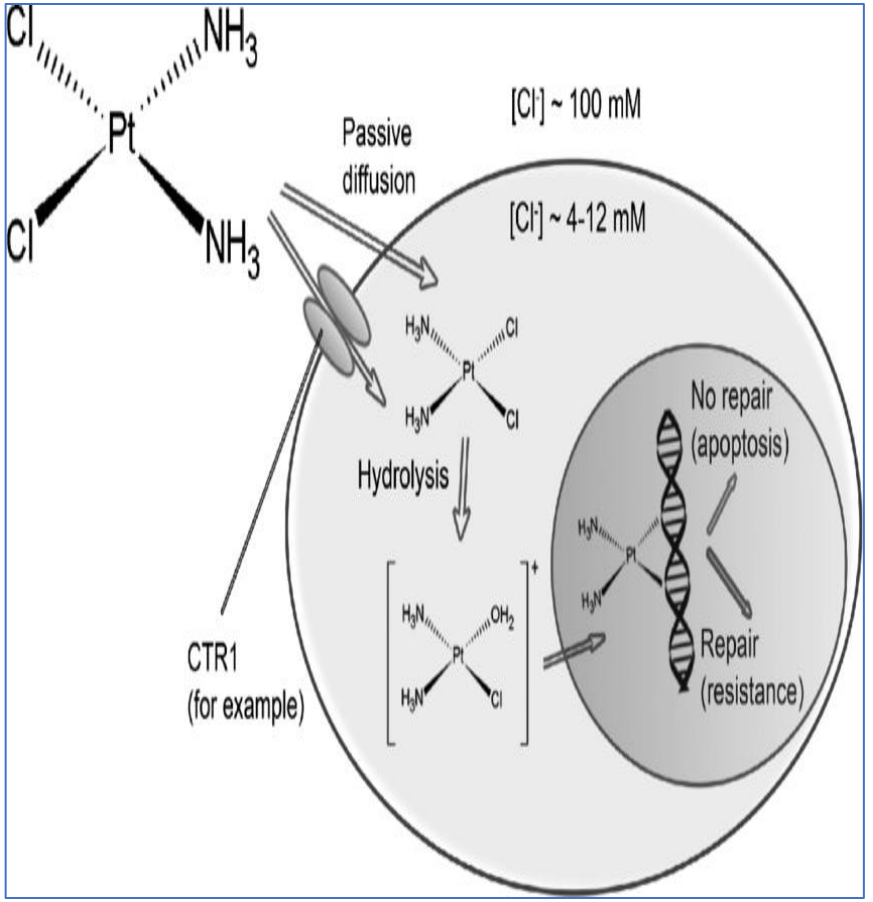
- **Carboplatin** is **used** when patients **cannot be vigorously hydrated**, as is required for **cisplatin** treatment, or if they suffer from **kidney dysfunction** or are **prone to neuro- or ototoxicity**.
- **Oxaliplatin** is a closely related **analog of carboplatin** used in the setting of **colorectal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



VI. PLATINUM COORDINATION COMPLEXES

1. Mechanism of action:

- The mechanism of action for these agents 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 chloride** in the **low-chloride** milieu.
- It **then binds** to **guanine** in DNA, forming **inter- and intrastrand cross-links**.
- 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**.



VI. PLATINUM COORDINATION COMPLEXES

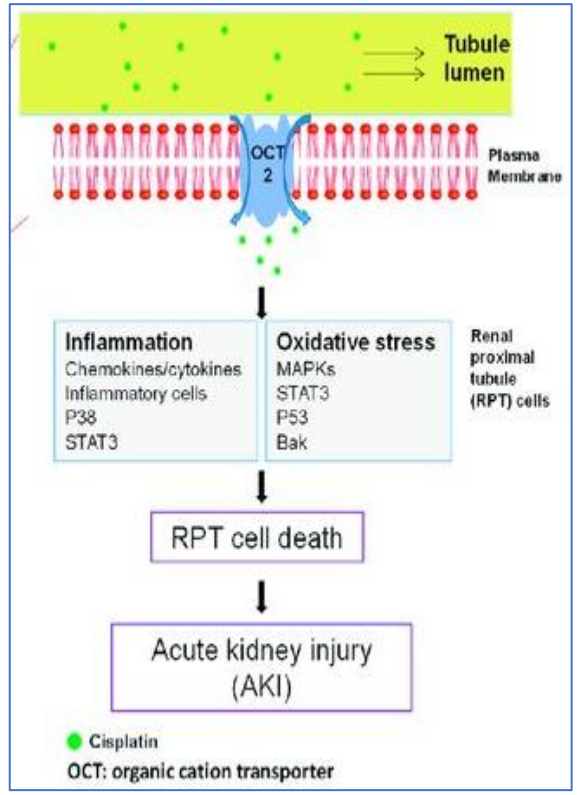
2. Pharmacokinetics:

- These agents are administered via **IV infusion**.
- **Cisplatin** and **carboplatin** can also be given **intraperitoneally** for **ovarian cancer** and i**ntra-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 CSF**.
- The **renal route** is the main pathway of **excretion**.

VI. PLATINUM COORDINATION COMPLEXES

3. Adverse effects:

- **Severe nausea and vomiting** occur in most patients **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.



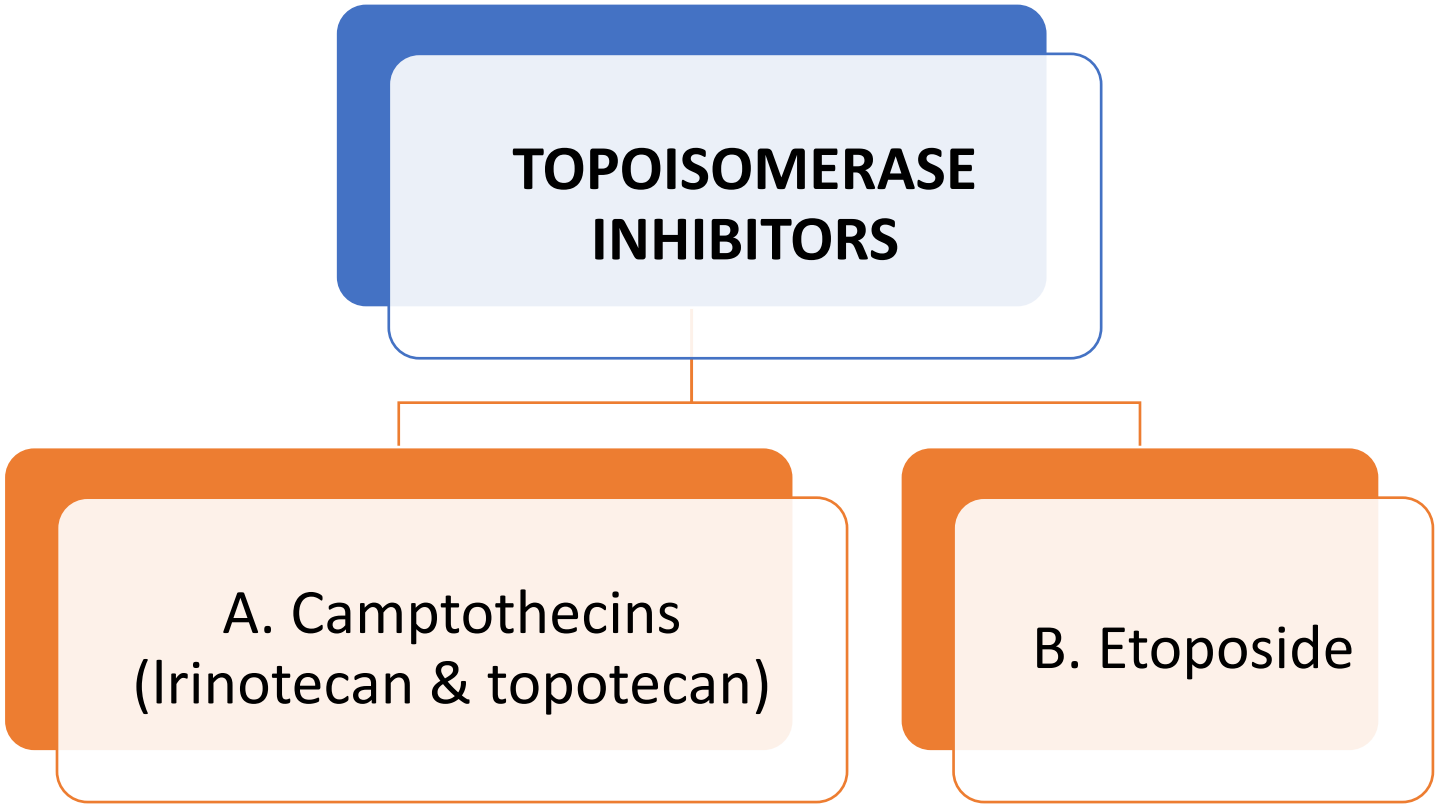
VI. PLATINUM COORDINATION COMPLEXES

3. Adverse effects:

- **Unlike**, cisplatin, **carboplatin** causes **only mild nausea and vomiting**, and it is **rarely nephro-, neuro-, or ototoxic**.
- The dose-limiting toxicity is **myelosuppression**.
- **Oxaliplatin** has a **distinct** adverse 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**.

VII. TOPOISOMERASE INHIBITORS

- These agents exert their **mechanism** of action via the **inhibition of topoisomerase enzymes**, a class of enzymes that **reduce the supercoiling of DNA.**



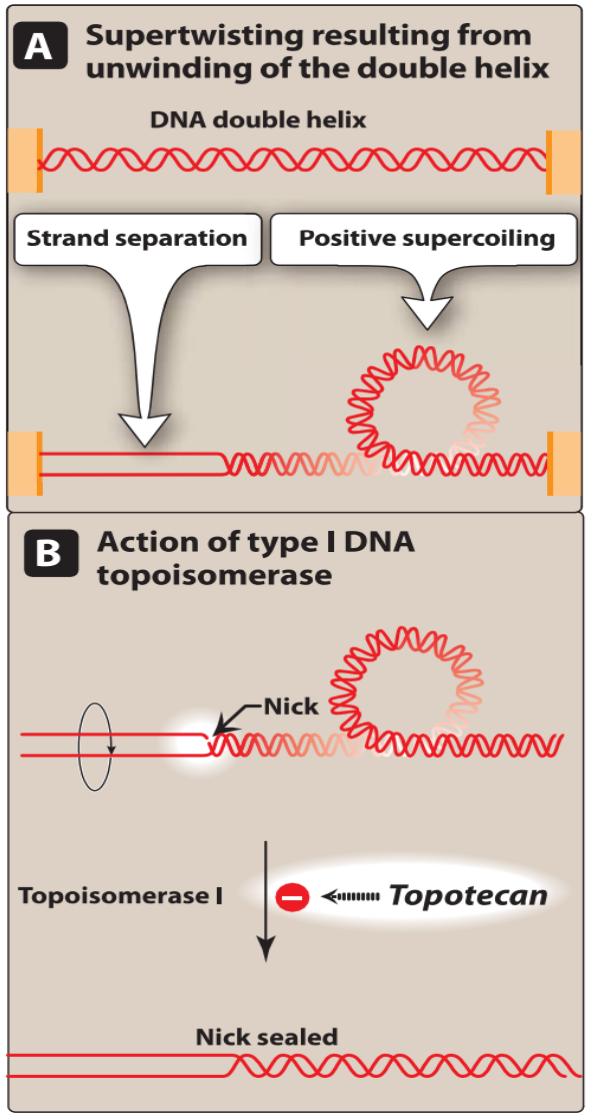
A. Camptothecins

- **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**.

A. Camptothecins

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**.



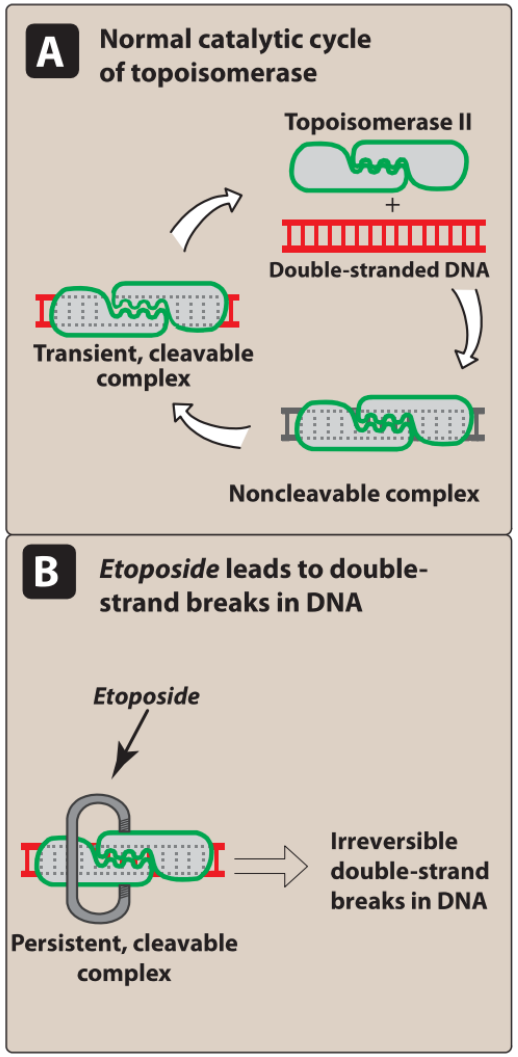
A. Camptothecins

2. Adverse effects:

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

B. Etoposide

- **Etoposide** is a **semisynthetic derivative** of the plant alkaloid, **podophyllotoxin**.
- This agent **blocks** cells in the **late S to G2 phase** of the cell cycle, and the major target is **topoisomerase II**.
- **Binding** of the drug to the **enzyme-DNA complex** results in the **persistence** of the **transient**, **cleavable form** of the **complex** and, thus, renders it susceptible to **irreversible double-strand breaks.**
- 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.

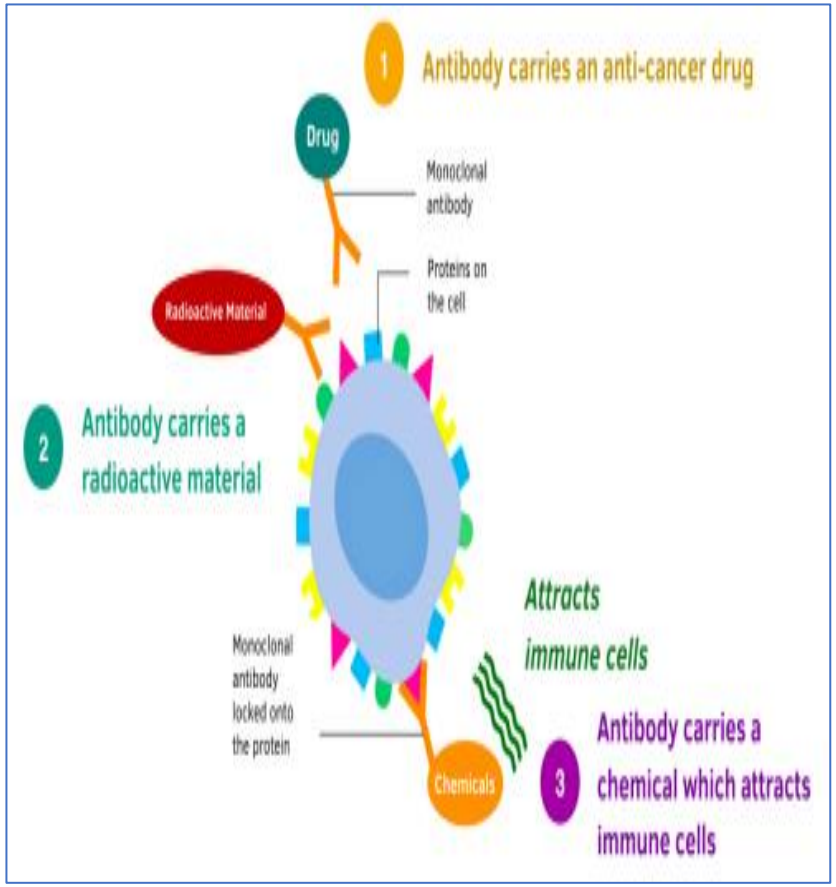


VIII. MONOCLONAL ANTIBODIES

- **Monoclonal antibodies** are an **active area of drug development** for **anticancer** therapy and other **nonneoplastic** diseases **because** they are:

1. **Directed** at **specific targets**
2. Often have **different adverse effect profiles** as compared to traditional chemotherapy agents.

- Monoclonal antibodies also find application in a number of **other disorders**, such as **inflammatory bowel disease, psoriasis, and rheumatoid arthritis**.
- All of these agents are administered **intravenously**, and **infusion-related reactions are common**.

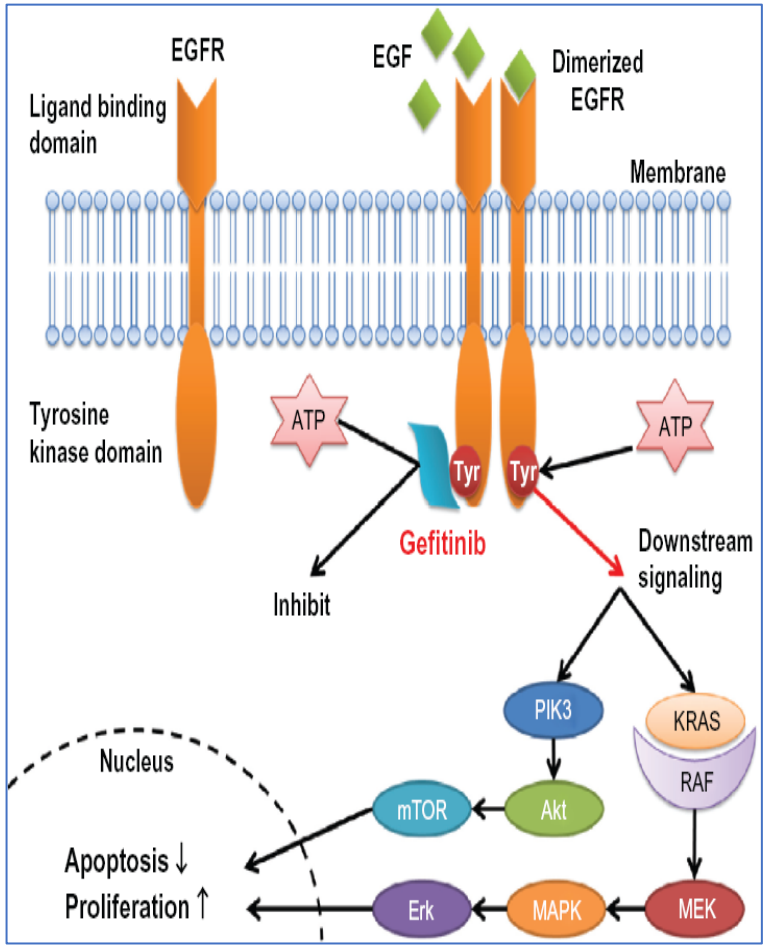


VIII. MONOCLONAL ANTIBODIES

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS	MONITORING PARAMETERS	NOTES
Bevacizumab	Binds VEGF and prevents binding of VEGF to its receptors on endothelial cells Inhibits vascularization of the tumor	Hypertension, GI perforation, proteinuria, wound healing problems, bleeding	BP, urine protein, signs and symptoms of bleeding	Hold for recent or upcoming surgical procedures
Cetuximab	Binds to EGFR and competitively inhibits the binding of epidermal growth factor and other ligands Inhibits tumor cell growth and increases apoptosis	Skin rash, electrolyte wasting, infusion reaction, diarrhea	Electrolytes, vital signs during infusion	Premedication with antihistamine required before infusion; rash equated with increased response
Daratumumab	Binds to the transmembrane protein CD38 on multiple myeloma cells and causes cell lysis	Infusion reactions, diarrhea, fatigue, pyrexia	CBC with differential, vital signs during infusion	Can bind CD38 on red blood cells Type and screen patients before starting therapy Premedication with antihistamines, antipyretics, and corticosteroids required
Ramucirumab	Binds VEGF receptor 2 and blocks binding of VEGF receptor ligands	Proteinuria, hypertension, wound healing problems, bleeding	BP, urine protein, signs and symptoms of bleeding	Hold for recent or upcoming surgical procedures
Rituximab	Targets the CD20 antigen expressed on the surface of pre-B lymphocytes and mature B lymphocytes	Fatal infusion reaction, TLS, mucocutaneous reactions, PML	Vital signs during infusion, TLS labs	Fatal reactivation of hepatitis B Premedication with antihistamine and acetaminophen required Increased risk of nephrotoxicity when given with *cisplatin*
Trastuzumab	Inhibits the proliferation of human tumor cells that overexpress HER2	Cardiomyopathy, infusion-related fever and chills, pulmonary toxicity, headache, nausea/vomiting	LVEF, CBC, pulmonary toxicity due to infusion reaction	Embryo-fetal toxicity Neutropenia in combination with chemotherapy Premedication with antihistamine and *acetaminophen* required

IX. TYROSINE KINASE INHIBITORS

- The **tyrosine kinases** are a **family** of enzymes that are **involved** in several **important processes** within a cell, including **signal transduction** and **cell division**.
- The **tyrosine kinase inhibitors** are administered **orally**, and these agents have a **wide variety of applications** in the treatment of cancer.



IX. TYROSINE KINASE INHIBITORS

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Afatinib	Inhibits EGFR tyrosine kinase	Diarrhea, rash, stomatitis, paronychia, nausea, vomiting, pruritus	P-gp inhibitors and inducers	CBC, CMP	Administer on an empty stomach Reduce dose for significant diarrhea Use effective contraception for female patients
Dabrafenib	Inhibits mutated BRAF kinases	Pyrexia, rash, arthralgia, cough, embryo-fetal toxicity	CYP3A4 inhibitors and substrates; CYP2C8 inhibitors and substrates; substrates of CYP2C9, CYP2C19, or CYP2B6	Glucose, symptoms of heart failure or bleeding, CBC, BMP, INR (if *warfarin*)	Use effective contraception for female patients Administer on empty stomach May cause new primary malignancies
Dasatinib	Inhibits BCR-ABL tyrosine kinase	Myelosuppression, fluid retention, diarrhea	CYP3A4 substrates, acid-reducing agents	CBC, BCR-ABL, electrolytes	QT prolongation
Erlotinib	Inhibits EGFR tyrosine kinase	Rash, ILD, hepatoxicity	CYP3A4 substrates, acid-reducing agents, *warfarin*	CMP	Rash equated with increased response
Ibrutinib	Inhibits Bruton tyrosine kinase	Neutropenia, thombocytopenia, diarrhea, anemia, pain, rash, nausea, bruising, fatigue, hemorrhage, pyrexia	CYP3A inhibitors and inducers	CBC, CMP, atrial fibrillation, BP, tumor lysis syndrome	Avoid grapefruit juice and Seville oranges Can cause hepatitis B reactivation Use effective contraceptive

IX. TYROSINE KINASE INHIBITORS

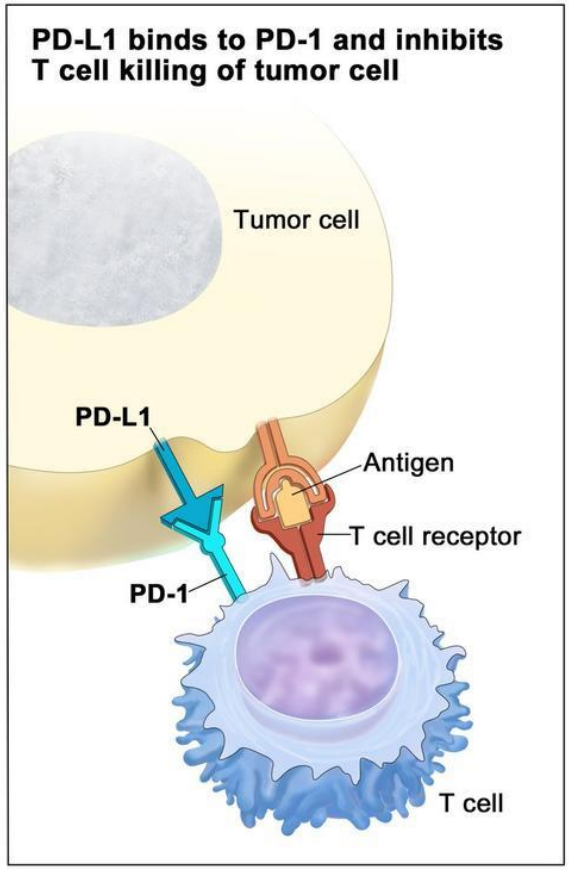
DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Idelalisib	Inhibits phosphatidylinositol 3-kinase	Diarrhea, fatigue, nausea, cough, pyrexia, abdominal pain, pneumonia, rash, neutropenia, infection	CYP3A inducers and substrates	CBC, LFTs, pulmonary symptoms, infection	Use effective contraception for female patients
Imatinib	Inhibits BCR-ABL tyrosine kinase	Myelosuppression, fluid retention, CHF	CYP3A4 substrates, *warfarin*	CBC, BCR-ABL	Monitor for development of heart failure
Nilotinib	Inhibits BCR-ABL tyrosine kinase	Myelosuppression, QT prolongation, hepatotoxicity	CYP3A4 substrates, acid-reducing agents	CBC, BCR-ABL, electrolytes	QT prolongation Administer on empty stomach
Osimertinib	Inhibits EGFR tyrosine kinase	Diarrhea, rash, dry skin, nail toxicity, fatigue	Strong CYP3A inducers	CBC, ECG, electrolytes	Use effective contraceptive for female patients
Pazopanib	Multi–tyrosine kinase inhibitor	Diarrhea, hypertension, hair color changes, nausea, anorexia, vomiting	CYP3A4 inhibitors, inducers, and substrates; CYP2D6 or CYP2C8 substrates; *simvastatin*; drugs that reduce gastric pH	ECG, electrolytes, thyroid function tests, LFTs, UA, CBC, BP	Use effective contraceptive for female patients

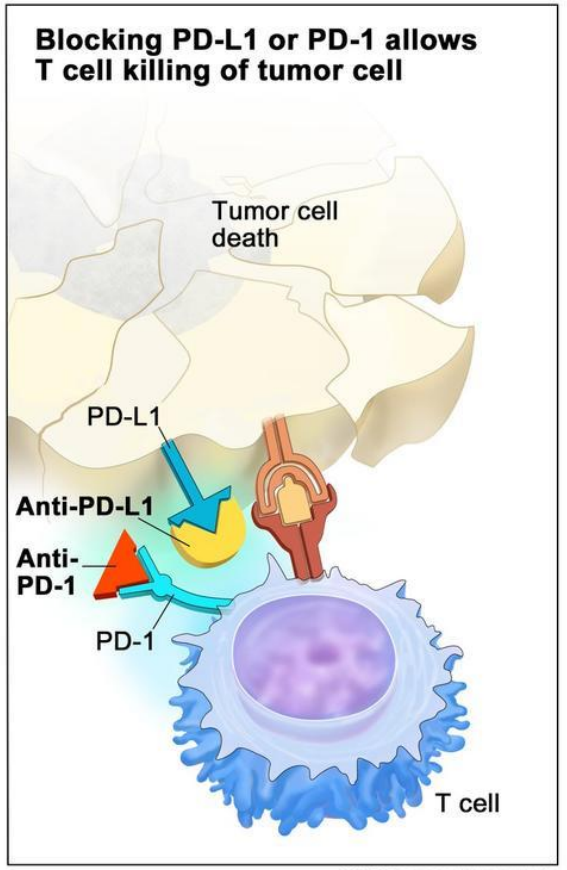
IX. TYROSINE KINASE INHIBITORS

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Sorafenib	Inhibits multiple intracellular and cell surface kinases	Hypertension, hand-foot syndrome, rash, diarrhea, fatigue	CYP3A4 inducers, *warfarin*	BP, CMP	Wound healing complications, cardiac events
Sunitinib	Multi–tyrosine kinase inhibitor	Hypertension, hand-foot syndrome, rash, diarrhea, fatigue, hepatotoxicity, hypothyroidism	CYP3A4 substrates	BP, CMP, TSH	Monitor for development of heart failure
Trametinib	Reversible inhibitor of mitogen-activated extracellular kinases	Pyrexia, rash, diarrhea, vomiting, lymphedema	CYP2C8 substrates, P-gp	Fever, new cutaneous malignancies, serum glucose, LVEF, CBC, CMP	Used in combination with *dabrafenib* Administer on empty stomach
Vemurafenib	Inhibits mutated BRAF serine-threonine kinase	Arthralgia, rash, alopecia, fatigue, photosensitivity, pruritus, skin papilloma	CYP3A4 inhibitors and inducers, CYP1A2 substrates	ECG, electrolytes, CMP, uveitis	May cause new primary cutaneous malignancies Use effective contraception in female patients

X. IMMUNOTHERAPY

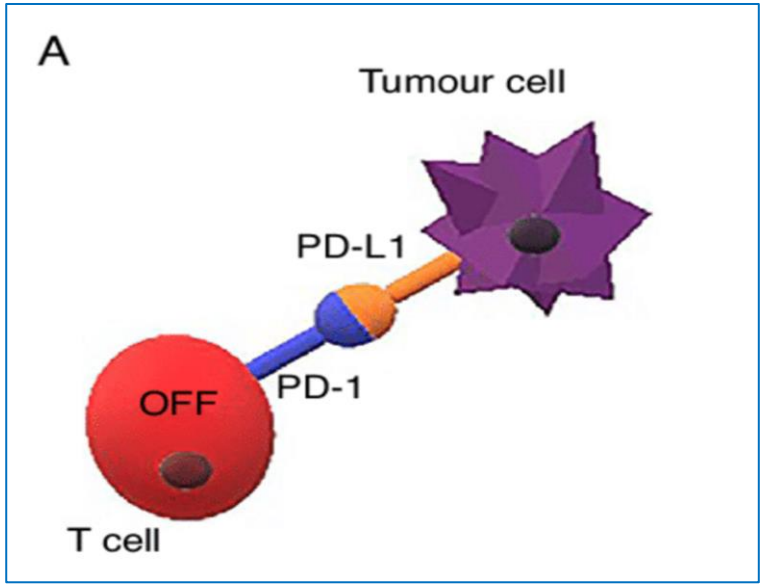
- Immunotherapy with **intravenous immune checkpoint inhibitors** is a rapidly evolving option for **cancer treatment**.
- **The goal of immune checkpoint inhibitors** is to **block** the checkpoint molecules, such as the **programmed death (PD-1) receptor**, that normally **help to keep** the immune system in check.
- **By blocking** these molecules, the **immune system** is **better able to attack** the tumor and cause **destruction**.

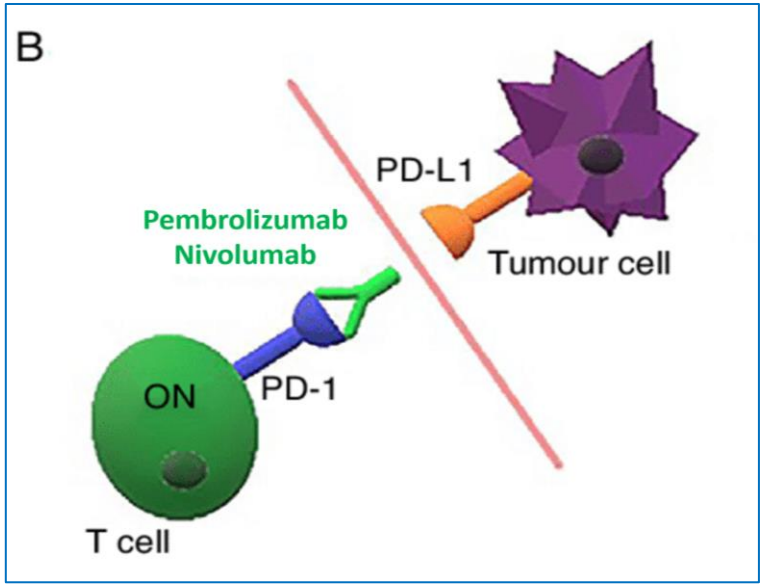




X. IMMUNOTHERAPY

- The **two most commonly** used checkpoint inhibitors are **pembrolizumab** (Keytruda®) and **nivolumab** (Opdivo®).
- The **adverse reaction profiles** of these agents consist **of potentially severe and even fatal immune-mediated** adverse events.
- This is **because** turning off the immune checkpoints **allows an attack of the tumor, but can also lead to** unchecked **autoimmune response to normal tissues.**





X. IMMUNOTHERAPY

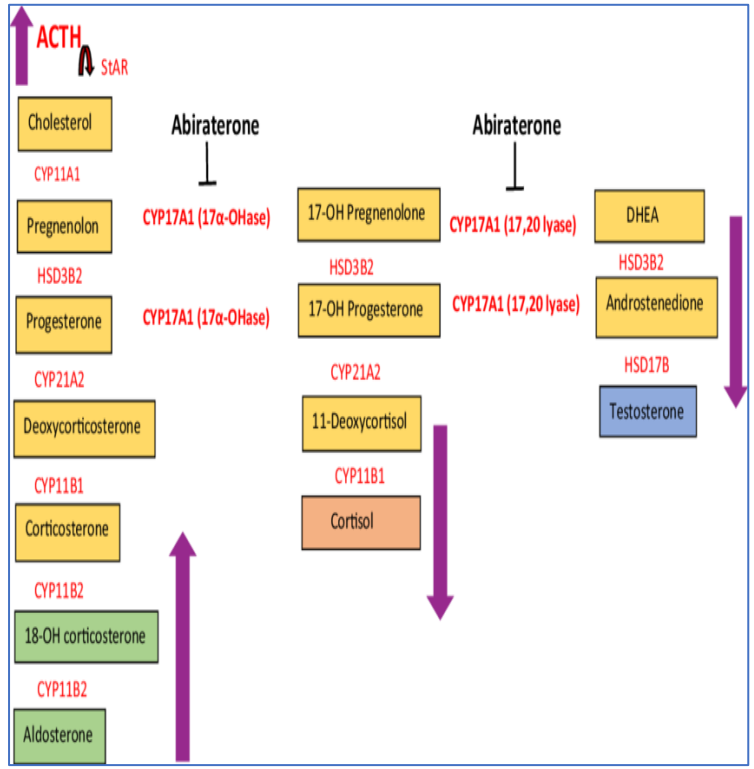
Adverse events:

- Adverse events include **diarrhea, colitis, pneumonitis, hepatitis, nephritis, neurotoxicity, dermatologic toxicity** in the form of severe skin rashes, and **endocrinopathies** such as **hypo- or hyperthyroidism**.
- **Patients** should be **closely monitored** for the potential development of signs and symptoms of toxicity and **promptly treated** with **corticosteroids** if **necessary**.

XI. MISCELLANEOUS AGENTS

A. Abiraterone acetate

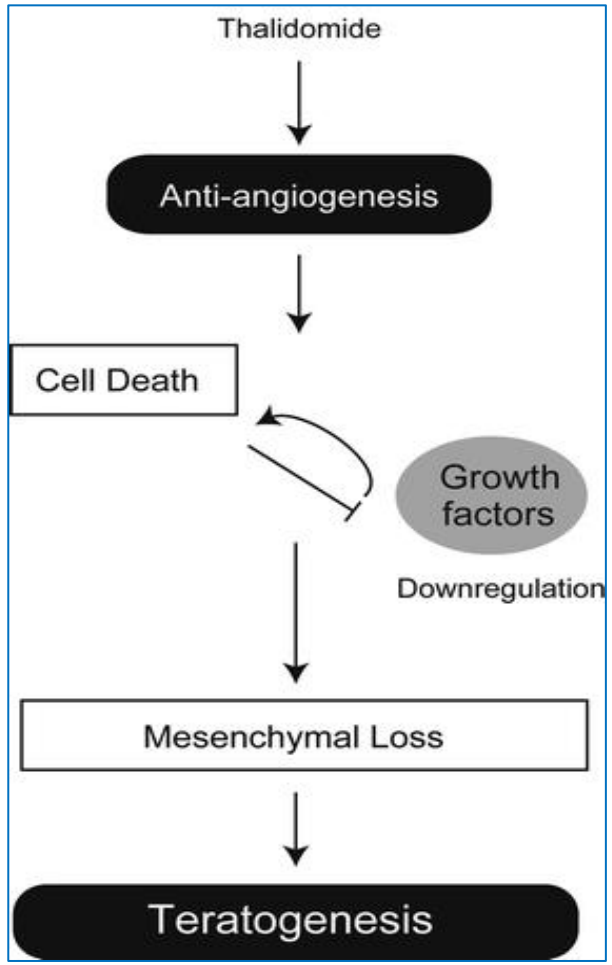
- It is an **oral agent** used in the **treatment** of metastatic castration-resistant prostate cancer **(mCRPC)**.
- It is used in **conjunction** with **prednisone** to **inhibit the CYP17 enzyme** (an enzyme required for androgen synthesis), resulting in **reduced testosterone production**.
- **Co-administration** with **prednisone** is required to help **lessen the effects of mineralocorticoid excess** resulting from CYP17 inhibition.
- **Hepatotoxicity** may occur, and patients should be **closely monitored** for **hypertension, hypokalemia, and fluid retention**.
- **Joint and muscle discomfort, hot flushes, and diarrhea** are **common** adverse effects.



XI. MISCELLANEOUS AGENTS

B. Immunomodulating Agents

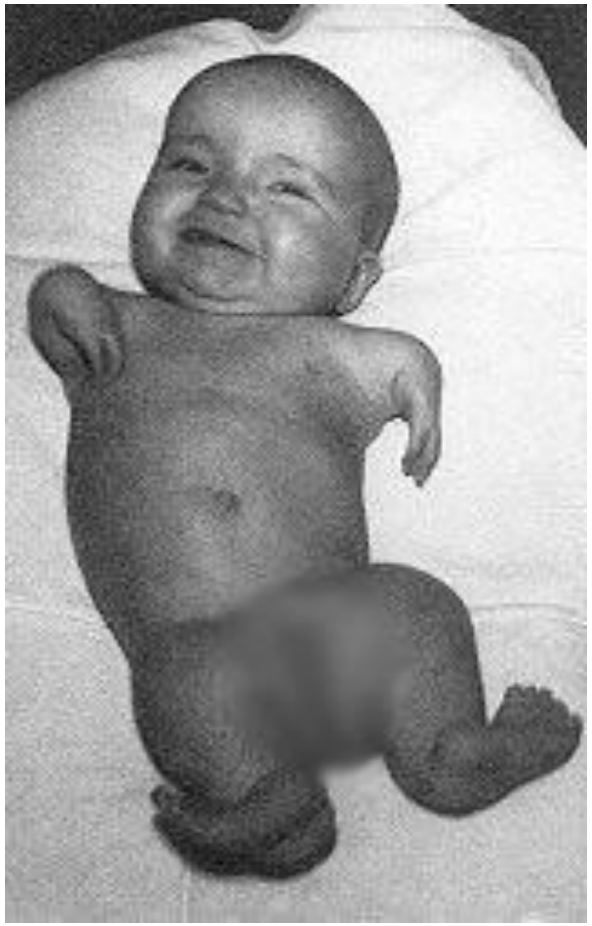
- **Thalidomide, lenalidomide, and pomalidomide** are **oral agents** used in the treatment of **multiple myeloma**.
- Their exact **mechanism** of action is **not clear**, but they **possess antimyeloma properties** including **antiangiogenic, immune-modulation, anti-inflammatory, and antiproliferative** effects.
- These agents are often **combined** with **dexamethasone** or **other** chemotherapeutic agents.



XI. MISCELLANEOUS AGENTS

B. Immunomodulating Agents Adverse Effects:

- It include **thromboembolism, myelosuppression, fatigue, rash, and constipation.**
- **Thalidomide** was **previously** given to **pregnant women** to **prevent morning sickness**.
- However, **severe birth defects** were prevalent in children born to mothers who used thalidomide.
- Because of their **structural similarities** to thalidomide, lenalidomide and pomalidomide are **contraindicated** in **pregnancy**.

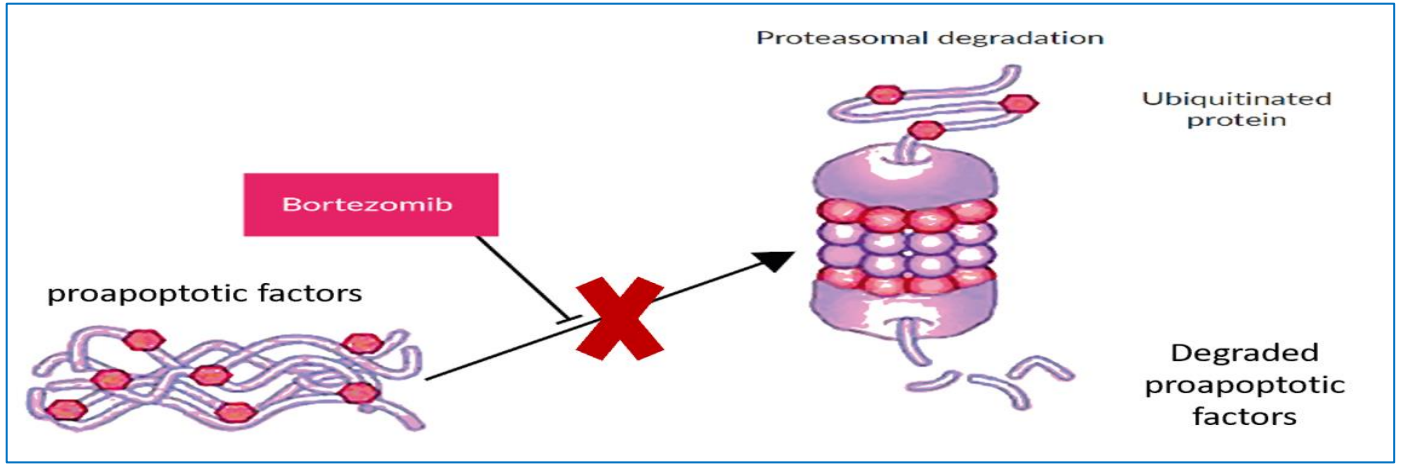


Limb abnormalities, including missing or shortened limbs

XI. MISCELLANEOUS AGENTS

C. Proteasome Inhibitors

- **Bortezomib, ixazomib, and carfilzomib** are **proteasome inhibitors** commonly used as **backbone therapy** in the treatment of **multiple myeloma**.
- These agents work by **inhibiting proteasomes**, which in turn **prevents the degradation of proapoptotic factors**, thus leading to a **promotion** of programmed cell death (**apoptosis**).
- Malignant cells readily depend on the suppression of the apoptotic pathway; therefore, proteasome inhibition **works well in multiple myeloma**.

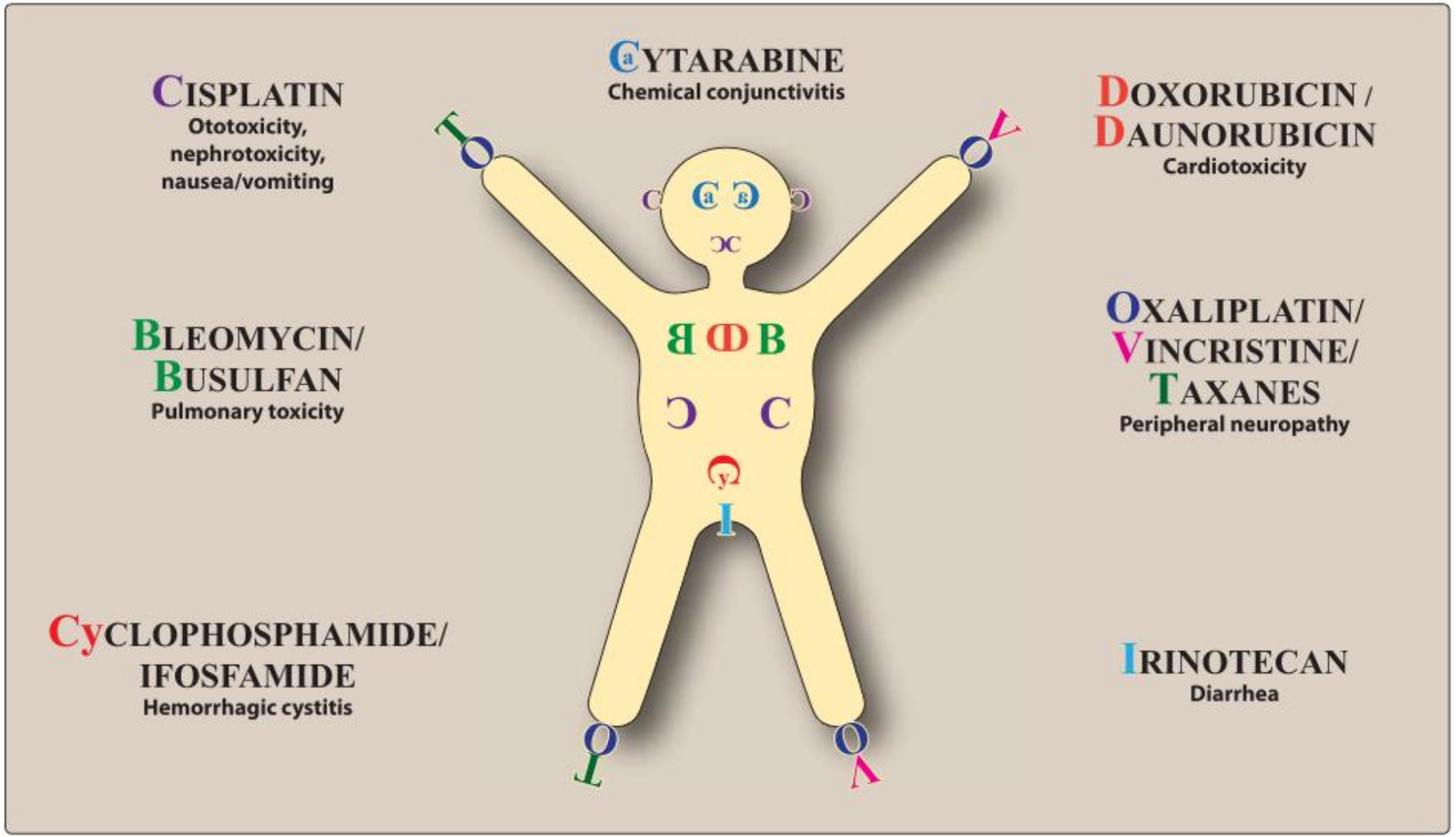


XI. MISCELLANEOUS AGENTS

C. Proteasome Inhibitors

- **Bortezomib** can be administered **IV**, but the **SC route** is **preferred** because it is associated with **less neuropathy**.
- **Other adverse effects** include myelosuppression, diarrhea, nausea, fatigue, and herpes zoster reactivation.
- Patients **should** receive **antiviral prophylaxis** if they are receiving therapy with **bortezomib**.
- **Ixazomib** is an **oral agent** with an **adverse effect** profile **similar** to **bortezomib**.
- **Carfilzomib** is administered **IV**, and common adverse effects include **myelosuppression, fatigue, nausea, diarrhea, and fever**.

CHEMO MAN



Chemo Man is a useful tool to help remember the most common toxicities of these drugs

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