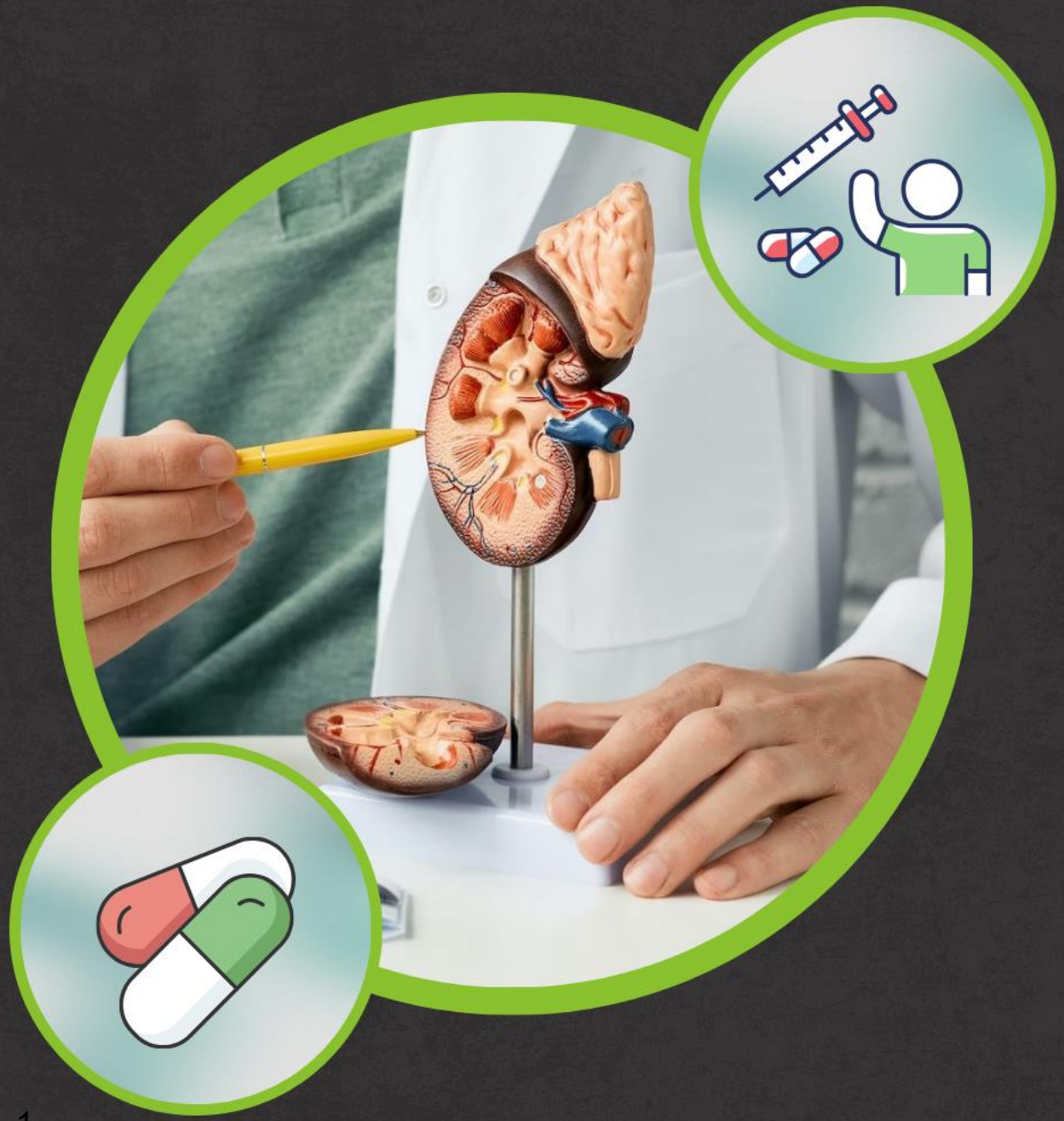

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Drugs Used in Neoplasms of the Urogenital System

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‼ الدكتور حكى انه نركز على بعض المعلومات خاصة و ان الموضوع يحتاج تخصص اكثر لعلاج هذه الأمراض
المعلومات المهمة سنحددها باللون الأحمر و الأقل اهمية تحتها خط بشكل عام الدكتور يقرأ كل شيء

‼ Common adverse reactions for antineoplastic Drugs:

1. Nausea and vomiting
2. Alopecia (most drugs)
3. Bone marrow Suppression
4. Mucositis

They affect both neoplastic and normal cells specially those with rapidly dividing ability such as hair follicles and Mucosa of GIT

‼ old drugs were cytotoxic ,affect both normal and neoplastic cells , Thus it has narrow risk benefit ratio , however, new drugs depends on interfering with specific pathophysiology in the neoplasm , in which monoclonal antibodies were used for particular neoplasm

‼ in hormone dependent neoplasms, we use drugs(monoclonal antibodies) that block hormone receptors ,stop the growing of neoplasm resulting, in a good response

Drugs for Breast Cancer

1. Cyclophosphamide
2. Methotrexate (MTX)
3. Anthracyclines (Doxorubicin)
4. Paclitaxel
5. Ixabepilone
6. Bevacizumab
7. Trastuzumab

1. Cyclophosphamide

- **An alkylating agent.**
- **It is inactive and needs [1]activation by microsomal enzymes to 4-hydroxycyclophosphamide and aldophosphamide. (Enzymatic step)**
- **These active metabolites are delivered to both tumor and normal cells, where [2]aldophosphamide is cleaved nonenzymatically to the cytotoxic forms phosphoramide mustard and acrolein. (non-enzymatic step)**

‼ Two steps for activation :

Mustard:means that the molecule contains nitrogen

Cyclophosphamide

Therapeutic uses:

- **Breast cancer**
- **Ovarian cancer**
- **Wilm’s tumor**
- **Others**

Cyclophosphamide

Toxicity:

- **Are dose-related, and occur primarily in rapidly growing tissues such as bone marrow, GIT, and reproductive system.**

1. **Nausea and vomiting.**
   - Du to the stimulation of chemoreceptor triger zone medulla oblangata
2. **Direct vesicant effects and can damage tissues at site of injection.**
   - ⛔ Not given IM , ✅ only IV
3. **Hemorrhagic cystitis which can be prevented by adequate hydration.**
   - the drug should be stopped and fluid intake should be given and urination

Cyclophosphamide

4. **Carcinogenic, with increased risk of secondary malignancies, especially acute myelogenous leukemia.**

   Since they are cytotoxic alkylating agents, causing mutations in the DNA

4. **Bone marrow depression may be associated with leukopenia and thrombocytopenia, and bleeding.**
5. **Alopecia** reversible

All anti cancerous agents cause vomitting and nausea, So patients takes premedications such as antiemitting drugs

2. Methotrexate (MTX)

- **It is a folic acid analog that inhibit dihydrofolate reductase and prevent the formation of tetrahydrofolate (THF).** Similar to antibiotic mechanism, however this one works on animal cells rather than bacteria
- **THF serves as the key one-carbon carrier in the synthesis of thymidylate, purine nucleotides, and the amine acids serine and methionine.** Interfere with Protein ,DNA Synthesis, and cell devision.

Methotrexate

MOA

- **Thus, it interferes with the formation of DNA and RNA and key cellular proteins.**
- **Intracellular formation of polyglutamate metabolites by folylpolyglutamate synthase, with the addition of up to 5-7 glutamate residues, is needed for the therapeutic action of MTX.**
- **MTX polyglutamates are selectively retained within cancer cells.** Relative selectivity

Methotrexate

Also cancer cells develop resistance

Development of resistance is due to:

1. **Decreased drug transport via the reduced folate carrier or folate receptor protein.**
2. **Decreased formation of cytotoxic MTX polyglutamate.**
3. **Increased levels of the target enzyme, DHFR, through gene amplification.** Decrease the inhibition

Methotrexate

4. **Altered DHFR protein with altered affinity for MTX.**
5. **Activation of the multidrug resistance transporter P170-glycoprotein.**

Increase in the expression of P170-glycoprotein on the surface of cancer cells inhibiting the entry of the drug

Methotrexate

- Pharmacokinetics

- **It is administered by oral, intravenous and intrathecal routes.**
  - ⛔ Not given IM
- **Mainly eliminated by the kidney through <u>active transport,</u> and <u>dose reduction is needed in renal dysfunction.</u>**
- **<u>Its renal excretion is inhibited by aspirin, other NSAIDs, penicillins, and cephalosporins</u>. Due to the competition over the active transport**

Methotrexate

When Leucovorin is used ?
antagonises MTX when overdose to rescue normal cells

- **The effects of MTX can be reversed by administration of leucovorin (5-formyltetrahydrofolate).**
- **Leucovorin rescue can be used in conjunction with high-dose MTX therapy to rescue normal cells from undue toxicity, and in accidental overdose.**

Methotrexate

Therapeutic uses:

- **Breast cancer**
- **Bladder cancer**
- **Choriocarcinoma.** Originated from Placental tissue and can be completely cured
- **Others.**

Methotrexate

Toxicity:

1. Mucositis (GIT), diarrhea
2. Hepatotoxicity specific for MTX

Liver has high capacity for regeneration ,thus it is affected by anticancer agents .

3. Myelosuppression with neutropenia and thrombocytopenia
4. Neurological & cognitive impairment

Intrathecal administration could damage neurons

5. Immunoallergic pneumonia leading to pulmonary fibrosis
6. Chemical pneumonitis

Pulmonary Fibrosis may be developed by two mechanisms Chemical and allergic

7. Renal dysfunction

3. Doxorubicin

- **Belongs to anthracyclines, the most widely used cytotoxic anticancer antibiotic drugs.**

Mechanism of action: mechanisms for cytotoxicity

1. **Inhibition of topoisomerase II.** Inhibits the repair system
2. **Intercalation to DNA.**
3. **Generation of semiquinone free radicals and oxygen free radicals (iron-dependent, enzyme- mediated reductive process), which cause cardiotoxicity.** specific for doxorubicin

نصيحة من الدكتور يعقوب ديروا بالكم على اكلكم لانه بأثر على مناعتكم في مقاومة السرطان
بكفي شاورما ☺

Anthracyclines

4. **Binding to cellular membranes altering fluidity and ion transport.**

Pharmacokinetics

- **They are administered IV.**
- **Metabolized extensively in the liver.**
- **~ 50% of the dose is excreted in bile, and dose reduction is needed in hepatic dysfunction.**

Anthracyclines

Therapeutic uses:

1. Breast cancer
2. Endometrial cancer
3. Cancer of ovary
4. Cancer of testis
5. Bladder cancer
6. Others.

Urogenital system cancers and others

4. Paclitaxel

- Belongs to taxanes.
- It is an alkaloid derived from the Pacific and European *yew* (صنوبريات) .
- It functions as mitotic spindle poison which results in inhibition of mitosis and cell division. It arrests cell division
- Metabolized by CYPs, and 80% of the drug is excreted in feces.
- Dose reduction is required in hepatic dysfunction.

It is eliminated via hepatic metabolism

Paclitaxel

Therapeutic uses:

1. Ovarian cancer
2. Advanced breast cancer
3. Prostate cancer
4. Bladder cancer
5. Others

Paclitaxel

Adverse reactions:

Because of the arrest of cell division

The primary dose-limiting toxicities are nausea (not specific), vomiting(not specific), hypotension, arrhythmias, myelosuppression, peripheral sensory neuropathy.

- **Hypersensitivity (5%), requires premedication with dexamethasone, diphenhydramine (H1- blocker) and an H2-blocker.**

To prevent hypersensitivity reactions when giving **IV paclitaxel**, patients must be treated with:

- Corticosteroids (dexamethasone)
- H1 blockers (diphenhydramine)
- H2 blockers ➡️ often forgotten but essential

Note: Many practitioners forget H2 blockers when treating allergic reactions. However, histamine acts on both H1 and H2 receptors, so both must be blocked during serious allergic events. This is a critical point to remember, especially in emergencies.

Paclitaxel

- **An albumin-bound formulation used for breast cancer does not require premedication, with milder myelosuppression and reversible neurotoxicity.**

5. Ixabepilone

- It is not a taxane, but it is a microtubule inhibitor. Mitotic spindle inhibitor
- Used for metastatic breast cancer.
- Main adverse effects are hypersensitivity reactions, myelosuppression, neurotoxicity, with peripheral sensory neuropathy.

The common adverse effects of microtubule poisons (whether taxanes or not) include neurotoxicity and bone marrow suppression, due to their shared mechanism of inhibiting mitotic spindles.

6.Bevacizumab (Monoclonal Antibody)

- **The growth of both primary and metastatic tumors requires an intact vasculature.**
- **The vascular endothelial growth factor (VEGF) signaling pathway is an attractive target for chemotherapy.**
- **Bevacizumab is a recombinant humanized monoclonal antibody that targets all forms of VEGFs particularly VEGF-A.**

- Solid tumors require a blood supply for growth. They stimulate **angiogenesis** through **VEGF** signalling. **Bevacizumab** blocks **VEGF-A**, thereby inhibiting the formation of new blood vessels, and suppressing tumor growth.

Monoclonal antibodies are originally developed in mice. To reduce immunogenicity, these antibodies are humanized ➡️ part of the molecule is derived from mouse origin and the rest from human sequences. This reduces allergic reactions when used in humans.

Bevacizumab

- **This antibody binds to and prevents VEGF-A from interacting with its receptor.**

Toxicity:

- **Hypertension** ➡ This is related to its effect on blood vessels
- **Arterial thromboembolism (TIA, stroke, angina, & MI)**
- **Wound healing impairment** ➡ Because wound healing involves new BVs formation
- **GI perforations and proteinuria** ➡ If a part of the GI tract becomes ischemic (due to impaired vascular supply), it may undergo infarction, making it susceptible to perforation.

➢ Proteinuria ➡ loss of protein in the urine.

➢ Not all adverse effects of bevacizumab can be fully explained by its mechanism of action.

7. Trastuzumab

- Is a recombinant, humanized monoclonal antibody that binds to human epidermal growth factor receptor (HER-2/neu), preventing the natural ligand from binding to the receptor, and it down regulates the receptor.
- Cause cardiotoxicity manifested as a reduced left ventricular ejection fraction ➡ causes heart failure
- It may be used in metastatic breast cancer in patients whose tumors overexpress HER-2/neu.

We need to determine whether the HER2 receptor is overexpressed in the breast cancer tissue. If HER2 is not overexpressed, trastuzumab will not be effective, as the drug specifically targets HER2-positive tumors.

REMEMBER: Doxorubicin can also cause cardiotoxicity 😊

Drugs for Prostate Cancer

1. Mitoxantrone

Drugs for Prostate Cancer

- **The treatment of choice is elimination of testosterone production, either by surgical castration or hormonal therapy.**
- **Discussed before.**

Mitoxantrone

- It is an anthracycline antibiotic.
- Act by intercalation with the DNA molecule, which in turn causes single- and double-strand disruptions and suppresses DNA repair via inhibition of topoisomerase II.
- Used for advanced, hormone-refractory prostate cancer. (when the cancer no longer responds to hormonal therapies like anti-testosterone or anti-androgens)

Mitoxantrone

Toxicity:

1. Myelosuppression, leukopenia, is the dose- limiting toxic effect.
2. Thrombocytopenia
3. Nausea and vomiting
4. Alopecia
5. Mucositis
6. A blue discoloration of fingernails, sclera, and urine is observed 1-2 days after drug administration. Specific toxicity

Drugs for Ovarian Cancer

Drugs for Ovarian Cancer

- Cisplatin, Carboplatin
- Cyclophosphamide
- Paclitaxel
- Topotecan
- Doxorubicin
- Altretamine

We will discuss the red ones
The blue ones were discussed previously

Platinum Analogs

Cisplatin, Carboplatin.

- **They exert their cytotoxic effects like the alkylating agents.**

Acts like alkylating agents but without alkyl groups.

- **They kill tumor cells in all stages of the cell cycle.**
- **Bind to DNA and form intra- and inter-strand cross-links, leading to inhibition of DNA synthesis and function.**

- The main **DIFFERENCE** between these two drugs is that **Carboplatin** is **LESS nephrotoxic** than Cisplatin, but it can cause myelosuppression

Cisplatin

Therapeutic uses:

1. **Breast cancer**
2. **Testicular cancer**
3. **Ovarian cancer**
4. **Bladder cancer**
5. **Others**

- **It is eliminated by the kidney and dose reduction is needed in renal dysfunction.**

Cisplatin

• Myelosuppression is allowed during treatment to an extent, but it requires monitoring.
•In severe cases (e.g. Hb 5–6 g/dL, neutropenia), supportive therapy is given between cycles to boost blood cell counts.

Toxicity:

1. **Nausea and vomiting**
2. **Nephrotoxicity**
3. **Peripheral sensory neuropathy**
4. **Ototoxicity** ➡ The only one in this lecture that causes this toxicity

REMEMBER: Ethacrynic acid can also cause ototoxicity 😊

- **Carboplatin is less toxic to the kidney, but its main dose-limiting toxicity is myelosuppression.**

Dose-limiting toxicity = the toxicity that prevents further dose increase.

- In cancer treatment, we follow structured regimens, not just single drugs like cisplatin. While there may be different acceptable regimens for the same cancer, especially with older cytotoxic drugs, targeted therapies like monoclonal antibodies and hormones are non-negotiable. These are based on solid evidence, not personal opinions

Camptothecins

- They are natural products derived from a tree grown in China.
- They inhibit the activity of topoisomerase I, the key enzyme responsible for cutting and re-ligating single DNA strands.
- This results in DNA damage and cell death.

REMEMBER: Mitoxantrone ➡ topoisomerase II

Topotecan

- **It is used for advanced ovarian cancer as second- line therapy following platinum-based chemotherapy.**
- **The dose should be adjusted in renal function.**
- **The main toxicities are nausea, vomiting and myelosuppression.** non-specific toxicities

So if a patient with advanced ovarian cancer is already receiving platinum-based drugs but is not responding, Topotecan becomes an option as a second-line therapy.

Altretamine

- It is an alkylating agent that forms DNA cross-links, resulting in inhibition of DNA synthesis and function.

Toxicity:

- Nausea and vomiting
- Myelosuppression
- Peripheral neuropathy
- Flu-like syndrome.

Drugs for Testicular Cancer

Drugs for Testicular Cancer

- **Cisplatin**
- **Etoposide**
- **Bleomycin**
- **Ifosfamide (similar to cyclophosphamide).**

Ifosfamide, which is a derivative of cyclophosphamide. It was designed to reduce the risk of **hemorrhagic cystitis**, a major side effect seen with cyclophosphamide.

We will discuss Etoposide and Bleomycin

Etoposide

- It is a semisynthetic derivative of <u>podophyllotoxin</u>, which is extracted from mayapple root ليمون الأرض او البدفيل .
- IV, and oral formulations are available.
- <u>Dose reduction is needed in renal dysfunction.</u>
- Teniposide is a related drug.

Etoposide

- **They inhibit topoisomerase II, resulting in DNA damage through strand breakage induced by formation of a ternary complex of drug, DNA, and enzyme.**

Toxicity:

1. **Nausea, and vomiting,**
2. **Hypotension** (in some cases)
3. **Myelosuppression**
4. **Alopecia.**

Non-specific

Camptothecins → topoisomerase I
Mitoxantrone → topoisomerase II
Etoposide → topoisomerase II

We don’t typically call these side effects "adverse reactions“ they’re more appropriately called **toxicities**, because these drugs are inherently toxic at therapeutic doses. The goal is to kill the cancer cells, but normal cells get hurt in the process. That’s why the term “toxicity” is more accurate.

Bleomycin

- **Anticancer antibiotic**
- **It is a small peptide that contains a DNA- binding region, and an iron binding domain at opposite ends of the molecule.**

DNA binding domain binds to DNA and alter DNA and iron binding domain generates free radicals

- **It acts by binding to DNA, which results in single-strand and double-strand breaks following free radical formation**(developed in an iron dependent mechanism)**, and inhibition of DNA synthesis.**

Bleomycin

- It is a cell-cycle specific drug that arrest cells in the G2 phase of the cell cycle.
- It is used also in squamous cell cancer of the cervix and vulva.
- Dose reduction is needed in renal dysfunction.

REMEMBER: Cisplatin and Carboplatin act on all cell cycle stages 😊

Bleomycin

- **Dose-limiting toxicity is pulmonary in the form of pneumonitis, cough, dyspnea, dry inspiratory crackles, and chest infiltrates.**
- **This is more in patients:**

a) **older than 70 years of age**

b) **who receive accumulative dose greater than 400 units**

c) **with underlying pulmonary disease**

d) **with prior chest radiation.**

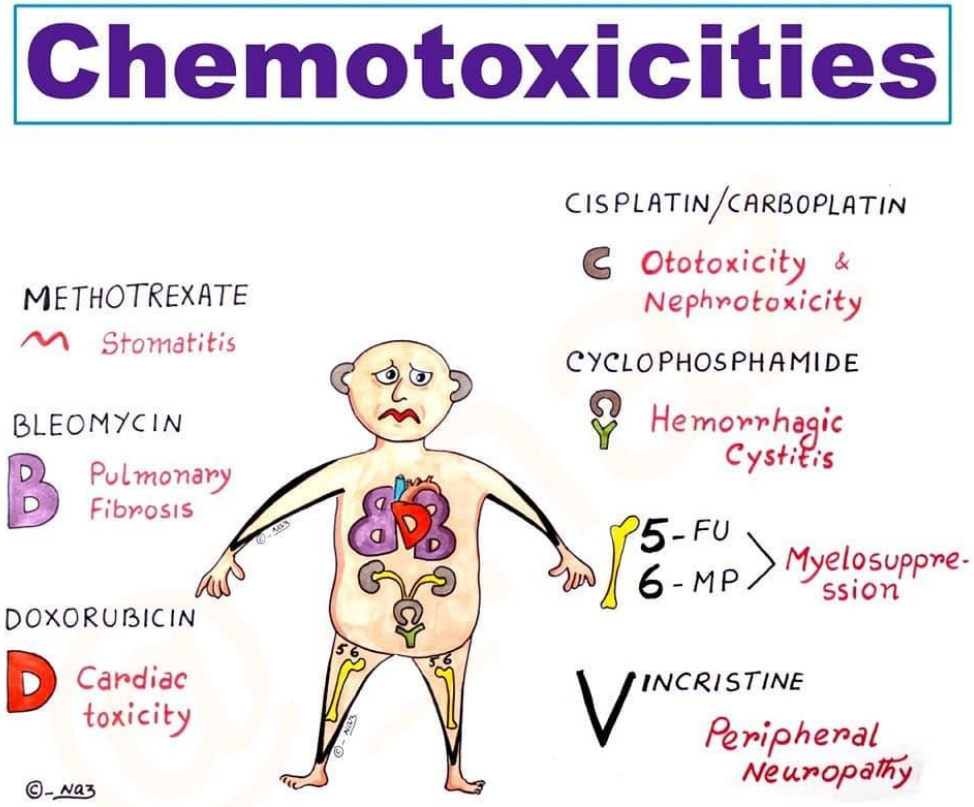
Some drugs, like penicillin or heparin, are dosed in units, not milligrams, because they aren't completely pure
we use units of activity instead of weight.
For bleomycin, the cumulative dose should not **exceed 400 units**, because of the risk of pulmonary toxicity, especially in patients with lung disease or prior chest radiation due to additive effects. **This is the main limiting toxicity.**

Pulmonary toxicity
Bleomycin
Methotrexate
Nitrofurantoin

Bleomycin

Other toxicities:

1. **Allergic reactions**
2. **Fever**
3. **Hypotension**
4. **Dermatotoxicity,**
5. **Alopecia,**
6. **Mucositis.** **inflammation and ulceration of the mucous membranes throughout the GI tract**



أبان مولدهُ عن طيبِ عُنصرهِ ***يا طِيبَ مُبْتَدَأٍ منه ومُخْتَتَمِ
يومٌ تفرَّسَ فيهِ الفرسُ أَنَّهمُ ***قَد أُنذِروا بِحُلولِ البؤسِ والنِّقَمِ
وباتَ إيوانُ كسرى وهو منصدعٌ ***كشملِ أصحابِ كسرى غيرَ ملتئمِ

اللهم يا من نصرت المسلمين في القادسية
انصرهم في غزة وائذن بتصدع الكيان الغاصب وانكساره

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!