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بسم الله الرحمن الرحيم

Drugs Used in Neoplasms of the Urogenital System

FINAL | Lecture 12

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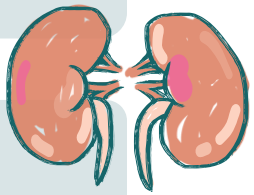
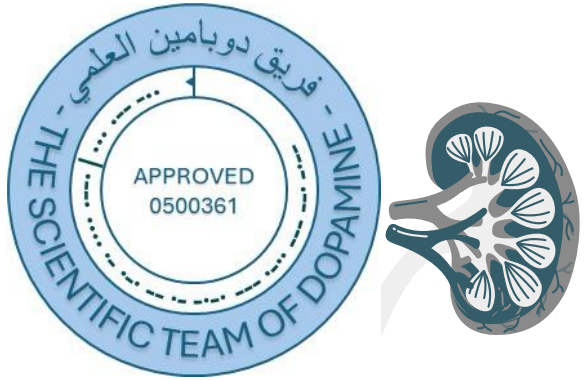


﴿قُلْ بِفَضْلِ ٱللَّهِ وَبِرَحْمَتِهِۦ فَبِذَٰلِكَ فَلْيَفْرَحُوا۟ هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ﴾



Introduction

- The lecture contains a large amount of information; therefore, not all details will be discussed. The focus will mainly be on the important points, for example the adverse effects and common adverse reactions of antineoplastic drugs.

- **Most cytotoxic drugs commonly cause adverse effects such as nausea, vomiting, alopecia, and bone marrow suppression**. These drugs affect both **neoplastic cells** and **normal cells** because they target rapidly dividing cells. Although neoplastic cells are more affected, some normal cells in the body also undergo rapid division, including bone marrow cells, hair follicle cells, and the mucosal cells of the gastrointestinal tract. Consequently, antineoplastic drugs may lead to bone marrow suppression, hair loss, mucositis, shedding of gastrointestinal mucosal cells, and other related adverse effects.

Introduction (cont.)

- Previously, treatment options mainly consisted of cytotoxic drugs that affected both normal and abnormal tissues. In reality, the therapeutic benefit of these agents compared with their associated risks was relatively limited, resulting in a **narrow risk to benefit range (therapeutic index).**

- Currently, newer drugs have been developed based on the pathophysiological processes involved in cancer. These include **monoclonal antibodies that specifically inhibit certain pathological pathways involved in particular types of neoplasms**. In addition, **hormonal therapy** is used for hormone-dependent neoplasms, which are tumors stimulated by hormones. Examples include **endometrial carcinoma** stimulated by **estrogen**, **prostate cancer** stimulated by **androgens**, and **some types of breast cancer** that are **estrogen-dependent** *so blocking the hormonal stimulus can inhibit neoplastic growth and may produce an adequate therapeutic response.*

Drugs for Breast Cancer

"اللَّهُمَّ إِنِّي أَسْأَلُكَ فَهْمَ النَّبِيِّينَ، وَحِفْظَ الْمُرْسَلِينَ، وَإِلْهَامَ الْمَلَائِكَةِ الْمُقَرَّبِينَ، بِرَحْمَتِكَ يَا أَرْحَمَ الرَّاحِمِينَ"

يعطيكم العافية، الدكتور حكى إنه هالمحاضرة فيها كثير معلومات يلي ما بنحتاجها بالوقت الحالي،
فالمفروض نركز على الأشياء المهمة يلي بحكيها وحطينا إلكم عندها علامة، لكن بشكل عام الدكتور
مر على كل السلايدات وقرأهم، بالتوفيق وادعولنا ☺

1- Cyclophosphamide

- **An alkylating agent.**

Two steps for activation : ❖ important

- **It is inactive and needs activation by microsomal enzymes to 4-hydroxycyclophosphamide and aldophosphamide.** – **Enzymatic Step** occurs within the cell, whether normal or cancerous.
- **These active metabolites are delivered to both tumor and normal cells** as the drug does not selectively target cancer cells, **where aldophosphamide is cleaved nonenzymatically to the cytotoxic forms phosphoramide mustard and acrolein.** – **non Enzymatic Step**

✓ Mustard:means that the molecule contains nitrogen

Cyclophosphamide

Therapeutic uses: ✓ not selective for a particular organ .

- **Breast cancer**
- **Ovarian cancer**
- **Wilm's tumor** pediatric renal tumor
- **Others**

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Cyclophosphamide

Toxicity:

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

1. **Nausea and vomiting.**
   - Due to the stimulation of chemoreceptor trigger zone in medulla oblongata.
2. **Direct vesicant effects and can damage tissues at site of injection.**
   - Therefore, intramuscular administration should be avoided because it may lead to vesication and local tissue injury. For this reason, the drug is administered intravenously.

Cyclophosphamide

3- Hemorrhagic cystitis which can be prevented by adequate hydration to maintain sufficient urine flow.

- This toxicity results from the **physical irritating effect of the drug metabolites on the urinary bladder.**

❖ **Related to CLINICAL**

patients receiving cyclophosphamide for the first time may develop hematuria, which can cause panic. In such cases, it is important to recognize that the bleeding may be related to cyclophosphamide toxicity, discontinue the administration if necessary, and provide appropriate management.

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

- **This is related to its action as an alkylating agent, which induces mutations in DNA, causing the cell to become highly dividing and subsequently contribute to malignant transformation**

رَبِّ إِنِّي فَوَّضْتُ أَمْرِي إِلَيْكَ وَتَوَكَّلْتُ عَلَيكَ فَكُن لِي خَيرَ وَكِيل
وَدَبِّر لِي أَمرِي فَإِنِّي لَا أُحسِنُ التَّدبِيرَ .

Cyclophosphamide

5- Bone marrow depression may be associated with leukopenia and thrombocytopenia, and bleeding. Patients are anemic

6- Alopecia

- Alopecia (Hair loss) is usually **reversible**. In some patients, the hair might be white or gray before falling out; however, after regrowth, the hair commonly returns to its normal color temporarily.

- **Nausea, vomiting, bone marrow suppression,** and **alopecia** are among **the most common toxic effects associated with anticancer drugs.** Therefore, in questions asking which anticancer drugs cause nausea and vomiting, the correct answer is "*all of the above*," since these effects are shared by many cytotoxic agents.

- Chemotherapy-induced nausea and vomiting are primarily centrally mediated. For this reason, **patients usually receive premedication with antiemetic agents before chemotherapy administration.** In many cases, **more than one antiemetic drug** is required to adequately control symptoms.

- **These drugs are generally administered systemically by injection rather than orally.**

2- Methotrexate (MTX)

❖ **Important : mechanism of action**

- **It is a folic acid analog that inhibit dihydrofolate reductase and prevent the formation of tetrahydrofolate (THF).**
  - ✓ similar in mechanism to antifolate antibacterial drugs, but it does not act on bacteria; instead, it targets human & animal cells.
- **THF serves as the key one-carbon carrier in the synthesis of thymidylate** required for DNA synthesis **, purine nucleotides, and the amine acids serine and methionine,** Consequently, it plays a major role in protein synthesis, DNA synthesis, and cellular division.

  - ➢ By **inhibiting tetrahydrofolate formation, methotrexate interferes with cell division and suppresses the growth and proliferation of neoplastic cells.**

Methotrexate

- **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: it may accumulate in highly dividing normal cells as well)

✓ If polyglutamation does not occur, the intracellular retention of methotrexate is reduced and its activity against cancer cells is diminished.

Methotrexate

Development of resistance is due to: which might lead to flare up in cancer patients

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.**

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DHFR = Dihydrofolate Reductase

Methotrexate

Connect with previous knowledge
Similar mechanisms of Resistance is seen with penicillin. Due to alterations in the target site, particularly changes in penicillin-binding proteins (PBPs). Since penicillins act by binding to enzymes involved in bacterial cell wall synthesis, structural modification of these proteins leads to reduced affinity and thus binding between the drug and its target enzyme.

4. **Altered DHFR protein with altered affinity for MTX.**
5. **Activation of the multidrug resistance transporter P170-glycoprotein.** influence the entry and distribution of drugs into cells
    - Another mechanism of resistance involves the development of altered drug transport systems, such as multidrug resistance (MDR) transporters (P-glycoprotein-like proteins) located on the surface of neoplastic cells. **These transporters may be present or expressed at low levels initially, but after exposure to the drug, their expression may be increased (overexpression), leading to enhanced drug efflux and reduced intracellular drug concentration.**

Methotrexate

- It is administered by oral, intravenous and intrathecal routes. Not IM
- Mainly eliminated by the kidney through active transport, and dose reduction is needed in renal dysfunction.

❖ important

- Its renal excretion is inhibited by probenecid, aspirin, other NSAIDs, penicillins, and cephalosporins. (Compete with the drug)

Methotrexate

❖ **Important : what to do in a case of MTX excessive effect ?**

- **The effects of MTX can be reversed by administration of leucovorin (5- formyltetrahydrofolate).** Derivative of folic acid
- **Leucovorin rescue can be used in conjunction with high-dose MTX therapy to rescue normal cells from undue toxicity, and in accidental overdose.**
  - High dose: large doses at weekly or monthly intervals rather than daily.

Methotrexate

Therapeutic uses:

- **Breast cancer**
- **Bladder cancer**
- **Choriocarcinoma.**
- **Others.**

✓ **Choriocarcinoma** is a malignant tumor that arises from placental tissue, It is considered **a highly treatment-responsive neoplasm** and, in many cases, may be completely cured with appropriate therapy. Therefore, the prognosis is not limited merely to five-year survival rates.

✓ *The term "others" refers to additional types of cancers and is not limited only to urogenital malignancies.*

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Methotrexate

❖ Important (2,4,5) and specific to MTX

Toxicity:

1. **Mucositis (GIT)** can also be observed with other anticancer drugs, **diarrhea**
2. **Hepatotoxicity** MTX specific toxicity ; since the liver cells are rapidly dividing and have capacity for regrowth.
3. **Myelosuppression with neutropenia and thrombocytopenia** common
4. **Neurological & cognitive impairment**
   - Since the drug can be administered intrathecally, improper administration or lack of caution during intrathecal use may result in neuronal damage.
5. **Immunoallergic pneumonia leading to pulmonary fibrosis** ❖ Very imp
6. **Chemical pneumonitis**
7. **Renal dysfunction**

✓ **Pulmonary fibrosis** may occur through both **allergic** and direct **chemical** mechanisms, and because the lungs are essential for gas exchange, pulmonary fibrosis can significantly **impair respiratory function** and may be associated with high mortality.

3- Doxorubicin

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

> ✓ The **immune system** plays an important role in protection against cancer. Neoplastic cells may continuously arise in the body; however, **under normal conditions, the immune system recognizes and eliminates these abnormal cells before they develop into clinically detectable cancer, and it can eliminate early small tumors** (قد حبة الحمص)

Mechanism of action:

1. **Inhibition of topoisomerase II.**
   - **Topoisomerase II** is involved in DNA repair, it regulates DNA structure by allowing controlled breaks and re-ligation of DNA strands, ensuring proper DNA organization and repair. **If this process is disrupted or fails, abnormal DNA changes may occur, which can contribute to cancer development.**
2. **Intercalation to DNA.**
3. **Generation of semiquinone free radicals and oxygen free radicals (iron-dependent, enzyme- mediated reductive process), which cause <u>cardiotoxicity</u>.** ❖ **Important and specific**

Anthracyclines

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

- **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.**
    - *Dr said that he will not be asking about when to reduce the dose (hepatic or renal dysfunction…)*

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Anthracyclines

These are examples of UGS cancers, It is applicable in other cancers as well.

Therapeutic uses:

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

5- Paclitaxel

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

Paclitaxel

Therapeutic uses:

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

Paclitaxel

Adverse reactions:

- **The primary dose-limiting toxicities are nausea and vomiting non-specific adverse effects , hypotension, arrhythmias, myelosuppression, peripheral sensory neuropathy neurotoxicity**
- **Hypersensitivity (5%), requires premedication with corticosteroids and anti histamines: dexamethasone, diphenhydramine (H_1- blocker) and an H_2-blocker respectively .**
  When administering a paclitaxel IV infusion, preparation of dexamethasone, diphenhydramine and H2-blocker syringes is **obligatory**.
- Usually, in the treatment of allergy, physicians forget **H2-Blockers**, even though they're a **crucial part of treatment**. ❖ important

Paclitaxel

- **An albumin-bound formulation used for breast cancer does not require premedication, with milder myelosuppression and reversible neurotoxicity.**
  - In an attempt at lowering paciltaxel's toxicity, a new albumin-bound formulation was created. It does **not** require the premedication of dexamethasone, diphenhydramine and H2-blockers. This new formulation also causes **less severe neuropathy and myelosuppression.**

6- Ixabepilone

- **It is not a taxane, but it is a microtubule inhibitor.** A mitotic spindle inhibitor, thus inhibits mitosis.
- **Used for metastatic breast cancer.**
- **Main adverse effects are hypersensitivity reactions, myelosuppression, neurotoxicity, with peripheral sensory neuropathy.**
- Similar to the adverse effects of paclitaxel. This is because both drugs are microtubule inhibitors. (Even if they're not the same class of drugs)

7- Bevacizumab

- **The growth of both primary and metastatic tumors requires an intact vasculature.** Tumors can also undergo **angiogenesis** (the **formation of new vasculature**). This enhanced vascularity is **essential for the tumor's survival.** Angiogenesis requires VEGF.
- **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.**

Monoclonal antibodies are originally produced using mouse cells. Because mouse proteins can be recognized as "foreign" by the human immune system, scientists modify these antibodies by adding human DNA sequences during drug development. This makes the antibodies "*humanized*" and reduces the likelihood of **immune rejection**.

Bevacizumab

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

Toxicity:

- **Hypertension** due to the **it's effect of normal blood vessels** .
- **Arterial thromboembolism (TIA, stroke, angina, & MI)**
- **Wound healing impairment** since **the process requires neo-vascularization.**
- **GI perforations and proteinuria** Damaged blood vessels **reduce blood flow** to certain tissues (**ischemia**). This may cause **infarctions**. **Infractions** weaken the structural walls of the affected organ, increasing the **susceptibility for perforations**.
- **VEGF plays a role in maintaining the structure of podocytes, its reduction damages podocytes, allowing proteins to leak into the urine.**

8- Trastuzumab

- **Is a recombinant, humanized monoclonal antibody that binds to** a specific type of **human epidermal growth factor receptor (HER-2/neu), preventing the natural ligand from binding to the receptor, and it down regulates the receptor.** Inhibits the natural substrate from binding, thus blocking its action. This drug is effective in **tumors sensitive to epidermal growth factors**. Not all breast cancers
- **Cause cardiotoxicity manifested as a reduced left ventricular ejection fraction** causes heart failure ❖ important
- **It may be used in <u>metastatic breast cancer in</u> <u>patients whose tumors overexpress HER-2/neu</u>.**

Drugs for Prostate Cancer

Drugs for Prostate Cancer

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

1- Mitoxantrone

- **It is an anthracycline antibiotic.**
- **Act by intercalation with the DNA molecule,** (The majority of cancer antibiotics intercalate with the DNA molecules). **which in turn causes single- and double-strand disruptions and suppresses DNA repair via inhibition of topoisomerase II.** It destroys DNA molecules.
- **Used for <u>advanced, hormone-refractory prostate</u> <u>cancer.</u>**
- **<u>Hormone-refractory</u>**: Unresponsive to hormonal therapy. Meaning, if the prostate cancer is not responsive to **anti-testosterone** drugs, you administer Mitoxantrone.

Mitoxantrone

Toxicity: unspecific symptoms with the exception of the discoloration.

1. Myelosuppression, leukopenia, is the dose- limiting toxic effect.
2. Thrombocytopenia by itself or with leukopenia
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. Stain caused by the drug.

Drugs for Ovarian Cancer

Drugs for Ovarian Cancer

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

We already discussed the drugs in blue

1- Platinum Analogs

Cisplatin, Carboplatin.

❖ important

The only difference between the two drugs is that **carboplatin is less nephrotoxic**

- **They exert their cytotoxic effects like the alkylating agents.**
  They're not alkylating agents (they do not contain an alkyl group).
  Though, the **platinum** in them **induces similar effects by DNA binding**
- **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.**

There are **4 stages in the cell cycle**. Some anti-cancer drugs are **specific to a certain stage**. For example, microtubules inhibitors inhibit mitosis, which is 1 stage of the 4 that encompass the cell cycle and are considered **cell cycle specific. Platinum analogs on the other hand, are not specific to a certain stage.**

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

Toxicity:

1. **Nausea and vomiting** non-specific
2. **Nephrotoxicity** Specific, caused by the elimination of the drug by the kidney
3. **Peripheral sensory neuropathy** Specific
4. **Ototoxicity** Platins are metals, they damage the inner ear by readily accumulating and causing oxidative stress.

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

- **Dose-limiting effect:** If said toxic effect occurred, you should not increase the dose, since the toxicity will only get worse. During cancer therapy, myelosupression is allowed. For example, some patients may reach 5-6 hemoglobin levels and develop neutropenia. However they are given agents between cycles to correct for the suppression
- **In the treatment of cancer**, you do not give the anti-cancerous agent by itself. There are time bound regimens. There could even be multiple regimens for the same cancer. The reason we have those regimens is because there are multiple nonspecific cytotoxic/cell cycle inhibitor medications.

2- Camptothecins

- **They are natural products derived from a tree grown in China.** The happy tree (Camptotheca acuminata)
- **They inhibit the activity of topoisomerase I** (not II)**,the key enzyme responsible for cutting and re- ligating single DNA strands.** This is essential for DNA repair
- **This results in DNA damage and abnormal cell death.**

Topotecan

- **It is used for advanced ovarian cancer as second- line therapy following platinum-based chemotherapy**: means that part of the regimen contains platinum and there was no response then shift to topotecan
- **The dose should be adjusted in renal function.**
- **The main toxicities are nausea, vomiting and myelosuppression.** Nonspecific adverse reactions

3- 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.**
- *again: non-specific toxicities occur with almost all anti-cancer drugs, such as alopecia and mucositis in the GIT.

Drugs for Testicular Cancer

Drugs for Testicular Cancer

- **Cisplatin**
- **Etoposide**
- **Bleomycin**
- **Ifosfamide (similar to cyclophosphamide).** It's a derivative of cyclophosphamide. However, it causes **much milder hemorrhagic cystitis** than seen in cyclophosphamide.

✓ **Ones in blue are already discussed**

1- Etoposide

- **It is a semisynthetic derivative of podophyllotoxin, which is extracted from mayapple root.** It's a part of the **Solanaceae family** الفصيلة الباذنجانية **encompassing eggplants, tomatoes and tobacco**.
- **IV, and oral formulations are available.**
- **Dose reduction is needed in renal dysfunction.**
- **Teniposide is a related drug.** They share the same drug class

Enjoy this story with Jeddo Yaqoub

There was a study done to figure out weather nicotine is formed in leaves or roots. When the tobacco shoot was placed over the tomato root, the leaves did not form nicotine. However, when the tomato shoot was added to the tobacco root, **the tomato stem and fruit accumulated nicotine. Proving that roots produce nicotine, not the leaves**

Etoposide

- **They inhibit topoisomerase II, resulting in DNA damage through strand breakage induced by formation of a ternary complex of drug, DNA, and enzyme.** Notice that many anti-cancer drugs inhibit topoisomerases

Toxicity: not adverse reactions but toxic reactions, since they're toxic at therapeutic doses.

1. **Nausea, and vomiting,**
2. **Hypotension** the only specific one ❖ important
3. **Myelosuppression**
4. **Alopecia.**

2- 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.** The DNA-binding domain binds to DNA and alters its structure. Whilst the iron binding domain generates free radicles.
- **It acts by binding to DNA, which results in single-strand and double-strand breaks following free radical formation, and inhibition of DNA synthesis.** The formation of free radicals in the body depends on iron.

Bleomycin

- **It is a cell-cycle specific drug that arrest cells in the G_2 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.**

Bleomycin

❖ important

- **Dose-limiting toxicity is pulmonary in the form of pneumonitis (will lead to fibrosis), cough, dyspnea, dry inspiratory crackles (crackling sound heard using a stethoscope) and chest infiltrates (opaque infiltrates on imaging, due to fibrosis.)**
- We also mentioned pulmonary toxicities in: **methotrexate and nitrofurantoin.**
- Again, dose-limiting toxicity means you should not increase the dose if toxicity occurred. You may even **stop the medication.**
- **This is more in patients:**

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

b) **who receive a cumulative dose greater than 400 units** other medications also measured via unit of activity (since there are not completely pure, it can't be dosed with mgs): **Penicillins, Heparin**

c) **with underlying pulmonary disease**

d) **with prior chest radiation.** Such as patients who have undergone pulmonary radiotherapy for lung cancer will lead to additive effect

Bleomycin

Other toxicities: the most important is the **pulmonary toxicity**

1. **Allergic reactions**
2. **Fever** drug-fever, a manifestation of allergy
3. **Hypotension**
4. **Dermatotoxicity**
5. **Alopecia**
6. **Mucositis.** Affects all the GIT from the oral cavity to the anal canal.

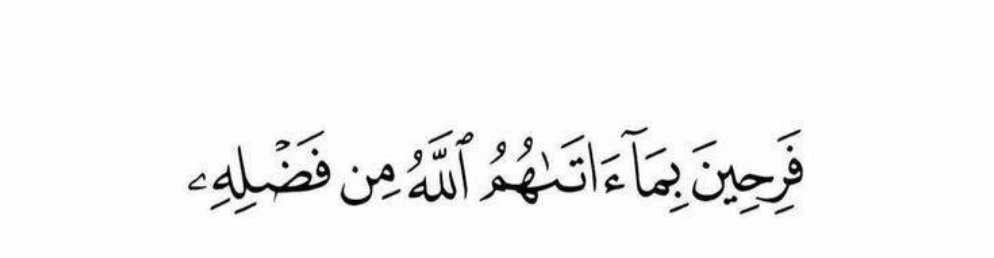
PHARMACOLOGY QUIZ

LECTURE 12

External Resources

رسالة من الفريق العلمي

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقِه من فتنة القبر وعذاب النار،
أنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم.



وهيك بنكون وصلنا لآخر موديفايد للفارما، نسأل الله أن يجعل هذا العمل خالصًا لوجهه
لا تنسونا من صالح دعائكم .الكريم، وأن ينفعنا بما تعلمنا، وأن يبارك في جهودنا جميعًا

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