Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 36

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SHEET

SLIDES

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Cancer Chemotherapy

Introduction:

Cancer is not a single disease. It is a group of more than 200 different diseases that are characterized by uncontrolled growth and spread of abnormal cells.

Cancers are **heterogeneous diseases**. Breast cancer is really different from colorectal cancer, colorectal cancer is different from prostate cancer, prostate cancer is different form testicular cancer, ovarian is different, lung cancer is different... and so on.

Each type of cancer has a distinguished phenotype. The bottom line that we really need to understand is that we treat every single type of cancer differently. By now, you don't need to know the treatment of all types of cancer, you can't memorize 190 types of cancer treatment.

Generally, cancers are a group of mutations within one cell. Cancer cells are of **monoclonal origin** that arise from one cell. As these cells replicate, new mutations appear ending up with a lump. This lump is a collection of heterogeneous cells.

Every cancer cell has a different mutation. This means that I am dealing with a heterogeneous target. A single therapy is not enough as it will kill one phenotype of cancer cells only. You need to deal with a **multiple therapy**. In treating cancer, we use ***3* drugs at minimal**. Some drugs will attack that type of cancer that has x-mutation, the other drug will attack cancer with y-mutation, some cancer cells will not be treatable so they'll come back and produce cancer again and again.

What is the percentage of getting cured after having a cancer?

It depends on the type of cancer. In most cancers we have **50:50 percent**, meaning that one patient will survive while the other will die within 5 years period, this is how we measure the survival period in cancer.

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Cancer treatment

"There are three major approaches to the treatment of the common solid tumors:

Surgery

Radiotherapy

Chemotherapy"

Surgery and radiotherapy are the real effective in the treatment (responsible for the 50% survival chance), so why do we have a chemotherapy?

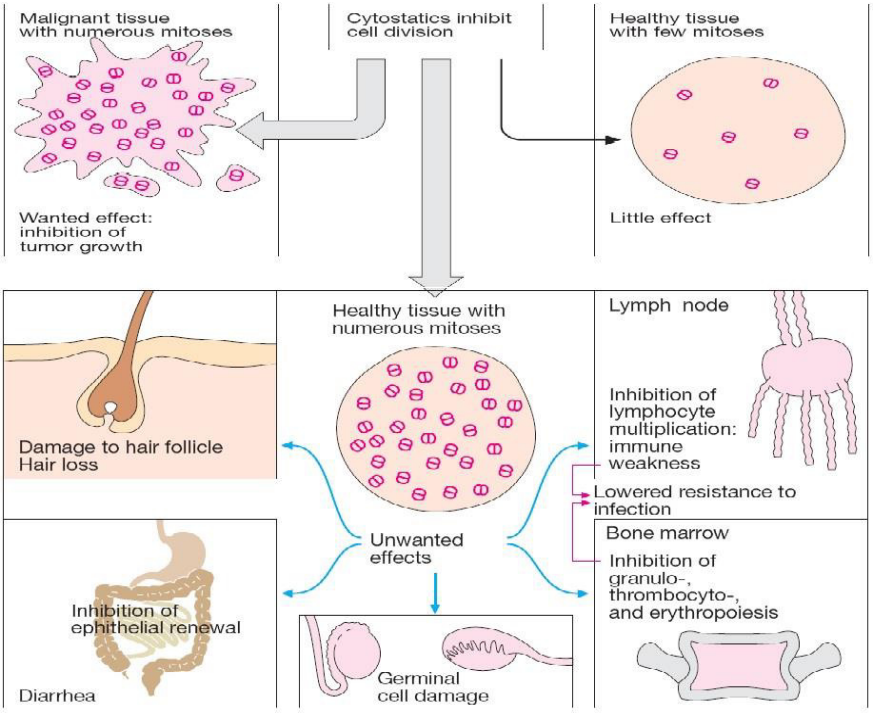
To help in the treatment. That means, we are doing surgery getting the lump out of the patient's body. However, that doesn't mean that we have got all the border cells of cancer. In order to make sure that there is nothing left of the cancer lump, we have to chemotoxic the patient .

What is meant by chemotoxic ?

It means giving the patient strong drugs that will kill every single replicating cell in his body.

Look at the picture to the right:

We are giving anti-cancer drugs that will kill every single replicating cell.



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What are the replicating cells in our body?

- **Hair follicles:** most of the cancer drugs produce alopecia. (تساقط الشعر)
- **Epithelial renewal:** epithelial cells within the gut are renewed every day, that means they are replicating.
- **Germ cells and bone marrow:** both are replicating.
- **Non-replicating cells are not affected by anti-cancer chemotoxic drugs.**

The problem of chemotoxic drugs is that they inhibit all the normal replicating cells in the body as well as the cancer cells which replicate continuously everyday. We don't have a real target, so **there is nothing called selectivity in chemotherapy.**
Cancer drugs are selective? absolutely no. Why?

Because most of them (90%) kill every replicating cell in the body.

Anticancer drugs side effects

The common side effects are:

- alopecia
- nausea
- vomiting
- emesis
- bone marrow suppression
- fatigue
- anemia
- weak immunity

- One of the most problems that they we are facing nowadays in King Hussein Cancer Foundation and Center is CMV (cytomegalovirus). We started using

Foscarnet now, which is principally **used for the treatment of resistant types cytomegalovirus (CMV)**.

- Pneumocystis also is being a real problem.

These diseases are common when there is bone marrow suppression, when the patient's immune system goes down, so the opportunistic bacteria and viruses will get the chance to infect the patient.

Types of treatment

Again you have to understand well that: "most of the 50% cure is effected by surgery and radiotherapy on non-metastatic tumours. "

Metastatic tumors usually cause death. Here, we need to do **palliative treatment** -العناية التلطيفية- , (the patient out of suffering). For example, if the patient is going to live for 6-months or a year with a metastasized cancer, during this time I need to give him palliative treatment.

The other two types of treatment :

- **Cure Treatment:**

  This the objective of therapy. It applies for:

  - Childhood ALL (Acute Lymphoblastic Leukemia)
  - Testicular cancer
  - Wilm's tumor in children (kidney tumor)
  - Basal cell carcinoma

  The previous four cancers are four of the most curable meaning after treating the patient, cancer will not come back again.

  While in other types of cancers, after treating the patient and suppressing the cancer, it will come back again within 5 or 10 years, and the patient is going to die:(

So, we do surgery just trying to delay this recurrence by inhibiting as much as possible of cancer cells. We can do surgery, radiation, chemotherapy,or combination of them.

- Usually we do surgery, then give drugs. Giving drugs after surgery is called **adjuvant treatment** – العلاج المساعد -(helpful treatment) in cancer science. Sometimes the cancer is too big, so we need to treat it with chemotherapy to reduce the edges of cancer trying to contain it, then we start doing surgery. When we give drugs before surgery it is **neoadjuvant treatment.**

Note:

Adjuvant treatment ⟶ Drugs after surgery

Neoadjuvant treatment ⟶ Drugs before surgery

Palliative therapy ⟶ Drugs are just to reduce the symptoms

Cocktail of Drugs

As what we have said in treating AIDS, we use a cocktail of drugs that act by different strategies. We use different types of drugs to reduce the number of resistant cells within the AIDS patient.

In cancer we have a heterogeneous lump, we need to kill as much as we can of this lump, so we have to hit and hit in different strategies, that is why we also give a cocktail of drugs.

- The doctor is reading from slides:
  - "Drugs are administered as a cocktail of three or more components at the maximum dose that can be tolerated by the bone marrow.
  - The cocktail is administered once a day by IV injection/infusion for a week.
  - The patient's haemopoietic system permitted to re-populate for three weeks and the process repeated up to half a dozen times."

This means that we hit cancer patient hard with the maximum dose for a few weeks, and the patient really gets tired. Usually we have three weeks to get bone marrow back as a free time, then we hit back again doing this for 6-7 times. We are doing this because our patient can't tolerate the maximum dose that we give.

Why not to giving a low dose for a long period of time (6-months) so that the patient can tolerate?

Actually, we can do this but the problem is that **low dose won't kill the resistant cancer cells**. So that, the best way to deal with cancer is to maximize the dose as much as we can, then giving a free period to get bone marrow to repopulate, as mentioned earlier.

- Again the doctor is reading from the slide:
  "The therapeutic cocktail comprises drugs whose:

  (1) Mechanism of action differ, the intention being:

  a. Additive or synergistic effect

  b. to delay the appearance of drug-resistant cells for as long as possible.

  (2) Major toxicity differ, non overlapping toxicity."

Cocktail of drugs has to have different mechanisms of actions for two reasons:

- One of them is **to maximize the effect** through additive and synergistic activities.
- The other thing is that it has **to have different toxicity**, we don't want to synergies toxicity, we only want to synergies the activity.

A student asked: Can the patient tolerate the toxicity?
Yes, actually we give the maximal toxic dose that the patient can tolerate because if we reduce the dose the cancer cells will resist. Cancers are very bad,

very aggressive, and genius that easily manipulate normal cells, mutations are very simple in these cancer cells (easy to occur) as they replicate fast.

Classes of anticancer drugs

Drugs currently being used in the clinic are:

1. **DNA Binding Agents**
   (intercalating and alkylating agents)
2. **Mitotic Spindle Inhibitors**
   (modulators of tubulin polymerisation)
3. **Antimetabolites**
   (anti-folates, pyrimidine and purine analogues)
4. **Hormones and Hormone Antagonists**
   like breast cancer, prostate cancer, and ovarian cancer that depend on estrogens and androgens.
5. **Miscellaneous anticancer drugs**
   we have drugs that are selective for cells that have mutations with philadelphia chromosome, abnormalities that are associated with CML (chronic myelocytic leukemia). We inhibits replication by inhibiting philadelphia chromosome products.

All these are called targeted therapy. These are the only drugs that do not produce bone marrow suppression nor alopecia or the other side effects because they target the oncogens that keep cells replicating.

We have drugs for other cancers like HER-2 positive breast cancer.
We are lucky that CML cancer is driven by a single driver (cause), while the problem of other types of cancer that they have multiple drivers. So, if we inhibit the first driver through targeted therapy, a second driver will take its

place so that the cancer will not stop. So that, **targeted therapy actually does not work except if the cancer is driven by 1-2 drivers mostly**.

DNA binding agents:

(1) Anthracyclines :

They are based on drugs called quinolones that bind gyrase.

A. Doxorubicin

- Doxorubicin or andriamycin, interacts with molecular oxygen causing single-strand breaks in DNA, so that the cell cannot replicate anymore. If the cancer cell can't replicate anymore, it will choose to go to apoptosis (programmed cell death) so we're basically driving cell to its suicide.
- Doxorubicin binds and inhibits (poisons) an enzyme called **topoisomerase-II**
- Doxorubicin is one of the most important and **widely used** anticancer drugs (has a nice activity against all tumors).
- Doxorubicin produces free radicals and **causes heart failure**. So, it is use is **limited** (500mg/kg/day) as treating a patient with it will end up with a cardiac toxicity (2% for low doses, 8-20% for higher ones).
- Doxorubicin also **causes bone marrow suppression**, **alopecia,** nausea, vomiting… . This is another kind of toxicity that it causes, in addition to the cardiac toxicity, but we give the patient 3 weeks to recover so we have no problem with this.

- A student asked: Is this drug selective to cancer cells only?

NO, it causes alopecia, nausea, vomiting, bone marrow suppression, and it affects the sperms and eggs, but it is really an effective drug.

- Another student asked: Does it doxorubicin cause anemia?

Yes, because the patient will suffer from bone marrow suppression which will lead to anemia, but it disappears rapidly (the patient has 3 weeks to recover).

Epidemiology of cancer in Jordan

Breast cancer ⟶ most common in ladies

Colorectal cancer ⟶ most common in men

AML (acute myelogenous leukemia) ⟶ most common in children

Lung cancer is lethal and not treatable; in 99.9% of the cases the patient will die. In the last few years, we had 525 lung cancer.

Anthracyclines are dose-limited, irreversible, and cause lethal cardiomyopathy. This cardiotoxicity may be a result either of the generation of free radicals, or of lipid peroxidation . In order to reduce free radicals we can use **Dexrazoxane** (anti-oxidant) .

We mentioned that **Doxorubicin** is used in all cancers, but keep in mind that it's **mainly used in breast cancer**. It the first drug of choice in breast cancer .

How to prescribe doxorubicin?

We give (4 doses) per (4 months) each dose is (100 mg/month) in order not to exceed the limiting dose (500mg). In breast cancer treatment, we give in the first 4 doses with a cocktail of drugs. Doxorubicin causes necrosis around the injection area.

B. Bleomycin :

Another antibiotic used in treatment of testicular cancer. Generally, we treat testicular cancer by 2 drugs, one of them is Bleomycin. Bleomycin affects and is toxic to the testicular cells and causes a little bone marrow suppression. (forget about other details of this drug).

Till now, we only have mentioned anthracycline drugs which attack and inhibit the DNA (topoisomerase-II complex) by DOXO. Another Class that attacks the DNA is Alkylating agents.

(2)Alkylating agents :

Another strategy for attacking the DNA..

Alkyl is a functional group of formula (C_nH_{2n+1}) whether it is a methyl (CH_3-),or ethyl (C2H6),...

We are going to add an alkyl group on the DNA. Usually drugs have 2 alkyl groups (one alkyl group on one side (N7 of guanine) , the other is on the second side of the DNA to stretch it, resulting in cross-linked products that will result in inhibition of the replication.

Like doxorubicin these agents have **no selectivity**, so they will also kill bone marrow cells, epithelial cells, immune cells, and hair follicles by their alkylating activity.

(Note: We are not required to know the mechanism of action for each drug)

A. Cyclophosphamide:

The second drug of choice in **treating breast cancer** (remember DOXO was the first drug used). About 90% of the patients take these 2 drugs in treatment of breast cancer.

Toxicity:

- **Hemorrhagic cystitis**, *inflammation of the urinary bladder*, resulting from the formation of acrolein, *a metabolite of cyclophosphamide*. We can reduce the toxicity of acrolein either by N-acetylcystein, or Mesna (2-mercaptoethanesulfonate). These two drugs neutralize acrolein reducing cystitis.
- **Nephrotoxicity**, (similar to acyclovir), and we reduce it by hydrating the patient.

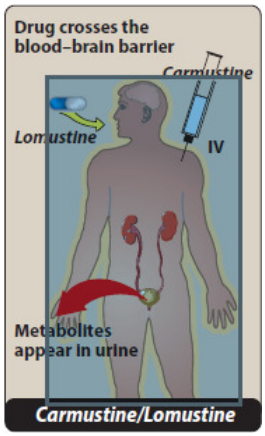
Most of the anticancer drugs are given IV except the alkylating agents , the most important one of them is cyclophosphamide.

When do we need to use an **oral drug**?

- When you have to tell your patient to go home. If the **treatment may take years**, like in case of children with **AML** who can get cured, or you need to treat patients with a palliative treatment (not IV), so we give them an oral cyclophosphamide.

- Another example is having a patient with a metastasized breast cancer, especially the **triple negative breast cancer**, the worst cancer that occur in ladies. We treat her, but the treatment won't cure her, even we cannot reduce the symptoms. So, we send her home and we give her a palliative treatment, and of course it has to be oral (cyclophosphamide).

B. Carmustine & Lomustine:



Considering **brain cancer (glioma)**, we use alkylating agents other than DOXO and CYCLO. We use **Carmustine (IV)** and **Lomustine (orally)** .

Why we don't use DOXO and CYCLO?

1- They don't cross the blood-brain barrier.

2- They don't have good activity against glioma.

The disease itself is heterogeneous so we use 2 drugs, carmustine and lomustine.

Sometimes to make sure that the drug stays in the brain, we use what is called biodegradable disc of lomustine which is inserted in the scalp and that will continuously produce the drug (for months), every time the cancer cells try to

come out ,it will find the drug. We call this post treatment suppression therapy (suppressing the recurrence).

Side effects:

Like the other drugs, bone marrow suppression and alopecia, ...

(3)Platinum analogs (i.e Cisplatin):

One scientist put 2 platinum electrodes to see the effects on bacterial cells. He noticed increasing in the bacterial size without division. Finally, he found that the replication process in the bacteria was inhibited . So, new drugs, called Platinum, was designed.

- In **colorectal cancer**, the main drug used is Platinum analogue, alkylating platinum, or cisplatin.

What is special about Cisplatin?

It produces a very **little bone marrow** suppression, and active against colorectal cancer.

Why platinum is not used in treating breast cancer?

Because cancer is a heterogeneous disease as we said, so each type has its own treatment (however, it could be used sometimes in breast cancer).

- Let me start reading: It is particularly effective in **germ cell tumours** (testicular cancer and ovarian tumours) and in breast cancer.
- Remember when we talked about **bleomycin** for testicular cancer, we said it causes LOW bone marrow suppression, so we can **combine it with platinum** to cure **testicular cancer .**

- Its main toxicities are to the kidney and to the ear. So, it **can't be combined with gentamicin** ,(also causes Nephro and Ototoxicity), **or vancomycin** because there will be any synergistic side effect activity .

  How to reduce the Nephrotoxicity?

  by hydration (للمرة المليون)

- Also, **cisplatin can't be combined with acyclovir** (IV) because of nephrotoxicity.

- Finally, cisplatin produces a relatively little myelosuppression, severe nausea, and vomiting.
- Don't forget that **cisplatin is mainly used to treat colorectal cancer**

Special Thanks to AMR AL-NAJJAR for helping me writing this sheet!

Good Luck All During Your Finals :)