PHARMACOLOGY

Number: 24

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Subject: Anticancer Drugs

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To recap the story back:

we said that we will talk about 3 types of cancer:
1- breast cancer
2- colon cancer
3- acute lymphocytic leukemia

They are the most important cancers in our community, because the most common cancer among **women is breast cancer**, among **men the colon cancer**, among **children is acute lymphocytic leukemia**.

Anti cancer drugs:

- Very important thing to understand in cancer treatment that it is not all about the treatment itself, it is also about how as a doctor you can deal with the adverse effects of anticancer drugs.
  You have to deal with the main 5 adverse effects which are very common when administrating of any Anticancer drug which are:
  1- Hair loss (alopecia)
  2- immunosuppression
  3- bone marrow suppression
  4- inhibition of epithelial renewal
  5- germinal cell damage

- in addition, you have to deal with every drug extra side effects which may not be shared between all anticancer drugs but specific for each one of them .(each anticancer drug has its specific side effect which another anticancer drug does not cause it and you have to deal with them all).

- There are 2 types of anti-cancer drugs: c**ell cycle specific** and **cell cycle non-specific.**
- In solid tumors, we have to use cell cycle non-specific drugs.

24.1 overview of DNA binding gents

1-Anthracyclines:
- DNA binding agents
- the most important one of them is **Doxorubicin**
- **Doxorubicin** used in treatment of **breast cancer**

2-Alkylating agents:

- ❖ alkylating the DNA “adding an alkyl group”, which Results in cross-linking thus breakage of the DNA , Ex:

  A-Nitrogen Mustards (cyclophosphamide) → going to be used to treat breast cancer as we said.

  B-Nitrosoureas (**Car**mustine and **lomustine**):
  Mnemonic: **limousine car**.
  -they can cross BBB (blood brain barrier), so they have been used as part of treating **brain tumors**.
  Only **lomustine can be given orally**.

3- Platinum analogs

The mechanism of action of this group is very similar to Alkylating agents, and there are many members of this group but the most important one that we required to know which cisplatin is**:**

- ❖ it is the backbone in treating all types of **colon cancer**
- ❖ The main adverse effect of cisplatin is **nephrotoxicity**.

- ❖ Note: whenever you are dealing with a nephrotoxic drug, you need to **hydrate** your patient to overcome this side effect, why??
  because the whole problem that causing nephrotoxicity is that the drug will precipitate in the nephrons causing nephrotoxicity , so when you hydrate your patient more and more , you will decrease the amount of precipitated drug.

24.2 Breast cancer treatment:

- Breast cancer is **solid tumor** so, How to treat solid tumors? -Always we have to stick with the story that we have to use drugs which are **not cell cycle specific**.

- so in treatment of breast cancer we use combine of two drugs :

1- Doxorubicin:

- it is an Anthracyclines
- Topoisomerase II poison.
- Has a limit of 500 mg/kg/day .If we exceed it, we'll end up with cardiac toxicity.

2- Cyclophosphamide:

- It's an Alkylating Agent!

Side effects:

- It can cause **cystitis** (inflammation of the urinary bladder): a metabolite of cyclophosphamide is **acrolein**, acrolein is toxic for the urinary bladder.

- The solution is to not only give an antidote for cyclophosphamide, but also for acrolein co-administer cyclophosphamide with N-acetylcysteine (or **mesna**).

24.2. A Therapeutic uses of these drugs:

- So, the first therapy for breast cancer is combination between **doxorubicin** and **cyclophosphamide**. (Doses are not to memorize)

- It is a very great therapy after doing the **eradication surgery (adjuvant therapy), in** order to hit hard the cancerous cells

that have escaped from the primary cancer (metastasized cancerous cells).

- The idea here is that we use double mechanism of action to destroy metastasized cancer cells.

- Why we don't use another drug with these ones?
  -It is very complex story but in brief, because **both cyclophosphamide and Doxorubicin are immunosuppressant** drugs, so if we use another immunosuppressant drug with these we are killing the patient actually. So it is very complicated story.

To sum up

- We need to hit hard!
- We need to use a nonspecific cell cycle drugs when dealing with solid tumors like breast and colon cancers.
- treating of breast cancer by using dual drug activity which are **cyclophosphamide and Doxorubicin.**
- treating of colon cancer (we took one drug for colon cancer until now) by using **cisplatin** which has cell mechanism of action similar to the Alkylating agents because it is Platinum analog.
- Cisplatin is a nephrotoxic drug.
- When dealing with any nephrotoxic drug, the solution is to hydrate your patient.

24.2. B mitotic spindle inhibitors

Now, we are done with the first mechanism of action, which is -generally speaking- DNA based, cyclophosphamide and doxorubicin.

The second mechanism of action that we are going to use is a totally different mechanism of action, as **here we are allowed to use cell-cycle specific drugs.**

We have dividing cells within the body, and those dividing cells will be targeted through their mitotic spindles- part of the cell cycle-, so when you're inhibiting those mitotic spindles; then **you are inhibiting the cell replication within the M phase.**

- ❖ You have two options, either you inhibit the array- which mitotic spindles come out from- or you inhibit the pull out:

1- If you are inhibiting the array from going toward the centromere or toward chromosomes, then you are inhibiting something called **POLYMERISATION**, these drugs are called *Vinca alkaloids.*

2- *If* you are inhibiting the degradation of those chromosomes after segregation, we call it inhibition of **Depolymerisation,** these drugs are called *Taxol "Paclitaxel*".

Those are great drugs; we find them very effective in treatment of breast cancer and they are effective in many places, so we actually use them for many cancers.

1-Taxol:

- ❖ The Texans, of which Taxol is the best known example, are isolated from the yew tree.

  P.S: Don't take herbalists as medication_ تخريف_! It's all about "dosing", when you are taking/drinking chamomile for example, you are not taking the actual dose!

Pharmacodynamics:

- ❖ They bind to tubulin but have the opposite effect to the "Vinca alkaloids" and stabilize microtubules to Depolymerisation, So we call them "mitotic spindle poison".

It is very critical to understand the difference between INHIBITORS and POISONS...

- ❖ **Poisons**; I'm using the component of the cell to induce the inhibition of replication, in other words, I'm using the cell to kill itself.

We generally call them Topoisomerase poisons, all these Taxols are poisons –not inhibitors- , and we call them so because we leave things happen then stop them, so what really kills the cell or cytotoxic the cell is the design itself.

So topoisomerase alters the supercoiled form of DNA, but in term of gyrase, gyrase cut the DNA but it cannot rejoin with the DNA, so we use the topoisomerase to bactericidal the drug in case of Quinolones.

So when we use (Taxols, topoisomerases, or fluoroquinolones) we are **not going toward the enzyme and inhibit it**, instead, we need the enzyme to work and after it works we target it to stop its work. And that's the difference between poisons and inhibitors.

Side effects:

- Taxanes are **more toxic than Vinca alkaloids**, the side effect here is something new and you need to deal with, it is the NEUROTOXICITY which is a peripheral neuropathy.

As we said before dealing with cancer drugs is complex, rather than all that problems that we cause to our patients "Anemia, leucopenia, thrombocytopenia, nausea, vomiting, and alopecia" still we have extra things with drugs.

Actually, it is not easy to convince the patient to take cancer drugs, an issue that we unfortunately don't take care of.
So you have to sit with your patient and tell him that we are going to take care of you, because these drugs are really toxic, really annoying. Your patient needs you to sit him down and tell him about his drugs, and that using them is our only option, and that we will support him from the beginning to the end!
Many Patients actually may refuse to take drugs, that's why we have to deal with this problem.

Although anticancer drugs have sever side effect but the patient should take them but he is not forced to do so, it's his option.

Note: no drug-drug interaction with anticancer drugs.

- The manifestations of the peripheral neuropathy (the side caused by Taxanes) include **numbness** & **joints pain**.

Clinical use of Taxons:

- We start treating by doxorubicin given in combination with cyclophosphamide
- Patient is treated with doxorubicin in 4 cycles, every cycle is 21 days; patient is dosed for 3-4 days and then left alone for approximately 2 weeks , patient not dosed for 2 weeks to allow bone marrow to return to normal.
- After the 4 cycles, **Paclitaxel** is given.

2-Vinca alkaloids:

Vinca alkaloids, like *Vincristine* (naturally product isolated from the periwinkle plant) & *Vinblastine*, act by **binding to tubulin & inhibit its polymerization into microtubules and by so prevent spindle formation during mitosis** arresting the dividing cell in metaphase. These drugs are widely used in cases of having **solid tumor**, **leukemia** & **lymphoma**.

Side effects:

- Peripheral neuropathy is a **trade mark for all mitotic spindle poisons** including Vinca alkaloids → no one knows why or how it's caused.
- Vinca alkaloids drug Vincristine has relatively **less myelosuppression**
- Note: **Vincristine** and **cisplatin** have less bone marrow suppression.

24.2. C other drugs used in breast cancer

1-Herceptin: (Trastuzumab –trade name-)

Pharmacodynamics:

- A monoclonal antibody →prescribed for those with epidermal growth factor type 2 (HER2) over expression (it's common to

be over expressed in breast cancer (~30% of cases in Jordan are HER2 +ve)).

- Being a HER2 positive breast cancer is bad, because breast cancer has many tribes and that is one of them, and it is be **more invasive**, have greater ability to metastasize, etc.

- Note that epidermal growth factor type 1 over expression is also related to breast cancer.

Side effects:

- Herceptin (like Doxorubicin) is cardio-toxic that's why we don't treat these cancers with Herceptin from the first place.

- Note: Herceptin & Doxorubicin shouldn't be combined together as the both of them cause cardio-toxicity.

2-Tamoxifen

If one single cancerous cell is left after the therapy course we don't want it to have a driver to derive a new cancer. So if the patient is ER +ve, estrogen is a deriver of cancer so we should deplete it either by **inhibiting the synthesis of estrogen** or by **giving the patient an anti-estrogen receptor** (estrogen receptor inhibitor).

Pharmacodynamics:

- It is a selective estrogen receptor modulator (SERM) which means that it has both estrogenic and anti-estrogenic effects on various tissues.

- Note that we said that tamoxifen is a selective **modulator** not a selective inhibitor! As this drug when it binds to one receptor it inhibit it, and when it binds to the same receptor in another site it will activate it.
- So in pharmacology when a drug has an unclear function as an agonist or antagonist we called its function as "selective modulator" drug.

- ❖ Backing to tamoxifen, this drug is an inhibitor in the breast while it is an agonist in the endometrium so if I'm treating a patient from breast cancer I may cause an endometrium cancer to arise! And that's why this drug has a limitation.

- ❖ This limitation leads us to do something which we call it the "cut off" process as a lady that is on this drug have to stop using it after 5 years or she will **develop an endometrium cancer.**
- ❖ So AGAIN, the patient must stop administration of tamoxifen after 5 years.

Note: There is a study called Atlas study said recently that if we use tamoxifen for 10 years instead of 5 years we will increase the incidence of producing endometrium cancer by only 1%, but that still under investigation.

Clinical uses:

- ❖ Patients with estrogen-receptor (ER) positive tumors are more likely to respond to tamoxifen therapy, while the use of tamoxifen in women with ER negative tumors is still investigational.
- ❖ Another important use for tamoxifen is that we use it as a prophylactic drug for patient with high incidence to have breast cancer; patients with braca-1, braca-2 mutations.

- ❖ It is active **orally** and is therefore particularly useful in maintenance therapy.

3-Trastuzumab

- ❖ It is a Her2 inhibitor which is an epidermal growth factor receptor family that is overexpressed in 25% to 30% of breast cancers.
- ❖ "mAb" in the end of its name means monoclonal antibody, and every drug that ends with "mab" has the same function.

Clinical uses:

- Trastuzumab is an anti-HER2 monoclonal antibody for HER2- positive metastatic breast cancer treatment as an adjuvant treatment (in combination with **doxorubicin**, **cyclophosphamide**, and **paclitaxel**).

- **Not** all breast patients have an over expressed Her2 gene so doctors are **not** allowed to give Her2 inhibitors unless they do a **test** that prove that this patient have a mutation in the Her2 gene.
- We use Her2 inhibitors for one year as one injection per month.

- Now, if the breast cancer were too big and you couldn't dissect it you have to use cyclophosphamide, doxorubicin and Taxol before surgery in order to **shrink** the tumor and then you do the surgery. "This process we call it neoadjuvant"

  **In this case we don't use Her2 inhibitor or tamoxifen as a neoadjuvant, we use them only after the surgery as adjuvant drugs.

To treat breast cancer...

1-adjevant therapy:

- 4 cycles of doxorubicin (SE :*cardiac toxicity*) + cyclophosphamide
- after these 4 cycles we use paclitaxel (SE : *neurotoxicity*)
- if the patient was HER2 +ve , we use Herceptin (it also cause *cardiac toxicity* , so never give it with doxorubicin)
- if patient ER +ve we use tamoxifen

2-**neoadjevant therapy: Trastuzumab** for patients who are HER2 +ve

3-prophylaxis: tamoxifen in patients with braca-1 and braca-2 mutations

24.3 Antimetabolites

- The most important thing about the antimetabolites that they are the most effective against **leukemia**.

- In leukemia and lymphoma we can't include a non-cell cycle specific drugs as in the liquid tumors don't ever inter the G0 phase as if they stop replication they will die.

1-Methotrexate

- The first drug from this group is **Methotrexate** which is a **folic acid analog.**
- This drug is very important in treating cancers and auto-immune diseases because it is an immunosuppressant drug. In auto-immune diseases absolutely the dose of methotrexate will be less than the dose that we use for treating cancer. You may link methotrexate to the **sulfonamides** as both of them are dihydrofolate reductase inhibitors.

- **Methotrexate** is widely used clinically, usually administered orally, it is used against **acute lymphocytic leukemia**.

2-Azathioprine (Mercaptoguanine) (Purine Analog): it is like the acyclovir, as it is a false metabolite that we can use to inhibit DNA elongation.

3-Fluorouracil which is a pyrimidine analog also it inhibits the DNA elongation.

- Fluorouracil, 5FU، incorporated into DNA and RNA, finally inducing cell cycle arrest and apoptosis by inhibiting the cell's ability to synthesize DNA. (S phase specific).

- It is widely used in **colon cancer** along with **cisplatin**.

So Colon cancer treatment **is 5-Fluorouracil** and **cisplatin.**

5-FU is effective in palliative management of carcinoma of breast, colon, pancreas, rectum and stomach in patients who cannot be cured by surgery or other means.

•Its main toxicities are myelosuppression and gut epithelial damage.

Side effects:

Antimetabolites drugs don't have special side effects, so they don't cause neuropathy problems or cystitis or any other problem

20.4Chemotherapy for acute leukemia

- Chemotherapeutic treatment is a complex of a long way of treatment up to 3yrs,during this period we have these phases:

1-Induction:

- We hit hard so we are trying to get rid of the disease completely, so we are trying to kill every cancerous cell in the child.
- In a period of 4-6 weeks we used these drugs:

A-Vincristine: which a mitotic spindle polymerization inhibitor It is not a strong bone marrow suppressor so we can dose it highly.

B- Glucocorticoid

C- L-asparaginase: Leukemia cells are the only cells cannot synthesize asparagine, so we deplete the asparagine from the blood, so it is kind of target therapy.

2-Intensification (aka: Consolidation):

We treat similar to the induction but with less frequency:

- **Methotrexate (MTX)** with **6-mercaptopurine (guanine like nucleotide).**
- **6-mercaptopurine is injectable.**
- **The oral form of mercaptopurine a prodrug called Azathioprine.**

3-CNS prophylaxis:

- Patients with **ALL (acute lymphocytic leukemia)** frequently have meningeal leukemia at the time of relapse (50-75% at one year in the absence of CNS prophylaxis) and a few Have meningeal disease at diagnosis (<10%).
- Simply as a result of the harsh treatment the leukemic cells may metastasize to the brain, and develop a brain tumor.
- **Intrathecal** (methotrexate, cytarabine, steroids).
- And for **adult high-dose systemic chemotherapy** (methotrexate, cytarabine, L-asparaginase).

4-Maintenance:

- Maintenance usually consists 1. **Weekly methotrexate** and 2. **Daily 6-mercaptopurine** as **Azathioprine**.
- 2-3 years
- Oral Drugs.

Bevacizumab

- **Bevacizumab** inhibits the action of VEGF (**Vascular endothelial growth factor**), a blood vessel growth Factor When VEGF is bound to Bevacizumab, and it cannot stimulate the formation and growth of new blood vessels.
- Prevents VEGF from binding to its receptor.
- Adds to the effects of chemotherapy in cancers like bowel and lung.
- FDA-approved for colon cancer.

- First-or second-line colorectal cancer treatment in combination with 5-fluorouracil and **cisplatin** chemotherapy.
- Remember that's such drugs cause fatigue so the mother could skip some doses (we have to be aware and warn her).

Imatinib (gleevec)

- The only active drug in target therapy (in reality)
- Philadelphia chromosome or Philadelphia translocation is a specific chromosomal abnormality that is associated with chronic myelogenous leukemia (CML).
- This translocation results in the Bcr-Abl fusion protein, the causative agent in CML, and is present in up to 95% of patients with this disease.
- The other 5% we use antimetabolite therapy.

The end ….