Anti-Cancer Drugs

Today's lecture is somewhat heavy, so you need to concentrate well.

- If you remember we talked about cancer and we have a problem in cancer called heterogeneity, other problems include: Tumor Cells Are Not Immunogenic, tumor stem cells, deregulation of apoptosis. These problems are making cancer treatment very difficult and to treat something difficult, we need to use something called combination therapy.
- If you remember H. Pylori, we used a regimen or a "cocktail", AIDS also require combination therapy. And with cancer we always deal with combination therapy, but combination of what? Different mechanisms of action. If you want to combine drugs together, it's non-sense to combine drug with the same mechanism of action, right? Simply you want to attack the cells from different points of view.

❖ What are the mechanisms (classes) that we have?

1. **DNA binding agents.** We want to deactivate the DNA through these drugs (intercalating agents and alkylating agents)
2. **Mitotic spindle inhibitors.** We want to inhibit the mitosis through the inhibition of mitotic spindle (Modulators of tubulin polymerization) we will take about it in details the next lecture.
3. **Antimetabolites.** We want to reduce the cell's metabolites to reduce the synthesis of purine and pyrimidine. If there is no purine and pyrimidine, there is no proliferation.
4. **Hormones and hormone antagonists.** If the cancer you're dealing with has hormonal parts, like breast cancer, we need to suppress the hormone.
5. **Miscellaneous anticancer drugs.**

- ✓ You should know that anticancer drugs are a lot, and every year new drugs are produced.
- ✓ When treating cancer, you should always remember that you are killing things beside cancer cells, like hair (leads to alopecia), Gastrointestinal epithelial cells (leads to nausea and vomiting), and bone marrow (leads to myelosuppression).
- ✓ We are going to speak about two cancers mostly, which are breast cancer and acute lymphocytic leukemia in childhood because they are common.

❖ How to treat breast cancer?? If we need to treat breast cancer, we need to use a regimen. This regimen depends on many things. The bottom line of the story is to use chemotherapy regardless if the patient were Estrogen receptor positive(ER+) or ER-. HER-2 positive or HER-2 negative, we have to chemotherapeutic this patient. How?

- The best regimen to use these days is (Anthracycline and Taxans) which is called Anthracycline-based therapy.
- What are the adds-on drugs?
  - If the patient is ER+ we must add a drug called tamoxifen (antagonist for ER receptors).
  - If the patient is HER-2 positive, I have to antagonize HER-2 with Herceptin (Trastuzumab) .
  - If my patient had high vascular endothelial growth factor, I may give her a drug for the angiogenesis activity.
  - If the patient has a metastatic breast cancer, then the situation is very different. We are going to hit her in many ways. We have a preferred first line therapy and second line therapy.

- This all to tell you that we are going to use a lot of drugs and different regimen for the different situation.

DNA binding agents

- We are going to talk about DNA binding agents, we are going to talk the prototype called Doxorubicin, and this is the best drug in cancer and the main component of breast cancer regimen. When we say Anthracycline dependent breast cancer treatment, this means depends on Doxorubicin because Doxorubicin is "anthracycline, a chemical structure".
- How Doxorubicin works? It's similar to Ciprofloxacin if you remember. When the DNA is open and undergo zipping there will be coiling, and topoisomerase is needed to resolve the coiling, so if there is no topoisomerase in the cell there will be no replication because the DNA will be coiled and unzipped. So Doxorubicin traps topoisomerase and prevent it from joining the DNA. You must remember that this activity is for all dividing cells in the body, so Doxorubicin has good activity on almost all types of cancers but with side effects that includes: alopecia, nausea, vomiting, bone marrow suppression, and immune suppression.
- Although that this drug is good for treating cancer, it produces free radicals which goes to the heart and may cause heart failure or what we call cardio toxicity. So we have a strange dose-limit which is, 400mg/kg/m^2 accumulated dose, if we increase the dose above that number then we increase the risk of cardiac toxicity. One of the ideas is to give an antiradical but it's not really working.

  - To sum up, this is the first drug in the treatment of breast cancer, with "the 5 common side effects" plus cardiac toxicity.

ALKYLATING AGENTS

- Now I need to give a drug with another mechanism of action targeting something else to synergize their activity, the second drug is the alkylating agent. It's a drug that binds to Guanine, how? The alkylating agent binds with two N7-Guanine residues in the DNA which results in the breakdown of the DNA and producing a cross-linked product. The name of this drug is Cyclophosphamide.
- However, it has the following side effects: alopecia, nausea, vomiting, bone marrow suppression, and immune suppression. It cause also Cystitis (inflammation of the urinary bladder) resulting from the metabolites of the drug (Acrolein), so we add Acrolein deactivator (N-acetylcystein or Mesna).

✓ We use this drug (Cyclophosphamide) because it's the best drug to combine with Doxorubicin.

Now we will talk regarding other cancers beside breast cancer for a moment. Other drugs from the Alkylating agents group are used to treat two cancers.

Nitrosoureas

- First is brain tumors (Glioma) , the drugs used here are called Nitrosoureas (Carmustine and Lomustine), these drugs can cross the blood brain barrier. After the brain surgery for the tumor we insert what's called degradable disk that contains these drugs (Carmustine or Lomustine) within the brain, this disk release the drugs over long period of time that can reach to 6 months, this method is called Post-treatment suppression therapy. So if there is a cancer cell that we couldn't take through surgery or chemotherapy, we don't want it to come back and produce another cancer.

Platinum analog

- Second is the colorectal cancer, we use a Platinum analog drug called (Cisplatin), this Alkylating-like drug is used in treatment of this cancer and has a special issue of selecting toward colorectal cancer but we don't know how. So when we give those drugs to the colorectal cancer patients they are very selective, in addition to provide little immunosuppression and this is called marrow-sparing, this let us use this drug in a higher dose than other drugs.

- This drug also used in testicular and ovarian cancers frequently leading to complete cure, the complete cure results from the bone marrow-sparing and the ability to give a high dose.

- However, it has other side effects related to the kidney and the ear, so we can't combine them with other drugs that cause kidney and ear side effects like Furosemide and Gentamicin. To reduce this toxicity we need to hydrate the patient by giving him normal saline.

Antimetabolite

We want to deplete the cells from the building blocks (purine & pyrimidine) so we'll have anti-purine or anti-pyrimidine.

➢ They are three types:

1. **Purine analogue :**
   - 6-mercaptopurine, azothioprine
   - Mechanism of action: It will be introduced to the DNA as a nucleotide but the polymerase can't continue the replication with it because it's FAKE nucleotide.

- We use purine analogue (e.g.: 6-mercaptopurin) for the treatment of breast cancer and childhood acute lymphocytic leukemia (ALL)

2. **Pyrimidine Analogs:**

5-fluorouracil will be used by DNA polymerase instead of uracil.

3. **Folic Acid Analogs:**
Trimethoprim and Methotrexate
Inhibit dihydrofolate reductase (DHFR), which results in inhibiting purine synthesis so the cell will not have purine therefor the cell can't go to cell cycle and eventually we will inhibit replicating all cells: cancer or even normal.

➢ Side effect is similar to other drugs and include bone marrow suppression, alopecia, epithelial GI problems, immune suppression

✓ 6-mercaptopurine, Azothioprine, Methotrexate are the most important, not because they are used in cancer treatment but because it's used in psoriasis, rheumatic arthritis and as an immunosuppressant in organs transplantation.

♣ To sum up the Antimetabolites: we either inhibit the enzyme that synthesis purine (methotrexate) or I give false purine (Azathioprine, 6- Mercaptopurine) or false pyrimidine (Fluorouracil)

Methotrexate

- Methotrexate is widely used clinically, usually administered orally. The most important use for Methotrexate is childhood acute lymphocytic leukemia and metastasized breast cancer.
- Main toxicity is myelosuppression because it's not selective
- The Antimetabolite (Methotrexate) they are very effective drugs which deplete the purines in the cells so if the dose is higher than needed, the patient will suffer from complete myelosuppression and that's a life threatening situation, we don't want to reach this situation so we need

to rescue the bone marrow therefor we give him Folic acid (calcium leucovorin).

✓ Acute lymphocytic leukemia main regimen contain either Methotrexate or 6-mercaptopurine (not together)

- Methotrexate, Azathioprine and 6-mercaptopurine are also used for rheumatoid arthritis, inflammatory bowel disease (IBD) and other autoimmune disorders. The idea is myelosuppression thereby suppressing the immunity but the dose here is lower than the dose we use in cancer, e.g.:
  - Methotrexate dose is 15mg/week for rheumatic arthritis and IBD But in cancer we hit hard more than 100mg/day, because in cancer we need to kill every dividing cell but in rheumatic arthritis and IBD we want to reduce the immunity a little

In metastasized breast cancer I can use 2 regimen:

I. Anthracycline based

II. Antimotabolite based (CMF) **C**yclophosphamide, **M**ethotrexate, **F**lurouricl

We can use any one of them and change to the other if needed.

DONE BY

EBRAHEEM ALABDALI