PHARMACOLOGY

◉ Sheets ○ Slides

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Done by: Lena Sarhan

Corrected by: Amer Sawalha

Subject: Anti-Cancer Drugs 2

Doctor: Malek Al-Zihlif

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Cancer "Cocktail"

- Cancer is something that is heterogeneous, meaning that it is very complex and needs a treatment that will target different aspects of the tumor.
- This is why we use a cocktail of cancer drugs→ using more than one drug that will target different things.
- The larger the cocktail, the better because more targets are being attacked.
- Something important to keep in mind is that the **major toxicity factors should differ; they should not overlap**→so drugs with similar side effects SHOULD NOT be given together.
- The cocktail should consist of drugs that have DIFFERENT targets.
  - *Remember: in antibiotics, when treating pseudomonas you would give an anti-pseudomonal penicillin in combination with an aminoglycoside or fluoroquinolone*

Treatment Response

- There are cancer patients that experience a resistance to anti-cancer drugs, **intrinsic resistance**. In general, any metastatic cancer can become resistant.
- There are some cancers that are treated, and the patient shows a great response, but after a while (can be a year or even 10 years), the patient returns with the same cancer. This is because there was a resistance during treatment, or the cancer was already resistant, and it could not be detected.
- There are 4 reasons for resistance/cancer coming back:
  1. **Genomic instability and hypermutability**
     - Tumors are not constant lumps, they are always changing; the primary tumor can be completely different from its metastatic deposits.
     - One person's cancer can be biochemically different from another person→one will respond to treatment and the other may not (the reality is that each patient can't have a specially designed treatment down to the last detail, so there is always the possibility that the main treatment used will not completely eradicate all of the cancer of one patient compared to another patient who the treatment is perfect for).
  2. **Tumor cells are not immunogenic**
     - Cancer cells do not have antigens.
     - They produce proteins that go to the immune system (T-cells) and inhibit its activity.
     - Cancer is not affected by the immune system, so even when it comes back, the immune system can't do much.

3. **The numbers game**
    - 10^8 tumor cells can be visible on an X-ray.
    - Cancer cells are hard to detect in early stages.
    - It is important to kill every cell for treatment, because remember tumor cells can evade the immune system.
    - If there are 10^{11} tumor cells present, killing 99.99% of them leaves 10^7 residual cells.
    - If there is one single cell left in the body of the patient, the cancer can come back.
    - That's why even after surgery when the lump is removed, chemotherapy is done to make sure the cancer cells are gone. This is called "**adjuvant therapy**".
4. **Poor tumor vasculature**
    - If there is no surgery, there is no way to get to the center of the tumor.
    - Angiogenesis of tumors are poor, so this leaves parts of the tumor without nutrients and oxygen (usually the center), creating a **hypoxic condition**.
    - Cells under hypoxic conditions do not divide (remain in G_0) and are resistant to all anticancer drugs.
    - After drug treatment, these cells may be re-populated and may get the opportunity to be re-oxygenated and this new cancer will be resistant to anticancer drugs.
5. **Deregulation of apoptosis**
    - The genomic instability of tumor cells leads to deregulation of apoptotic pathways.
    - Results in generalized reduction in sensitivity to all forms of cellular insult.

Anti-cancer Drugs

- There are 5 classes of drugs:
    1. DNA binding agents
    2. Mitotic spindle inhibitors
    3. Antimetabolites
    4. Hormones and hormone antagonists
    5. Miscellaneous anticancer drugs
- There are 2 types of anti-cancer drugs: **cell cycle dependent/specific** and **cell cycle non-specific**.
- Cell cycle specific drugs work on the cell cycle.
- Not all tumor cells enter the cell cycle and divide. There is a **growth fraction**, and usually only 10-20% of tumor cells grow in a solid cancer. So cell-cycle specific drugs will target 10-20% of the cells in a solid tumor.

- Therefore, in solid tumors, non-cell cycle specific drugs need to be used as well.
- Non-cell cycle specific drugs are very toxic; they kill everything (dividing and non-dividing cells).
- Cell cycle specific drugs do not work well in solid tumors because the growth fraction is low.

Breast Cancer

- Most breast cancer patients will start treatment with a non-cell cycle dependent drug→**Doxorubicin**

Doxorubicin

- It is an anthracyclin.
- It is a **topoisomerase II inhibitor**.
- Every single patient affected with breast cancer will take doxorubicin.
- It has a side effect that limits its activity→shouldn't be given in high doses.
- **Given in combination with cyclophosphamide** (alkylating agent).
- 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.
- During treatment, patient will suffer from fatigue.
- During the cycles the patient will be immunocompromised.
- Treatment with doxorubicin SHOULD NOT exceed a certain amount→ there are dose-limiting side affects associated with the drug.
- Cardiomyopathy is a dose related side effect.

Alkylating Agents

Cyclophosphamide

- It can be taken orally, but when treating breast cancer it is injected.
- In palliative therapy, oral treatment of cyclophosphamide is given.
- It can cause **cystitis** (inflammation of the urinary bladder) → a metabolite of cyclophosphamide is acrolein; acrolein is toxic for the urinary bladder→ so the solution is to not only give an antidote for cyclophosphamide, but also for acrolein→ co-administer cyclophosphamide with **N-acetylcystein** (or **mesna**).

~Below is off topic from breast cancer treatment, doctor continued to speak about other alkylating agents

Nitrosoureas

- There are 2 really good drugs that **can penetrate the blood-brain barrier** under this category→ **Carmustine** and **Lomustine**.
- They are drugs of choice in treating brain tumors.

Cisplatin (Platinum Analogue)

- It's not as effective as doxorubicin.
- It has an efficacy against a wide range of neoplasms.
- Main drug used against **colon cancer**.
- It is **nephrotoxic**→ its nephrotoxicity can be reduced by hydrating the patient.

~Back to breast cancer

- After the 4 cycles of treatment, cells need to be inhibited from proliferating.
- If the mitotic spindle is inhibited, the result would be an M Stop.
- Mitotic spindle inhibiting drugs are M phase specific (cell cycle specific drugs).
- After the 4 cycles, **Paclitaxel** is given→ inhibits degradation.

Paclitaxel

- Isolated from yew tree
- Side effect: peripheral neuropathy

- If breast cancer patient has tumor that is estrogen positive, then should be given anti-estrogen drug → Tamoxifen.
- If patient is epidermal growth factor positive, then should be given drug to inhibit epidermal growth factor.
- Breast cancer has overexpression of HER2; an epidermal growth factor present in 25-30% of breast cancer patients.
- If there is HER2 overexpression then the patient should be given Herceptin, but it is usually not given in the beginning (when given, it's an injection each month for a long period of time).