CANCER THERAPY

• We will have some lectures to talk about anticancer drugs, cancer treatment from a pharmacological point of view, this will be something very challenging because if you really want to learn how to treat cancer we need more lectures and to get an extra lecture is something more challenging than the treatment itself.

• We will not memorize most of anticancer drugs, just memorize the prototype of each class.

• This lecture is just an introduction about cancer; to know the most important features of cancer, to help us understand the mechanism of cancer therapy [*actually it's a very easy lecture most of the information are already known by most of us*] .

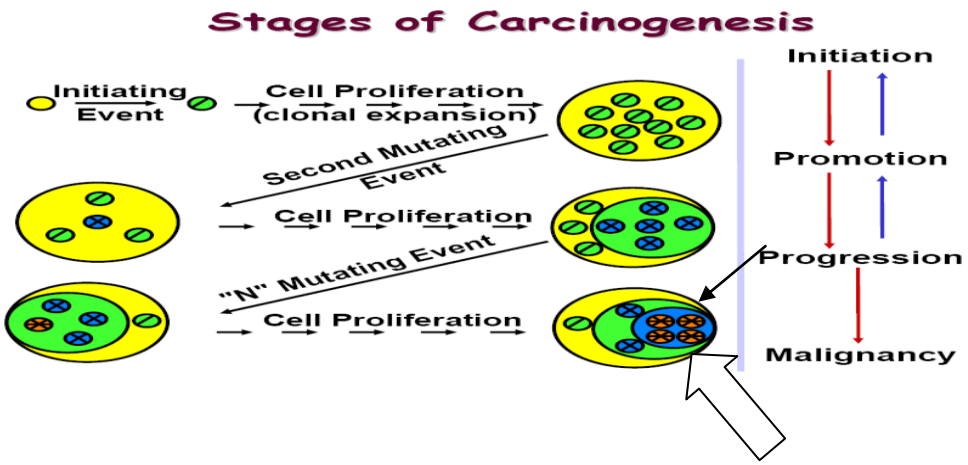
• Some of the information is not logical and contradicts our knowledge of cancer but that's what has been said in the lecture.

•The points between the {} are read by the doctor from his slides

***The main difficulty of cancer treatment is its **heterogeneity** between the population (between cancer patients); if we assumed that we can identify 200 types of cancer, within these 200 types we have another million subtypes.

→Because of this heterogeneity the Survival Rate of cancer patients with treatment will be very broad even if we are comparing patients within the same class of cancer and taking the same medication.

→ Remember, cancer is **MONOCLONAL IN ORIGIN** ; a single cell will build up the whole cancer mutations, so the heterogeneity originated from the building up of mutations through stages (steps of mutagenesis) within the same cell ; the normal cell is being hit by mutations resulting in its conversion into an abnormal one (this cell will build up more chance to become cancerous) .



→As you see from the previous diagram , we have a lot of mutations, in pharmacology we need to hit all of them(all the circles within the pointed malignant cell) ,so we need to combine drugs to treat cancer ;one drug will not work on all levels of mutations .here comes the term **cancer drug cocktail /cancer drug regimen .**

→***So as a rule ; there is no cancer patient who can be treated with only a single agent except CML patients***.

***Remember CML(chronic myeloid leukemia) have a chromosomal translocation which results in the **Philadelphia chromosome** and this Philadelphia chromosome is the only driver (leader) in CML so if you inhibit/damage it you will damage the cancer, and that's the rule by which our magical drug **Imatinib** works, which is used to treat CML, but again and again this is an exception .

Imatinib is a tyrosine-kinase inhibitor used in the treatment of multiple cancers, most notably Philadelphia chromosome-positive (Ph^+) chronic myelogenous leukemia (CML).

•Summery of the next point "مشان الله لا تدخنوا":

→ Statistics showed that Lung cancer has become the leading cause of death in ladies and 95% of Lung cancer is related to smoking ((here, the doctor mentioned ladies because from his point of view Jordanian smoking Men are a hopeless case :P)) .

HALLMARKS OF CANCER:

1- **Tumor suppression genes level** mutations which start at the very early beginning of the cancer so the cell will proliferate without stopping = no breaks.

2- **Oncogenes Level** mutations, the cell will have a very fast proliferation.

3- **DNA repair genes level** mutations.

4-The cell will **adapt to resist apoptosis**.

5- **Reduction of immunogenicity,** so immunity can't recognize cancer.

→By these mutations/ Hallmarks the cell now is transformed into a cancerous cell= the cell will have Tumorigenicity (tends to produce tumors) and by this tumorigenicity the cancer cells will proliferate more and more, so they will need

more *nutrition* and *blood supply*; as a result they will produce **VEGF-2 and PDGF** to start building their own angiogenesis.

HOW TO TREAT CANCER ?

1- **Surgery**; mainly for primary tumors (A **primary tumor** is a tumor growing at the anatomical site where tumor progression began and proceeded to yield a cancerous mass) .

2- **Radio-therapy**; done by targeting/hitting the DNA of the dividing cells, resulting in the breakage of DNA which will induce apoptosis of the cells, but remember, many cancer cells have become resistant to apoptosis (this is one of the mechanisms where we have resistance for cancer treatment).

3- **Chemotherapy**(our major concern now) ; only effective in 10% of the patients .

→The Dr noted that in the slides it's written as follows:

{Most of the 50% cure is affected by surgery and radiotherapy on non-metastatic tumours .};this 50% not only by mono-therapy but combined therapy (surgery with radio or with chemo) .

▪We have three important terms to deal with in cancer treatment:

CURATIVE

▪ Here, cancer patients will not get the cancer again in their lives = we can rub out the cancer, but chemotherapy doesn't produce remission (isn't curative) except in 4 types of cancer:

1-**Childhood ALL** = 90% of the chemotherapy which is done for patients with ALL is a successful treatment; we can cure the cancer ….. And yes, this percentage is here in Jordan at KHCC.

2-**Basal cell carcinoma** is very curable with chemotherapy, most common form of skin cancer.

3-Testicular cancer.

4-Wilms' tumor : it is a cancer of the kidneys that typically occurs in children, rarely in adults.

-another curable cancer that we mentioned before is CML where we have the magical **imatinib, so we have a total of 5 curable cancers**.

*we can use the term **remission** (A decrease in or disappearance of signs and symptoms of cancer) referring to curative.

*ALL : acute lymphoid leukemia .

TREATMENT

▪Here, we give the patients the medication and this medication will suppress the cancer for a while i.e. for certain duration and this duration can vary between patients very broadly depending on:

1- The mutations profile of the cancer.

2- Pathological stage of cancer; *advanced cancer* OR *late stage cancer*.

3- Invasiveness of the cancer.

PALLIATIVE THERAPY

▪We just help the patient to live better by eliminating the symptoms.

▪We help Improve the quality of life.

▪ The situation of the tumor here is very bad; we give the patient chemotherapy to alleviate symptoms and/or pain, but we almost know it's hopeless case.

▪it's a common therapy with an already metastasized tumor, like:

♯ **Breast cancer with Triple negative** which commonly metastasize**.**

♯**Non small cell lung cancer** = worst case; most likely death.

→A very important thing to remember is that when we are talking about chemotherapy we are targeting every dividing cell within the body whether it's a normal cell or a cancerous one, so in addition to cancer cells we are targeting :

A- normal skin cells (hair follicles) **B**-Epithelial cells of the gut

C- hematopoietic cells (BM cells including immune cells).

♯As a result the patients who are receiving chemotherapy will have:

Alopecia (hair loss) **, Nausea**, **Vomiting , Diarrhea , BM suppression** (anemia; fatigue and immune suppression →Because of this Immunosuppression we give the patient ; antifungal, antiviral and antibiotics.

♯We give the chemotherapy in cycles; divide the huge dose which is supposed to eliminate the cancer, into smaller doses over intervals of days between each dose. (In general, chemotherapy treatment is given in cycles. This allows the cancer cells to be attacked at their most vulnerable times, and allows the body's normal cells time to recover from the damage)

♯WHY WE GIVE THE CHEMOTHERAPY IN CYCLES?

1- Because of the aforementioned side effects, the large dose needed to eliminate the cancer is intolerable, so we give the patient the highest tolerable dose in cycles and give time for Erythropoietin to induce the Hematopoiesis.

2- The angiogenesis for the cancer is very poor, so we are reaching the cancer by cycles; the first cycle will reach the outer layer, then by cycles we give this poor angiogenesis time to supply the next deeper layer so we are able to kill this deeper layer. This enables us to penetrate as much as we can into the cancer lump, until we reach the cancer stem cell.

**these side effects are not present in targeted therapy.

***GOALS OF CANCER THERAPY*:**

1- Curative; total eradication of cancer; (remember the five types of cancer which were mentioned above as curative because the dr repeated them many times).

2- Palliative therapy.

3- Adjuvant therapy:

- It is helpful for surgery.
- Attempts to eradicate microscopic cancer after surgery
- e.g. breast cancer & colorectal cancer

→ given in cycles to make sure that we got rid of those microscopic cells.

4- *Neoadjuvant* therapy; the administration of therapeutic agents before a main treatment (before doing the surgery to excise huge masses, we give some chemotherapy esp. if the edges are not clear).

SO WHY ARE WE NOT CAPABLE OF TREATING CANCER?

1- ***Genomic Instability and Hypermutability***

- { The de-regulated genome →→ genetically heterogeneous tumour
- Damage to DNA repair genes is critical → → more heterogenousity as the disease progresses.
- From a pharmacological perspective, at the biochemical level the tumour is a constantly changing target.
- Thus, the primary tumour can be biochemically distinct from metastatic deposits.
- and one person's colon cancer can be biochemically different from another person's.}

→ if we are treating pnt A and pnt B with colon cancer and they are at the same stage and receiving the same medication, Their response will be different because they are very heterogeneous even within the same class, because of this we are moving toward the **personalized medicine**)).

2-Tumour Cells Are Not Immunogenic

▪ We call them " **الخلية الملساء** " **;** nothing within the cell can be recognized by the immune system **.**

▪ The cancer drugs have to kill every single dividing cell, But there aren't any immunogenic factors to help us recognize the cancer cells (we are not talking about antimicrobial drugs where we can reduce the load of the organism in conjunction with the immune system).

→To sum up: the immune system ***cannot recognize the cancer*** cells and ***cannot help the chemotherapy in any way or another***.

→ How the cancer cells evade the immune system:

{▪Tumour cells evade immune detection by down-regulating their MHC antigens

▪So they can't be recognised by antigen-presenting and activated killer T-cells.}

▪ The cancer cells will send out an immune inhibitory factor and some CDs that will bind toward the immune system cells and suppress them.

☻ One of the new treatments targets the immune inhibitory factor.

3-The Numbers Game:

→ This is the worst thing cancer treatment can face; it tells you that you cannot detect any abnormal cells if the number of cancer cells is below **10^6 .**

→ remember that cancer is monoclonal in origin ; so this cell will divide and build up it's heterogeneity and tumorigenicity without being noticed, before the number of cancer cells become 10^6 or above ((at the time of diagnosis the cell is already a heterogeneous and cancerous cell)) .

→ let's assume that we diagnose a cancer with 10^8 cancer cells, and we start treating the patient, we will continue our treatment with chemotherapy till we reach any number below 10^6 (how much are we below 10^6 we cannot know) and that's the REAL problem; maybe we cured the patient completely [kill all of the cancer cells], and maybe we reached number just little below 10^6 [kill the weak cells and keeping the bad ones] .

♯Why do we have a higher percentage of curative outcome if we precede the chemotherapy by a surgery?

1- We reduce the number of cancer cells to be killed by the chemotherapy.

2- We remove the inner layers of cancer cells which are the most resistant cells to the chemotherapy (we already removed the CANCER STEM CELLS).

{▪1×10^8 tumour cells are visible on an X-ray.

▪1×10^9 cells is a palpable lump weighing a gram.

▪1 x 10^{12} cells weigh a kilogram and the patient is dead. Cancer is hard to detect in its early stages and may already have grown to 10^{10} - 10^{11} cells at presentation.

▪You've got to kill every single cell by drug treatment,

▪No immunological mopping-up of residual tumour!

▪If there are 10^{11} tumour cells present (100g), killing 99.99% of them leaves 1 x 10^{7} residual cells.

▪1 L1210 leukaemia cell will kill a mouse.}

(4) Poor Tumour Vasculature

{ ▪Tumour masses can only grow to a diameter of about 200 microns before they run into trouble with nutrient supplies.

▪To grow larger they must develop their own vascular supply which they do by producing **angiogenic growth factors**.

▪However, these blood vessels are of a poorer quality than normal blood vessels which leaves parts of the tumour without nutrients and oxygen.

▪Thus, hypoxic cells become a pharmacological sanctuary from which the tumour can be re-populated after a round of drug treatment when surviving cells may get the opportunity to be re-oxygenated.}

→ imagine that you have a lump of cancer cells composed of superficial and deep layers, and this lump has a very poor vasculature, the blood supply will be only enough to supply the superficial layers, but not adequately to the deep ones.

WHAT WILL HAPPEN TO THE CELLS IN THE DEEP LAYERS ?

1- Necrosis, but this is not for cancer cells which are **resistance to necrosis,** so only part will become necrotic.

2- Escape, where it has two options:

A- To go into G0 stage where it will become a HYPOXIC CELL; avoiding the cell cycle so no division →no need for oxygen and blood supply.

B- or to become a **CANCER STEM CELL** , which also doesn't divide, so they can live without oxygen for a long time.

→ These two cells are resistant to all anticancer drugs, and they are the reason of the recurrence of the cancer after years of treatment by chemotherapy [they are the Polar Bear who appears when the sunlight appears].

♯So the Real reason of why we are *not capable of treating cancer* is the DRUG RESISTANCE; which is not because the patient cannot tolerate the drug's side effects but because of the cancer cell itself.

#The patients either presents with:

1. a tumor that is already non-responsive or

2. the tumor initially regresses only to return later in a drug-refractory form.

→ remember, our target is to inflict damage on all dividing cancer cells in our body, by breaking the DNA so the cell will go into apoptosis except some cells who resist apoptosis i.e. some patients will not even respond to the therapy.

Cancer Drug Classes :

1. **Antimetabolites** (anti-folates, pyrimidine and purine analogues) →their mechanism of action is like that of sulphonamides *(they deplete the metabolites so no DNA → no dividing cells,* non-dividing cells are not affected because this DNA problem appears during replication*).*

2**. Mitotic Spindle Inhibitors** (modulators of tubulin polymerisation) → for the cell to divide it must send out mitotic spindles toward the centromere (if we inhibit this mechanism we inhibit the cell division, we kill the dividing cells -the non-dividing cells are not affected).

3. **DNA Binding Agents** (intercalating and alkylating agents that break DNA down).

4. **Hormones and Hormone Antagonists**→ if the drivers are Hormones (breast cancer positive estrogen receptor, ovarian cancer, endometrial cancer and prostate cancer-these cancers can be hormone dependent).

5. **Miscellaneous anticancer drugs** (targeted therapy) → these are our magical drugs like **Imatinib** and **Avastin.**

☻ **Avastin** : it's a monoclonal antibody toward VEGF works by inhibiting the angiogenesis thus inhibiting the cancer growth.

☺Thanks to Ahmad Al Tamimi for correcting the sheet .

بالتوفيق في الإمتحان ☺

وكما قال الحكيم حمزة نمرة

""واهو كله بيعدى افهم بقى يا افندى
مش واقفة على حاجة ولا حتى محتاجة
ان انت تزعل كل ده""