Sheet ○Slides

number : 17

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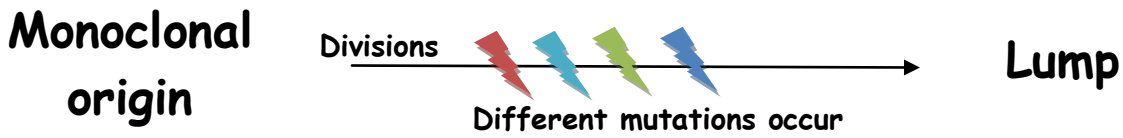


The main problem we deal with in cancer is **mutations**. We start with a monoclonal origin (one cell), and each time a cell divides , new mutations appear in the new cells so … new type of cells ! These new cells end up forming a lump (كتلة سرطانية)

THE LUMP PROBLEM: this lump has different cells --> different genotypes and phenotypes --> **different targets** to treat --> **different response** to drugs.

So using a cocktail of chemotherapeutic drugs , with different mechanisms of action to delay cancer cells' drug resistance as long as possible, and to treat cancer is ***A MUST!!***

- Number of cells in the lump when targeted reaches billions , scanning with X-Rays or CT – scan (Computed tomography التصوير الطبقي المحوري) can discover a lump with $1*10^7$ cells already in the patient's body (most cases in reality are discovered by the time it reached $1*10^9$ cells) .

- Are they similar ?? NEVER !!

>>**Why ?** We may have lost Oncongenes , Tumor suppressor genes , DNA repair genes but ..

We gained metastasis , Angiogenesis , which produced the heterogeneous lump (cells are NEVER alike) . It's heterogeneous between cancers and between cancer cells itself .

For example , breast cancer is completely different from colon cancer and colon cancer is completely different from lung cancer and so on . Moreover , patient A and patient B may have colon cancer , for example , stage 3 but genetically they are really different , and if you take a cross section from the lump itself and examine different . So remember this **note** : cancer is not one disease , it is 200 disease , and the same disease itself is heterogeneous (the cells are completely different from each other in the same lump)

* Note: In all cancers there are many things to target (many drivers) , the only known cancer until now which has a target is Chronic Myeloid leukemia (CML) . It results from translocation (rearrangement) of ABL gene on chromosome 9 and BCR gene on 22 to form a new fusion gene (Philadelphia chromosome) . Since the target is now specific and well known, the treatment became easier and this type of cancer became as any chronic disease. **Imatinib** is now the drug of choice ; it's taken daily in form of oral tablets .

^ Slide 8 ; Hall marks of cancer :

1. Gain of oncogenes.

2. Loss of tumor suppression genes.

3. Loss of immunity (non immunogenic , can't be recognized by the immune system).

4. It invades the immune system by sending inhibitors to T-cells (Body check points against foreign bodies).

5. Loss of apoptotic activity (cancer cell won't die).

6. Ability to metastasize (ex. by matrix metallo-proteases that degrade extra cellular matrix).

7. Endless replication, so endless mutations and no check points for mutations' correction.

SO what are we dealing with?? A monster that needs to be showered with all available weapons in hope to be killed !

- Now as you know , or going to know :P , the main goal of chemotherapy is **targeting all highly dividing cells** (since it's cancer cells nature) , so it'll cause the 4 common side effects between all cancer drugs (slide 13) :

1. Alopecia (hair loss)

2. Nausea , diarrhea , vomiting (GIT disturbances)

3. Bone marrow suppression (causing anemia)

4. Immunosuppression (no division of B and T- lymphocytes)

In addition to certain specific side effects for some drugs which we try to avoid giving those that produce the same specific side effect in the same time .

" We can't prevent the common 4 , but at least we don't want the patient to suffer from the fifth ."

- Because cancer cells have many mechanisms of resistance , the most aren't apoptotic (if some are killed , some will stay) while normal cells are, SO body cells will respond more to cancer drugs.

- Kidney, brain , heart and liver cells are not affected since mitosis isn't active much there , so drugs don't kill them.

** 2.00 min – 13.00 min , slides covered : 8 – 11 **

- Due to these harsh side effects the patient will have to face each time taking chemo, there is a cycle that regulates when to take the next dose and how many times should it be taken .

Ex. The 1st dose of chemotherapy is given for 2 – 3 days , then the patient leaves the hospital for 21 days to recover, after this period ends , he gets back to take the 2nd dose and so on ..

Of course # of cycles differ according to disease nature, and what determines how many times is something called (chemical trials) ; we keep on giving chemo until we can no longer see the lump .

^ slide 12 : ***The goal of cancer treatments** (the doctor explain them later in different locations but it is good to understand them from now) :
>> Curative :
-Total eradication of cancer cells

-Curable cancers include testicular tumors, Wills tumor
>> Palliative:
-Alleviation of symptoms

-Avoidance of life-threatening toxicity

-Increased survival and improved quality of life
>> Adjuvant therapy :
-Attempt to eradicate microscopic cancer after surgery

-e.g. breast cancer & colorectal cancer

- Why do we fail to treat cancer ?

^ slide 14

Keep this in your mind : NO SURGERY , NO TRETMENT !

If the tumor is not dissectible (ex. It metastasized), it can't be treated . chemo only cures 10% of cancer patients , others if not treated by surgery , mostly they'll die ! (In some books it is said to be 50% of cancer patients are likely to be cured and this may be accepted because of surgery !!)

- Why are drugs non-effective ??

Mainly because of drug resistance not a lack of selectivity for tumor cells .

^ slides 15 – 21 , here the doctor read the slides , and we put the slides' sentences themselves with some explains .

1. <u>Genomic instability and hyper mutability</u> :

The de-regulated genome ›››› genetically heterogeneous tumour . Damage to DNA repair genes is critical ›››› more heterogeneousity 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 persons.

2. <u>Tumor cells are not immunogenic</u>: All cancer cells should be killed, that's not easy
Tumor cells evade immune detection by down-regulating their MHC antigens
So they can't be recognized by antigen-presenting and activated killer T-cells.

3. The number game:

>> 1 x 10^8 tumor cells are visible on an X-ray.

>> 1 x 10^9 cells is a palpable lump weighing a gram.

>> 1 x 10^12 cells weighs 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 moping-up of residual tumor!
" If there are 10^{11} tumour cells present (100g), killing 99.99% of them leaves 1 x 10^7 residual cells."

Dr.Malek said a very important thing about it : " if you were very successful in treatment of cancer , and in drugs you're using , and killed 99.9% of cancer cells existing in patients body that you actually can't see of it by scanning less than $1*10^6$ or $1*10^7$ (in Jordan it's $1*10^9$ to $1*10^{10}$) , 1 x 10^7 residual cells will remain which you may not see and will sure cause a recurrence !! "

4. Poor tumour vasculature " HORRIBLE ! "

Tumor masses can only grow to a diameter of about 200 microns before they run into trouble with nutrient supplies. Now to grow larger they must develop their own vasculature which they do by producing angiogenic growth factors. However, these blood vessels are of a poorer quality than normal which leaves parts of the tumor without nutrients and oxygen.

What is happening here ?? Part of the tumour is going to be necrotic, and part of it is going to leave the cell cycle and enter G_0 phase, and since Chemotherapy targets only dividing cells, those dormant cells will never be affected !!!!!

5. Deregulation of apoptosis (The big Daddy of them all)

The genomic instability of tumor cells inevitably leads to deregulation of the apoptotic pathways. This results in a generalized reduction in the sensitivity to all forms of cellular insult. THE REAL BRICK WALL!!

Why does this happen?

1. We have no immunity to act on cells after decreasing the load by chemo.
2. High # of invisible cancer cells.
3. Some cells entered g_0 phase.
4. Some cells are non- apoptotic.

21.45 min – 22.10 min : missing slide that talks about how can we deal with this? Drugs are administrated as a cocktail of 3 or more compounds as the maximal dose that can be tolerated by the bone marrow " we have to hit and hit HARD." The cocktail is administrated once a day by IV injection (infusion for a weak) , the patient hemopoietic system (blood cells formation system) is left to recover in 3 weeks . the process is repeated until reaching half a dozen or more .

- In easier words ?!

We consider bone marrow tolerance because we plan to destroy superficial cells , let vasculature reach inner cells and get them back to life , then the 2nd dose will kill them , the inner will get vascularised and alive so we'll hit another time , and so on , in order to at least shrink the tumour or let it disappear (not seen but perhaps still there).

Ex. " 40% of breast cancer cases experience a recurrence , even though it's considered treatable ! " , Why ??

The lump is removed by surgery, but cells which escaped and divided to make another tumour somewhere aren't, these cells took the characteristics of their origin, and formed a small gathering that may not be seen, this is chemo goal here!

* Slide 18 will be explained next lecture .
** 13.00 min –24.40 min, slides covered : 14 -21 **

^ slide 22 ; **What are Cancer drugs ?**

They are **KILLERS** , used in chemo to target cancer cells by 4 mechanisms :

1. **Cell cycle specific** (kill dividing cancer cells) :
a. Anti-metabolites (kill during S phase)

Like sulphonamides , they stop synthesis of purines or pyrimidines and so DNA replication won't occur and mitosis will stop .

Many drugs of this type are used in chemotherapy .

b. Mitotic spindle inhibitors (kill during M phase)

Act on spindles that binds to centromeres in mitosis . Taxol and Vincristine are most known ones .

2. **Non- cell cycle specific** (gets inside non- dividing cells and break DNA) :

a. Intercalating agents like Topoisomerase inhibitors .

Just like quinolons ; they enter , bind DNA , and in the moment topoisomerase start to cut , the inhibitor binds to it and causes DNA fragmentation.

b. Alkylating agents .

They have 2 alkylated sides to bind both strands irreversibly, and break DNA.

3. **Hormones and Hormone Antagonists**

Act on hormonal dependent cancers like endometrial cancer , breast cancer and prostate cancer , all which depend on either estrogen or testosterone .

4. **Miscellaneous anticancer drugs**

New drugs which have a specific job; to target things that don't exist in normal cells . It's a new strategy that has an additive activity used to help in cases a target DOES EXIST !

The best example on them and the one used alone without any other drug is the previously mentioned drug to treat CML (Imatinib).

AGAIN : In all cancers , a Drug combination of all previous mechanisms **Must** be given!

** 24.40 min -31.00 min , slides covered : 22 **

Now we'll start a new interesting topic : Breast cancer 101

- Most common diseases in Jordan are :

1. Breast cancer in females

2. Colon cancer in males

3. Childhood acute lymphocytic leukemia

- What is the problem we're facing with breast cancer ??

Close lymph nodes, so cancer metastasis (lymph node involvement) is common , and breast cancer is in turn staged according to lymph node involvement and lump size .

- A brief Overview :

* SURGERY

A must as a first step, either by breastectomy (the whole breast is removed) , or only by removing the lump (according to the situation) .

* Chemotherapy " as adjuvant therapy "

Since in most cases lymph nodes are involved , many cells may have escaped to the lymph nodes and reached far places , made cancer there and they're still invisible .

^ slide 23 ; Breast cancer therapies are :

1. Chemotherapy
2. Biologically – targeted therapy (Miscellaneous anticancer drugs)
3. Endocrine therapy (hormonal therapy)

^ slide 25; Breast cancer treatment differs according to the condition :

- If the tumor metastasized , it'll become non-curable , and we'll have to treat by palliative chemotherapy (تلطيفي)

* Metastasis means that the patient is unfortunately gone !

- If breast cancer metastasized , it'll go to axillary lymph nodes , or to bone if no lymph nodes are involved .

^ slide 26; Drugs used to treat breast cancer :

1. Tamoxifen
2. Doxorubicin (Trade name : Adriamycin)
3. Cyclophosphamide (Trade name : Cytoxan)
4. Paclitaxel (Trade name : Taxol)
5. Trastuzumab (Trade name : Herceptin)

These drugs are used with both metastasized and non-metastasized cases, and cancer treatment is built upon them !

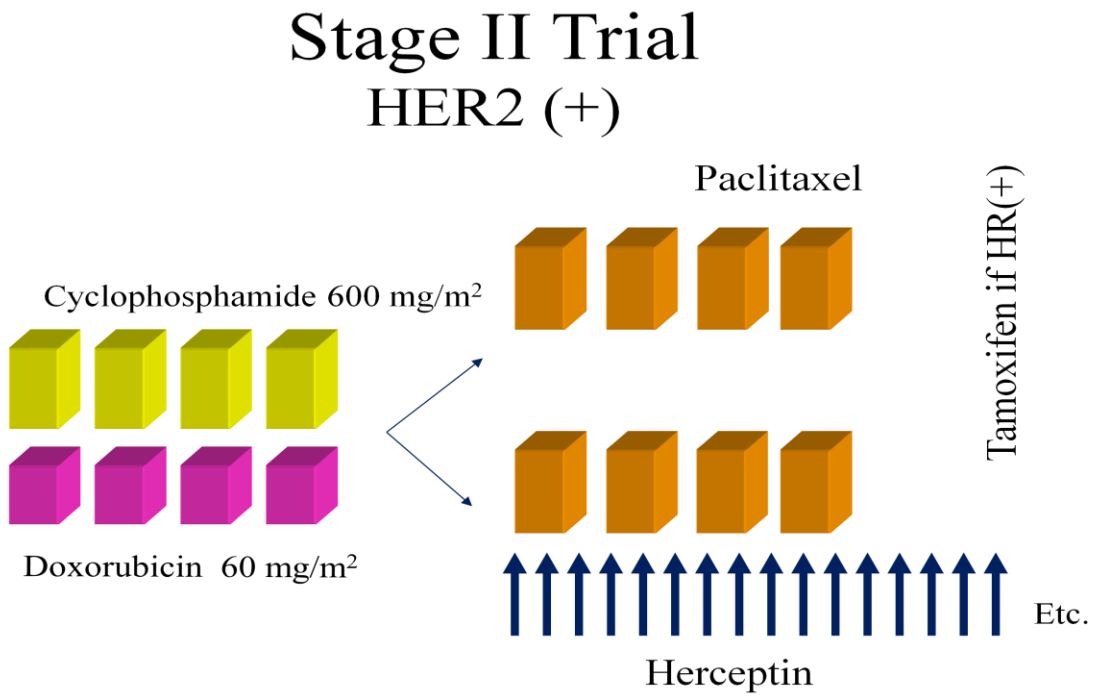
* Notes on slide 27 :

1. 4 cycles of doxorubicin and cyclophosphamide are given together .

2. Then 4 or 8 cycles of paclitaxel are given.

3. During treatment with paclitaxel , cycles of hercipten can be given.

4. Then, tamoxifen is given.



** 31.00min – 38.10 min , slides covered : 23 – 27 **

- Starting to understand more about these drugs one by one :

1. Doxorubicin (THE BEST EVER DRUG FOR CANCER *.*)

- Belongs to anthracyclin Family.

- A non–specific cell cycle, intercalating drug that kills dividing and non- dividing cells that didn't enter G_0, but it doesn't affect cells in G_0 phase nor non-apoptotic cells .

- It acts like aminoglycosides in binding to membranes and altering fluidity.

- For all cancers it's a favorite; however, in addition to the common 4 side effects , it produces a bizarre side effect when its free radicals ;which are good to destroy cancer; reach places that it shouldn't reach like heart , and thereby cause **Cardiotoxicity** . (Refer to slides 28-29)

- Because of Cardiotoxicity, there is dose limitation when it's given , which is 400mg/m^2 as maximal accumulating dose (whole dose among 4 cycles) .

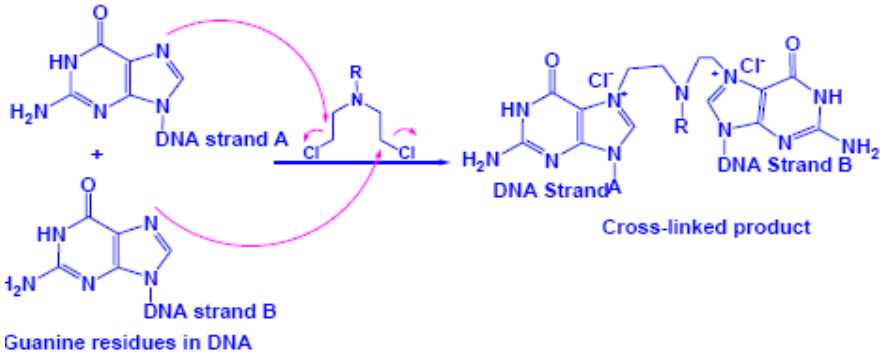
Wait ! m^2 O.O ??

YES ! Since chemo drugs are killers, you need to measure the suitable **tolerated** dose accurately by considering your patient's body surface area .

^ Slide 63 (the last slide) concludes that incidence of developing Cardiotoxicity will jump from 2% to 10% when exceeding the 400mg limit, so now there's a limiting point for its administration : " **not** to be given more than 400 mg of this drug. "

2. Cyclophosphamide

- A non-cell specific , alkylating agent that binds to Nitrogen #7 of guanine on both strands . by having to active sides , it binds and pulls until it breaks DNA and produce a cidal activity (it kills cells) .



- Its specific side effect is Cystitis (inflammation of urinary tract)

* Remember that all 5 drugs in addition to causing common 4 side effects , each of them has a specific side effect you'll get to know , our goal is not to reduce common 4 because the ugly truth is " we can never, " but at least we'll try not to administer for example 2 drugs that produce Cardiotoxicity together !

** 38.10 min – 48.32 min , slides 28- 31 **

**Note : The doctor will talk about previous drugs in more details next lecture .

** *Don't forget to check the doctor's slide ..*

THE END

A thing I wish to say: this sheet language and layout were built upon your opinions, I hope you've seen an improvement !

I wish to all of you the best of Allah's guidance through your semester and to the rest of your life, and remember ..

" Whom is guided by Allah is never lost " :D

Stay blessed CURE ♥