◉ Sheet ○ Slides

number : 16

doctor : Malek

done by : Renad Zakaria

correction : Abdullah Kadi

Previously *on Pharmacology…*

-The last group of antibacterial drugs which are **Quinilones** (we name them without generation; like is it **Cipro** or not)

-We talked about **Ciprofloxacin** which used to treat:

1- Urinary Tract Infection (Prostatitis)

2- Gastroenteritis (*Salmonella, Shigella, E. Coli*)

-If it was **Trichomonas** infection we use Metronidazole to treat it.

*We will take it in urogenital system in the 3rd year (The doctor said it's in the GIT system but I think he mistaken it with Urogenital because its a sexually transmitted infection :p)

-Then we talked about **Levofloxacin** and **Gemifloxacin** they are 'Respiratory Quinilones' and bactericidal and are used for community acquired pneumonia in life threatening situation. They're active against all causes of community acquired Pneumonia (*Streptococcus Pneumoniae*, *H. Influenzae, Klebsiella Pneumonia, Chlamydia ,Legionella and Mycoplasma*)

Q. Are they active against Pseudomonas?

A. Yes, but we prefer Ciprofloxacin because it stronger.

**That was a quick revision for the previous lecture so lets start our lecture:

-Quinolones Side Effects:

The limiting factor of using Quinolones, that they cause something called 'Arthropathy'.

Fluoroquinolones may damage growing cartilage and cause an Arthropathy, particularly in young individuals. So, its contraindicated in children (under 18) except in special cases (Like : Cystic Fibrosis).

**Important conclusion: Do NOT give Quinolones to growing children, pregnant and breastfeeding women.

So assume that a pregnant woman had UTI. What is the drug of choice in this case?

At first we her give 2nd and 3rd generation cephalosporins (it acts on *E. Coli* and most of *Gram Negative* bacteria). But what do we do if we have ESPL and the patient had a serious condition and we must give antibiotic that cover gram negative? We use a famous drug named **Co-trimoxazole**.

*Lets talk about the history of this drug: **Co-trimoxazole**

Sulfonamides were used in the past but not anymore. It may be used for burns and some skin infections but not common because they are old drugs (even older than Penicillins!) so the resistance's already there.

So a brilliant man came up with an idea to revive these drugs. So he combined two drugs from the Sulfonamides group: **Trimethoprim** and **Sulfamethoxazole** (Synergistic Effect) and produced **Co-trimoxazole** which covers *Gram Negative* and especially *E. Coli*, *Salmonella*, *Shigella*, and effective for UTI and Gastroenteritis.

-Especially used for women (Why? Because Men do not get pregnant so the risk for them to develop UTI is much less than Women) and can also be used for children.

-There's a special feature about this drug: like we took in microbiology that some bacteria produce Dihydropteroate Synthase that is inhibited by sulfamethoxazole, and bacteria can produce dihydrofolate reductase and this enzyme inhibited by Trimethoprim. So after we combine these two drugs (Co-trimoxazole) there are two pathways to inhibit so when the bacteria try to resist the drug simply it can't because the bacteria can over express one of the two enzymes not the both so we conclude that the resistance can't be developed for this drug which is great!

*The trade name is Co-trimoxazole and the scientific name is Oral Trimethoprim sulfamethoxazole (TMP/SMZ).

** We already talked about Teicoplanin, we said that if the patient has high suitability to kidney failure and you can use it instead of vancomycin.

*The below box is ***not*** included because we don't have VRE and MRSA. But in case you face something like this in the future ☺

The drug of choice to treat VRE (V**ancomycin-resistant *E. faecium* infections) is Linezolid.** It can also be used for Nosocomial Pneumonia, Community-Acquired pneumonia, and skin infections; complicated or uncomplicated.
-It should be reserved for treatment of infections caused by multidrug-resistant gram-positive bacteria.

-This drug is highly expensive; it costs 1400JD! So you will never prescribe it to you patients in the future.. At least in Jordan. :P

I mean the **Linezolid** and the antibiotic in pregnancy

*But in general, avoid giving Tetracyclines and Quinolones for pregnant women. Instead, you can prescribe Penicillins and Cephalosporins.

-**X Category** in the table means: Teratogenic; which means it causes malformations in the fetus. Avoid prescribing any of the drugs in this category.

-**D Category**: shows teratogenic and malformation in animals but not to humans, try to avoid this category as much as you can (risk/benefit ratio).

-**C category**: is between the two above there is no evidence for its safety (risk/benefit ratio).

-**B & A category** is really safe.

- There are no Antibiotic that cause malformation (An example about Malformation is a baby born with short hands like a seal, this is caused by a drug named Thalidomide, women took it as anti-nausea and vomiting)

-Most Antibiotics fall in category D. It means they are approved, they have an effect on fetuses but it is ***not*** Teratogenic.
(Example: Tetracyclines and Aminoglycosides which cause teeth discoloration and bone deformities. So minimal effects not malformations)

E. Coli is the strongest bacteria that can develop resistance even stronger than *Pseudomonas*

*Conclusion: -

Penicillins and Cephalosporins are the safest drugs for pregnant women, keep in mind ESPL problem.

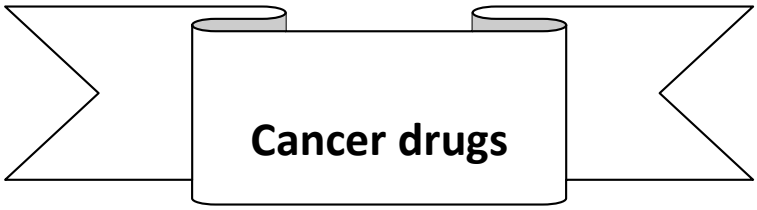
-For pregnant women with Gram Negative infection (especially *E. Coli*) we use Co-trimoxazole. It's a safe drug as well.

the end

of

Antibiotics.

let's start with our new topic anti cancer drugs



We took a lot of lecture about cancer and neoplasia in Pathology, and here we will discuss the drugs for it.

-Treating cancers with drugs is very hard, so what makes it treatable or not is actually if the surgery is possible or not.

*Before we start you should know basic things:

-When we say effective drug it does not always mean curable.

-Cure/Curable: means complete removal of cancer (or any pathogen in general) and the cancer will not reoccur ever in the patient's life. Like, ever. :P
–Treatment: The patient may or may not respond to the drug.
–Remission: Disappearance of the cancer and it may reoccur or not.

⇨ So when we treat cancer we try to increase the remission until we don't see the cancer, in reality for example we have a five year survival period in which the patient actually might have the cancer again in its severe form and actually kill the patient. This applies for Leukemia, Lymphoma, breast cancer the cancer may not appear after 5 years so we think its curable but keep in mind there are some cancers that reoccur even after 10 years!

-There are five types of curable Cancer:

1- Childhood Acute Lymphocytic Anemia (ALL) one of the most common cancers. 90% of the patients are cured and they will have normal life after treatment and cure which lasts for 3 years. In adults, acute lymphocytic anemia is 70% curable.

2- Testicular cancer in men.

3- Basal cell carcinoma in the skin.

4- Chronic Myelogenous Leukemia curable because of phelidelphia chromosome and imatnib (recall pathology lecture)

**The other cancers aren't curable we will say why in the coming lectures in pharmacological view.

**the doctor read a sentence about smoking related to lung cancer and the smoking ethics and its disadvantages.

*As we know cancer is monoclonal in origin from one cell we have cancer.

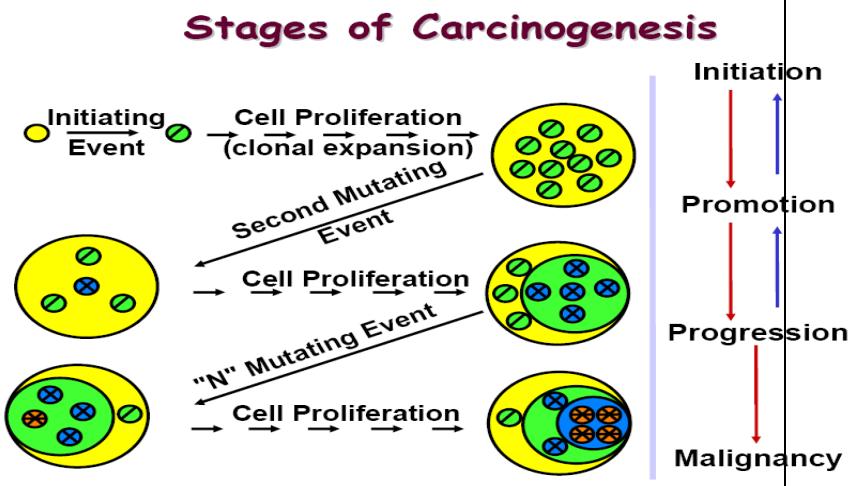
1- At the initiating event we have mutations in oncogenes.

2- At the second mutating event we have mutations in tumor suppressor genes.

3- Mutations in DNA repair genes.

4- Mutations in apoptosis,

metastasis and immunology genes.



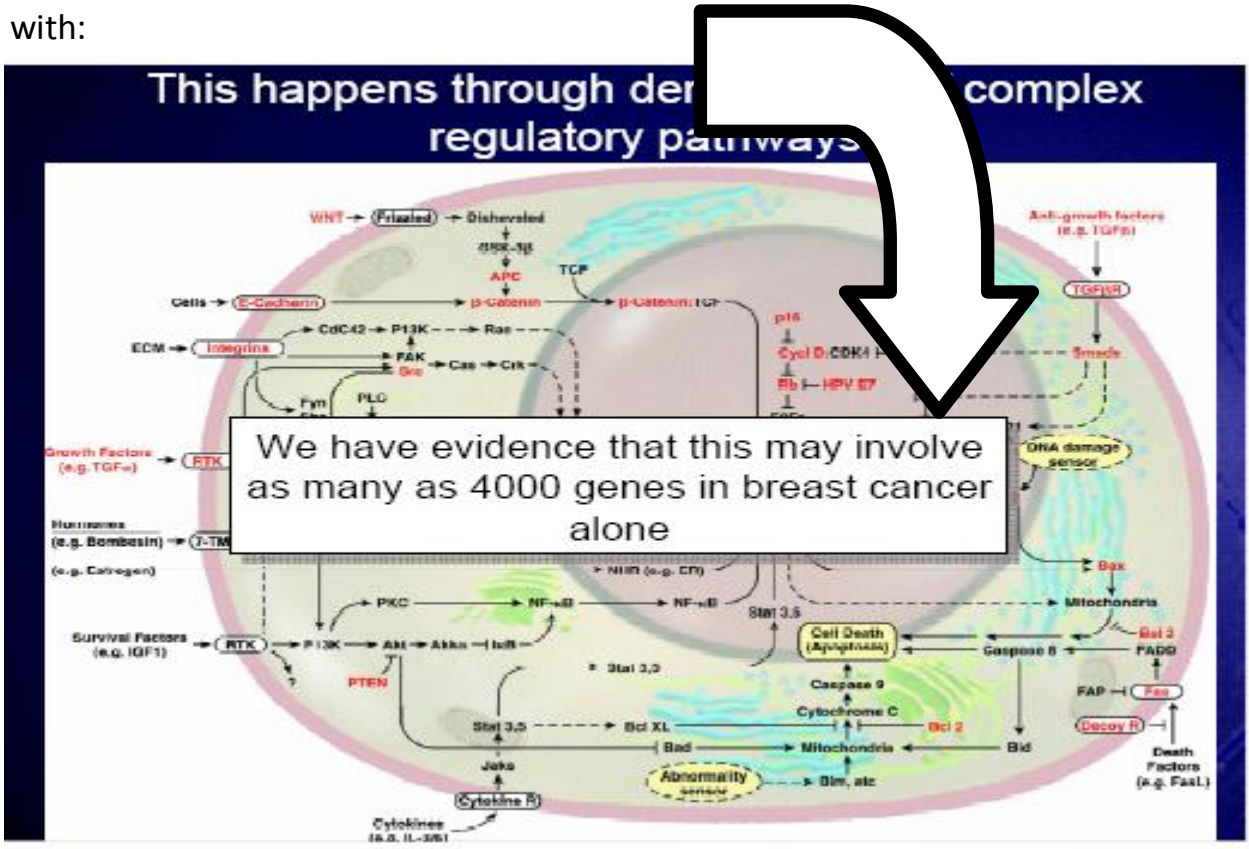
All of those mutations together make up a lump which is composed of different types of cells; some of them contains multiple mutations and others contain hundreds of mutations.

Q. So what do we target to treat cancer? Or what's the problem that we face when treating cancer?

1- Unfortunately, there is no single mutation or receptor to target. For example if we took a sample for colon cancer patients and made DNA sequencing to know the cause of cancer, we found out that a lot of mutations and factors take place to make cancer, it's a **heterogeneous** disease which means that the lump, by it self, has multiple fractions of different cells (changeable target).

2- Other problems we face; for example when we apply DNA sequencing to breast cancer patients, we found out there are, for example, two patients who have the same lump size and almost histologically the same. But after sequencing there are different mutations that cause the cancer and it's a problem (we can't simply prescribe same treatment for each of them!)

*For point 1&2 it was a project that apply for colon and breast cancer they collect samples and make studies they assume that at the end of this project they will find for example the number of specific genes that cause the breast cancer and same to colon, but the reality and the results were the opposite and they end up with:



3- Cancer itself is also mutable which means that mutations can occur and develop, because there are no DNA repair gene, oncogenes are becoming unstoppable and tumor suppressor genes turn off. So during the treatment of cancer, there's no guarantee that it's not changeable, therefore, the treatment will be not effective.

*In chronic **Myelogenous Leukemia** we found out that the cause is one mutation on chromosomes 9,22 so we're able to treat it. But that's not applied for other cancers, so how do we treat?

-We took about hallmarks of cancer in pathology lecture so let's proceed to the treatment of cancers and we use our knowledge about them to treat cancers.

At first you must there are three patches to treat cancer:

1- Surgery 2- Chemotherapy 3- Radiotherapy

The primary tumor is removed by surgery. If it has not metastasized then the surgery may prove curative. As we said the death to survival ratio of the patient is 50:50, and we perform a surgery ***only*** when the percent of survival is more than 50%. But if it's not dissectible (Surgery isn't possible) we won't be able to perform surgery; therefore, cancer isn't curable.

Radiotherapy, irradiation with high energy X-rays (4 to 25 MeV), may be applied subsequent to surgery to help prevent re-growth of the primary tumour.

Surgery plus radiotherapy is a common treatment modality.

Tumors that are not dissectible may be treated by radiotherapy alone, most of the 50% cure is effected by surgery and radiotherapy on non-metastatic tumors, if the disease is found to be metastatic then systemic chemotherapy is administered after surgery and radiotherapy.

Cancer drugs are not specific for cancer cells but are cytotoxic to all proliferating cells in cycle.

So when do we use chemo therapy?

1. When the cancer's already spread out in the body, we need to treat the metastasized section of the cancer (the most common case); for example if we have breast cancer patient and the cancerous cell reach the lymph nodes we need to get rid of it cause it may spread to another tissue so we give chemotherapy and apply surgery.

2. But if the cancer's already metastasized and spread throughout the body and reach deep tissues (like reaching the cervix in the breast cancer) here we treat cancer with chemotherapy as a mitigation treatment just to prolong the patient's life and make what's left of his/her life easier.

Conclusion: curing only happens if we perform surgery and radiotherapy. In realty, cancer drugs don't make a lot of change except for sure to many cases, we use them for prolonging the expected life of the patients which makes a different in their life and it's the real value of these drugs. Remember ***not*** for curing.

*There is a way to measure the effectiveness of the drugs by what we call "event free survival" which means the time that the patient spends without the reoccurring of cancer after the treatment.

**there are four types of treatment :

1. **Curative:** which means total eradication of cancer cells
   like: ***Testicular tumor***, ***Wilms tumor*** (Kidney tumor that affects children - very rare)

2. **Palliative**: allevation of symptoms, avoidance of life threatening toxicity, increase survival and improve quality of life. This will ***not*** cure the patient, it'll only prolong his life expectancy period with less difficulty, patients at the last stage in cancer commonly take this type of treatment like lung cancer and pancreatic cancers.

3. **Adjuvant Therapy**: an attempt to eradicate microscopic cancer after surgery. Sometimes, after the patient goes in to surgery, the cancer spreads out (we can't see the spreading cancer) so we treat him/her with chemotherapy. This chemotherapy is now called adjuvant therapy just to make sure it kills all the cancerous cells.

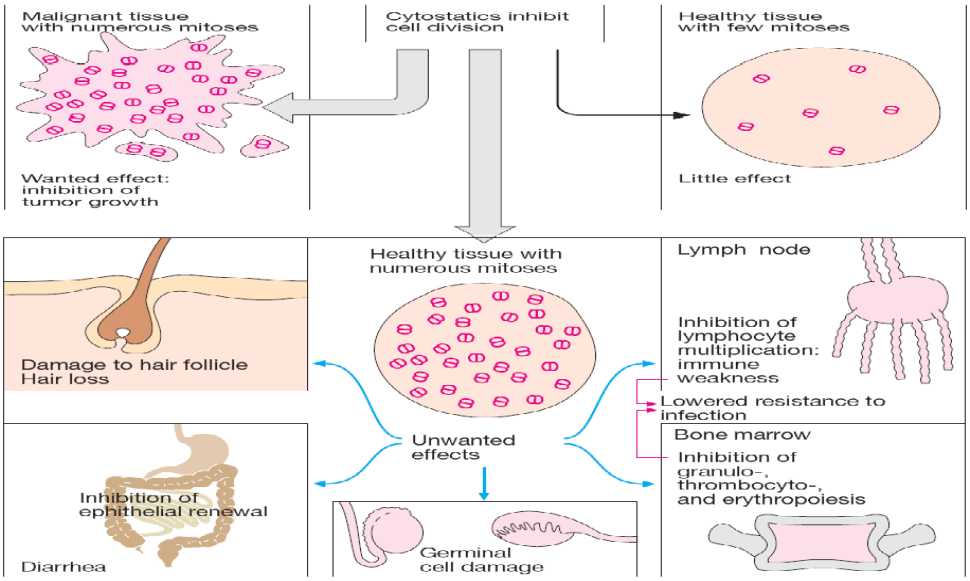
4. **Neoadjuvant Chemotherapy:** we use this type of chemotherapy when the tumor is so big that we can't remove through surgery, so we use anti-cancers to shrink it. Only then do we perform a surgery.

**in the coming lectures we will go through common Jordanian breast cancers and colon cancers only and with them we will discuss pharmacogenetics.

*So the best solution to treat cancer that has no changeable target with no identity is to hit hard (kill normal and cancer cells), kill all reproductive cells with chemo therapy.

**the non reproductive cells will not be affected like: brain, kidney and liver.

In the picture below you will notice some side effect because cancer drugs are cytotoxic and it will produce:



Affect the cell that in mitosis phase and reduce its division and reproductive:

1. Hair loss: affect the hair follicle.

2. Immunodeficiency (Immune weakness): due to the effect it has on lymph nodes and therefore inhibits lymphocyte.
3. Anemia, because it decreases the bone marrow cells.
4. Severe nausea and diarrhea, because the drug kills the lining epithelial of GIT.

*Therefore these side effects are the dose limiting toxicity (sometime some patient their bone marrow/GIT/lymph nodes cant endure the dose that we give to kill the cancer and that will cause massive damage in it so keep in mind toxicity), and keep in mind the resistant cancer cells for the drugs.

**there are some side effect that are related to other causes since we stop proliferation to all dividing cells in the body.

**So that's why we called the cancer drug chemotherapeutic agents because they burn all reproductive cells (cancer and normal cells), but unfortunately normal cells respond for the drug more than cancer cells because they don't contain mutations and they have repair, oncogenes, tumor suppressor genes. So it's a drug that produce side effect more than the effect.

$$ All cancer drugs except the target drugs therapy (like imatnib) when there is no target, we give chemotherapy.

Sorry for any mistakes, please refer to the slides ☺