◉Sheet ○Slides

number : 20

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In the previous lecture we talked about personalised medicine and genetic polymorphism in patients:

We talked about tamoxifen as an example on personalised medicine and genetic variation between patients (pharmacogenetics). We said that it is a prodrug that should not be taken for more than five years, and we prescribe it for treatment, prophylaxis, or as post adjuvant therapy to make sure there is no recurrence of the cancer. It is a very valuable drug and is metabolized by an enzyme called CYP2D6, so if you have a non-functioning CYP2D6 or you lost the two alleles and the enzyme became defective you will lose the function; it will not convert tamoxifen to endoxifen so the patient will not benefit from this drug . If the patient is an ultrarapid metabolizer (has more than two alleles, for example four) that means the patient is a fast convertor of tamoxifen to endoxifen so he is going to respond more but with more side effects, so keep in mind that you have to lower the dose to avoid toxicity.

If the patient lost one allele (intermediate metabolizer) you may need to increase the dose.

We applied this also on transporters like P glycoprotein**,** if we lose the two alleles, we lose its function (remember that it is responsible for decreased drug accumulation in multidrug-resistant cells), so losing this transporter is like drinking grapefruit juice with a drug. To avoid that, keep in mind pharmacogenetics (genetic variations) to avoid unexpected side effects due to this problem.

Let’s start with our topic for today

Colorectal cancer:

It is a common cancer within the Jordanian population, It is the most common cancer among men (lung cancer is becoming more and more common).

Colorectal cancer has four stages:

Stage 1	too small, too tiny, removed by surgery, no need for chemotherapy also no need for adjuvant and neoadjuvant therapy, curable
Stage 2	surgery and adjuvant therapy, curable
Stage 3	no metastasis but big mass, some involvement of lymph nodes, give aggressive chemotherapy or give similar therapy to stage 2, almost curable not all the time
Stage 4	It is metastasised already, patient mostly lives for five years , 5% or 8% may live more than five years

**We approach every stage with different ways

it is treated in a different way from breast cancer with different drugs (no linkage between the two (different mutations)). In colorectal cancer there are **mutations in RAS and RAF and **involvement of epidermal growth factor 1**. The nature of it is different, it is more dependent on angiogenesis compared with breast cancer (remember: the way you treat cancer depends on the pathophysiology of the cancer).

** So let's start with its treatment in which you need four drugs (it is an adjuvant therapy):

1- **Oxaliplatin** 2- **5-fluorouracil** 3- **leucovorin** 4- **bevacizumab**

-Oxaliplatin, 5-fluorouracil, and leucovorin are named together **FOLFOX.**

- We may give another drug with **FOLFOX** which is Irinotecan, we rarely give this drug, only 5% of the patients take it.

-we treat 90% of colorectal cancer with **FOLFOX** for stages 2 and 3.

Also used for stage four but we combine other drugs with them.

1- Oxaliplatin:

-It is a platinum-based antineoplastic (alkylating agent), it contains reactive platinum with four methyl groups, and so it can bind DNA in four different regions (which causes breakage of DNA).

-Platinum drugs are three:

1-cisplatin 2- carboplatin 3- oxaliplatin

*we do not use cisplatin and carboplatin because they produce nephrotoxicity, more GIT damage, severe nausea and vomiting and peripheral neuropathy, according to the global guideline we use oxaliplatin, but here in Jordan we use cisplatin (because oxaliplatin is expensive).

They all have the same effect but oxaliplatin is the best with low side effects comparing to the other two.

- Although they are alkylating agents, so from pathology lectures we know that they cause cancers (leukaemia), we use these drugs widely because they have good activity on colorectal cancers.

Comparison of Platinum Toxicity

Table 5. Comparative adverse effect profiles of platinum drugs

Adverse effect	cisplatin	carboplatin	oxaliplatin
Nephrotoxicity	++	+	-
Gastrointestinal toxicity	+++	+	+
Peripheral neurotoxicity	+++	-	++
Ototoxicity	+	-	-
Hematologic toxicity	+	++	+
Hypersensitivity	-	+	-

-used to treat also breast, ovarian and testicular cancers

-First of all we give this drug at first with 100 mg/m^2, IV in day one.

2- 5-Fluorouracil:

-It is an antimetabolite drug.

-it's given 3000 mg/m^2, IV, continuous infusion on days one and two, for 46 hours.

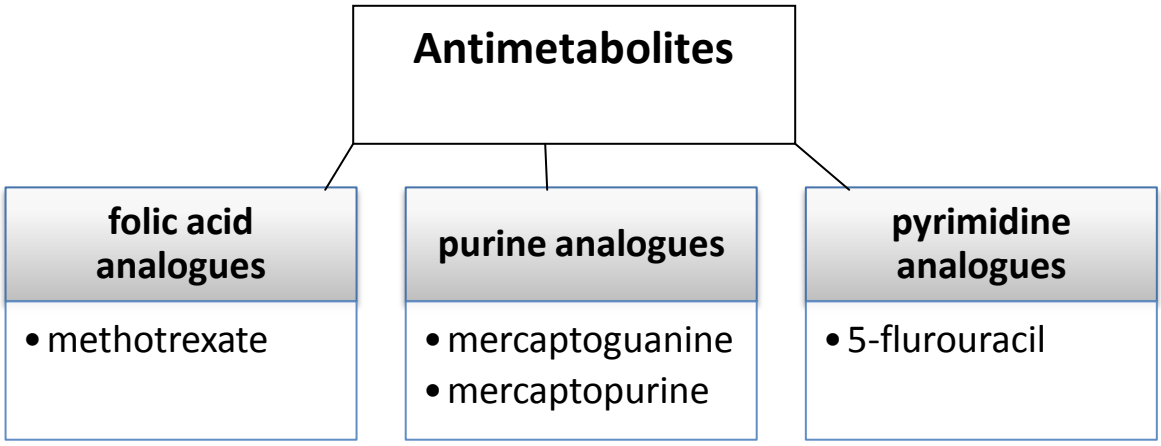
Let's recall some information on antimetabolites:

Antimetabolites are three types:

Base analogues: 1- Pyrimidine analogues similar to cytosine and thymine.

2- Purine analogues similar to guanine and adenine.

3- Antifolates (folic acid analogues): which deal with folic acid synthesis (like sulfonamides).



-It is a uracil-like drug (keep in mind we have thymine instead of uracil in DNA)

- When the body is making building blocks of DNA, an incorporation for such a false nucleotide (5-flurouracil is an example) in the place of a normal nucleotide occurs, normal

nucleotides come to join the false nucleotide but no connection between the two occurs, so the elongation of DNA ends (the DNA stops replicating and the cell is arrested in the S phase). In general, all antimetabolite drugs are S phase specific, not only 5-flurouracil.

Let's talk about 5-flurouracil, so instead of giving uracil we give 5-flurouracil and that inhibits the replication of cancer cells (competitive binding).

But what is the relation between uracil and DNA?

At first Uracil will be converted to thymine by the action of an enzyme called **thymidylate synthase (TS)** , in this pathway we need a methyl group that is obtained from **N^5,N^{10} Methylene- THF** , so deoxyuridine monophosphate (dUMP) will be converted to dTMP (that takes place in DNA).

Our drug 5-flurouracil **inhibits TS by binding to it tightly (after it is converted in the body to fluorodeoxyuridine monophosphate (FdUMP)), so it blocks the synthesis of thymine (dropping in thymine level) so the fast growing cancer cells will stop because thymine is needed for DNA replication (arrest cells in S phase).

**if we accelerate the above reaction by adding folinic acid that can drive the reaction, this will increase the availability of the methyl donor THF and this how it accelerates this pathway, when we accelerate the reaction and we already had given 5-flurouracil, so its increase the inhibition of TS, so that why we give a drug named leucovorin (folinic acid).

**look at the pictures below it summarize all of it:

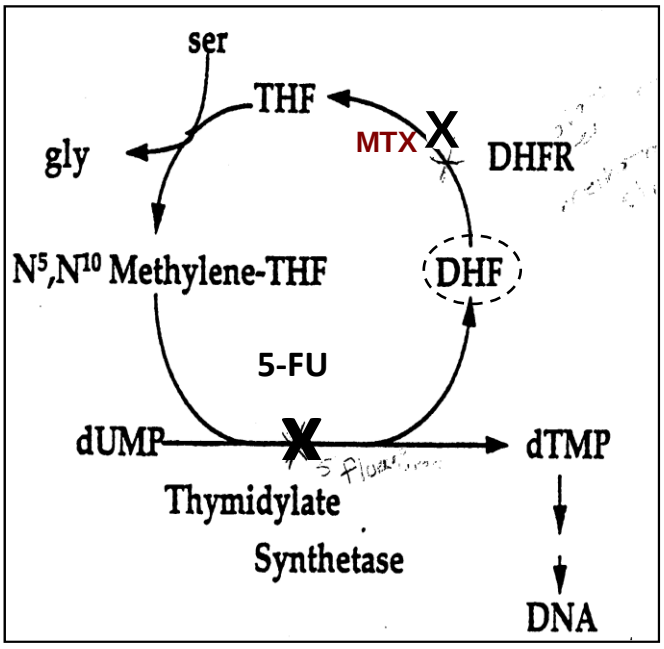


Figure 1. This figure illustrates the effects of 5-FU on the biochemical pathway in formation of dTMP

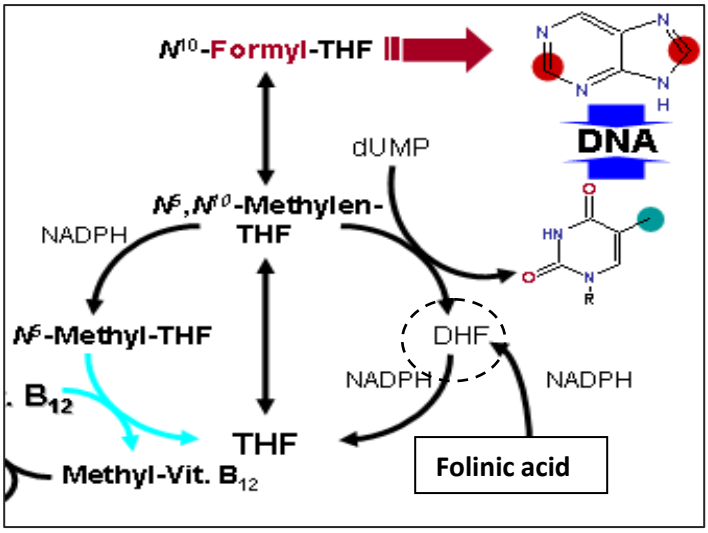


Figure2. This figure shows the effect of adding folinic acid, which makes abundant THF.
-it does not require the action of dihydrofolate reductase for its conversion to THF.

**side effects of 5-flurouracil: myelosuppression, bone marrow suppression and gut epithelium damage (all side effects of cancer drugs in the previous lectures mainly).

3-Leucovorin:

-A potentiating drug, used to potentiate other drugs.

- We give 400 mg/m^2 IV on day one as a 2-hour infusion before giving fluorouracil dose, why?

Because when we give 5-FU after leucovorin, 5-FU will find high availability of **N^5, N10 Methylene- THF** so it will act fast and ideally, so the survival increases and life expectancy of the patients increases.

- It is not an anti cancer drug, its folinic acid which helps enhance the activity of 5-flurouracil as we said before.

**in the past they used to give oxaliplatin and 5-flurouracil alone, and then they found a drug with potentiating activity (how? Like we said before by driving the reaction which makes more THF, so more methylene is available for TS). Pay attention we drive it on the false nucleotide 5-FU and that's how we inhibit this enzyme)

So we give at first oxaliplatin, then leucovorin, then fluorouracil for day one, we repeat this cycle of taking theses three drugs for two weeks (sometimes three weeks) it depends on the cancer but mostly we give seven cycles.

4-Bevacizumab:

-we use this drug when we especially treat stage four where the incidence of recurrence is very high. Pathophysiology of colorectal cancer depends a lot on angiogenesis unlike the breast cancer.
- It has an anti-angiogenic activity (VEGF antagonism), it affects the formation of growth factor that produced by cancer to the endothelial cell to produce angiogenesis.
-angiogenesis is stimulated by Vascular endothelial growth factor (VEGF), it is more aggressive in stage four of colorectal cancer, because the size of cancer will be bigger in this stage so more angiogenesis.
-its trade name is avastin, and it is a monoclonal antibody (like trastuzumab).
-so patients with advanced or metastasised colorectal cancer (stage 4) are treated with bevacizumab that inhibits VEGF (slows the growth of new blood vessels).

-so for stage 4 patients only, we used to treat with bevacizumab with FOLFOX drugs. We do not use bevacizumab with stage 2 and 3 patients, why?

Because in clinical trials when they used the drug on them there was no difference (used it or not it was the same)

-And for stage 4 patients this drug prolonged the expected life of them, from 8-12 months.

-When we end the therapy (end FOLFOX) or during it we give bevacizumab since the interaction between drugs is very low.

**let's talk about the history of this drug:

It was discovered by a scientist named Judah Folkman (he was a surgeon, at the year of 60 he left his job and started working as a scientist, he was the first one to discover and define angiogenesis of the tumour) after that, scientists had tried to discover the factors that stimulate angiogenesis until they discovered VEGF, so they made an antibody (bevacizumab) that binds receptor A (one of VEGF receptors), and it was approved for breast cancer, lung cancer, brain tumour, GIT cancer, and colorectal cancer.

After six years they found that this drug in realty is active and has effects only on colorectal cancer, by finding that the survival years increased only in colorectal cancer patients, so now it is contraindicated for treatment of breast cancer, but it is still used for lung cancer because it increases the survival period by 2 months (intermediate survival period for lung cancer is 8 month, so when we use bevacizumab it will add 2 months so it has a real value).

-Can you live without VEGF?

The answer is no, because it has other functions in repair and wound healing, according to that this drug will produce **impaired wound healing**, **bleeding**, **bowel perforation**, a bizarre side effect which is **high blood pressure**, and affect repair and healing

-We want to put this drug in a target therapy like herceptin, however it has many side effects. It is a very expensive drug (1000 JD). If the patient took this drug after the adjuvant therapy, the patient will have to take bevacizumab until s/he dies.

Please refer to the slides, have a good time while studying.