SHEET NO. 22

PHARMACOLOGY

DOCTOR 2019 | MEDICINE | JU

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مرحبا ☺

كلام الدكتور باللون الاسود و السلايدات باللون الاخضر.

Last time we talked about cancer drugs, and we started with 'why we have a failure in cancer treatment' and we summarized it with 5 problems; which are:

1) heterogeneity (which is very high in cells).

2) the absence of immune-genic activity (where cancer cells teach the immune system cells on how to deal with it and consider it as a friend).

3) the number game plays a very important role in this process.

4) that there is loss of apoptotic activity in these cells so when we treat using drugs, we can see that the treatment isn't responding because we can't drive through the apoptotic process.

5) we also talked about the big issue which are the hypoxic conditions and we have to understand that this condition creates a case of dead cells (not really dead, but entering the G_0 phase where there is no response to any kind of drugs) and this is what cause the recurrence of cancer.

We depend on strategies in treatment for cancer and these strategies depends on:

- cocktail (combination/regimen) of drugs; it contains number of drugs (for example 5 drugs) and each of these drugs will have a different mechanism of action (this mechanism must be known to produce a side effect which has to be different from other drugs) and this is due to heterogenesity; having high heterogenesity means that we are using every weapon we have.

  ○ there will be side effects (sever ones) so we try to gather drugs with different side effects in the regimen (synergism is not only in the activity, we don't want it to happen in side effects and this is why we try to gather cancer drugs that are as far as possible from having the same side effects.

  ○ why do we use it? Because we are dealing with cells without apoptosis, cells with different cell cycle situation and cells themselves could be heterogeneous, so we are using different types of drugs which produce different activity in order to make sure that we are killing all the cells that are present in the body. (monoclonal origin of a cancer means that we have to mope out all cancer cells and this is what we call regimen).

CANCER DRUG CLASSES

• The classes of drugs currently used in the cancer clinic are:

1. Antimetabolites (anti-folates, pyrimidine and purine analogues).

- here cancer cells are dividing and they will need a lot of metabolites and these metabolites need nucleotides in order to undergo replication, so actually we can deprive cells from these metabolites and this depression will produce a pause in S phase of the cell cycle.

Folic acid is important in the synthesis process of purines and pyrimidine; by which we are reducing the concentration of folic acid.	The enzyme dihydrofolate reductase will inhibit the synthesis of purines which will force cells to stop in the S phase.	Antimetabolites are S phase specific/cell cycle specific which means that they stop proliferation and keep cells in S phase.

- purines and pyrimidines analogues: instead of giving the cell cytosine, we give it something similar-to it (like acyclovir in anti-viral), they recorbilate within the DNA and they will stop the cell's proliferation in the S phase.

2. Mitotic Spindle Inhibitors (modulators of tubulin polymerisation) – also cell cycle specific

- in order for mitosis to occur there should be overlapping with the mitotic spindles (which are responsible for separating chromosomes, so we can do this inhibition by preventing their rresurrection by using drugs such as vincristine and vinblastine OR Inhibition by preventing their separation (after they have formed) from the chromosome, so cell will undergo inhibition of cell cycle (M phase specific; stop cell cycle in M phase).

3. DNA Binding Agents (intercalating and alkylating agents) – non cell cycle specific drugs

- Intercalaters will enter the DNA and stay there without linking within the DNA and they bind to topoisomerase; this binding will cause segmentation of DNA and this results in cell death despite being in S or M phase or any other phase of the cell cycle.
- Alkylating agents are different since they bind DNA from one side and another DNA from the other side and then it causes crosslinking which will result in the braking of the DNA and it will destroy the cell.

3. Hormones and Hormone Antagonists

- We are talking about cancers that depend on hormones, in case of breast cancer-estrogen and in case of prostate cancer-androgen.
- The idea here is preventing hormones from binding to their locations and driving cancer.

4. Miscellaneous anticancer drugs (it will be explained later in this lecture ☺)

Breast Cancer Systemic Therapies

- Breast cancer is the most common cancer in Jordan, and it is found in ladies more than men.
- Breast cancer could be hormonal dependent vs non-hormonal dependent, aggressive vs not very aggressive.
- In diagnosis; there will be a lump in lady's breasts and we want to treat it, the first idea will be to remove it by surgery and by doing this, the main lump will be removed.
- Micro-metastases; they have escaped the original lump and went either to lymph nodes or other places which we aren't able to see (because they are less than 10^6 cells).
- After removing the main lump, we start with chemotherapy; we try to give systemic chemotherapy and erase all the unseen micro-metastases in order to delay the recurrence of cancer.

• Drug treatments that can attack cancer cells throughout the body

– Endocrine therapy (hormonal)

– Chemotherapy

– Biologically-targeted therapy

Treatment of Early Stage Breast Cancer

• Breast cancer most curable when detected early

– Micro-metastases (undetectable) can exist at time of diagnosis in many patients, leading to eventual recurrence (even if the cancer is small and detected early, we are afraid of the presence of micro-metastases).

• Multidisciplinary care critical for best outcomes.

Usually in stage 1 cancer we only do surgery, but in most cases, we see the patient presents with stage II cancer which means that the cancer is more than 2 cm in length, and this indicated the presence of micro-metastases.

– Surgery.

– Radiation therapy (to clear all the residual leftovers of the cancer).

– Adjuvant systemic (drug) therapy reduces risk of recurrence and death.

Treatment of Metastatic Breast Cancer

• Metastatic breast cancer is not curable (so here we are using palliative treatment) but can be very treatable.

• Goals:

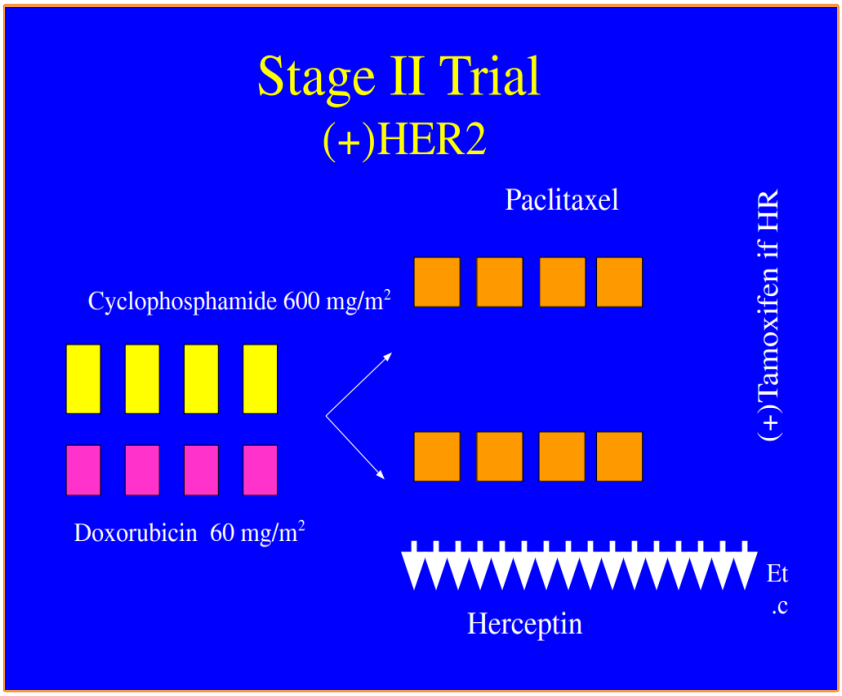
1) Control and regression of disease.	2) Prolongation of life	3) Improvement in symptoms and quality of life.

Medicine List

• Antineo-plastics relevant to treatment of breast/cervical cancer

– Tamoxifen
– Doxorubicin (Adriamycin)
– Cyclophosphamide (Cytoxan)
– Paclitaxel (Taxol)
– Trastuzumab (Herceptin)`

Not all patients will be taking all 5 drugs, some will take 5 and some will take 4 and some take only 3.



- when a surgery is performed on a lady, cycling is done (each 21 days we give a dose); we give her cyclo-phospho-amide and doxorubicin, we give the two drugs in 4 cycles…why? Because these chemotherapeutic agents will inhibit the bone marrow, lymphocytes (lymph system), alopecia and also problems in epithelial lining of the gut.

- We can't give the patient 4 doses of cyclophosphoamide at once, so we give it as cycles and let the bone marrow have a chance to recover, because these two drugs are considered generally as strong ones (they are chemotherapeutic agents that are able to segment the DNA). (from me: further explanation of this figure has been made as lecture progressed so just go on and everything will be cleared ☺)

Doxorubicin (very well-known drug to be associated with cancer)-also known as Adriamycin.

• The drug has a red colour (rubicin in French means red).

• DNA strand scission via effects on Top II enzyme (topoisomerase poisons) – it inhibits DNA.
- topoisomerase 4 (gyrase); when there is unwinding in the DNA (opening the DNA and replicate), there will be coiling of the DNA and this is solved by Top II which cuts, tightens and connects.
- doxorubicin prevents re-joining of DNA by binding after the cut by Top II is done (trapping topoisomerase in its cutting form mechanism).
- this process is called poisoning because doxorubicin doesn't cut the DNA, it allows the enzyme to cut it, then it comes and bind to the DNA, so it's called topoisomerase poisons.
• Non cell-cycle specific.
• High-affinity binding to DNA through intercalation, resulting in blockade of DNA and RNA synthesis.
• Binding to membranes and altering fluidity
• Generation of the free radical and oxygen radicals

Anthracycline (doxorubicin is one of the antibiotics of anthracyclines)

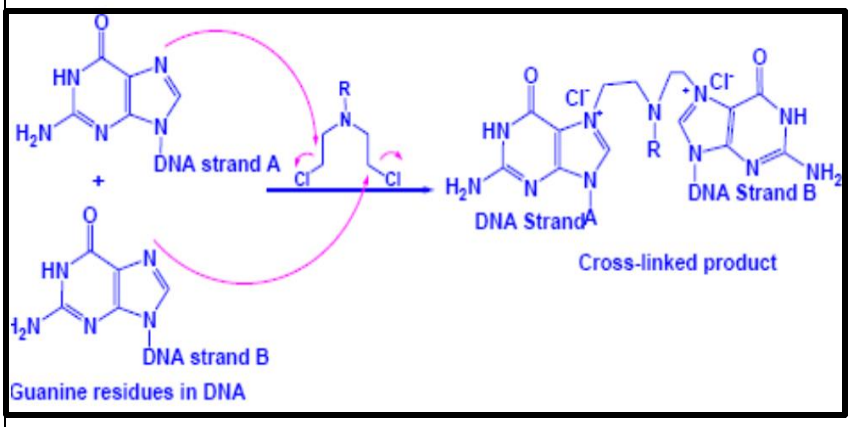
• Their main toxicities are:-
- Bone marrow depression
- Total alopecia

If doxorubicin doesn't produce cardiotoxicity, we would have solved a lot of cancer's problems.

• doxorubicin affects the heart; BUT the anthracyclines have a strange dose-limiting irreversible and lethal cardiomyopathy. (why do we still use it? Because doxorubicin is needed in order to destroy cancer by we keep an eye on the heart).
- one of the solutions is by giving avoid giving more that 500 mg per m^2; if we used 500 mg per m^2 then the percentage of people who would have toxicity would be 5-20% but if we used 400 mg then the percentage of people having cardiotoxicity would be 1-2% and this is why we don't exceed 400 mg (cut off) so we don't reach more incidence of cardiotoxicity which will cause cardio-failure and cardiomyopathy.
• This cardiotoxicity may be a result of the generation of free radicals and lipid peroxidase.

ALKYLATING AGENTS

• Alkylating agents bind irreversibly to DNA and function by crosslinking the two Watson-Crick strands, thereby inhibiting strand separation and preventing DNA replication.



-we have guanine residues in both strands, alkylating agents are like clips; chlorine is lost from both sides and then these agents cross-link the products which breaks the DNA.
-they are non-cell cycle specific.

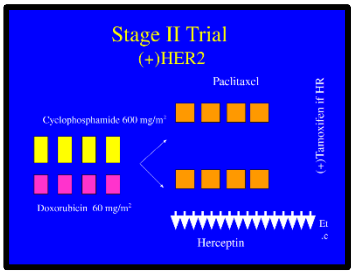
Nitrogen mustards

Cyclophosphamide

1. most commonly used alkylating agent used in lymphomas, leukemias, sarcomas, carcinomas of breast or ovary, as well as childhood malignancies.

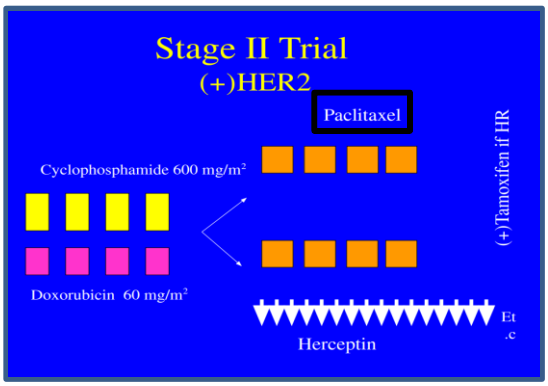
2. has a special place in the maintenance therapy for breast cancer. (when the patient has metastasis and we want to slow/make the progression easier, prolong her life & reduce chances of complication so we give her cyclophosphoamide).

- It is taken orally.
- Doesn't really produce bone marrow suppression (known as bone marrow sparing drug), compared to doxorubicin which is a very strong bone marrow suppresser.
- Cyclophosphoamide is a prodrug; large amount of it is stimulated/activated inside cancer cell (it gets stimulated in other areas like lymphocytes but mostly it's activated in cancer cells), because the enzyme that stimulated it is over expressed in cancer cells so it's a type of relative targeting.

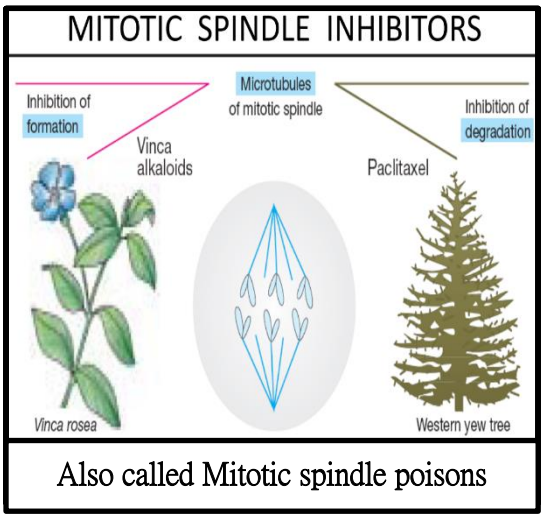


- this allowed us to use cyclophosphoamide and doxorubicin together in these cycles to tackle the cancer cells by different mechanisms of action and they don't have the same side effects.
- giving doxorubicin and cyclophosphoamide in these cycles won't exceed 400 mg/m2 so we haven't exceed safety limits.

3. Cystitis (inflammation of the urinary bladder) may result. (after cyclophosphoamide is metabolized and about to be excreted, its converted into acroline which causes inflammation and hematourea, so either we hydrate the patient by giving cyclophosphoamide in long doses that are diluted or drinking high amounts of water or we give him saline and by hydrating the patient we will get rid of acroline OR co-administered with N-acetylcystein or 2-mercaptoethanesulfonate (mesna) which binds to acroline and reduce the toxicity of cyclophosphoamide. Both are thiols that neutralized acrolein.



- these is another mechanism of action to make sure that all cancer cells have died, so in the next four cycles we will give the patient a drug called Paclitaxel and with it we will give another drug called Herceptin.



Also called Mitotic spindle poisons

-mitotic spindle inhibitors are cell cycle specific and divided into two types; inhibition of formation (vinca alkaloids- vincristine and vinblastine) and inhibition of degradation (paclitaxel). These drugs prevent the separation of chromosomes from the mitotic spindles by binding to the separation place (same as topoisomerase poisons; letting the mitotic spindle to kill the cell in M phase).

-vincristine is used to treat colon cancer and for breast cancer; paclitaxel is used.

Emission of tubules: polymerization.

Contraction of mitotic spindles: depolarization.

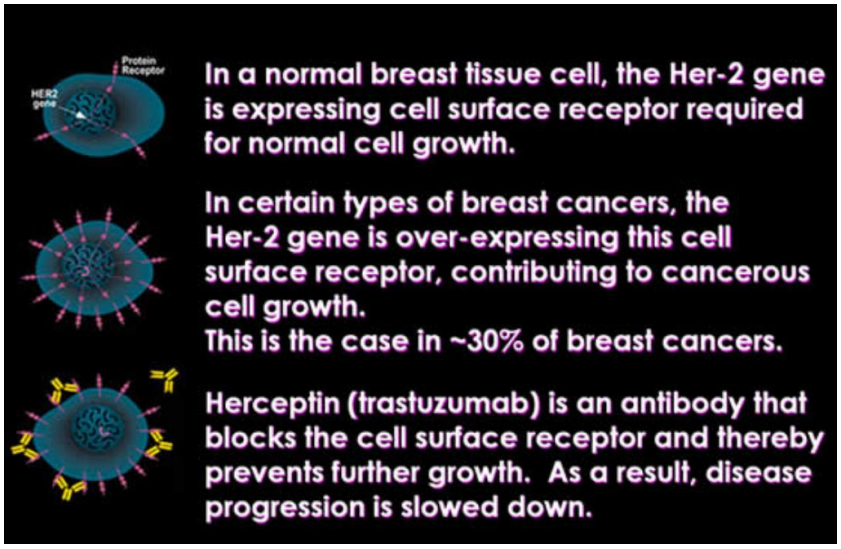
INHIBITORS OF TUBULIN DE-POLYMERISATION

• The TAXANES (mitotic spindle poisons), of which Taxol is the best known example, are isolated from the yew tree.

• They also bind to tubulin but have the opposite effect to the Vinca alkaloids and stabilise microtubules to depolymerisation. (mitotic spindle poison)

• The taxanes are generally more toxic than the Vinca alkaloids and side-effects include myelosuppression (that is why they are separated from doxorubicin) and Peripheral neuropathy (they cause severe pain in neuronal endings in hands and feet).

- Cyclophosphoamids, doxorubicin and paclitaxel are given generally in all types of cancer (there are exceptions); in breast cancer we take a biopsy from the patient, we send it to the lab and the lab would tell us that this cancer is ER(+)-estrogen receptor positive, or BR(+); when it's ER+ It will be BR+.
- HER2 (epidermal growth factor 2) which drives proliferation.
- 25% of cancer patients are not just ER+ (estrogen dependent cancer and overexpression of estrogen receptor), but also there is overexpression of HER2 receptor. The solution is inhibiting these growth factors.
- Trastuzumab (Herceptin) is a drug for HER2.



- in normal breast cells, we have HER2 expressing cell's surface in low amounts.

- not just overexpressing, its multiplying the expression of this cell surface receptor.

- trastuzumab: monoclonal antibody

- this drug is used with paclitaxel (they have different side effects), a side effect of trastuzumab is cardiac toxicity and this is why it hasn't been used with doxorubicin.
- this drug is given to the patient for 2 years (or 1 if progression disappeared); dose injected each month.

-Her-2 overexpression in breast cancer

•About 20-30% of breast cancers overexpress HER-2 protein (usually because of gene amplification).

• Monotherapy with anti-HER-2 monoclonal antibody (trastuzumab/Herceptin) has a 30% response rate in HER-2-positive metastatic breast cancer. (we are using palliative treatment not cureness).

• Combination of trastuzumab plus chemotherapy improves time to progression and overall survival in advanced HER-2 positive breast cancer. (even if the primary tumor was ER+ and HER2+ we will give the patient HER2 inhibitor).

- Reduces recurrence by 1/2 & deaths by 1/3 when added to chemo in early stage breast cancer.

•Trastuzumab plus anthracycline (cyclophosphoamide) results in a 20% incidence of cardiotoxicity and this is why they are given separately.

- If the lab results of the patient stated that she is ER+, we will inhibit ER by giving a drug called tamoxifen which is an inhibitor of estrogen receptors (for 5 years because it is safe and we want to be sure that there won't be recurrence of cancer for the patient).

HORMONE ANTAGONISTS

• Tumours derived from hormone-sensitive tissues may be hormone-dependent.

• Their growth can be inhibited by

(1) hormones with opposing actions. (2) hormone antagonists. (3) inhibit hormone synthesis.

Tamoxifen

•Selective estrogen receptor modulator (SERM) so it either causes inhibition or induction of estrogen receptors and it is present on bone (increase density-agonist), endometrium (causes cancer by inducing proliferation-agonist) or breast cancer (increase its growth-antagonist because breast cancer tissue is different; the receptor has a cell organ specific activity) , have both estrogenic and antiestrogenic effects on various tissues.

• When used prophylatically, tamoxifen has been shown to decrease the incidence of breast cancer in women who are at high risk for developing the disease

• Side effects include hot flashes, depression, increased risk of uterine cancer and blood clots (similar to entering menopause, caused by decreased estrogen).

• Taken daily by mouth for 5 years. (because uterus cancer incidence is increased 1-2% id used for 5 years but if will reach 4% if more that 5 years and this is why we limit the use for 5 years).

Are there drugs that prevent the occurrence of cancer (prophylaxis)?

- yes, tamoxifen is taken by patients that have a high risk of cancer like those who have mutation in BRACA 1 and BRACA 2 or patient who have a history of cancer in her family so she is given the drug before cancer occurs (in Jordan breast cancer occurs during 40s) so she is given prophylactic drugs between 35-40 years of age and it should be only for 5 years because if the period extended we will risk the occurrence of endometrial cancer.

The doctor skipped the slides from 40-47 and started with colon cancer chemotherapy but I will put at the end of the sheet just in case they were included as self study ☹.

Chemotherapy as adjuvant in CRC (colorectal cancer)

Oxaliplatin + 5-flurouracil + leucovorin (MFOLFOX7)

- folfox treatment depends on oxaliplatin which is the same as cyclophosphoamide (a drug used as an alkylating agent and generally speaking; we call this alkylating agent -bone marrow safe drug), the side effects of oxaliplatin is kidney toxicity.
- 5-flurouracil is an antimetabolite, it is converted into thymidine analogue, so it enters the DNA and also it stops cell cycle in S phase, its side effects is very sever bone marrow suppression and this is why leucovorin is given with it.
- Leucovorin (folic acid supplement) is used to drive the normal cell to produce more DNA so we don't have complete bone marrow suppression.
- In case of colon cancer, leucovorin is either given with 5-flurouracil to refine its activity in cancer cells but if the patient suffers from bone marrow suppression; then we give leucovorin to drive the bone marrow to proliferate.

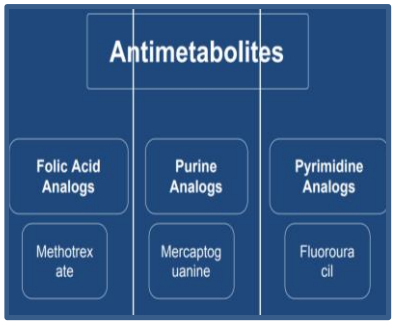
Oxaliplatin: 100 mg/m² IV on day 1
5-Fluorouracil: 3000 mg/m² IV continuous infusion on days 1 and 2 for 46 hours
Leucovorin: 400 mg/m² IV on day 1 as a 2-hour infusion before 5-fluorouracil
Repeat cycle every 2 weeks

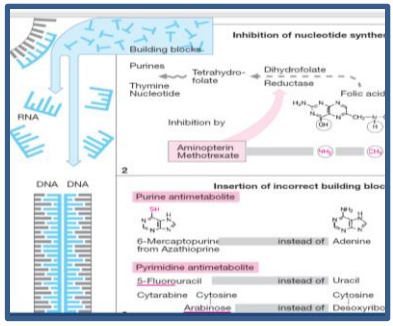
- Colon cancer induces epidermal growth factor 1 and there is a monoclonal antibody that inhibits growth, its pharmacological response isn't very high because the epidermal GF is not overexpressed in high amounts in colon cancer.

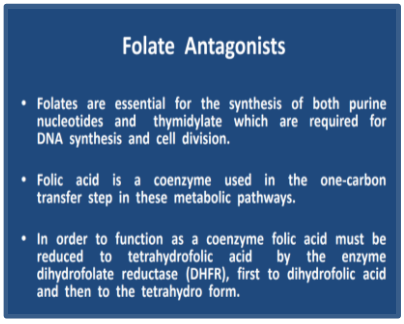
And this is the treatment of cancer, regimen with different side effects and different mechanisms of action which result in reducing micrometastases after surgery (then we give this adjuvant therapy).

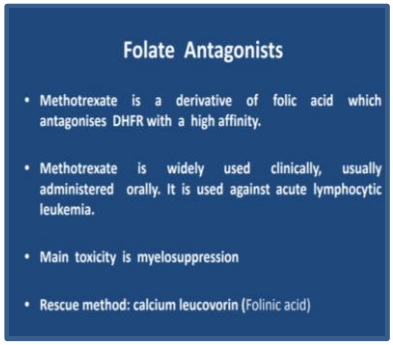
- We can give these chemotherapies before surgery, because sometimes the cancer is very large and the surgent won't be able to see the edges and these are neo-adjuvant therapy (not just adjuvant) in order to reduce the size of the cancer and to be able to decrease its size.

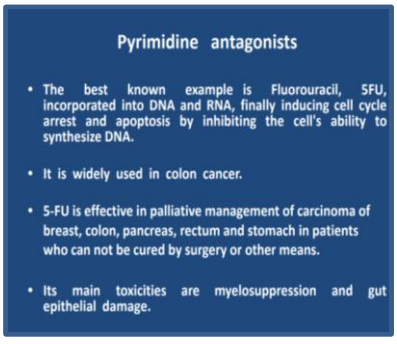
Slides that haven't been explained in the lecture











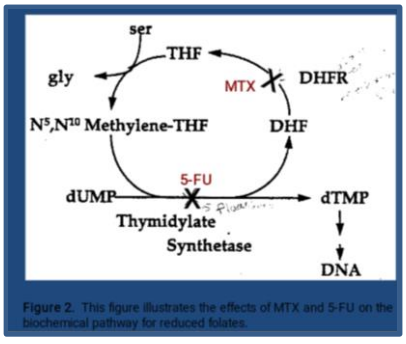


Figure 2. This figure illustrates the effects of MTX and 5-FU on the biochemical pathway for reduced folates.

Leucovorin

- Derivative of FH_4
- Given as "rescue" by repleting intracellular FH_4 pools
- Selective for rescuing normal cells more than malignant cells

Platinum analogs

- In the clinic, cisplatin behaves very similarly to the organic alkylating agents and finds widespread use.
- Cisplatin has efficacy against a wide range of neoplasms.
- It is particularly effective in germ cell tumours (testicular cancer and ovarian tumours) and in breast cancer.
- Its use in combination chemotherapy has revolutionised the treatment of testicular and ovarian tumours, frequently leading to complete cure of testicular cancers in young men.

Platinum analogs

- Its main toxicities are to the kidney and to the ear,
- produces relatively little myelosuppression but can cause severe nausea, vomiting.
- Carboplatin is a second generation platinum analog that has less renal toxicity and gastrointestinal toxicity.
- Though Carboplatin has widely replace cisplatin in chemotherapeutic regimen.

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	-	+	-

Bevacizumab

inhibits the action of VEGF, a blood vessel growth

Factor When VEGF is bound to Bevacizumab, it cannot stimulate the formation and growth of new blood vessels

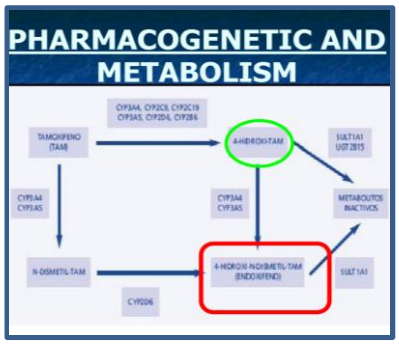
- prevents VEGF from binding to its receptor
- adds to the effects of chemotherapy in cancers like bowel and lung
- FDA approved for:
  - First-or second-line Colorectal cancer treatment in combination with 5-fluorouracil-based chemotherapy
  - Unresectable, locally advanced, recurrent or metastatic nonsquamous non-small-cell lung cancer in combination with carboplatin and paclitaxel

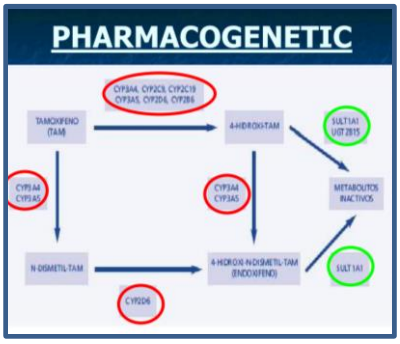
Bevacizumab

Serious side effects include:
- bowel perforation
- impaired wound healing
- bleeding
- kidney damage

More common side effects of Are:
high blood pressure
- tiredness/weakness
- clots in veins
- diarrhea

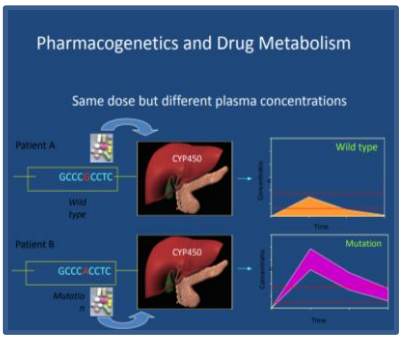
- The probability of developing impaired myocardial function based on a combined index of signs, symptoms, and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m2 of Doxorubicin, 3 to 5% at a dose of 400 mg/m2, 5 to 8% at 450 mg/m2, and 6 to 20% at 500 mg/m2. The risk of developing CHF increases rapidly with increasing total cumulative doses of Doxorubicin in excess of 400 mg/m2.





Tamoxifen Metabolism

- Tamoxifen is converted to endoxifen principally by a noninducible P450 enzyme that is coded for by the most polymorphic, and most studied, gene in the cytochrome P450 system: CYP2D6.
- In one study, **breast cancer** patients treated with tamoxifen who were homozygous for a poor metabolizer genotype (*4/*4) had significantly lower serum concentrations of endoxifen than those with the active.



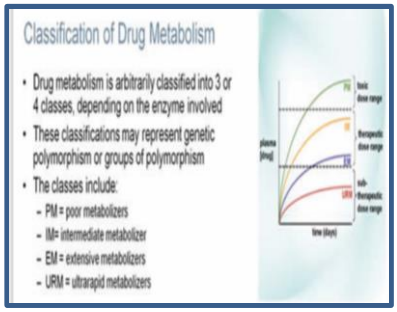
Phenotypes of CYP450

Poor metabolizer (PM). 1
has low metabolic capacity-
has two mutant alleles-

Intermediate metabolizer (IM). 2
has metabolic capacity between PM and EM-
has one reduced activity allele and one null -

Extensive metabolizer (EM). 3
has regular metabolic capacity-
has at least one and no more than two-
normal functioning alleles

Ultrarapid metabolizer (UM). 4
has higher metabolic capacity than EM-
has multiple copies of functional alleles-



Frequencies of the CYP2D6 genotypes and in Jordan Zihlif et al 2012

Predicted Phenotype	Count (192)	Frequency (%)
Poor metabolism	5	2.6
Intermediate metabolism	41	21.1
Extensive metabolism	120	62.5
Ultra-rapid metabolism	**26**	**13.5**

Zihlif et al 2012
Genetic testing and molecular biomarkers 16 (10), 1201-1205

THE END ❤