*Combination therapy:

- Cancer is heterogeneous, and resistant anticancer drugs are common, so combination of drugs together is needed in order to attack cancer.

*Cancer drugs are divided into groups:

I) DNA binding agents (Intercalating and Alkylating agents)

2 types:

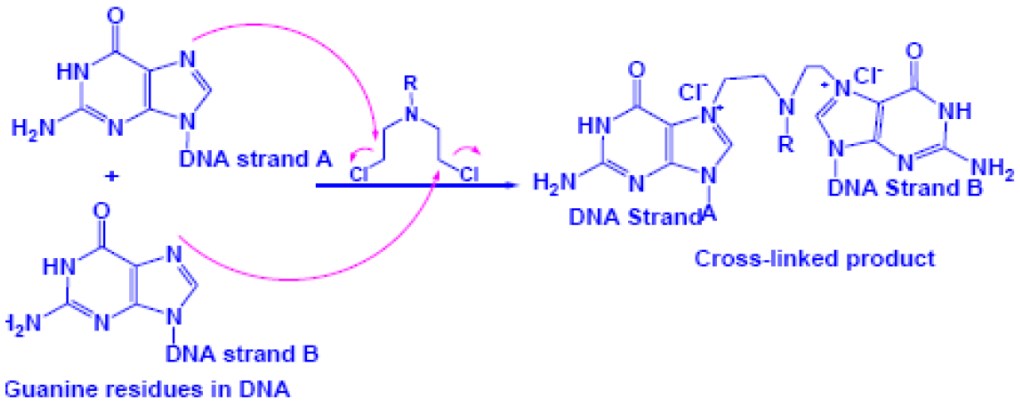
1) Poisoning the DNA itself.
2) Topoisomerase poisons.

Doxorubicin

- The main drug of the DNA binding drugs.
- Belongs to **Anthracyclins** (Which are two types doxo- and dauno-rubicin).
- The base for all **breast cancer treatments**.
- Treatment by this drug is called Anthracyclin based treatment.
- **Cardiotoxicity** is the most important side-effect. You have to adjust the dose you give your patient "not to exceed 400ml/kg/m^2 " in order to avoid it.

*Alkylating agents:

- Used in **breast cancer treatment**.
- The alkyl group is attached to the guanine base of DNA, at the number 7 nitrogen atom of the purine ring → Crosslinking the two DNA strands together → Breakage of the DNA → Forcing the cell to undergo apoptosis.



Carmustine and ***Lomustine***

- Alkylating agents.
- belong to **Nitrosoureas**.
- Used in **Brain tumors treatment**.

*Post-treatment suppression therapy:

- Placing a disc within the brain to suppress any new growth for any residual tumor cells.
- Done because In spite of using a lot of drugs in chemotherapy we still think there is a residual tumor.
- Must be a part of the treatment of every cancer patient.

Cisplatin

- **Alkylating-like drug** (or **Platinum Analog**).
- The main drug that is used for **treatment of colorectal cancer** (The most common cancer in Jordanian males).
- Treatment by this drug is called Cisplatin based therapy.
- works like the alkylating agents.
- **Little bone borrow suppression**, so it is called a "**bone morrow sparing drug**".

*Notes:

- What happens in DNA binding agents group is similar to what we do in radiation therapy, which is break on the DNA.
- Radiation therapy is usually used after surgery, before chemotherapy.
- Sometimes it is used before surgery, and in this case it is called **Neoadjuvant therapy**.

II) Antimetabolites

- Have a great effect against **leukemias and lymphomas**. (There is no treatment for leukemias nor lymphomas without antimetabolites.)
- Have a great effect in treatment of **Children Acute Lymphocytic Leukemia**.
- two mechanisms to hit the cancer cells:

1- Inhibition of nucleotide synthesis.
2- Inhibition of DNA Polymerase by introducing false metabolites (Insertion of incorrect building block).

- **Side-effects:**

Bone morrow suppression, Immuno suppression, Alopecia, Nausea, Vomiting.

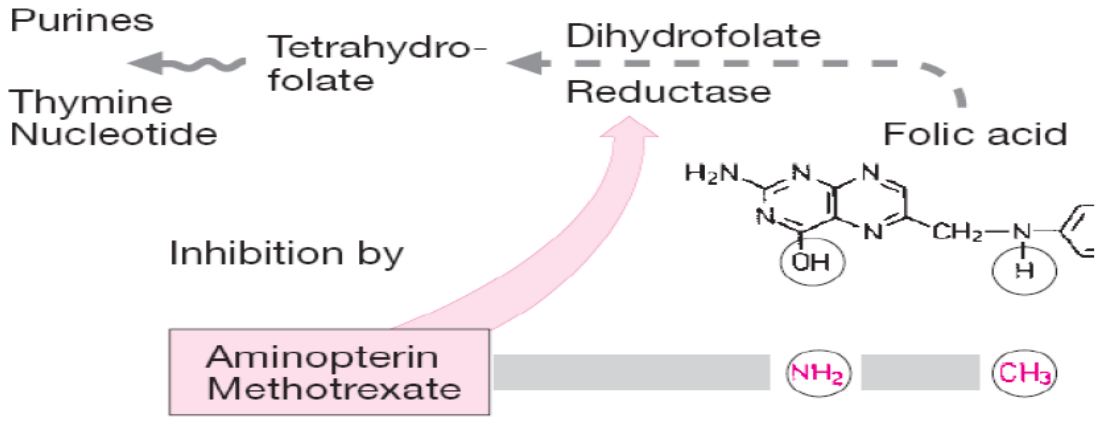
- There is no special side-effects like the DNA binding agents.

- 3 Drugs mainly:

1) ***Methotrexate***.
2) ***6-Mercaptopurine***.
3) ***5-Flourouracil***.

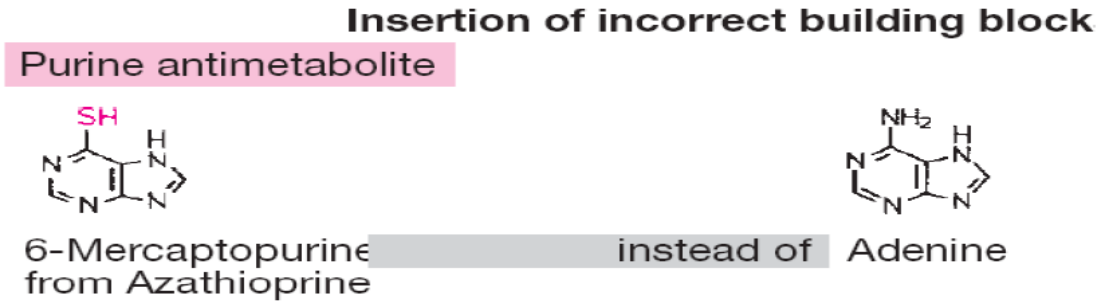
1) Methotrexate

- Inhibits Dihydrofolate Reductase enzyme → **Inhibits Purines synthesis** → The cell will not have enough nucleotides → Cannot replicate anymore.



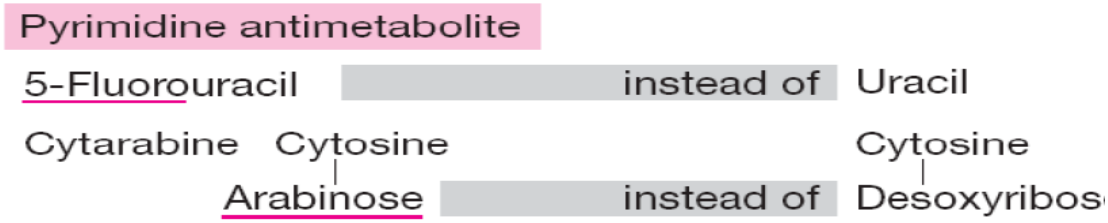
- Used also in **psoriasis, rheumatic arthritis, blood diseases and inflammatory bowel diseases**.
- In treatment of diseases other than cancer, we only want to reduce the immunity, so it is given in very low doses "7.5mg twice weekly" or 15mg once weekly.
- In treatment of cancer, we give the patient the highest dose he can tolerate "15 mg per square meter".
- Notice that the same drug can be used in different doses.

2) 6-Mercaptopurine = *Azathioprine*



- ***6-Mercaptopurine*** → Injectable.
- ***Azathioprine*** → Oral.
- ***6-Mercaptopurine*** is used in leukemias esp. childhood Acute Lymphocytic Leukemia (ALL).
- The patient is going to take it **for years** as a treatment.
- Used in the **maintenance phase**"will be explained in the sheet" in the treatment of ALL.

3) 5-Flourouracil



- Used for treatment of **colorectal cancer**.
- Combined with ***Cisplatin***.
- Every patient with colorectal cancer is going to take the **FOLFOX regimen**.
- **FOLFOX regimen** = ***Cisplatin*** + ***5-flourouracil*** + 3rd drug "wasn't mentioned by the Dr."

*Notes:
- Teatment of breast cancer may take about 6-8 months.
- Treatment of Childhood ALL may take years and consists of phases.
- Breast cancer and colorectal cancer are considered solid tumors.
- Leukemias and Lymphomas are considered liquid tumors.

III) Mitotic Spindle Inhibitors

- Have been taken from plants.
- 2 Drugs mainly: 1) ***Vincristin*** 2) ***Taxol***

- 2 Types:

1) Inhibitors of Tubulin polymerization → *Vincristin* and ***Vinblastin***

- This type is called Vinca.
- The **Vinca Alkaloids (*Vincristin* and *Vinblastin*)** are natural products isolated from the periwinkle plant.
- They act by **binding to Tubulin** and inhibit its polymerization into microtubules.
- Thereby preventing spindle formation **during mitosis**. This causes dividing cells to arrest at metaphase → Cells will die or undergo apoptosis.
- They are widely used in treatment of **solid tumors**, **Leukemias** and **Lymphomas**.
- **Little bone morrow suppression "bone morrow sparing drugs"** (like the Cisplatin)
- Relatively **non-toxic**, generally having mild myelosuppressive activity, but they cause sensory changes and neuromuscular abnormalities frequently. (because neuromuscular junctions are attacked when attacking Tubulin.)
^ according to slide 51 this is only about Vincristin Not Vinblastine 😐

Vincristin

- The most important drug in this group.
- Can be given in large doses.
- Used in the induction phase of ALL in children and adults.

2) Inhibitors of Tubulin De-polymerization → *Taxol*

- The Taxanes (of which ***Taxol*** is the best know 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 de-polymerisation. (mitotic spindle poison)
- ***Taxol*** is the 3rd drug that is used in **breast cancer treatment** after ***Doxorubicin*** and ***Cyclophosphamide***"was mentioned in the previous lectures."
- The Taxanes are generally more toxic than the Vinca Alkaloids.
- Side-effects:

Myelosuppression and **Peripheral neuropathy**.

*Related to breast cancer treatment:

- **Old regimen:** 6 cycles of these three drugs together (***Doxorubicin***+***Cyclophosphamide***+***Taxol***) but here the patient will suffer a lot because of myelosuppression.
- New regimen"Used worldwide nowadays": 4 cycles of ***doxorubicin***+***cyclophosphamide***, after finishing the 4 cycles we start 8 cycles of ***taxol***.
One cycle = 21 days.
- Sometimes you cannot combine certain drugs together, as if you combine a lot of drugs with the same side-effects this is going to destroy the patient!
- The three drugs cause all the side-effects so the idea here is to give them separately.
Doxorubicin → Cardiotoxicity + the other side-effects.
Cyclophosphamide → Cystitis + the other side-effects.
- When you start the 8 cycles of taxol, you have to be concerned about the **peripheral neuropathy**, as the patient will have muscles and joints pain and paresthesia.

*Notes:

- Most of the drugs we use are natural drugs.
- 90% of the anticancer drugs are natural products.
- You - as a doctor - should be both natural and synthetic, as you believe

the idea plants have a nice activity.
- Herbal medicine is nice, but the main problem of it is the dosing.
- A certain plant may be useful for a cancer patient and at the same time have no response on another patient that has the same cancer!

*Targeted Therapy:

- Drugs that only target cancer cells.

Asparginase

- The 1st drug used in targeted therapy.

*Mechanism of action:

- L-aspargine is needed for building of any cell.
- Human cells and most of the cancer cells can synthesize L-aspargine.
- Some of the cancer cells cannot synthesize L-aspargine, so they uptake L-aspargine from the circulation.
- If we give Asparginase → L-aspargine will be destroyed → **Inhibition of L-aspargine uptake** by the cancer cells → metabolism and replication of the cancer cells will stop.
- This type of targeted therapy is used with **Leukemias esp. childhood ALL cells** because they cannot synthesize L-aspargine.

*Side-effects:

- **hypersensitivity reaction** manifested by fever, chills, nausea and vomiting, skin rash, and urticaria.
- Different from those of the chemotherapy.
- No myelosuppression, Alopecia, Epithelial gut or immuno problem.

Dr. read slide 53:

- Asparaginase (L-asparagine amidohydrolase) is an enzyme that is isolated from various bacteria for clinical use.
- The drug is used to treat childhood acute lymphocytic leukemia.
- It hydrolyze circulating L-asparagine to aspartic acid and ammonia.

Because tumor cells lack asparagine synthetase, they require an exogenous source of L-asparagine.

*Phases of ALL treatment:

1) Induction(or Initiation) Phase:

a- ***Vincristin***

b- ***L-asparginase***

c- Glucocorticoid (***prednisone***, ***prednisolone*** or ***dexamethaone***) → Steroids normally have anti-proliferating effect against the fast-growing cells either they were in the immune system or the hemopoietic.

(We induce with ***Vincristin*** + ***Asparginase*** + ***Dexamethazone*** or ***Prednisolone***)
- These drugs stop proliferating cells esp. in lymphomas and leukemias.
- Intensive chemotherapy.
- You need to dose the patient highly in this phase.

2) Consolidation(or intensification) Phase:

- Another chemotherapy different from the first chemotherapy.
- Once normal hematopoiesis is achieved, patients undergo consolidation therapy.

a- ***Methotrexate*** with ***6-Mercaptopurine***. (What is usually used)
b- High dose ***Asparginase*** over an extended period. (Not used much)
c- Reinduction treatment (a repetition of the initial induction therapy in the first few months of remission).
(We consolidate with High dose ***Methotrexate*** + High dose ***6-Mecaptopurine***)

3) Maintenance Phase:

- To make sure 100% that cancer cells that were not killed in the first two phases, or cancer stem cells or resistant cells won't get a chance to re-grow, so the patient won't get the cancer back.
- It is similar to post-treatment suppression therapy.
- 6-Mercaptopurine or ***Azathioprine*** (orally) on a daily basis.
Boys → for 3 years.
Girls → for 2 years.
Adults → for 2 years.
- Methotrexate may be taken also in addition to ***6-mercaptopurine*** but weekly.
- This is the longest treatment of cancer!
(We maintain with weekly Methotrexate + daily 6-Mercaptopurine)

4) CNS Prophylaxis → *Methotrexate*

- Done in order to protect the brain from the escaping of some leukemic cells during treatment, as they may escape to the brain and make brain tumors.
- Patients with ALL frequently have meningeal leukemia at the time of relapse (50-75% at one year in the absence of CNS prophylaxis).
- We give high dose ***Methotrexate***.
- Given Intrathecally (in the CSF) through the spinal canal.

*Notice that ALL requires Methotrexate-dependant treatment.

IV) Hormonal Agents

- Hormones are the drivers of cancer growth in some cases.
- Examples: Estrogen and Androgen receptors.
- Estrogens induct breast cancer, endometrial cancer, ovarian cancer and uterine tumors.
- Androgens induct prostate cancer.
- The most important and what we are concerned about is breast cancer.
- Hormonal agents inhibit the hormonal induction.

Tamoxifen

- ER antagonism activity.
- Selective Estrogen receptor modulator (SERM).

Why is it called Selective Estrogen receptor "Modulator" not "Antagonist"?
Because it has both estrogenic and antiestrogenic effects on various tissues, so it cannot be called an agonist nor an antagonist.

- Used in Breast cancer treatment.
- Patients with Estrogen-receptor (ER) positive tumors are more likely to respond to Tamoxifen therapy.
- After finishing the 4 cycles of Doxorubicin+Cyclophosphamide, at the time we start giving Taxol we give Tamoxifen with it (Some doctors start giving Tamoxifen from the beginning).
- The use of Tamoxifen in women with ER negative tumors is still investigational.
- The patient has to take ***Tamoxifen*** **for 5 years**.
- If a woman has BRCA1 and BRCA2 mutations and a family history of breast cancer, then she is at high possibility to get breast cancer, so she needs a prophylaxis with ***Tamoxifen*** **for 5 years also**.

Why for 5 years?
To make sure that you are suppressing the growth of cancer by inhibiting Estrogen if there was a cancer growth initiation.

Why not more than 5 years?
Because ***Tamoxifen*** is an **agonist for ER on endometrial cells**, so if you give it for more than 5 years it may reach the endometrium and the patient may develop endometrial cancer!

Flutamide

- Antiandrogen.
- Binds to Androgen receptors.
- Effective in the treatment of prostate cancer.
- Pure antagonist, so we may use it for a long time as it doesn't develop another cancer.

Slide 64: Read it if you like :p

Imatinib

- Associated with CML (Chronic Myelogenous leukemia).
- Inhibits Philadelphia chromosome (the cancer driver).
- Never used with another drug.
- Patient resistance percentage is about 10%.
- If there is a resistance, you return back to the antimetabolite chemotherapy (Vincristine, 6-mercaptopurine……).

Bevacizumab

- Avastin is the trade name.
- Anti-angiogenic drug.
- Inhibits the action of VEGF (Vascular Endothelial Growth Factor), 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.
- It was thought that this drug is going to deplete the blood supply to the breast cancer cells and stop the cancer growth and get rid of it, but it didn't really work and lost its FDA approval.

Other uses:

1- Used in treatment of **colorectal cancer**. (Remember Colorectal cancer treatment is by ***Cisplatin***, ***5-Flourouracil*** and ***Bevacizumab***)
- It prolongs the life of colorectal cancer patient for six months.
- Although, it is not covered by the ministry of health as it is very expensive, one injectable dose = 1000JD!

2- It is injected in the eye to **reduce diabetic retinopathy**.
- As a result of changes that follow hyperglycemia, the retina becomes hyperperfused, so one of the solutions is to deplete perfusion by using ***Bevacizumab*** to stop angiogenesis.
- 3 or 4 times, once monthly.

****

Sorry for any mistakes ☺