Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 37

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SHEET ■

SLIDES □

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Cancer Treatment-2

In this lecture, we are going to continue our talking about cancer Drug Classes.

I couldn't split the sheet into many small parts because everything is connected to everything. don't worry, I tried to avoid leaving paragraphs without clear headline or without numbering. You'll find the revision at the end of the sheet ☺

-Strategies we are going to use in treatment of cancer:

Actually, each strategy is related to a specific drug class.

1-First strategy ➔ Poisoning Of Topoisomerase:

Class of drugs➔ intercalator drugs.

A member in this class ➔ Doxorubicin:

- Side effects:
  - has a limit of **500 mg/kg/day** .If we exceed it, we'll end up with cardiac toxicity.
- Applications:
  - Breast cancer

2-Second strategy ➔ alkylating the DNA "adding an alkyl group", which results in cross-linking thus breakage of the DNA

Class of drugs ➔ Alkylating agents.

Members in this class➔

- ✓ Cyclophosphamide:
  - Side effects:
    - Cystitis, but we can reduce it.
  - Applications:
    - Breast Cancer

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✓ Carmustine and Lomustine:

- Applications:
  - Active against glioma (They cross the blood brain barrier)

✓ Cisplatin :

- Side effects :
  - very little myelosuppression (bone marrow suppression) activity; giving us the opportunity to give high doses
  - Nephrotoxicity and ototoxicity
- Applications:

1) Treatment of testicular cancer :

The golden therapy of testicular cancer which is going to produce complete remission is composed of two drugs :

1. Cisplatin (main reason to cure testicular cancer)
2. Bleomycin (an intercalating agent /side effects: very little myelosuppression and Pulmonary fibrosis)

Both of them have a side effect of a very little myelosuppression, so we can dose the patient as much as we can if we kept an eye on the nephrotoxicity and ototoxicity of Cisplatin -and Pulmonary–because of the pulmonary fibrosis the Bleomycin cause-.

2) Colorectal Cancer: (one of the most common cancers in Jordan)

It's not actually Cisplatin. We rarely use Cisplatin. Because usually when we use Cisplatin for Colon cancer, cancer cells will develop resistance against Cisplatin(you may be asking yourself why this resistance doesn't develop in case of testicular cancer,this is because of two reasons:First, because you can dose the patient as much as you can in testicular cancer .Second, testicular cancer can't develop resistance against Cisplatin as it is –its nature-.

So, we use **Oxaliplatin**; which is very similar to Cisplatin. Oxaliplatin is modified to be more resistant to DNA repair induced by colorectal cancer so it can't develop resistance against it .

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Let's stop for a moment and talk about :Heterogeneity of Cancers:

This example-testicular cancer treated with Cisplatin and colon cancer doesn't-reflects the high heterogeneity of cancers(different cancers have different characteristics) that requires us to use the "differential treatment of cancers"; 200 type of cancers we have to deal with them differentially.

Also, the combination of therapies reflects this characteristic –high heterogeneity within the same cancer itself- .the lump itself has different types of cancers so we have to use more than one therapy.

For breast cancer we use cyclophosphamide plus doxorubicin (for 4 cycles), as for colon cancer we use oxaliplatin plus another drug we'll mention it later, for acute lymphocytic leukemia we use 3 totally different drugs. All of them are called "cancer" however each one has its own treatment

In the slides, both intercalating agents and Alkylating agents are classified under one class which is DNA binding agents.

Now, Let's get back to our strategies:

3-third strategy ➔ inhibiting synthesis of Purines and Pyrimidines:

Class of drugs ➔ Antimetabolites

Members in this class ➔

- ✓ Methotrexate(Folic acid antagonist) :
  - Mechanism:

Methotrexate is similar to trimethoprim (a Dihydrofolate Reductase Inhibitor – DHFR-Inhibitor , in bacteria, that we add to Sulfamethaxazole and produce co-trimoxazole, that's used in UTI "for prophylaxis" and Pneumocystis) .but Methotrexate is a DHFR in humans.

- Advantages:
  - can be taken **orally** and for a long duration.
- Side effects :
  - Since it's an antimetabolite it causes *Myelosuppression* {that's why we use it in auto-immunity problems, When the immune system attacks the body itself. (Rheumatoid Arthritis, psoriasis, IBD, and problems in eyes).To attack those diseases we reduce the immunity but with *low*

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doses, in comparison with that in the case of cancer, and problem is going to be solved.}

- Applications :

  In general, all **antimetabolites** are usually active in Leukemias and Lymphomas (chronic lymphocytic leukemia, CML, ALL...); in the beginning we don't use doxorubicin or cyclophosphamide, we deal with them by antimetabolites "Methotrexate"

  - Used for treatment of :

    Psoriasis
    IBD (Inflammatory Bowel Diseases)
    Rheumatoid Arthritis
    Used as an Immunosuppressant for kidneys' implants

  - Childhood Acute Leukocytic Leukemia (ALL):

In the case of ALL we sometimes combine Methotrexate with another purine analog called 6-mercaptopurine (6-MP)

Treatment of ALL is in "phases method" . we have two phases for treating it :

First Phase➔ Induction Phase :

-Goal: In this phase we try to abolish ALL leukemia cells in the child's body. (that's why this phase is the strong phase)

-Drugs: we use three drugs:

Methotrexate, vincristin(we'll talk about it later) , Promethazine(a steroid/we're not going to discuss it).

-those are really **toxic** drugs, they rescue the body of the patient and doctors can easily over-treat their patients (not intentionally) but to the fact that some patients respond differently. In some cases these drugs may produce **severe** myelosuppression (grade 3 or 4!), which is a Life-threatening and may cause death .So, we try to reduce it to grade 1 or 2 by reducing the side effects of methotrexate. but ,how?

Let's think together: DHFR are enzymes that help in the participation of Folic acid in the synthesis of purines which are important for the cell.

Methotrexate is a DHFR-Inhibitor . it inhibits it by antagonizing folic acid .so, it is a folic acid antagonist. This may affect the normal rapidly

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growing cells like cells in bone marrow and cause bone marrow suppression.

To help solving this problem we give "folinic acid"/trade name: Calcium Leucovorin; which is very similar to folic acid, it will not run around metabolic pathways Methotrexate want to block.so, it's only an antidote that is going to reduce its side effects. It has an excellent absorption and will cause myelosuppression recovering.

The Second Phase we'll talk about it in the next drug.

- ✓ 6-Mercaptopeurine (purine antagonist):
  - Side effects:
    - Toxicity to the bone marrow and Liver." بهدّ الحيل".
  - Applications:
    - As post-treatment suppression therapy of ALL (second phase).

Second Phase of treating ALL ➔ Maintenance Phase:

-in this phase we try to suppress any regrowth.

-we use 6-Mercaptopeurine for two years (post treatment). We give oral treatments at home and make sure the patient will come each month to check on his liver and bone marrow.

- ✓ 5-Fluorouracil "5FU" (Pyrimidine Antagonist):
  - Applications:
    - Part of the **FOLFOX**, which is a chemotherapy regimen for treatment of colorectal cancer.(composed of three drugs : Oxaliplatin , 5FU, leucovorin)

**chemotherapy regimens are done after a long journey of experiments that tend to find the best combination of drugs that work on a specific type of cancer

** NOTE THAT all antimetabolites produce bone marrow suppression except Acyclovir. Even Sulfonamides, since they're antimetabolites. But they have a little selectivity towards bacterial enzymes.

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* Recap:

	Drugs of choice	Side-effects
Breast Cancer	doxorubicin	Cardiac toxicity
	Cyclophosphamide	cystitis
Colorectal Cancer	5FU	Myelosuppression
	oxaliplastin	Nephrotoxicity; hydration Is recommended
Acute lymphocytic leukemia	"induction" Methotrexate	Severe myelosuppression "rescue the patient with folic acid agonist {Folinic Acid}
	"maintenance" Azithropin or 6-MP (2years)	Bone marrow and liver toxicity

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4-Fourth strategy ➔ Inhibition of Mitotic Spindles (either inhibit Polymerisation "sending the mitotic spindle toward the chromosomes" OR De-Polymerisation "getting out of the chromosomes")

- Polymerization Inhibitors:

*Polymerisation is sending mitotic spindles toward chromosomes.

So, If I inhibited them then I'm inhibiting mitosis!

*Drugs used ➔ Vinca alkaloids:

- Source: Periwinkle plant (most drugs are natural)
- Types:
  a) Vinblastine
  b) Vincristine :
     -More active ,
     -produce relatively low myelosuppression,

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-Active on many solid tumors and childhood ALL (when we need low myelosuppression in the induction phase "instead of the golden treatment with the methotrexate because it produces severe myelosuppression").it is also used for Lymphomas, breast cancer, sarcomas and various childhood neoplasms.

The 3 drugs used in the induction phase of ALL:

(the BEST regimen found for ALL)

i) Methotrexate ii) Vincristine iii) Prednisone (not required)

- Side effects:
  - The whole group (polymerisation and depolymerisation) produce sensation problems, or neuromuscular problems in sensation ,neural side effects, *sensational neural problems*.تعددت الكلمات و المعنى واحد.
    It'll cause pain in joints, and in the neuromuscular ends, and even peripheral neuropathy frequently with mild myelosuppression. (so it's relatively non-toxic)

De-polymerization inhibitors:

*Drugs used → Taxol :

- Side effects: myelosuppression and neuronal side effects.
- Applications:
  - Breast Cancer:
    it has proven beneficial in late stage in breast cancers.as long as we can't use cyclophosphamide and doxorubicin for more than four cycles, because of the cardiac toxicity that is caused by doxorubicin, we need to look for another strategy because of the number games in cancer. But,what's the number game?

The number game says that we can't detect cancer with X-ray if there weren't more than 10^8 cancer cells –that was in 2006.now,it's maybe 10^6.

this means that if we finished treatment and not all the cells were killed (10^4 for example are still in the body) and we wanted to check if we achieved the complete cure, we may find from the X-ray that there are no more cancer cells as long as we can't detect it because of the small number of cells. However, cancers are of a monoclonal origin .so, even a

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single cell can develop a cancer and the patient will suffer from **recurrent** cancers after few years.

Actually, 40% of women in Jordan who had breast cancers suffered from recurrent cancers (after 2-3 years) although they made a surgery and took adjuvant therapy. So, this means that a single regimen of 4 cycles of cyclophosphamide and doxorubicin are not enough even if they killed 99.9% of cells. If there's still one more cell left it'll be able to cause recurrent cancer. That's why we use Taxol (4 cycles or 8 cycles,it depends on the case) and this is the same reason why we have induction and maintenance phases in treatment of ALL .so, we suppress things we can't see by using a different strategy, if it didn't die by the first one it will by the second.

Let's have a rest and revise together everything we have learned until now!

- Poisoning Of Topoisomerase done by → intercalator drugs:

E.g.Doxorubicin:
- limit of 500 mg/kg/day .with it, we'll end up with cardiac toxicity.
-used in treatment of Breast cancer.

- Directly Damaging DNA by alkylating it "adding an alkyl group", which results in cross-linking thus breakage of the DNA→ Alkylating agents.

E.g.1)Cyclophosphamide:
-Causes Cystitis
-used in treatment of Breast Cancer.

2)Carmustine and Lomustine:
-Used in glioma(cross the blood brain barrier)

3)Cisplatin:
-Cause Very little myelosuppression,Nephrotoxicity
-Treatment of testicular cancer with the intercalating agent Bleomycin which causes very little myelosuppression and Pulmonary fibrosis.

4)Oxaliplatin:
-used for treating colorectal cancer (platinum compound)

- inhibiting synthesis of Purines and Pyrimidines done by →Antimetabolites

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E.g. 1)Methotrexate:
-Folic acid antagonist (DHFR-inhibitor)
-can be taken orally and longly.
-causes Myelosuppression
-used in treatment of auto-immune problems (Rheumatoid Arithritis, psoriasis, IBD, and problems in eyes), Childhood Acute Leukocytic Leukemia (ALL)/induction phase.
-Rescue method: "folinic acid"/trade name: Calcium Leucovorin, reduces myelosuppression.

2)6-Mercaptopeurine:
-purine antagonist
-causes Toxicity to the bone marrow and Liver." بهدّ الحيل".
-used in treatment of ALL / maintenance phase.

3)5FU :
-Pyrimidine Antagonist
-used in treatment of colorectal cancer.

- ❖ Inhibition of Mitotic Spindles→
- Polymerisation Inhibitors→ Vinca alkaloids:

E.g.1)Vinblastin

2)Vincristin :

-More active

-causes relatively low myelosuppression,sensation and neural problems (whole group).

-Active on solid tumors, childhood ALL (induction phase) ,Lymphomas, breast cancer, sarcomas and various childhood neoplasms.

- De-polymerization inhibitors→Taxol :

-causes myelosuppression and neuronal side effects.

-used in Breast Cancer in the fifth cycle for 4 or 8 cycles.

When diagnosing breast cancer; we test for 3 things:

1- ER: estrogen receptor
2- PE: progesterone receptor
3- HER-2: epidermal growth factor-2 "oncogene"

According to the results we get on each one (either positive or negative) we choose the appropriate therapy, which differs from one case to another as we'll discuss later.

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Now, Let's continue the classes of cancer drugs far away from the strategies :P

Hormonal Agents

Examples on Hormonal Agents:

✓ Tamoxifen:

- Applications:
  - ER-Positive breast cancer(80% of Jordanian breast cancer patients): **ER stands for "Estrogen Receptor"**

ER-Positive breast cancer means that this cancer is hormonal dependent and Hormones (in this case Estrogen) helps in the growth of this cancer. So, we have to inhibit it by an Anti-Estrogenic.

note that this's not enough alone as a treatment of breast cancer, we have to give the chemotherapy to abolish (kill) cancer cells. Anti-estrogen is given only to inhibit any **regrowth** or the increase growth of the cancer and not to abolish it.

- prophylactic purposes:

when there is a high chance of developing the breast cancer especially in the western world (history of cancer, old age, mutation in cancer susceptible genes). Tamoxifen should be taken for 5 years

- Mechanism:

Tamoxifenstrogen actually is not an antagonist of Estrogen .it's a selective estrogen receptor **modulator**(SERM) ,which means that it is "tissue specific receptor function" .its activity depends on the tissue it's working on. it is an antagonist of estrogen in breast and an agonist of estrogen in endometrium.

- Side effects:
  - temporary **menopause** signs and symptoms(due to reduction of estrogen activity):
    Hot flashes,
    fluid retention (causing edema)
    nausea ,
    osteoporosis(so we have to watch the bones: strength and density….etc)
  - Endometrial cancer:

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if it was given for a patient for a long time (more than 5 years), it'll cause a prolonged Estrogenic activity in the endometrium which will lead to endometrium cancer.

But it's not so common. The percentage is 1% in patients who use it for less than five years and this percentage jumps to 1.5% for patients who use it for more than five years (for 10 years as post-treatment suppression therapy).

There's no other choice ,we have to use it. We can't ignore treating an already present cancer because we are afraid of developing another one which develops in only 1% of the patients.

Even in cases of prophylactic application, Endometrium cancer with a probability of 1% is better than breast cancer with probability of 50% or more.

NOTE: the patient has to sign an agreement before taking Tamoxifen for **prophylaxis, since there'll be a chance for developing endometrial cancer while she doesn't have any cancer yet. However in **treating** breast cancer we don't ask for the patient's agreement, because this treatment is considered as a guideline → every ER+ve patient must take Tamoxifen for 5 years.

**NOTE: we can start giving it with the chemotherapy or we can wait until the fifth cycle.

**Since Tamoxifen works as anti-estrogen; the lady taking it generally won't get pregnant since there'll be defects in all her hormones, but in case she got pregnant; the drug won't harm the embryo.

**In Jordan breast cancer isn't very common; 1 out of 10-12 females has breast cancer; and this is a low percentage in comparison with western world were 1out of 4 females has breast cancer.

- Similar drugs:
  Same as tamoxifen, is raloxifen(a new drug) with NO osteoporosis, milder hot flashes and nausea, and even less endometrial cancer.

  ✓ Flutamide (Antiandrogens):
  - Applications:
    - Prostate cancer:

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Testosterone (or dihydrotestosterone) will bind its receptor and induce growth of cancer. So, we have to inhibit it by an anti-androgen like Flutamide.

- Side effects:
  - impotence (less fertility)
  - decrease spermatogenesis.

Let's revise what we have taken in Hormonal agents before we move to the next station:

Hormonal Agents:

❖ Tamoxifen:

-Used in ER-Positive breast cancer (Estrogen Modulator /SERM) and for prophylactic purposes .

-causes temporary menopause signs and symptoms(Hot flashes, fluid retention, nausea ,osteoporosis) and Endometrium cancer.

-Similar drugs: raloxifen(no osteoporosis and even less endometrial cancer.)

❖ Flutamide (Antiandrogens):

-used in Prostate cancer (inhibit testosterone)

-causes impotence and decreases spermatogenesis.

Now, we are going to take about a new class which is sometimes considered a part of the previous one and is called:

Targeted Therapy

Drugs that are members in this class:

- ✓ Trastuzumab(Trade name: Herceptin): **-mab stands for monoclonal antibody**
  - Applications:
    - HER-2 Positive breast cancer(20% of Jordanian patients):

Back to the breast cancer, you may hear about a breast cancer patient who is "HER-2 –positive".and the question comes: what does this mean?

It means that the oncogene HER-2 (epidermal growth factor-2) is *overexpressed* in this cancer. and it's inhibited by targeting Trastuzumab on the receptors of the overexpressed gene (HER-2).

Generally speaking, HER-2 gene is normally found all over the body in adequate amounts (not over-expressed); so upon giving this drug, most of

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it will go to the over-expressed HER-2, that's why Trastuzumab has some **selectivity** {targeted therapy}.

- Side effects:
  - cardiac toxicity

So, I can't start with it as in case of Tamoxifen.because I have to start with doxorubicin which is also cardiotoxic. So, if I gave them at the same time I'll synergize the activity of cardiotoxicity. So, we have to start it in the ***fifth cycle*** for 1-2 years (it has been designed to stay in the patient's body for a month; so we give **monthly** injection of antibodies, or actually 3 weeks)

This drug is very expensive; one dose costs 3000jds, luckily the government covers it since it has been highly approved to be beneficial.

* Recap the whole story of **breast cancer**:

4 cycles of doxorubicin and cyclophosphamide, followed by 4-8 cycles of Taxol

Herceptin if the patient is HER-2 positive

Plus ER antagonist (tamoxifen); stared either with or after the chemotherapy

However, if the patient was (ER-ve, PR-ve, HER2-ve) → called "triple negative", which is the worst case of breast cancer; it has different treatment than the mentioned above. Luckily this aggressive type of breast cancer accounts for only 7-8% of breast cancer patients in Jordan.

✓ Imatinib:

- Applications:
  - Chronic Myelogenous Leukemia CML: **mainly caused by one driver**

Imatinib is the **single** drug of CML that's taken **orally** and for treatment and maintenance for around 15 years. It's actually the treatment of CML when it is caused by Philadelphia translocation (as in 97.5% of cases / it is translocation of a chromosome section that produces something called Bcr-Abl which causes *continuous kinase activity*) .

If it was caused by something other than Philadelphia translocation then the treatment is so different. It's a combination of therapies and usually those patients don't live for a long time because there's no complete

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remission. So we have to test for Philadelphia chromosome for CML patients before starting the treatment.

- Side effects: (not so common but they may occur) :
  Liver toxicity (take care of liver enzymes)

  Nausea

  Muscle pain

  Fluid swelling

  Diarrhea

  Low white blood counts

✓ Gefitinib:
This's an old drug that didn't work (complete failure) .It is an inhibitor of the Epidermal Growth Factor Receptor (EGFR) which is a good idea, but they noticed that at the beginning , patients will respond for 1-2 months but after that cells become resistant and more aggressive. So there was a complete failure of this drug.

✓ Bevacizumab (avastin) **-mab: monoclonal antibody**

Angiogenesis: the growth of blood supply towards the cancer driven by messages that come out of the cancer those messages are VEGF and the fibroblast growth factor, VEGF is the most important.

Angiogenesis is considered to be a big problem in cancer, since you are supplying blood to the <u>outer surface</u> of the tumor, but the **center** of the tumor will become necrotic, cells there will shrink and enter the G_0 phase of the cell-cycle due to hypoxia (as a result of their poor blood supply), so these central tumor cells won't be replicating since they're arrested at the G_0 phase and thus they <u>won't respond</u> to any cancer treatment (because cancer treatments target rapidly replicating cells). After finishing the treatment (after 2-3 years) the cancer will come back again, as a result of nourishment of those cells so they get out from the G_0 phase and start replicating. this is the worst issue in our life.

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If I inhibited binding of VEGF toward the blood vessels by this drug so I really inhibit Angiogenesis thus inhibiting cancer growth and reducing cancer diameter. This drug worked perfectly on animal samples. However when we tried this drug on humans, it was a complete shock because it showed no difference in many cancers.

It succeeded only in treating **colorectal cancer**

FOLFOX: 1) oxaliplatin 2) 5-FU 3) Bevacizumab

We found that when patient takes Bevacizumab with the FOLFOX combination, it will have more effect on prolonging life of the patient up to about 6-8 months. That's why it has been approved to be used in cases of colorectal cancer.

In Jordan, FOLFOX is not used, since avastin costs 1000jds per dose and it's not covered by the government because they feel that 6-month of life prolongation isn't worth it; which is wrong according to the dr.

This drug is also used in cases of **Lung cancer**, where it also prolongs life of the patient by 2 months, which is good since patients with lung cancer die quickly.

It has been approved to have some activity in breast cancer, but through clinical trials we found that it doesn't have any activity in breast cancer. So there is no place for anti-angiogenic drugs for breast cancer.

This drug is related to eyes; we prescribe it to patients suffering from **diabetic retinopathy** in uncontrolled diabetes (diabetic patients may suffer from problems in blood supply to the retina). So avastin is given by injection to the eye.

Let's Revise :

Targeted Therapy:

- ✓ Trastuzumab(Herceptin):
  -used in HER-2 Positive breast cancer
  -causes cardiac toxicity
- ✓ Imatinib:
  -used in chronic Myelogenous Leukemia CML caused by Philadelphia translocation.
  -may cause liver toxicity, Nausea, Muscle pain, Fluid swelling ,Diarrhea, Low white blood counts

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- ✓ Gefitinib:
  (complete failure) ,It is an inhibitor of the Epidermal Growth Factor Receptor .patients will respond then it'll back more aggressive.
- ✓ Bevacizumab (alvastin)

- Cancers we know how to treat till now:
- Treatment of breast cancer :
  Doxorubicin and cyclophosphamide for four cycles >>
  Then, Taxol (4-8 cycles)
  with Trastuzumab (Herciptin) for HER-2 positive breast cancer
  and Tamoxifen for ER-Positive breast cancer (we can also start with it)
  *Note: if the breast cancer is HER-2 negative
  ER-negative PR-negative (progesterone receptor)
  It is called :Triple Negative Breat Cancer (TNBC) and it is hard to be treated.
- Treatment of Colon cancer:
  FOLFOX: Oxaplatin, 5FU, Bevacizumab (alvastin)
- Treatment of ALL:
  Methotrexate, vincristin, Promethazine.
  Then, 6-Mercaptopeurine
- Treatment of Testicular Cancer:
  Bleomycin , Cisplain
- CML:
  Imatinib

"Tell your heart that the fear of suffering is worse than the suffering itself. And that no heart has ever suffered when it goes in search of its dreams, because every second of the search is a second's encounter with God and with eternity."

May all your dreams come true ☺

Raya Abdalhameed Al Majali

Thanks go to Elaf Bataineh for helping me in this sheet .

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