# Pharmacology sheet 1

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# Treatment of Acute Leukemias

**Overview**

Chronic leukemias are simple to treat generally like for example **Chronic myelocytic leukemia** that is treated with **Imatinib- a tyrosine kinase inhibitor of BCR-ABL (Philadelphia chromosome fusion gene in CML**) and the disease will be controlled simply through taking one tablet every day for nearly 20 years.

So CML is becoming like any chronic disease (eg. Hypertension)

Acute leukemias are divided into two subtypes; Acute lymphocytic leukemia and acute myelogenous leukemia. We treat each one in a different way.

ALL is easier to treat

ALL is the most common leukemia in children (80% of leukemias in children)

- Death ensues within 2-3 months if left without treatment
- You need to **eliminate** every single cancer cell. And that is possible ONLY in ALL. 80% of children with ALL will be completely cured, but with lots of side effects.

- AML is not curable unless with bone marrow transplantation. However with ALL the leukemia will be cured just with drugs; but if it relapses BM transplantation could be made.

** So…

ALL cure with drugs

AML **control** with drugs, then bone marrow transplantation.

**Note :**

in AML and ALL you have to treat your patient quickly , and if not , he will be finished after 2 to 3 months . unlike CLL and CML which need a very long time to give a clinical manifestation , and it seems the same if you start treatment at the moment of discover or you wait for it to be clinically manifested .

****Use MULTIPLE drugs:**

WHY? 1.One agent can not treat a heterogeneous disease (because of instability of the DNA). So you need to hit from different points of view

2.overcome resistance

3.we can not increase the dose so much because of side effects(we avoid giving a combination that contain two drugs have the same side effect )

4. To target leukemic cells at different phases

these drugs should have different mechanisms of actions and different side effects

****Five side effects common for all cancer drugs (except targeted therapy):**

1.alopecia
2. Oligospermia
3. BM suppression
4. Immunosuppression
5. GI manifestations

- ALL manifestations: immunosuppression; infections, anemia, bleeding. So you need to intervent quickly.

- Complete remission (CR)= cancerous cells don't exceed 5% of peripheral blood cells. So our goal in the beginning of treatment is to reach CR.
Reaching CR doesn't mean you got leukemia-free survival!
Leukemia free survival = cure

## Treatment of ALL including 4 steps :

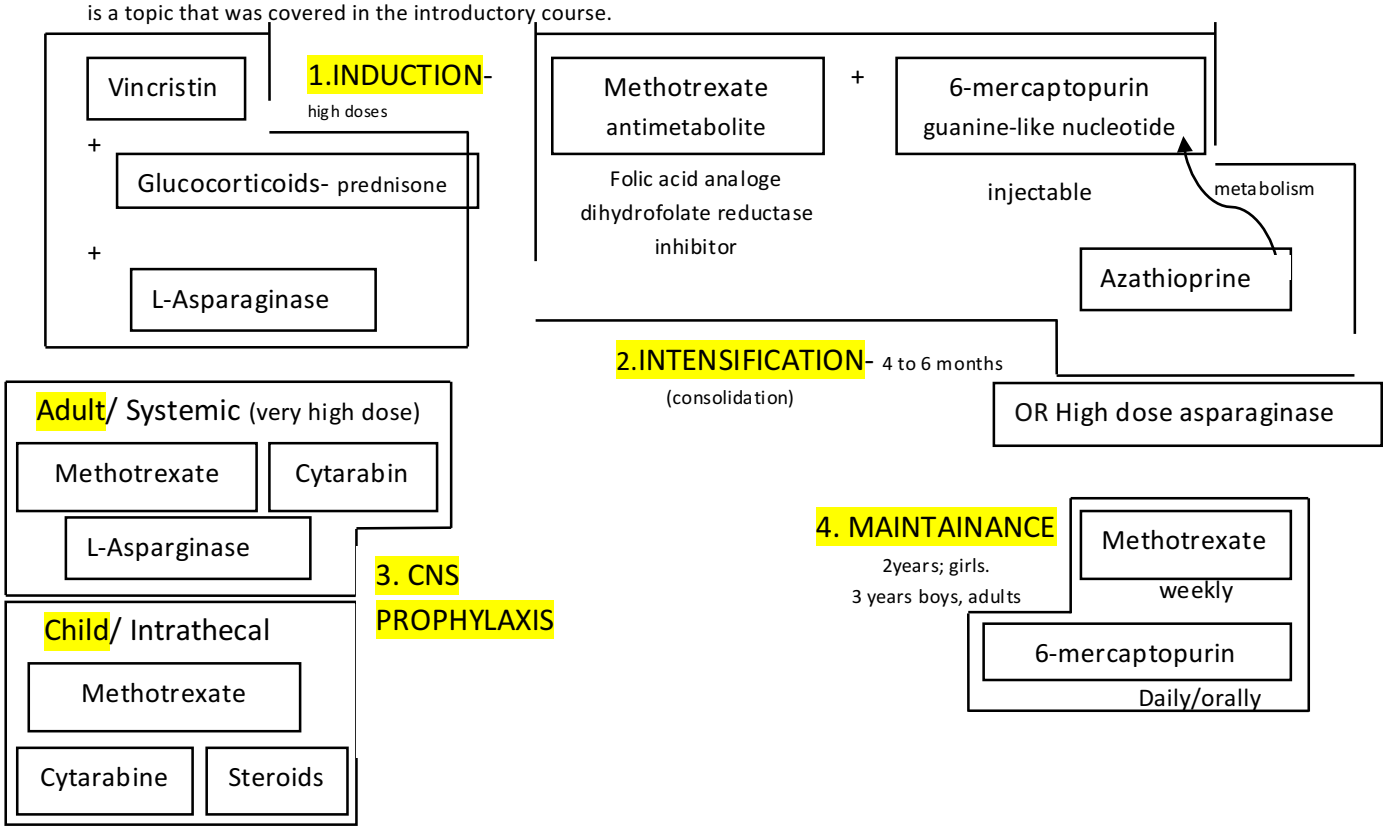
1- induction ( where we apply complete remission )
2- intensification
3- CNS prophylaxis
4- maintenance
*every step has group of drugs that we use in .

**in the next page there are scheme contain the drugs used in each step of these**

**Remember :**

cancer is a disease of monoclonal origin
that means if you want to cure your patient you have to kill every single cancerous cell in his body , because it can regenerate just from one single cell if it left .

## Treatment of Acute Lymphocytic Leukemia (ALL) -For those of you who remember; this is a topic that was covered in the introductory course.




**- Induction phase: goal is to induce CR; reduce the no. of cancerous cells very quickly to save the life of the patient.**
**in this step there is sth known as tumor lysis syndrome , because we induce a very high number of the cancerous cells to commit apoptosis , these cells will secrete their contents in the blood which can result in many manifestations , most important of them is hyperuricemia (large amounts of uric acid in the blood ) , also it may cause kidney failure because of the high pressure on capsule of kidney .**
**so , the idea is that we are killing very huge number of cells which body cannot tolerate at some cases , its common treatment is giving high doses of diuretic drugs to help the body to get rid of these damaged cells out of the body.**

**- Then change the drugs you are using and give high dose- because these cells that remained are resistant to the previous drugs. This gets us into..**
**Intensification (or consolidation) phase is to make sure CR will stay long**
**Consolidation: oral mostly**

****After consoldation phase a biopsy of the BM should show no leukemic cells.**

**- In ~60% of patients some of the malignant cells escape to the brain (because of the high pressure produced on them) producing leukemia in the brain (meningeal leukemia. So, CNS prophylaxis is a must to prevent that.**

**- Maintainance: to make sure no single cancerous cell will come back and kill our patient. This step stand for**

## To summarize the previous scheme (for those who didn't understand it ) :

**4 steps to treat ALL**

*First :*

**induction** which involve combination of 3 drugs given in a very high doses :

1-Vincristin (mitotic spindle inhibitor)

2-Corticosteroids (antiprolifrative drug )

3- L-asparaginase (destroy the amino acid aspargine )

*Second* :

**Consolidation** (intensification ), also involve combination of drugs given for 4 to 6 months :

1-Methotrexate (an antimetabolite) it is a dihydrofolate reductase inhibitor

2- 6-mercaptopurin (a guanine-like nucleotide and considered as anti metabolite )

* in some cases they give L-asparginase with them

*Third* :

**CNS prophylaxis**

for children we give the drugs **intrathecally**

1- methotrexate

2- cytarabine

3- steroids

for adult we give the drugs **systemically in high doses**

1-methotrexate

2-cytarabine

3- L-asparginase

*forth*:

**maintenance** by giving

1- methotrexate weekly

2- 6-mercaptopurin daily in oral form

| Drug | Mechanism | Side effects | |
|---|---|---|---|
| **Vincristine** | Decrease microtubular polymerization (tubulin inhibitor)- inhibit mitotic spindle formation | Peripheral neuropathy<br>Constipation | minimal BM suppression (marrow sparing). So it has a large therapeutic window (You can give a high dose) |
| **Glucocorticoids (prednisone)**<br>High dose | Antiproliferative activity | Increase appetite ,Cushing's, hypertension, hyperglycemia, Baffalo hump, moon face , psychological changes(nervous, depression, changes in personality) , osteoporosis, fluid retention (swelling) . | |
| **L-asparaginase** | Reduce protein synthesis (only works on leukemia because leukemic cells can't make their own asparagine) so this drug depletes it from the body of your patient and when it cannot make it. IT DIES. | ↓insulin synthesis leading to →hyperglycemia.<br>↓albumin→edema, ascites<br>↓Vit.K production- decrase production of vit. K dependent clotting factors→ can cause **thrombosis** (decrease of *factors ii, vii, ix, x*) OR **hemolysis** (decrease of *protein C and protein S*)—UNPREDICTABLE! | Patients stay at the hospital to be monitored for insulin, albumin and coagulopathies. |
| Anti – metabolite **Methotrexate** | Dihydrofolate reductase inhibitor | | |
| Anti – metabolite **6-mercaptopurine** | DNA polymerase inhibitor | | |
| **Topotecan** | Topoisomerase inhibitor | | Not used anymore |

- Corticosteroids are called the magical drugs.
- In the induction phase the drugs are *relatively* not very dangerous so you can give high doses

## Treatment of Acute Myelogenous Leukemia (AML)

More resistant to treatment; you won't get into remission in lots of cases. We also use bad drugs
☹
So, it most cases we cant kill every single cancerous cell after treating with these bad drugs(in most cases we cant reach CR ) , so we go toward bone marrow transplantation in most of the cases , and if not the disease can relapse easily .

| Drug | MOA | Toxicity- SEVEE BMS |
|---|---|---|
| **Daunorubicine** | Topoisomerase inhibitor | Cardiac toxicity |
| **Cytosine arabinose** | antimetabolite | Ataxia, very bad **Dizziness** |

## AML treatment :

1. Induction

**using two drugs :**

**1-Anthracyclin** (very strong drug) for three days.

**2-Cytosine arabinose** for seven days

** These drugs cause severe BMS (bone marrow suppression ), which means it cause pancytopenia .

***Extra***:

**Anthracyclines** (or **anthracycline** antibiotics) are a class of drugs used in cancer chemotherapy. The first **anthracycline** discovered was **daunorubicin**

Supportive care in needed in this step :we give antiviral drugs , antifungal drugs , antibiotics (all prophylactically) as well as platelets, IL-11 (for your patient to produce platelets) and EPO.

2. when finished induction we have two choices :

Either Consolidation- Cycles of drugs 4 to 6 weeks (higher risk of relapse) using the same drugs of induction step but in higher doses ,, OR go to **BM transplantation .****Core treatment for AML

in most cases they go toward BM transplantation because it is more effective

CNS leukemia is not common after treatment so prophylaxis isn't needed .

# THE END