HEMATOLOGY
&LYMPH SYSTEM

Pharmacology sheet

Number	7
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Cancer therapy for Leukemia

"What's required in this lecture is what's written in this sheet, anything in the slides that wasn't mentioned here is not required". *Take a deep breath, and smile, you're a PRIDE to many :D!*

If you remember from last year in introduction to pharmacology course, we talked about anticancer drugs in sheet 17, and we said that the main problem we deal with in cancer is **mutations**. We start with a monoclonal origin (one cell), and each time a cell divides, new mutations appear in the new cells so … new type of cells!

This applies to what we see in ALL, AML, CLL, CML, Non Hodgkin and Hodgkin lymphoma; A heterogeneous populations of cells WITHIN the same cancer population due to many accumulating mutations, however, we can sometimes find a **predominant mutation in these cells**, like translocation (rearrangement) of ABL gene on chromosome 9 and BCR gene on 22 to form a new fusion gene (Philadelphia chromosome) which is seen in **CML** (**C**hronic **M**yeloid **L**eukemia).

Note: Translocation t (9:22) can also be found in ALL, specially B cell-ALL, but it's the type with bad prognosis and it's the one occurring in adults (Source: Pathoma 2017 edition, p. 55)

THE MAIN PROBLEM: This population has different cells --> different **genotypes** and **phenotypes**

--> **Different targets** to treat --> **different response** to drugs.

So, we use a cocktail of chemotherapeutic drugs with different mechanisms of action to (1) delay cancer cells' drug resistance (most importantly), and to (2) target and kill the highest number of cancer cells as we're trying to target every single cancerous cell in the patient's body.

Important Note: In all cancers, there are many things to target (many drivers), the only known cancer until now which has a target is Chronic Myeloid leukemia (CML). The good news is that since the target is now specific and well known, the treatment became easier and this type of cancer became as any chronic disease. **Imatinib** is now the drug of choice; it's taken as daily, oral tablets.

****Key words before proceeding:**

ALL: Acute Lympho**blastic** Leukemia (also called acute lymphocytic leukemia)

AML: Acute Myeloid Leukemia

CLL: Chronic Lymphocytic Leukemia (Naïve B cell leukemia)

CML: Chronic Myeloid Leukemia

In ALL, CLL, AML we face the issue of heterogeneousity, that's why we have to treat in cocktail; in order to:

1. Obtain **Synergistic** متآزر action.
2. **Minimize side effects** of drugs.
3. Attack leukemic cancer cells in **different phases of mitosis**.
4. **Delay the onset of malignant cells' resistance**: It's easy for leukemia and lymphoma to develop resistance against single drug therapy "Cancer cells are smart enough to resist your single drug therapy!!"

That's why we use combination therapy, and we're going to follow-up this patient for a long time, why? You must bear in your mind that treatment of Leukemia and Lymphoma is longer than solid tumors due to **the high chance of recurrence**!

Treatment will take 3 years for ALL, 5 years for some of the other types, and so on.

**A little thing that'll be explained further later: in CLL we treat by "watch and wait"; we watch the patient, and depending on what happens with him or what symptoms appear, we start to act.

We'll start discussing first ALL, then AML, then CLL, and lastly briefly we'll talk about CML. Lymphomas won't be discussed.

(1) ALL therapy

The good news about using combination therapy, especially in ALL is the elevating cure rate (the patient completely healing from cancer); we now are reaching a very satisfactory rate of cure, which ranked ALL as the **highest cured cancer** especially in childhood (upon giving therapy, Childhood ALL reaches a cure rate of almost **90%).** In adults cure rate reaches 60-65%.

** (1) **Testicular cancer**, (2) **Basal cell carcinoma of the skin** (BCC; a carcinoma that arises in the skin's basal cells, which line the deepest layer of the epidermis), and (3) **Wilm's tumor** (also known as nephroblastoma; it's a cancer of the kidneys that typically occurs in children) are also an exception with **high cure rate** as well.

In other cancer types like in breast cancer, we reach a good response rate; however, recurrence happens in 30 – 50% of cases.

In leukemia it's amazing that we have a high DONE AND GONE cure state, but until reaching that, the patient will have to ride chemotherapy bumpy roller-coaster.

Agents used in treatment of ALL didn't change much over time, but we changed their **method** of usage, that's why we witnessed an elevated cure rate!

In 50s and 60s: cure rate was 30%

In 70s: Elevated to 60%

In 80s: to 70%

In 2000s: it settled on 90% "Nowadays cure rate "

We didn't introduce new drugs; we kept on using known chemotherapeutic agents usually used, we will talk about details later.

It's now all about using normal mechanisms:

1. **DNA** attack using **Topoisomerase inhibitors** (intercalating agents, work by freezing topoisomerase once it unwinds DNA helix), **alkylating agents** (2 alkylated sides to bind both strands irreversibly, and break DNA), **antimetabolites** (drugs acting as false nucleotides), or **tubulin inhibitors** like Vincristine or Taxol (acting on Mitotic spindles)
2. Cortisone
3. L-asparaginase: Using this drug was since a relatively old time

In a new way of management; a new way of giving these drugs: Phasing of ALL treatment.

Previously, we were depending on cycling "as we did in breast cancer therapy"; we bring the patient and we start giving drugs in cycles (12-15 cycles), and then we're done. Nowadays, we treat leukemia in **phases**:

1. Induction
2. Intensification
3. CNS prophylaxis
4. Maintenance therapy

Remission: Population of leukemic cells in the bone marrow is now less than 5%

Pathoma: "ALL; neoplastic accumulation of lymphoblasts (>20%) of bone marrow"

This is the management method used for treatment of **leukemia and lymphoma**.

Notes:

1. In phase of **induction**: you need to hit your patient hard enough "sorry for these heart-breaking words" to **induce** remission and to clear his body from cancer.

2. In **remission** phase: we usually don't see any leukemic cells in the biopsy we take from the patient's bone marrow; we also don't see any leukemic cells in the peripheral blood. We can say that once reaching 5%, the patient's body is **cleared from the disease**; HOWEVER, if we depended on remission only, which they depended on in old times, we'll be exposing the patient to high chance of **RECURRENCE!**

** **Please Remember** a very important thing Dr. Malek said last year: "if you were very successful in treatment of cancer, and in drugs you're using, and killed 99.9% of cancer cells existing in the patient's body that you can't see of them by scanning less than $1*10^6$ or $1*10^7$ (in Jordan it's $1*10^9$ to $1*10^{10}$), 1×10^7 residual cells will remain which you may not see and will sure cause a recurrence!! "

"It doesn't mean if you can't see, that there's no cancer in your patient's body"

3. **Post – remission therapy** has made ALL enter the "post-remission ERA ", this era where we prevented recurrence or at least decreased it very much!

0.00 min – 10.36 min, Slides covered (1, 2, 4)

** ALL treatment phases

1. **Induction "HIT HARD!":** Combination of drugs that we give in **high doses**.
   As a future General Practitioner طبيب عام or specialist, you'll have to keep an eye on an important thing while combining drugs, which is "drugs side effects". If you remember in cycles of breast cancer treatment, we didn't give Herceptin (Trastuzumab) and Doxorubicin in the same cycle because both of them had Cardiotoxicity as side effect!

   The Combination: High dose of **Vincristine** (mitotic spindle inhibitor) **+ L-asparaginase** (reduce asparagine available for cancer cells to use for surviving) **+ glucocorticosteroids**.
   This combination is given **for 4 to 6 weeks --> Induction time**.
   ** Sometimes we add to this combination:
   1) **Daunorubicin** (Anthracycline family; **Intercalating agent**)
   2) **Cyclophosamide** (**alkylating agent** that binds to both DNA strands then breaks them)

A. **Vincristine (M phase specific):** if you remember in breast cancer we talked about a drug called Taxol (Paclitaxel); Taxol worked in **M phase** of cell cycle (Mitotic phase) by inhibiting the spindles from getting back after binding chromosomes (Degeneration or depolarization inhibitors). Vincristine works in another way by **inhibiting generation or polarization of spindles**; it prevents their release in the first place, so it belongs to (polarization inhibitors).

In Arabic: يمنع عملية ابتعاث الخيوط المغزلية نحو الكروموسومات المصطفة في منتصف الخلية خلال عملية الانقسام

- **Side effects**: Very near to those of Taxol; **peripheral neuropathy** (Nerve Irritation) which manifests as tingling وخز in hands and numbness خدران in legs. It also produces **constipation** (which is common during Vincristine usage).
- **Bone Marrow Sparing "Very nice characteristic for Vincristine":** Vincristine produces a very low effect on healthy cells of bone marrow; somehow, it has some sort of selectivity toward cancer cells rather than normal bone marrow cells. So, bone marrow inhibition or suppression is **minimal** through Vincristine. Taxol on the other hand has NO selectivity toward cancer cells.
- Vincristine along with a drug called **Cisplatin (alkylating agent)** have the characteristic of bone marrow sparing (Sparing الاستغناء عن ، ترك).
  Having this amazing characteristic enable us to dose the patient high without worrying much, and we keep on having a very good results. This is the main idea here: we can dose Vincristine as much as we can as long as we keep the bone marrow.

> **Remember from last year: the 4 common side effects between all cancer drugs:**
> 1. Alopecia (hair loss), 2. Nausea, diarrhea, vomiting (GIT disturbances), 3. Bone marrow suppression (causing anemia), 4. Immunosuppression (no division of B and T- lymphocytes).

B. **Glucocorticosteroids:** we talked about them in Immunopharmacology.
In immune suppression therapy, you use corticosteroids to inhibit lymphocytes proliferation, same here is applied for cancer treatment; we **inhibit proliferation of leukemia lymphoblastic cells**.
Used corticosteroids are: Prednisone (used **to induce remission** in the treatment of Hodgkin and non-Hodgkin lymphoma as well), Prednisolone, and Dexamethasone.
In KHC (King Hussein Cancer center) they give Dexamethasone, it has more activity on Leukemia cells than Prednisone or prednisolone. However, Dexamethasone has a **very bad side effect** which is "**Avascular Necrosis**".

** Medscape website: "Avascular necrosis (AVN) نخر لا وعائي is defined as cellular death of bone components due to **interruption of the blood supply**; the bone structures then collapse, resulting in pain, loss of joint function and long-term joint damage.
AVN usually involves the **epiphysis** (end part of a long bone), such as the femoral and humeral heads and the femoral condyles, but small bones can also be affected. In clinical practice, AVN is **most commonly encountered in the hip**."
Unfortunately, after Dexamethasone administration, **5%** of Leukemia children experience Avascular necrosis in their hips "Because it mostly happens there" due to reduced blood supply, and often undergo **Hip replacement**. It's In Jordan more than other countries. Once avascular necrosis is suspected, we change the drug to **prednisone**. If avascular necrosis irreversibly happened, a hip replacement is a required.

- **Side effects for corticosteroids:**
  1- **"Most important": Depression, and change in personality (e.g. nervousness)**
  2- **Osteoporosis** (bone pain), and **Hypercalcemia** (muscle cramps and weakness).
  3- Hypertension
  4- Trouble in sleeping, increased appetite, fluid retention and swelling, indigestion, restlessness, headache, blurred vision, increased blood sugar level.

C. **L-Asparaginase "special drug only for ALL":** ALL cells depend **ONLY** on **Exogenous Asparagine** obtained from the diet for their survival; they **can't synthesize asparagine** inside them.
Remember that Asparagine is not an essential amino acid; being non-essential means it can be "**synthesized** in sufficient amounts from intermediates of amino acid metabolism, or from essential amino acids" –Lippincott's Biochemistry; p.261; 6th edition.

- CML may show little Exogenous Asn. dependency but the dependency in ALL is much higher comes from ALL.
- **ADD TO YOUR INFO - Lippincott's Biochemistry; P.262:** "some rapidly dividing leukemic cells are unable to synthesize sufficient asparagine to support their growth. This makes asparagine an essential amino acid for these cells, which, therefore, require asparagine from the blood. ***Asparaginase,*** which hydrolyzes asparagine to aspartate, can be administered systemically to treat leukemic patients. *Asparaginase* lowers the level of asparagine in the plasma, thereby depriving cancer cells of a required nutrient."
- Normal cells are able to synthesize asparagine thus they're less affected (but are still non-selectively affected) by the rapid depletion produced by treatment with L-asparaginase.
- Upon administration of L-asparaginase, ALL malignant cells are affected to a great extent because of rapid hydrolysis of Exogenous Asn which they depend on for survival; this

hydrolysis of intracellular Asparagine will cause **a decrease in protein synthesis and <u>apoptosis</u>** so these malignant cells will rapidly decrease in number.

- **Side effects:** due to the asparaginase existence and the chance of it getting into normal cells, its Hydrolysis to intracellular Asparagine will cause a **decrease in protein synthesis "impaired protein synthesis"** but NOT apoptosis.

When thinking of impaired protein synthesis, which proteins' deficiency will mostly affect us??

1) **Insulin.** Decreased insulin production results in <u>hyperglycemia</u> secondary to hypoinsulinemia. This hyperglycemia is transient, and it resolves تتبدد upon discontinuation of the drug. However, blood sugar must be monitored when using L-asparaginase.
2) **Albumin.** Hypoalbuminemia could be severe, resulting in <u>peripheral edema and ascites</u> "accumulation of excess fluid in peritoneal cavity – Robbins basic pathology; p.609; 9th Ed "

> **ADD TO YOUR INFO -Robbins Basic pathology; p.609:**" Involved mechanisms in ascites pathogenesis are: (1) Increased movement of intravascular fluids into the extravascular space of Disse (peri sinusoidal space around hepatic sinusoids), caused by sinusoidal hypertension and **hypoalbuminemia** (2) Leakage of fluid from the hepatic interstitium into the peritoneal cavity".

- These side effects are actually limiting factors for usage of L-Asparaginase

3) **Vitamin K- dependent Co-Factors "IMPORTANT TO UNDERSTAND".**
   These factors are part of hematology system; Vit.K dependent <u>clotting</u> factors AND endogenous <u>anticoagulants</u> such as protein C, protein S and anti-thrombin 3. Did you get the idea here?? It's "see-saw" principle.
   Do you remember when we talked about Tamoxifen last year in treatment of breast cancer? (sheet #18): Selective estrogen receptor **modulator** (SERM), have both estrogenic and Anti-estrogenic effects depending on the type of tissue; it is found to be estrogen antagonist in cancer cells (breast tissue,) but agonist on bones and endometrium.
   Here it's the same principle, it's either **thrombosis** if Protein C and S and Anti-thrombin 3 are inhibited, **or bleeding** if clotting factors were inhibited; this state is referred to as **"Coagulopathy".** Coagulopathy sate "which line is going to be affected more?" <u>depends on the patient</u>.
   Polymorphisms between people give the different tendency to either face thrombosis or bleeding.

- Monitoring coagulation parameters during L-Asparaginase therapy is a must.

- L-asparaginase therapy is used cautiously بحذر in patients with **preexisting coagulopathy** like **hemophilia** (Inherited genetic disorder that impairs the body's ability to make blood clots. This results in people bleeding longer after an injury, easy bruising, and an increased risk of bleeding inside joints or the brain- Wikipedia), **or hepatic disease.** Patients with limited hepatic synthetic function may be unable to tolerate the effects of L-asparaginase. Why? "Liver is the site of synthesis of clotting factors, coagulation inhibitors, and fibrinolytic proteins"- PubMed
- Intramuscular injection may cause bleeding, bruising كدمة , and hematomas due to coagulopathy

10.38 min – 20.40 min, slides covered (5- 9, 11-13)

****Remember this: Why do we care a lot about these side effects??** Because these drugs are used in ALL, and ALL is the most common cancer we'll see and we'll have to deal with in young patients, accounting for 80% of childhood leukemias.

- **Other L-asparaginase side effects:**
  1) **Mild Nausea/ vomiting (GIT disturbances)**: **Anorexia, abdominal cramps, general malaise, weight loss:** shared with all anti-cancers.
  2) **Tumor Lysis syndrome:** Hyperkalemia **(↑ K^+)**, Hyperphosphatemia **(↑ PO_4^-)**, Hyperuricemia **(↑ Uric acid),** Hypocalcemia **(↓ Ca^{+2}),** decreased urine output, **severe <u>Renal Insufficiency.</u>**

     What is happening here??? Many malignant cells are undergoing apoptosis, they're contents are flushing toward everywhere in the systemic circulation including renal glomerulus, this causes an unstable homeostasis in the body + renal stenosis, renal blockade and so insufficiency.

  Medscape website: "Tumor lysis syndrome refers to the constellation كوكبة of metabolic disturbances that occurs **when large numbers of neoplastic cells are killed rapidly**, leading to the release of intracellular ions and metabolic byproducts into the systemic circulation."

In Induction phase, we give a combination of drugs; we give them at high doses; we expect high levels of side effects, that's why during this period of 4 to 6 weeks, MONITORING is needed. The patient remains in the hospital for medical observation; because the least side effect in this case would be dangerous. Remember, however, that ***bone marrow suppression in Induction phase isn't really clearly seen because <u>none of induction-phase drugs have that real effect in suppressing bone marrow</u>.*** Want to check right? Feel free: refer to page 5, and page 6).

*** Note: Previously when Daunorubicin -or Doxorubicin- was used, we usually were worried about bone marrow suppression.

How would we now maintain the remission achieved after induction??!

2. Post– remission therapy

A. Consolidation الدعم "Intensification": Once normal hematopoiesis is achieved (the patient passed **remission** state), the patient undergoes Consolidation therapy. We have to act like there's nothing in the patient's blood; however, we act in reality like there's still something, so we have to consolidate.

HOW to consolidate? We do a regimen using **one way** of the following:

1) Methotrexate (Antimetabolite that kills during S phase; it's a Dihydrofolate reductase inhibitor) WITH Mercaptopurine (Antimetabolite).
2) **High dose of L-Asparaginase** over an extended period of time.
3) **Repetition of the initial induction therapy** in the first few months of remission: Same Induction-phase drugs (Corticosteroids, Vincristine, and L-asparaginase).

Again repeating: why do we do consolidation?? Because after reaching remission, we can't be sure that leukemia is DONE AND GONE, that's why we consolidate bearing in our minds that it might be still there even if we can't see it. Want a further proof? If we didn't do consolidation, and gave maintenance therapy directly after induction phase, recurrence will rise to **50%-60%.**

B. Maintenance therapy الحفظ: Even after doing consolidation, there's still a chance for a cell to be there hiding somewhere!

- What do we give? Weekly Methotrexate and Daily Mercaptopurine**.**
- For how long? In males for 3 years, in females for 2 years.
- How is it given? Injection for Methotrexate (It can also be taken orally, but it's preferable as injection), and Daily Oral Mercaptopurine (Given as Azathioprine; Azathioprine is a prodrug that is non-enzymatically converted to 6-Mercatopurine).

C. CNS prophylaxis

Very important note: Remember that as you're fighting this cancer hard, **some "smart" cancer cells escape to the brain "especially common in ALL",** so you have to make sure that you're giving a **PROPHYLAXIS FOR CNS** (remember that it was a part of post-remission therapy).

ALL Patients frequently have **meningeal** leukemia at time of relapse الانتكاس، عودة المرض.

At 1 year of treatment in the **absence of CNS prophylaxis** from ALL treatment, there's **50%-75% risk** of having meningeal leukemia upon relapse. Few ALL patients even **if CNS prophylaxis was given**, there's a **10% risk** that they'll have a meningeal disease at relapse diagnosis time.

- In Children: **Intrathecal** داخل الدماغ(injection into the spinal canal or into the subarachnoid space so that it reaches the cerebrospinal fluid (CSF); they pass a needle through the skull parietal bone) **Combination** of Methotrexate + Citrabin (antimetabolite) + Dexamethasone (glucocorticosteroid).
  This combination used to prevent meningeal leukemia is very common to be done for children having ALL.
  ** These days, some hospitals don't use the previous combination; they rather give a high dose of a Methotrexate, Citrabin and L-Asparaginase as a combination.

- In adults: Guide line treatment for adults is the exception we mentioned above; a high dose of a Methotrexate, Citrabin and L-Asparaginase as a combination.
- CNS prophylaxis is sometimes given many times; Intrathecal combination can be given once; or once every 3 to 6 months; sometimes during maintenance therapy if the situation was risky, the suitable thing is done depending on the patient status.

** Summary for ALL therapy (Slide 3):

1. Vincristine -----> arrest cell mitosis
2. prednisone ----> Lympholysis
3. L- asparaginase
4. Doxorubich (adriamycin)----> inhibit DNA synthesis
5. 6. M.P. (6 Mercaptopurine; Given as azathioprine "pro-drug") ----> inhibit DNA synthesis.
6. Methotrexate ----> Inhibit RNA and protein Synthesis

20.40 min – 30.15 min, Slides covered (3, 10, 14-16)

Back in History: if you remember when we started talking about cancer, we said that every single type of cancer is a disease on its self.

This reflects on how we manage each type of cancer, for example we manage ALL in totally different way than AML; AML doesn't respond very well to Vincristine, doesn't have a good response toward L-Asparaginase, Glucocorticoids don't have that high activity in AML. This has led us to use other drugs in management of AML.

(2) AML Therapy

1. Induction Phase:

A. Anthracycline family: Doxorubicin, Daunorubicin, Idarubicin (Old; now replaced with enhanced form). All work as **topoisomerase II Inhibitor**. Topoisomerase usually separate DNA strands during replication, anthracyclines leave Topo II to cut DNA, then they **TRAP** Topo II in a cleavable complex, this produced complex drive the cell into **apoptosis**.

- Side effects:
  1. **High** bone marrow toxicity (Myelotoxicity).
  2. **Cardiotoxicity.**

B. Citrabin: Citrabin Arabinoside (Cytosine Arabinoside; Ara-C) is a drug that looks like Cytosine.

** Induction here follows a principle called "**3+7**". We can't give these drugs together because both of them are very bone marrow toxic, especially since we give High doses of drugs in induction phase, so **if given together, you'll get a really harsh bone marrow suppression**.

- For that not to happen: We give Idarubicin or Duanorubicin for **3** days, **then**, we give Citrabin for **7** days.
- After Induction phase, we observe the patient's status to see if remission was achieved or not.
- Since this is a heavy induction phase for the patient (2 Very myelotoxic drugs), most patients will suffer **3 to 5 weeks of Pancytopenia** including Anemia, so they might require blood transfusion (Supportive care red cell and platelet transfusions). Also, prophylactic Antibacterial, Antifungal and Antiviral drugs are administered because you've suppressed immune cells production.

What is noticed here is absolutely different than what we have seen in ALL; you were lucky in ALL to dose as much as you want since you have **Vincristine** which was a **bone marrow sparing drug**, **Glucocorticosteroids** that had **minimal effect** on bone marrow, **L- asparaginase** that also had **a little if none** effect on bone marrow. Here in AML, nevertheless, we have a real issue of Bone marrow suppression to deal with.

We have to see that remission rate after induction phase isn't that high like that of ALL (which was >=90%); However, **Cure is still higher after timed-sequential induction therapy (42% vs. 27%).**

What does the previous statement mean?

Timed-sequential induction therapy **العلاج المحفز المتسلسل و الموقوت زمنياً** means that I have repeated the induction phase many times for my patient over a period of time. But even though, I noticed that my patient's remission rate of 27%, had only rose ارتفع 25% (from 27% to reach 42%) after I repeated the therapy, compared with if I didn't repeat it.

That's why we need Consolidation after remission state.

2. Post-Remission Therapy:

A. Consolidation "Intensification" phase:

Consolidation is either done by:

1. 3-4 cycles of **hi**gh **d**ose of Citrabin "Cytosine Arabinoside" (**HiD**AC) administered approximately every 5 to 6 or 5 to 12 weeks.
2. **Bone marrow** (peripheral blood stem cell) **transplantation BMT** (Very common in AML).
   "Here gather your mind please because it's really important"
   From what was told to you just shortly, you can see that even when you end induction phase and your patient is going toward remission, **his remission rate in best cases is still less than 50%!!**
   That's why **mostly** after doing induction to guarantee as much as possible that the disease won't come back, we resort نلجأ to bone marrow transplantation to provide the patient with hopefully healthy bone marrow, with no leukemic cells. In case BMT succeed, remission rate will rise very high, while if BMT failed, it'll decrease very much.
   Of course all of this after all depends on the degree of risk

B. CNS prophylaxis:

- **CNS leukemia is less common than in ALL; prophylaxis may be accomplished with high dose Ara-C +/- intrathecal Daunorubicin** "mistake in the slide corrected in the lecture".

C. Maintenance therapy: Not existing in AML therapy because remission is already hard to be reached. Patients were previously undergoing maintenance therapy but no beneficial effect was achieved, plus the percentage of patients who'll response to maintenance therapy was little. That's why after doing many clinical trials, they've reached a conclusion that there's no value to maintain, and that it's better to only consolidate and give CNS prophylaxis.

**Common side effects for AML treatment:

More than 10 in every 100 people have one or more of the side effects listed below.

1. **Bone Marrow suppression**
2. Fatigue (tiredness) during and after treatment – most people find their energy levels are back to normal after 6 months to a year.
3. Soreness ألم at the injection site (if you are having injections under the skin).
4. Women may stop having periods (Amenorrhea; an abnormal absence of menstruation) but this may only be temporary.
5. Special side effects for certain drugs
   a. Dizziness for **Citrabin;** that's why sometimes it **cannot be given to the elderly** because they already experience dizziness in times of their normal day.
   b. Cardiotoxicity for **Duanorubicin** (plus the high myelotoxic effect).

(3) CLL Therapy

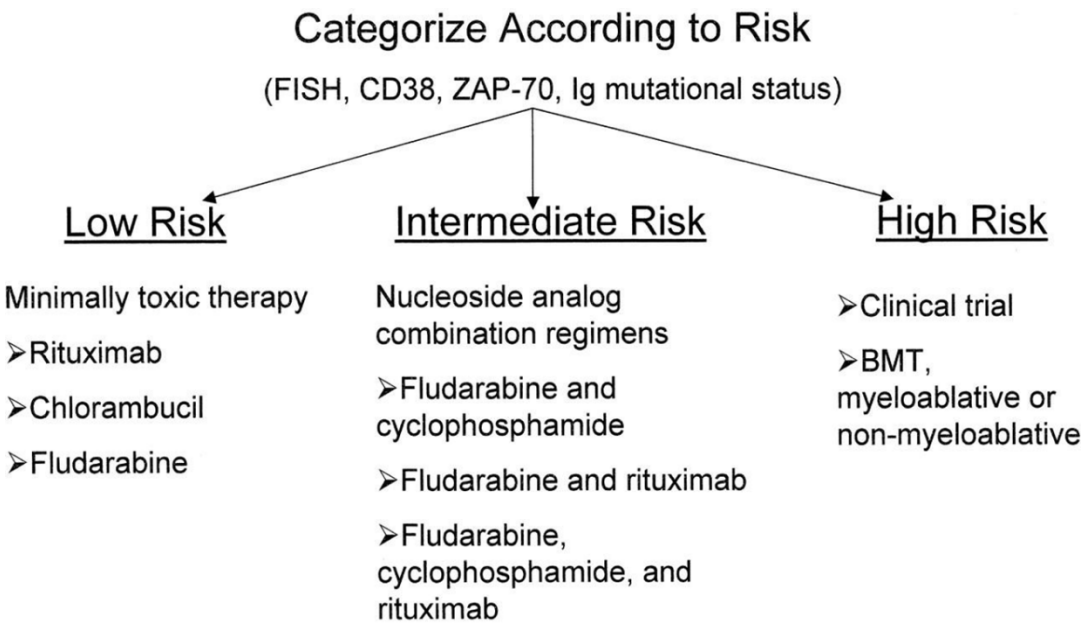
Drugs used in chronic lymphocytic leukemia are absolutely different than these used in ALL or AML; here we depend on degree of risk.

In page 2, we mentioned that treatment of CLL is to "Watch and Wait", now it's time to explain …

In Watch and Wait, we know that our patient has the cancer, yet we don't yet treat him. We Watch the patient's progression, and Wait until symptoms appear, then we start to interfere.

Determining when to start treatment and by what mean بأي طريقة؟ Is often difficult; studies have shown that **there is no survival advantage to treating the disease too early**.

It's kind of a complex Story! Signs and symptoms might take years until they appear (e.g. 8 to 10 years), so until they do, you really shouldn't treat you patient, you rather just watch him. However, some doctors once discovering CLL in their patient, treatment is initiated. Which is better? There's no survival advantage as mentioned previously, so to treat or not to treat is a really long story!



Take a fast look; we'll explain all of what's required below.

*****Mainly the treatment of CLL depends on Rituximab AND Fludarabine except in elderly over 60 whom we treat only with Rituximab.**

1. Low degree risk: Signs and symptoms are not so apparent; number of cancer cells is not high.

We use ONE of the following:

a. Rituximab - MabThera©: Anti CD20 antibody; remember that –**mab** suffix means (**m**onoclonal **a**nti**b**ody). CD20 is a CD marker for B cells, and it exists on the surface of Naïve B cells that are the leukemic cells in CLL.
b. Chlorambucil : Alkylating agent.
c. Fludarabine: Antimetabolite; works like Ara-C as a false nucleotide "like-nucleoside".
   * Side effect: strong bone marrow suppressor; that's why it's harsh enough to be contraindicated in elderly's treatment.

2. Intermediate degree risk:

Rituximab AND Fludarabine are given together, which is nowadays guideline treatment.

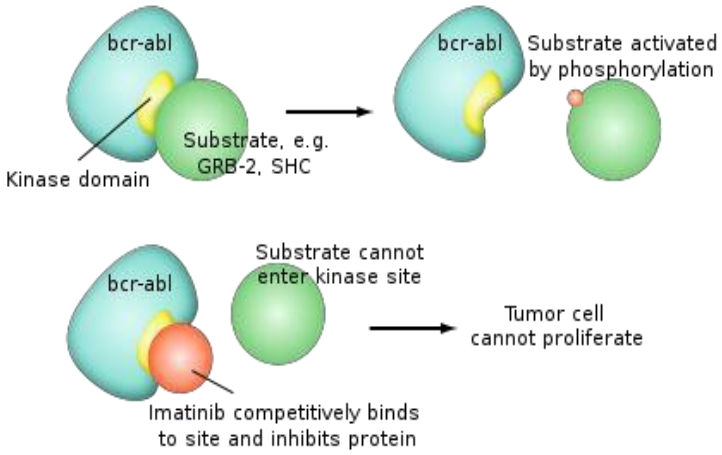
3. High degree risk: Not treated by drugs, **BMT** is done.

*** The conclusion**: Since CLL extends over a long period of time and starts also after a long time, to decide whether to treat or not depends on when did we diagnose the patient; which symptoms do we have; what treatment to start on "depending on risk degree".

30.15 min - 41.05 min, Slides covered (17-24"except 21, 23")

(4) CML Therapy: Imatinib – Gleevec© is the drug of choice

As mentioned before, majority of chronic myeloid leukemia patients (up to 95%) share gene translocation t (9:22) or also called Philadelphia chromosome; what Imatinib simply does is that it targets this ongoing fusion gene and inhibits it.



Application of Colony stimulating Factors in medicine

In hematology course we took some growth factors involved in hematopoiesis, a family of them was called "colony stimulating factor" family. Today we're going to talk about medical applications of some of colony simulating factors especially in Oncology.

1. Granulocyte-colony stimulating factor (G-CSF):

- G-CSF plays a central role in **neutrophil** formation; usually its levels are low but it may increase during **infections or inflammatory state**.
- Mutations in G-CSF receptor will severe congenital neutropenia ---> this is G-CSF therapy target.
- G-CSF is used to treat neutropenia, which is seen mostly in cancer patients after suppressing the bone marrow by chemotherapy: Given in **AML** after giving high dose of **Citrabin** and **daunorubicin** during Induction phase (After 7+3, if the bone marrow suppression was harsh enough to produce pancytopenia).
- G-CSF is sold under names like **Filgrastim** (the one we should know), or Linograstim.
  This drug is given in a frequent way to reduce neutropenia: Typically, we would need to use G-CSF for 7 days (1 each day) after each round of chemotherapy. Again this is especially used during AML therapy because both Citrabin and duanorubicin cause bone marrow suppression.
- Overall Indications for Filgrastim usage:
  a. Severe chronic neutropenia (Congenital, Cyclical, Idiopathic)
  b. To mobilize peripheral blood stem cells for transplantation: done to reactivate hematopoiesis.

c. **Mentioned before**; To accelerate neutrophil recovery in neutropenic patients receiving chemotherapy (either hematologic or oncologic malignancies).

- Filgrastim side effects:
  a. Splenic rupture; Filgrastim is known to cause a very common side effect which is splenomegaly that may lead to splenic rupture.
  b. Bone pain (up to 30% of patients).

2. Granulocyte Monocyte-colony stimulating factor (GM-CSF)

If you remember, granulocytes and monocytes started from the same lineage then as they got closer to maturation, they committed to a single line. Mostly in treatment we care about G-CSF more than GM-CSF.

- GM-CSF increases production of **neutrophils** as well as **macrophages**
- GM-CSF increase antigen presentation by macrophages (remember that macrophage is one of the antigen presenting cells APCs).
- IMPORTANT: GM-CSF deficiency will not cause pancytopenia, but will cause **human pulmonary alveolar proteinosis** (Since macrophages will not be there to clear excess surfactant in the alveoli).
- GM-CSF is sold under name of Sargramostim.
- Overall indications for GM-CSF use:
  a. To Improve neutrophil production in patients with delayed engraftment after transplantation
  b. To Mobilize autologous ذاتي peripheral blood stem cells for collection: if you wanted to get a high yield mobilization, you use GM-CSF.
  c. To Promote neutrophil recovery after autologous (collection and reinfusion of the patient's own blood cells) or allogeneic (Transfusion of blood cells from one person to another) stem cell transplant.
  d. To Reduce risk of death due to infections in patients older than 55 years old undergoing induction chemotherapy for AML.

**** Erythropoietin "EPO"**: It's another growth factor, involved in RBCs production.

Erythropoietin is used to induce production of red blood cells in cases of anemia that might happen

1. After **AML induction** phase.
2. In **Dialysis** غسيل الكلى patients: because they lose a lot of RBCs so you need to make up this loss.

However, during erythropoietin treatment you have to keep an eye on **blood pressure** (EPO. elevates blood pressure and may cause hypertension), and **thrombosis** (EPO. may cause some cardiovascular events "Cardiotoxicity" by blocking the coronary arteries).

41.05 min - 49.40 min, slides covered (25 – 32)

Sorry for the long sheet, *we wish this was an easy-going sheet, and hopefully we wish that you've enjoyed it. If anything was to be further enhanced please don't hesitate to inform us with!*

"What happened to you was to never miss you, and what missed you was to never happen to you "- Holy Hadith ♥