Hematology

Pharmacology

☑ Sheet ☐ Slide ☐ Handout

Number: **2**

Subject: **Chemotherapy of CLL, HL & NHL**

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Price:

This lecture is both interesting and up-to-date – enjoy ☺

Contents of this sheet:

- ☑ Treatment of CLL
- ☑ Treatment of Hodgkin's lymphoma
- ☑ Treatment of non-Hodgkin's lymphoma
- ☑ Myeloid growth factors (briefly)
- ☑ Vaccination/ leukemia (briefly/ not mentioned in slides)
- ☑ Summary

A quick review of ALL and AML:

	ALL	AML
Cureness	Only with drugs	Drugs with BM transplant
L-asparaginase use	Is a must	Cannot be used
Consolidation	Only oral drugs	Drugs (30-40)% cureness, or BM transplant (50-60)%
CNS prophylaxis	Is a must	Not needed
Expected age	Most commonly in children	Most commonly in adults

AML induction therapy: AML is an aggressive leukemia and it's very complex, so you need to use a combination therapy of:

- *Cytarabine* (*Cytosine arabinoside*, *Ara-C*): an antimetabolite, it is the most active drug in AML. In this situation we use a very high dose of *Ara-C*, up to 3000 mg/m^2. (In other cancers, when *Ara-C* is used in treatment, the dose is around $400mg/m^2$.)
  Clinical trials have shown that this drug is the most active one against AML.
- *Daunorubicin (Anthracycline)*: a topoisomerase inhibitor. It has some cardiotoxicity problems, like *Doxorubicin*.

By this we might be able to induce remission. However, for many patients the leukemia will relapse, and here we have two options:

- **Consolidation**, by giving around 3 to 4 cycles of high dose *Cytarabine* approximately every 5-6 weeks. (even after this, around 50% of the cases are going to relapse)
  OR
- **Bone marrow transplantation**, which is more effective.

- Chemotherapy alone gives 30-40% cure rates, while bone marrow transplantation raises that to 50-60%.
- Younger patients can tolerate the drugs used for AML more than old aged ones.

Common side effects:

- Fatigue as a result of anemia.
- Soreness at the injection site, obviously because all these drugs are toxins, especially if there is an extravasation.
- An occasional side effect: **Dizziness** especially in elders (they also suffer from delirium).
- In addition to the five common side effects of all cancer drugs.

Remember: *Daunorubicin* is cardiotoxic, and *Cytarabine* causes dizziness.

CLL Treatment

It is a chronic leukemia, not curable in many cases with a survival rate of approximately 10 years, we treat differently according to the signs and symptoms.

1- Watch and wait:
Even if you really know that your patient has CLL, you should not intervene until symptoms appear (anemia, bleeding...). Studies have shown there is no survival advantage to treating the disease too early, so whatever you do, the survival rate is usually around 10 years.

This breaks the general rule in cancer treatments, which says "If you detect the cancer early, you have higher curing chances." i.e. if you treat early you treat more.

2- Low risk CLL:
Low risk means that the patient has CLL, but he didn't start showing severe symptoms or any at all. Treat with a single oral agent, i.e. monotherapy (remember it is a chronic disease, so it needs a long term treatment).
Fludarabine (a purine analogue) *OR Chlorambucil OR Rituximab*.

Do we need to give high doses in low risk patients?
No need; because CLL is a chronic disease, so the idea of totally curing the patient isn't an option, we actually only control the symptoms.

Table 1: Fludarabine vs Chlorambucil as CLL treatment	
Fludarabine	***Chlorambucil***
An antimetabolite (like *Cytocine arabinoside*)	An alkylating agent (like *Cyclophosphamide*)
Orally	Orally
Stronger	
Aggressive side effects (high immunosuppression, increasing the risk for infections and hemolytic anemia)	Mild side effects

Which one should be used in low risk CLL?
This depends on age, if the patient is under 65 years old, the drug of choice is *Fludarabine*, but if he is over 70 years old, he cannot tolerate the side effects of *Fludarabine*, so we administer *Cholorambucil*.

There are no special side effects for both of these drugs other than the 5 common ones. ☺

<u>*Rituximab*</u> (Anti-CD20): is a monoclonal antibody.
Don't use it unless your patient is not responding to both *Fludarabine* and *Chlorambucil*. (It's given with *Cyclophosphamide*)

Remember: CD20 is a B-lymphocyte antigen, so *Rituximab* is specialized for destroying lymphocytes, B-cells more specifically.

3- Intermediate risk CLL:
Oral treatment (*Fludarabine* + *Rituximab*) OR in intolerant patients (*Cyclophosphamide* + *Rituximab*).

4- High risk CLL:
Fludarabine + *Rituximab* cycles with BM transplant.

Dr.Malek read this slide, though he said it's not important:
- *Rituximab* monotherapy is moderately active in CLL and its activity is dose dependent (between 500–2250 mg/m^2).
- *Rituximab* acts synergistically with other cytotoxic agents in vitro.
- It increases *Fludarabine* activity in NHL cell lines.
- It increases the activity of *Bendamustine*, *Mitoxantrone* and other chemotherapeutic agents in CLL cells.

☒ Determining when to start treatment and by which means is often difficult, as you know from pathology that CLL and non-Hodgkin's disease are very similar.

☒ **CML** treatment is **Imatinib**, Dr.Malek didn't explain this part since we took it in the introductory course.

Hodgkin's Lymphoma

- Hodgkin's lymphoma (HL) is characterized by Reed-Sternberg cells.
- Overall 10 years survival = 80%.

  - ❖ Hodgkin's that involves only **one** lymph node (low stage) is treated with radiotherapy.
  - ❖ Hodgkin's that involves **more than one** lymph node on both sides of the body is treated with chemotherapy.
  - ❖ More than that (like in the spleen and lower side lymph nodes), **aggressive** type, we treat with high dose chemotherapy and radiotherapy.

Chemotherapy

(ABVD) Four drugs with four different mechanisms of action:

Table 2: ABVD regimen for HL lymphoma

Adriamycin	Topoisomerase inhibitor	Side effects: • Secondary malignancy: (leukemia, NHL), solid tumors- lung, breast • Infections • Cardiac (*Adriamycin*), pulmonary (*Bleomycin*), and endocrinal abnormalities
Bleomycin	Intercalation and Iron chelation	
Vinblastin	Mitotic spindle inhibitor	
Dacarbazine	Antimetabolite	

- Higher doses are given for those who go through relapses, or younger patients with poor prognostic features.
- Most cases are curable, so the patients are lucky they have Hodgkin's and not Non-Hodgkin's lymphoma.

Remember: Pulmonary fibrosis can result from:

1- Bleomycin
2- Amiodarone
3- Asbestos

Non-Hodgkin's Lymphoma

- Non-Hodgkin's lymphomas (NHL) are more common than HL.
- Affect males more than females, and the median age of presentation is 65-70 years.
- B cells 70% , T cells 30%
- Here in pharmacology we are not concerned with pathology-classifications of non- Hodgkin's lymphoma, we rather classify them as indolent and aggressive.
- Ironically, the aggressive form of NHL is the curable form (50% chance), not the indolent. The indolent type is similar to CLL, you can treat it but cannot cure it.

What is the reason behind this?

Cancer drugs target active mitotic cells, these cells are much more in the aggressive form of NHL, which makes it highly treatable by these drugs.

Table 3 : Indolent vs aggressive NHL

indolent	aggressive
Long natural history (patients can live for many years untreated)	Short natural history (patients die within months if untreated)
Disease of slow cellular accumulation	Disease of rapid cellular proliferation
Generally incurable with chemotherapy	Potentially curable with chemotherapy
Cure is rarely the goal. Control is the goal	Cure is often the goal

We treat –the aggressive (high/intermediate) type– with a combination of drugs called **CHOP**:

- ***C****yclophosphamide*
- *Doxorubicin* ***H****ydrochloride*
- *Vincristine (****O****ncovin®)*
- ***P****rednisolone*

- Each one of these drugs has a different mechanism of action, we kick hard.
- Notice that in lymphoma, unlike leukemia, the treatment is not phasic, meaning there is no induction then consolidation and maintenance.
  We treat them as solid tumors, and so the treatment goes as cycles.
- Administration is every 3 weeks, for at least 6 cycles.

Side effects:

- ***C****yclophosphamide*: it causes **C**ystitis (inflammation in the bladder), we manage this by hydration.
- *Doxorubicin*: cardiac toxicity
- *Vincristine*: peripheral neuropathy
- *Prednisolone*: can cause many side effects (those of corticosteroids), like hypotension, hyperglycemia, fatigue, personality changes, depression… etc.

"The results of the treatment of patients with NHL have been improved impressively by the use of antibodies directed against the lymphoma cells."

Rituximab (*Mabthera*®) for NHL

Rituximab is a monoclonal antibody (unmodified Ab) used in both NHL and CLL, since lymphocytes in both of these pathologies express CD20, and *Rituximab* is Anti-CD20.

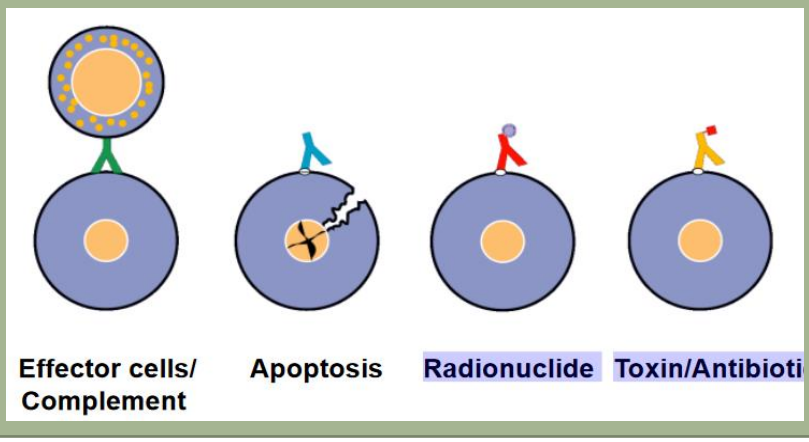
Actually, patients treated for NHL without rituximab only reach 50% of CR (complete remission). That's why, and especially in the aggressive form, we add this to the treatment from the start. So, in 2008 CHOP became R-CHOP (the R refers to *Rituximab*).

There are other MoAbs (monoclonal antibodies) that could be used, like: *Obinutuzumab*, *Ofatumumab*, *Epratuzumab* and *Lucatumumab* (just notice they all end with "mab").

How can these antibody-based drugs kill cancerous lymphocytes? (Figure 1)

1. If the antibody was alone it could induce **apoptosis** of cancerous cell.
2. The antibody can be **modified** by attaching it to a radionuclide, a toxin or an antibiotic, and so we'll kill the cell.
3. The antibody can sensitize or gather **other immune cells** like cytotoxic T-cells to come and kill the cancerous cell.

Figure1: Rituximab kill cancerous lymphocytes



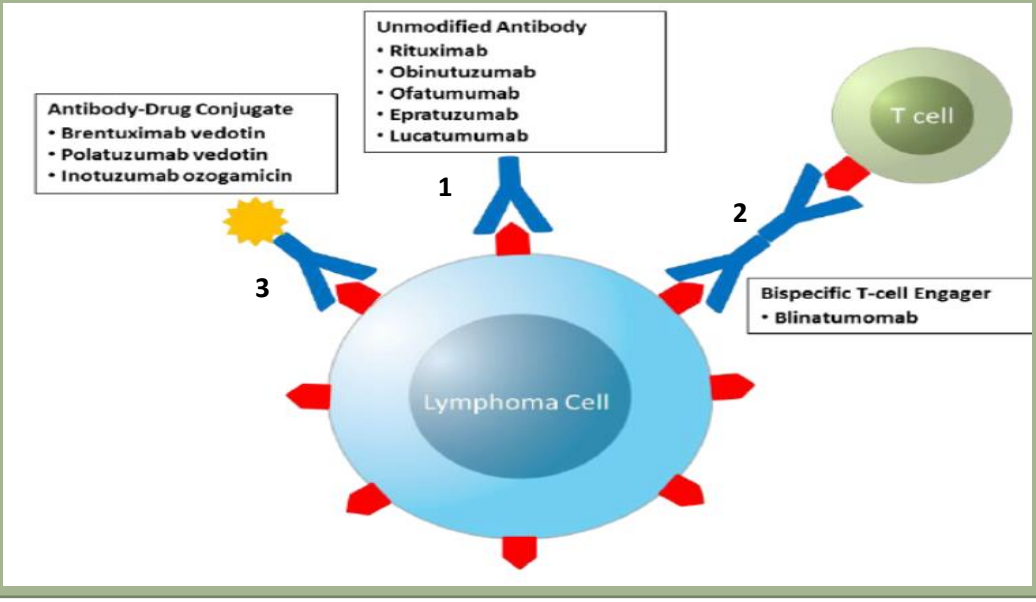
Modifications on MoAbs: (Figure 2)

- ✓ **Bispecific T cell engager**:
  Two antibodies (Abs) are used in this method.
  The first Ab recognizes the CD20 on lymphocytes by its Fab region and at the same time its Fc portion is attached to the Fc portion of the second Ab. The second Ab's Fab portion will be attached to another "killer" cell. By this high specificity is yielded.
- ✓ **Ab-drug conjugate:**
  In this method we attach a very toxic drug or a radioactive material to the antibody. One example is *Vedotin*, which is a very cytotoxic drug, even considered a toxin not a drug, and it won't be activated unless binding occurs.

As we learned from the immunology course, Abs are very specific so using them as drugs is very effective. So, why exactly do we use Abs as drugs to treat NHL?

- With present chemotherapy there's no, or insufficient cure.
- Treatment of minimal residual disease after chemotherapy might improve prognosis.
- Antibodies are more specific than cytostatic drugs.
- Antibodies are less toxic.
- Antibodies have a different mechanism of action.

Figure 2: modifications on Abs used in NHL treatment



Abs used in NHL treatment can be:
1: unmodified: like Rituximab

Or modified:
2: bispecific T cell engager (notice how 2 Abs are fixed on each other's Fc-Fc engagement)
3: Ab-drug conjugate

Side effects of *Rituximab*:

the side effects are based on the fact that *Rituximab* is an Ab, so when you inject it into the body, there will be a slight immune activation, manifested by:

- Fever, chills
- Temporary drop in blood pressure, dyspnea
- Rare: antibodies against rituximab (may cause death)

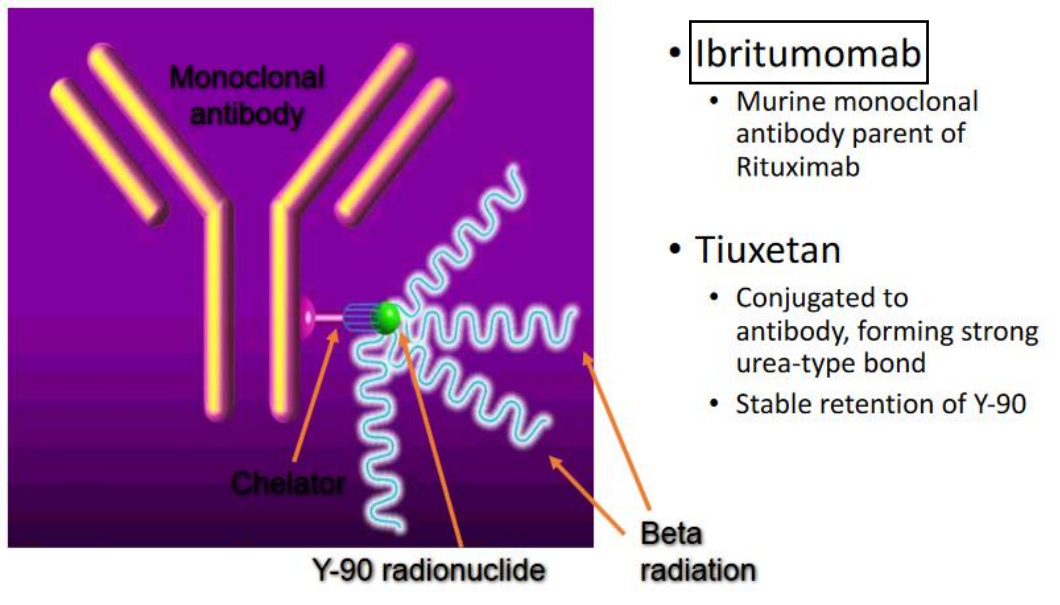
Those side effects are mild and transient, mainly during first infusion.

The doctor didn't focus on the details here in the box, but it is cool to know them.

Radio-immunotherapy

We've said that one of the modifications that can be used in NHL is Ab-drug conjugate. In Radio-immunotherapy the drug that will be conjugated is a radioactive substance – that will emit rays which will kill the lymphocyte.

Look at this figure: identify the Ab, the radionuclide and the beta rays that it emits. This Ab will be fixed on cancerous lymphocyte and *BAM!* the lymphocytes will be killed.



These info where also mentioned in the slides:
Radiolabeled anti-CD20 antibodies in the treatment of relapsed follicular lymphoma

•Response % higher than with "naked" anti-CD20

•Response duration ~ similar to "naked" anti-CD20

•High dose: response (5-10 years) cure?
•Also effective in patients resistant to "naked" anti-CD20
-Notice how lovely science evolves >> first we had CHOP >>then R-CHOP >> then radio-immunotherapy.

Myeloid Growth factors

This topic has been discussed by Dr. Munir, however Dr. Malek emphasized on some high-yielded principles regarding this topic.

First remember that anemia can be induced by **chemotherapy**, and when this happens we give the patient erythropoietin EPO (make sure that the patient is not iron or folate deficient before giving erythropoietin). In addition to that, patients who require **BM transplantation** need EPO. And of course those suffering from **kidney failure** and those who require dialysis need EPO as well.

Also notice that we did not talk about platelet growth factors, as nothing was approved with regard to their use in thrombocytopenia, instead we use IL-11 to activate the production of platelets (but this really has a lot of side effects and isn't used much). Thrombopoietin can be used here as well.

But, in reality we just transfer platelets for thrombocytopenic patients, using fresh frozen plasma, which provides platelets to the patient.

Now, **myeloid growth factor (GF)**:

- These are G-CSF and GM-CSF (Granulocyte/Granulocyte-Macrophage colony stimulating factor, respectively).
- So, we use them in cases of neutropenia, but why do we worry about neutrophils in this context?
  In cancer treatment, one of the limitations that prevents us from giving higher doses is neutropenia, as the body must have sufficient amounts of neutrophils (without neutrophils infections will disseminate).
  Also, If we induce neutropenia we give the patient myeloid GFs.
- Trials showed that prophylactic use of G-CSF reduces the time of neutropenia by half as well as neutropenia fever.
- 7 days of one injection after each round of chemotherapy.

We give G-CSF especially with **AML** as we use massive dose of *Cytarabine* (up to 3000 mg/m^2), the dose is really high and can easily induce neutropenia.

G-CSF:

- Play a central role in neutrophil formation.
- Increase during infection and inflammatory states.
- A mutation in its receptor results in congenital neutropenia.
- ***Filgrastin*** is a recombinant drug.

GM-CSF

- ***Saragramostin*** is the recombinant drug.
- Increases the production of neutrophils and macrophages.
- Increases antigen presentation by macrophages.

Febrile Neutropenia

- ✓ Life threating situation in which the patient has fever, chills and neutropenia.
- ✓ Managed by giving **broad spectrum antibiotics**.
  Remember: broad spectrum antibiotics like *Carbapenems*
  (e.g. *Imipenem- Tienam* الذي لا ينام), *Piperacillin/Tazobactam*.
  And we give myeloid GFs to correct neutropenia and Abs because the patient simply does not have immunity as he is neutropenic.

Side effects of *Filgrastin* (G-CSF):

These are built on the fact that you are giving immune-activating agents, side effects include:

1- Splenomegaly and there may be spleen rapture.
2- Bone pain in 30% of patients (as the production of new neutrophils occurs there).

Other uses for GM-CSF (do not memorize them, just the last one):

- Improve neutrophil production in patient with delayed engraftment after transplantation.
- Mobilize autologous peripheral blood stem cells for collection.
- Promote neutrophils recovery after autologous or allogenic stem cell transplantation.
- *Reduce risk of death due to infections in patients over 55 years old undergoing induction chemotherapy.

- **Autologous vs Allogenic**
  BM transplant is done either from yourself (**autologous**) or someone else (**allogenic**) that grow into a healthy hematopoietic system.
- We really use GM-CSF rather than G-CSF in strong cancers like AML and breast cancer.

Vaccination/ Leukemia

Like autologous BM transplantation we collect the patient's lymphocytes (activated T-cells), and in vitro we expose them to antigens and then reinject them into the patient. This can be done for lymphoma, too.

This sheet has been corrected and edited

Summary

ALL/AML

- ALL : Induce (*Vincristine*, *Glucocorticoid*, *L-asparaginase*) then consolidlate (Methotrexate with mercaptopurine or High-dose asparaginase).
  Maintenance Methotrexate (W) Mercaptopurine (D) + CNS prophylaxis.

- AML: Induce (Arabinoside + Daunorubicin +/-Thioguanine) and BM transplant.

CLL

- CLL: Watch and wait
  Mild >> *Chlorambucil/ Cyclophosphamide* + *Prednisone*
  Intermediate >> mab drug Imatinib is Bcr-Abl fusion protein of Philadelphia chromosome inhibitor.
  Aggressive >> BM transplant

HL /NHL

- HL : highly curable, [ABVD] *Adriamycin*, *Bleomycin*, *Vinblastine*, *Dacarbazine*
- NHL:
  Aggressive : CHOP-*Cyclophosphamide*, *Doxorubicin Hydrochloride*, *Vincristine*, *Prednisolonone*. R-CHOP (*Rituximab*) or radio-immunotherapy.
  Indolent : incurable.