INTRODUCTION TO MEDICAL

IMMUNOLOGY

SLIDE SHEET

NUMBER	23
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In the previous lecture we've mentioned the targets of immunotherapy and it could be either enhancing or suppression the immunity. We need to suppress the immunity in two main cases: organ transplantation and autoimmune diseases (hyper-activation of the immune system).

We've mentioned also the immunosuppressive drugs and finished talking about the 1st two groups; Glucocorticoids and Calcineurin inhibitors.

*We give 500 mg glucocorticoids before the transplantation then we reduce the dose.

*Calcineurin inhibitors (Tacrolimus and Cyclosporine) are the corner stone for all transplantations and we build our regimen mainly based on these drugs. Remember that they need monitoring because they are very narrow therapeutic index.

These two groups of drugs are efficient but sometimes they are not enough and even combining both of them won't reach our therapeutic target. Furthermore, we need other inhibitory mechanisms for the immune system. (To make sure that the immune system will not work we have to inhibit more than 1 step).

3-Anti-metabolites

They are the cornerstone drugs in so many diseases, non selective anti-cancers (inhibiting both T and B cells and all other replicating cells). They are false nucleosides which undergo phosphorylation in the body and become nucleotides. These nucleotides will be incorporated into the DNA and terminate the replication; so these drugs are anti-replication.

They are used as anti-cancer drugs and at lower doses (1/5th of the dose) as immunosuppressive drugs .

Examples: **Azothioprine**, **Methotrexate** and **Mycophenolate**.

1- **<u>Azathioprine</u>** is converted into **6-mercaptupurine** by xanthine oxidase enzyme.
So Azathioprine is metaolized by this enzyme, and this enzyme is inhibited by many other drugs, for example Allopurinol. Thus if your patients is on Allopuranol, you have to decrease the dose of Azathioprine to prevent its increasing levels and toxicity (BM suppression).

**This is called drug-drug-interaction.*
**Allopuranol is used in gout and hyper urecemia and it inhibits xanthine oxidase.*
****We start with Azathioprine in most of kidney transplantation**.*

2- **<u>Mycophenolate</u>** is a pure immunosuppressant that cannot be used as anti-cancer because it has a different mechanism of action which makes it more selective towards T and B cells.
It reversibly inhibits the enzyme IMPDH (inosine monophosphate dehydrogenase) which leads to the depletion of Guanosine nucleotide(anti proliferative) . And by inhibiting this enzyme specifically you are selectively inhibiting both B and T cells , and thus you will end up with lower effect on BM .

USES OF MYCOPHENOLATE:

- It's more effective that Azathioprine in preventing acute rejection (that's why if rejection appears we change Azathioprine to Mycophenolate)
  ((We start treatment with Prednisone, and then we add Tacrolimus and cyclosporine and azathioprine. If rejection appears and the graft is not functioning well, so there must be a problem either in the toxicity and levels (which is not the case here since you are monitoring the levels) or in the regimen itself. So you have to change the regimen, and this is one of the ways to change it! You will see this paragraph again with other solutions to change the regimen))

- If you are afraid of rejection and you are expecting a rejection (if there is no relation between donor and recipient, there is no matching in HLA antigens) we give Mycophenolate from the beginning because it's more selective.
- If the patient can't tolerate Cyclosporine and Tacrolimus because of their nephrotoxicity, we stop them and give him instead Mycophenolate and Prednisone.
- Mycophenolate Mofetil is used in solid organ transplant patients for refractory rejection.

**This drug is kind of selective towards B and T cells, sparing normal cells. But at high doses the selectivity is lost.*

**IMPDH enzyme is found in hematopoietic cells but its selectivity is more towards T and B cells.*

**Methotrexate also deplets Guanine.*

3- **Methotrexate** it's part of DMART (disease modifying anti rheumatoid arthritis drugs) , and it inhibits dihydrofolate reductase. It's used as a treatment of Rheumatic Arthritis.

4- IL-2 Receptor Inhibitors

If we are highly expecting an acute rejection, we use IL-2 receptor inhibitors (monoclonal antibodies) before the transplantation. They are expensive but they have an add-on activity which helps in boosting the activity of the regimen .

Remember the autocrine effect cause by IL-2 binding to its receptor CD25, so by inhibiting its receptor we inhibit the whole cycle and make sure there is no IL-2 secretd.

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monitoring the levels) or in the regimen itself. So you have to change the regimen, besides the Mycophenolate you can add IL-2 receptor inhibitors.))

Examples on IL-2 receptor inhibitors are Basiliximab and Daclizumab. These drugs have long half life and they differ in their humanization percentage.
(We bring these drugs from animals and then the animal portion is changed into a human portion, so the percentage of the humanized portion is what we mean it here.)

	Basiliximab	Daclizumab
Percentage of humanization	75%	95% (less allergy)
Half life	7 days	20 days
Blockage of the receptor remains	30-40 days	120 days
The dose	Twice or 3 times (two hours before transplantation, and the 2nd dose 4 after the transplantation)	Once, 4 days before the transplantation

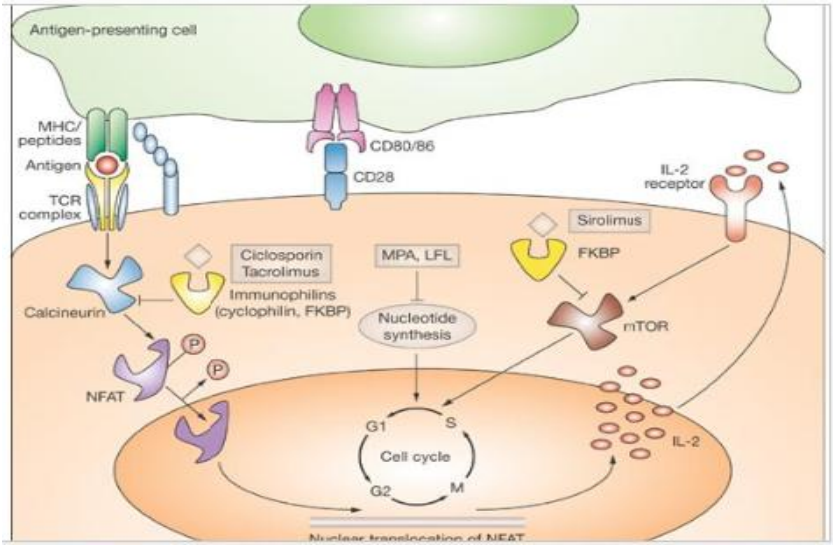
5- m-TOR inhibitors

The last drug we'll talk about in transplantation is Sirolimus which is an m-TOR inhibitor (mammalian target of rapamycin inhibitor). We use it as alternative of Tacrolimus and Cyclosporine and it inhibits a very important component in the cell cycle.

Sirolimus can also cause nephrotoxicity but much more less than the nephrotoxicity caused by Cyclosporine and Tacrolimus. Also it has a wider therapeutic window!

**Be careful of combining Sirolimus with Cyclosporine and Tacrolimus and any other nephrotoxic drug because the toxicity will be highly exacerbated.*

**It has an application in cancer also.*
**its trade name is RAPAMUNE.*



Look at this picture again; in order to end and inhibit the proliferation of T cells, you can target many mechanisms. And when you cannot give Tacrolimus and cyclosporine because of their nephrotoxicity we change into <u>a Sirolimus-based one (including Sirolimus, Mycophenolate and corticosteroids). Furthermore we can boost the regimen by adding IL-2 receptor antagonists.</u>

** Anti-CD3 **

There is a final drug used here but it is not used anymore in the market because of its high toxicity (It causes flare in the immunity) which is anti-CD3 Muromonab. This drug is an antibody towards a CD3, which is part of the T cell receptor. The important thing you have to know here that this antibody is NOT an antagonist! **It's an agonist** but when binds to the receptor it can't come out of it thus inhibiting further activation.

It causes hypersensetization and flare, therefore it is customary to premedicate the patient and give him **methylprednisolon** (he is usually on oral methylprednisolon but we boost it with injection), **diphenhydramine** (an anti histamine) and a 1 gram injection of **acetaminophen** which is a painkiller.

<u>QUESTION: How do we combine these drugs in real life?</u> *Guidelines may differ from one place to another and from a time to another.*

1- **Methyl predinsolone** 500mg IV just prior to transplantation and again at 24 hours. "we need to totally remove the immunity"

2- **Tacrolimus led triple therapy**
   - Tacrolimus 0.1mg/kg/day given as two doses at 10:00 and 22:00
   - Predinsolone 20mg once daily at 8:00
   - Azathioprine 1-2mg/kg (usually 75-100 mg) at 8:00 and initially 1-2 mg/kg once daily. Maintenance 1 mg/kg once daily.

   This is kinetic; you have to stick with the time! The regimen here is a time-dependent regimen so again and again you have to monitor and stick with time.

3- Patients with **high risk** for rejection are given **Tacrolimus led therapy with Mycophenolate instead of azathioprine**.

4- Basilixumab is also given in patients with increased risk of rejection and to patients with expected delayed graft function. It's given as 20mg 2 hours prior transplantation and 20 mg given on day 4 post transplantation. "if we are afraid of rejection"

Autoimmune diseases

They are an immune reaction toward a self antigen; examples:

1- Rhuematoid Arthritis: is very common in the Jordanian community and if it's left without treatment it leads to deformities
2- Systemic Lupus erythematosus, SLE: more common in females around the age of 30, and if left without treatment it leads to kidney faliure
3- Multiple Sclerosis MS: is rare
4- Insulin dependent Diabetes Mellitus

The only thing we can do for these diseases is to suppress the immunity. And the main target of the drugs used is to modify the span of the disease because the patient will live with the disease for his whole life.

QUESTION: How we control the autoimmunity and what are the drugs used in autoimmune diseases?

- In Systemic lupus sometimes flare appears and it's treated by high dose methylpredinsolon (300mg)

- In asthma**,** sometimes the patient is not responsive to anything (corticosteroid and IL-2) so we give him **Anti-IgE**. These monoclonal antibodies bind to the IgE preventing it from binding to mast cell, so there will be no release for Histamine. (so we prevent the asthmatic attacks)

- In Rheumatoid Arthritis we used **DMARDs** including (methotrexate, leflunamide , azathioprine and hydroxichloroquine) and we carry them using **glucocorticoids**. (To bridge them toward their activity because these drugs need 6-8 weeks to work).
  "This is just mentioned briefly by the doctor because we took them before"

- **Infliximab** and **Adalimumab,** these are biologic drugs, they act as anti TNF-alpha. (We use monoclonal antibodies against an important mediator in rheumatoid arthritis which is TNF-alpha. Anti-TNF-alpha is directed towards macrophages and T cells). They are used when DMARD is not working as injections. But in 2017 an oral one was developed.
  ***Anti TNF-alpha causes cardio-toxicity and reactivation for the latent TB.*
  ***The biologics are the last drug resort since they are expensive*

- **Rituxizumab** is an anti-CD20 (that means it's an anti B-cells). It's first approved in 1997 for use in B cell lymphoma so it has a variety of application in cancer and in rheumatoid arthritis; sometimes Rheumatoid arthritis involves B cells more than T cells "usually the opposite!"
  So this can be a reason for non responsiveness of some rheumatoid arthritis patients to DMARDs and Biologics. As their disease is more dependent on B cell so they are treated with Rituxizumab.

  **This drug is expensive with side effects including Bone marrow*

suppression and it is given in combination with methotrexate in rheumatoid arthritis.

QUESTION: how we can stimulate and boost the immunity?

- **IL-2**: They thought that why not to give IL-2 to cancer patient; since the main problem in cancer is that cancer cells invades the immune system because it's week so by boosting it with IL-2 the immune system will be stronger and attack the tumor? And they tried using IL-2 in melanoma, renal cell carcinoma and in Hodgkin disease.
  This assumption is wrong! Because the immune system is not weak. The immune system is there but it's not functioning! The cancer cells are sending inhibitors toward the immune system.

  **T cells have both activating (CD28 and TCR) and inhibitory receptors (CTLA4 and PD1)*
  **It's very toxic and produces flu-like symptoms without real effects.*

- **INF-alpha** is used as anti-viral drugs and as immunomodulators if we want to boost the immunity in cancer. The main target for it is to activate the immune system to attack the virus or cancer.
  Ribovirine was (and still in some countries) the drug of choice for hepatitis-C but now it's a cured disease.

Recently they discovered that the tumor produces proteins which bind to the inhibitory receptor on the T cell deactivating it. This can justify the presence of filtration of T cells in an isolated tumor. The T cells are there but cannot kill the tumor. (Not because it cannot see it but because it 's inhibited from it).
And by understanding the previous concept, new drugs developed as anti inhibitory receptors. And **Immunotherapy** appeared!

Examples on these check points inhibitors: Anti CTLA-4 and anti PD-1, these drugs will block the inhibitory receptors leads to the activation of the immune system.

**NOTE: Not all cancers can produce the ligand for these inhibitory receptors.*
**NOTE: The doctor will not ask us about the names of these drugs as they are many, but the most important one is Imelunomab.*

These drugs are first tested in melanoma and now they are being used in many different cancers. They showed a real success and a complete remission of some melanomas and lung cancers.

The effectiveness of these drugs is around 20-40% because as we mentioned not all cancers produce the ligands for the inhibitory receptors and only the ones that use CTLA-4 and PD1 as a way to invade the immune system can be treated with these drugs.

Other cancers use different mechanisms such as hiding or mutating their antigens so these cancers are not antigenic anymore and we have to recognize the mutated antigen. These cancers can be treated by adoptive T cell therapy.

Adoptive T cell therapy is a new and very effective method in which we take tumor cells as well as T cells from the patient. Then we expose the tumor antigens to T cells (we are helping the T cell in the recognition part), boost them (by give IL-2 for example) and finally re-inject them again into the patient.

*A final note: the cells we are injecting into the patient again cells are considered foreign cells (although they are from the same patient) so we add IL-2, IL-7 and IL-10 to activate the new immune system and make it stronger.

*Please excuse any typographical and grammatical errors

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