In previous lectures, we talked about selective anticancer drugs; the first one was Asparaginase, which hydrolyzes asparagines which in turn can't be synthesized in leukemia cells, and this drug is used only in the induction phase of ALL treatment in adults & children.

Also, we talked about Imatinib, it targets Philadelphia chromosome – which harbors BCR-ABL oncogene that is in turn activated in CML - & this drug acts by inhibiting the binding pocket of PCR-ABL oncoprotein & thus the cancer cell can't go into its cycle & proliferate, don't forget that there are no "real" side effects of Imatinib, since it acts selectively on CML cells & thus the patient can take it daily for 10 or even 15 years without having side effects.

Further more, we talked about Bevacizumab which is an antiangiogenic drug & is approved only for colorectal cancer – prolonging life expectancy to 6-12 months in the best cases - & lung cancer – prolonging life expectancy to 1-2 months - , why is it approved for lung cancer? Because the life span of a lung cancer patient isn't that long, so, prolonging life expectancy by 1 - 2 months in such a case can actually do a substantial difference.

The last target drug is Trastuzumab (Herceptin), simply if the patient has **HER 2 positive** breast cancer, we have to give her Trastuzumab.

{{What is HER 2? There are in our bodies Epidermal Growth Factor receptors , which are 4 types; EGFR-1, HER-2 which is EGFR-2, HER-3 & HER-4 … these receptors' genes if are over-expressed will become oncogenes, and are actually found so in many types of cancers.}}

When do we give Trastuzumab? We don't start with it, because we start with doxorubicin, also we can't combine it with doxorubicin , simply because Trastuzumab has a cardiotoxic activity.

So the first and last drugs we talked about in treatment of breast cancer are doxorubicin and Herceptin, both of them have a cardiotoxic activity –a principle known as synergism-, don't combine these two drugs together, so we start Trastuzumab after the forth cycle of cyclophosphamide.

Recently, there are talks about Trastuzumab activity on other types of breast cancer, even if the breast cancer is HER 2 negative, how? The selectivity of Herceptin isn't absolute, i.e. it binds to HER 2 as its inhibitor, but also, some of Herceptin will actually bind to & inhibit HER-1 & thus inhibits proliferation too, so in case of HER2 negative breast cancer, we can use this drug to inhibit over-expressed EGFR-1 for example,,, also it has an activity on ovarian cancer – since in some ovarian cancers, there's also over-expression of HER 2-, this leads us to another fact, which is that ovarian cancer too is hormonal dependant & HER 2 may play a role in that.

Note: Herceptin is now used mostly in breast cancer, but other uses may rise in the future.

Don't forget that Trastuzumab is a drug with no side effects.

The doctor showed a video about immunotherapy in treating cancers, the important issue about it is inhibition of the inhibitors, in other words, it's about inhibition of certain protein receptors found on the surface of immune cells like CTLA-4 & PD-1, which –these receptors- upon binding to their ligands; dampen down/ down-regulate an ongoing immune response at some stage to prevent collateral damage to the surrounding normal tissues, so, if there were already presented immune cells within the tumor & were activated &then we inhibited these inhibitors –blocked the receptors from binding to their ligands-, we can actually guarantee a continuous immune response to cancer cells, with a great outcome.

One example on these inhibitors of inhibitors, is anti PD-1and another important one is anti CTLA-4 known as Ipilimumab, which is FDA approved for Melanoma, which in turn is the worst cancer ever; being 100% fatal just as lung cancer, however melanoma is much faster than lung cancer (that's why melanoma patients go to such immunotherapy clinical trials having no hope but these trials), however, 30% of melanoma patients are actually responding to immunotherapy these days, i.e. NOW, immunotherapy is effective in many but not all cancer patients, & this is due to heterogeneous nature of cancer… luckily, melanoma isn't common in Jordan.

The main problem with cancer is immunity, any cancer emerging in the body is supposed to be suppressed by immunity, but unfortunately this isn't how it goes, that's why there is a big focus nowadays on immunotherapy, hoping to activate immunity to face & fight cancer.

Note: Immunotherapy isn't included in the exam material.

Anti viral drugs

* The head of a pin can hold five hundred million rhinoviruses (cause of the common cold). One sneeze can generate an aerosol of enough cold viruses to infect thousands of people... the aerosols keep circulating in the surrounding air for 25 minutes, so, cut it short & sneeze gently :P

The problem in the virus is that it hijacks the cellular machinery, it is an intracellular parasite (it's not meant as "the" parasite family that we know, the dr meant that it's an offending intracellular agent), so when the virus infects the cell, it will use the cellular machinery to produce its proteins and to spread out again, so what is it in the virus to select to be a target for antiviral drugs? And how do we treat it?

It is very difficult because we don't have a selective target, so we have to kill the dividing cells here too, i.e. if we treat a viral infection, there will be side effects (such as bone marrow suppression, but not all side effects of chemotherapy in cancer will be seen here; like alopecia), and this was until 1982, after that, selective drugs were produced, which we use now.

Viruses are the smallest infective agents, effectively consisting of nucleic acid (DNA or RNA) enclosed in a protein coat.

Viruses are intracellular parasites with no, or little, metabolic machinery of their own.

They have to borrow the biochemistry of the host cell to succeed and grow (this is what makes selective antiviral therapy so difficult).

***The life/infectious cycle of viruses may be divided into the following stages:**

1- *Adsorption or Attachment*: the virus will attach to specific receptors at the host cell membrane.

2- *Penetration*: entrance into the cell, through several mechanisms; one of them is receptor mediated endocytosis... in case of herpes virus, it's via fusion.

3- *Uncoating*: is the process when the viral capsid is removed.

4- *Synthesis of proteins and viral genome: here begins the hijacking:* the viral nucleic acid [RNA or DNA] will be free inside the cell, the RNA will get translated into proteins or the DNA [of the virus] will be replicated and translated too.

5- *Assembly of the viral particles which will surround the genomic core:* new viruses will be formed.

6- *Release of the viruses outside the cell:* Viruses may escape from the host cell by causing cell rupture (lysis). Enveloped viruses (e.g., HIV) typically "bud" from the host cell. During the budding process, a virus acquires the phospholipid envelope containing the embedded viral glycoproteins, and then the viruses will spread over to new host cells.

Pharmacologists try to target these steps of viral life cycle, the first step –adsorption- is targeted by Amantadine and Ramantadine , both work on inhibition of adsorption while other antiviral drugs work **within** the cell.

Tamiflu, generally, it's an antiviral drug administered to patients having influenza, it works on the last stage – release stage- … this drug was also administered to swine flu patients.

Every virus has different treatment and there is no wide spectrum antiviral drug except Interferons; because they increase the immunity to fight against the viruses –any type of viruses-, but actually we don't use it much except for hepatitis C.

The golden treatment of hepatitis C is interferon-alpha, why?

Because we want to synergize the immune system to fight against the viruses.

HERPES VIRUSES

-They are DNA viruses [including CMV, HSV 1, HSV 2 and VZV].

-HSV is the most common virus affecting us.

Anti-metabolites:-

Used to be administered in the treatment of viral infections, one of these anti-metabolic drugs is Vidarabine, it's an old drug, it looks like guanine, so, we're actually giving false guanine to the cell to inhibit DNA polymerase of both (human and viruses), so it is not selective, it causes bone marrow suppression in 30%-50% of patients administering it, again why? Because it's an anti-metabolite, however, this suppression isn't as severe as bone marrow suppression accompanying chemotherapy in cancer, why? Because the dose used in viral infections is different than that in cancer.

Note: Vidarabine is a nucleoside analog that will be converted into its triphosphate active form by kinases present inside the cells.

ACYCLOVIR: is the golden drug used in the treatment of Herpes viruses, it's a selective drug (the most selective).

GANCICLOVIR: this is somewhat a selective drug.

Mechanism of action of ACYCLOVIR:-

Acyclovir is a pro-drug, having no attached phosphate groups to it & is a nucleoside –Guanosine- analog; in order for this pro-drug to function, it has to be converted into a nucleotide analog (having 3 phosphate groups attached to it) & that is done through the following mechanism:

Acyclovir is converted into acyclo-guanosine monophosphate (acyclo-GMP) by viral thymidine kinase ONLY (since viral thymidine kinase affinity is 200 times more than the mammalian thymidine kinase towards Acyclovir), i.e. if this drug reaches a non-infected healthy cell, it won't function; due to the absence of VIRAL thymidine kinase in healthy cells & thus we blocked the first step in the conversion of acyclovir into acyclo-GTP. Subsequently, the *monophosphate* form is further phosphorylated into the active *triphosphate* form, acyclo-guanosine triphosphate (acyclo-GTP), by cellular kinases (which add the 2nd & 3rd phosphate groups) and now we have Acyclovir in its nucleotide active form.

Acyclo-GTP has approximately 100 times greater affinity for viral than cellular polymerases. As a substrate, acyclo-GTP is incorporated into viral DNA templates, resulting in chain termination, and the viral enzymes cannot remove acyclo-GTP from the chain, which results in inhibition of further activity of DNA polymerase, so it will cause inhibition of replication and proliferation of the virus.

- It is the most important drug used for treatment of herpes viral infections; in ACYCLOVIR we will not see bone marrow suppression; because it is selective.

Resistance to Acyclovir: viruses can easily become resistant & it's actually common; due to high mutation rates –even more than bacteria-, what's the mechanism of resistance?

Decreased activity of VIRAL thymidine kinase + altered DNA polymerase –change in its structure- to escape/ avoid inhibition by acyclo-GTP (escape from being a target for this drug).

- Clinical uses:-

Acyclovir is indicated for the treatment of HSV infections, including:-

- Genital herpes, it's a common infection being more in ladies, affects the genital tract… regarding the treatment, Acyclovir is given 4 times daily throughout the whole infection period, also, we have to prophylact the patient from recurrence of genital herpes, esp if it was frequent; between 3-4 times yearly, the prophylaxis may last up to 6 months, [we use **oral** acyclovir].
- Oral labialis (cold sores), it's common, upon stress or following common cold, there will be decrease in immunity & thus there will be reactivation & recurrence of the infection in the form of cold sores – don't forget that herpes viruses are opportunistic viruses that use immunesuppression for their own benefits - [recurrence occurs 4-6 times yearly].
- Herpes encephalitis.

Also, Acyclovir is indicated for the treatment of VZV infections, including:-

- Shingles.
- Chickenpox in immunocompromised patientsm (AIDS patients, cancer patients on chemotherapy, diabetics, elderly, etc…)

Also, Acyclovir is indicated:

- As a prophylaxis in the pt's treated with immunosuppressant drugs or radiotherapy, who are in danger of infection by reactivation of a latent virus.

-Acyclovir can be administered orally, IV (to treat herpes encephalitis) or topically as a cream or ointment in the cases of oral herpes.

Note:-
The prophylactic dose is always less than the treatment dose (i.e. half of the dose) [i.e. if a patient takes the treatment dose 4 times daily, each dose is 500-600 mg, then the prophylactic dosage will be 500-600 mg twice daily.]

- Why is Acyclovir administered 4 times daily? Because its bioavailability is low, i.e. it has a high first pass metabolism.

-The poor oral bioavailability is solved by administering valacyclovir (present on a wide base in pharmacies) which is (acyclovir + ester group), the ester group protects acyclovir from first pass metabolism, Valacyclovir is then converted to acyclovir by esterases upon hepatic first-pass metabolism. We give valacyclovir twice a day instead of giving acyclovir 4 times a day. In prophylaxis, Acyclovir is given twice a day but valacyclovir is given once a day for a long period of time (6 month) as in the case of frequent recurrent genital herpes esp. & more commonly in ladies, however, sometimes –not the general rule-, we may dose the lady with Acyclovir every couple of days not daily, but again, this isn't how it generally goes.

Note: we still use Acyclovir although Valacyclovir seems to be better & this is due to many reasons, most importantly is the fact that Acyclovir is cheaper.

- After all, there is a problem in treating viral infections, which is that we're not really curing the infection through the drug, instead, we're reducing the duration of it, for example, when it comes to oral labialis or genital herpes, the duration of infection each time is usually 5-7 days WITHOUT treatment & then it heals alone, If we treat with Acyclovir from the beginning of the infection, the duration will be shortened by 2 days only, so the duration WITH treatment will be 3-5 days, i.e. we're not reducing the duration from 5-7 days into one day, and actually, this doesn't apply to Acyclovir only, it applies to all antiviral agents & different viral infections whether influenza, herpes, etc… they all don't reduce the duration time of infections substantially, so, is it really necessary/ worth it to give the patient Acyclovir 4 times a day for 7 days, or Valacyclovir twice a day for 7 days? **No,** Usually it's **not** necessary & **not** of a great added value, however, if administered, you need to tell your patient not to expect full recovery the next day.

- Oral acyclovir has multiple uses. In first episode of genital herpes, oral acyclovir shorten the duration of symptoms by approximately 2 days , the time to lesion healing by 4 days and the duration of viral shedding by 7 days. In recurrent genital herpes the time course is shortened by 1-2 days.

- Oral acyclovir is only modestly beneficial in recurrent herpes labialis.

- Topical acyclovir cream is substantially less effective than oral therapy for primary HSV infections. It is of no benefit in treating recurrent **genital** herpes.

- Another drug administered topically is Docosanol, it has the same idea of the previous point; it only shortens the duration by 18 hours out of the 5-7 days duration of infection with oral labialis.

Again, Acyclovir is the golden treatment for herpes simplex virus (usually oral labialis and genital herpes).

- If the lady has genital herpes, we treat her with oral acyclovir; since there is no beneficial activity of the cream.
- For oral labialis, the cream only reduces the symptoms for not more than 1 day.
- We use ACYCLOVIR more towards prophylaxis in recurrence of genital herpes (again, more common in ladies).
- If a man or a lady has recurrent oral labialis, also here, ACYCLOVIR is used prophylactically.
- Still, in the prev. 2 cases, Acyclovir can be used in addition to prophylaxis as a treatment, IF the patient is suffering a lot.

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