Host-Pathogen Interaction (Immunology)
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Lecture – 26
Application of Interferons in Therapies

So, in previous session we have learned a lot about the cytokines, their mode of action and other properties and then we have also learned about the other mediators non-proteinaceous mediator, such as a ~~r~~vae~~-~~soactive amines. We have learned lipid~~-~~-based mediators which induces a particular kind of responses in the immune cells. We have learned in great length about inflammation various kind of inflammation how it is induced? What are the factors so and so forth.

So, now, I will take you to the application of these active molecules, which we call it as a cytokine. We also call it as a chemokine, interleukin~~-~~ and monokine and we also call it as a interferons. So, let us begin with interferons. So, interferon is a very important in modifying the immune responses. Interferons not only acting on immune cells but it also acts on other cells. They have a two major property.

One is that they are antiviral in nature and they are also having a anti-proliferative or pro-apoptotic property. So, these two properties are mainly associated with in type I interferon. There is a also one interferon which we call it as a type II interferon. So, these type II interferon basically play a very important role in activation of innate immunity, as well as adaptive immunity. It has a great influence in adaptive, immunity, also.

What I mean to say that they activate variety of adaptive immune cells like T cells. There is a specialized T helper cell. They modify one of the sub type of T helper cell and they basically play a very important role in activation of some antigen presenting cells such as macrophages which is ~~harboring~~harbouring some kind of microbial pathogen. And they are also playing important role in activation of some innate immune cells.

Macrophage is a of course, the innate immune cell but on another hand they are also playing important role in activation of natural killer cells. Anyway, we will discuss these interferons

in great detail when we take respective topics. So, when we will discuss about the viruses at that time, I will talk in great length about type I interferon and there is a one more. There are basically three classes of interferon.

One is type I, type, II, and type III, so, type I and type III plays a very important role in antiviral immunity. So, I will discuss in great length when I will take the host pathogen interaction and you in that we will discuss about the viruses. And I will talk about interferon gamma in innate immunity as well as when I will discuss about the T cells.

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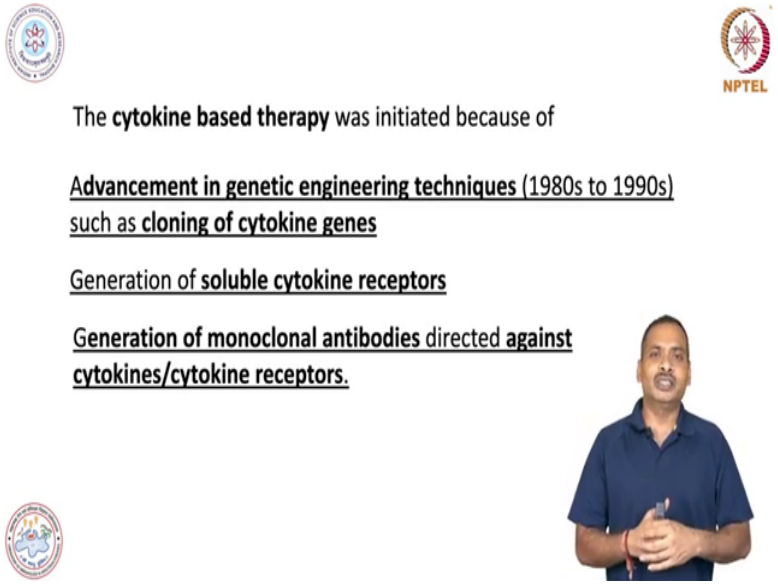

So, let us begin with these interferons and their application in therapy. So, when this therapy came in picture. At that time, it was basically having at that time the field of molecular biology. Molecular biology means where we can clone the gene where we can manipulate the nucleic acid. We can amplify the nucleic acid. We can make protein out of nucleic acid at that time. This cytokine-based therapy came in picture.

It is a basically very strongly associated with advancement of genetic engineering technique, as I have explained you which is roughly begin around 1980's and it was in quite high peak between 1980's to 1990's. At that time, the cytokine-based therapy concept or this idea came in picture. People learned about the cytokines, people now know how to make the cytokines and then the people wanted to use it for some or other diseases.

So, the cytokine is basically, if you want to isolate the cytokine from cells or tissues, I do not know it is very, very difficult. It is, why? Because it is producing in extremely low amount

and they have a quite huge biological effect. So, purification is a not a good option in order to make it for therapy. So, when this cloning and genetic engineering technique came then it is a quite cost effective. So that is why this cytokine therapy came in picture.

People started making soluble cytokines, soluble cytokine receptors. Probably you might be aware that there is a some biophysical chemistry or biophysical biotechnology kind of fields are there where their aim is to make the protein soluble. It is not easy to please remember, it is not easy that you just express any protein and it will be a soluble. So that is a big challenge. There are a lot of physics, chemistry and biology is needed.

Sometimes we change some amino acid which will not change the structure of protein and then it will become a soluble. Sometimes we add some small chemical agent which will make it soluble. Another is sometime these molecules, the half-life is very short. So, we have to increase their half-life I will tell you in this session that there is a one family of cytokine or interferon whose half-life is only 7 to 10 minutes.

So, in order to enhance their half-life, they add some small molecules which stabilizes under physiological condition. So, all these techniques were there, so that is why this cytokine-based therapy initiated. Another, a very big achievement in this field is people got it through the discovery of monoclonal antibody in my previous session or in my earlier session, I just discussed a bit about monoclonal antibody.

This monoclonal antibody was basically discovered by César Milstein and George Kohler~~-Caesar Myelstein and George Collar~~. They discovered this monoclonal antibody and it has a huge application and I think I have told you it has application in research. It has application in diagnosis. Variety of diagnostic is based on monoclonal antibody and it has a huge application in therapy. So, these things enables us to use the cytokine or as a therapy or we can target the cytokine for therapy.

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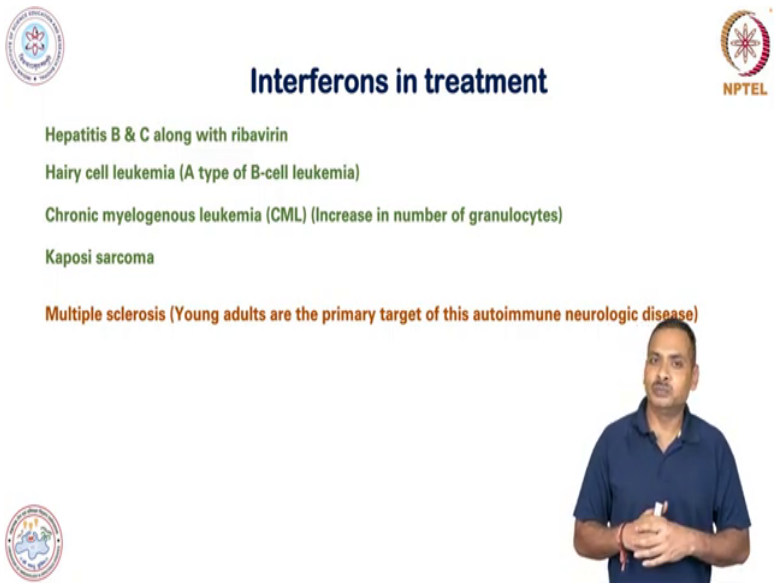

So, let us see about the interferons. So, in this session I will mainly focus on the interferon. So, probably you might be aware there is a some virus infection which cause the hepatitis which eventually result to the jaundice or that may result to the oncogenesis. So, Hepatitis, B and C infection is basically treated by interferons. This interferon is basically given along with some antiviral drug, as you can see in this slide, the name of drug is ribavirin.

So, this is quite effective. So, generally, this interferon is given along with this ribavirin. So, people are not very clear about that how much interferon is playing a role in overcoming this virus infection? So, there are some loop and holes and but still it is in clinical practice. Another is hairy cell ~~leukemia~~leukaemia, it is a type of B cell ~~leukemia~~leukaemia. In that the B cells develop a kind of projection hair like projections and this is quite fatal.

So, this kind of ~~leukemia~~leukaemia can be also treated by interferons. Another is chronic myelogenous ~~leukemia~~leukaemia, CML, where there is an increase in number of granulocytes. You remember when I have discussed about the cells of cells of immune system. Over there I discussed about the blood and blood has a white blood cell and white blood cells are mainly consist of two kinds of cells. One is granulocyte and another is agranulocyte.

I am just kind of refreshing for you and granulocytes are basically consists of neutrophils, basophils, eosinophils. So, there in this disease, in case of CML, there is a increase in number of these granulocytes and this is also treated by this interferons. Kaposi sarcoma, so, kaposi

sarcoma is a skin cancer. And this skin cancer is mainly associated with some kind of acquired immunodeficiency.

And when I say acquired immunodeficiency, so, one virus infection came come in picture. That is the infection of human immunodeficiency virus which cause acquired immunodeficiency syndrome, AIDS, so, the individual who is infected with the human immunodeficiency virus. They are prone to this kaposi sarcoma. They also develop some kind of fungal infection.

So, those individuals are kind of vulnerable, their immune system is kind of compromised and if you remember or probably you may know that this is a simple general knowledge in case of AIDS patient, the number of CD4 T cells are significantly reduced. And CD4 T cells is a central in adaptive immunity. So once this this cell will reduce then that will affect various arms of immunity and when immunity is compromised then people will tend to develop one or other types of cancer.

So, in case of AIDS, the kaposi sarcoma is a one of very unique cancer associated with AIDS. Another disease is infection of mycobacterium tuberculosis, and there is a some fungal infection. So, these are a kind of signature of acquired immunodeficiency. So, whatever I have explained you so far which is in green font. So, all these these conditions are basically treated by interferon alpha.

And now, I will talk about the multiple sclerosis. It is a very bad disease, a neuronal disease and it is mainly present in young adults. And this is the autoimmune disease. Basically, what happens if you remember the structure of neuron so, there is a myelin sheath, in axon region? So, this myelin sheath is necessary for nerve, conduction, and due to some some activation of non-specific activation of immunity.

These our immune cell start damaging these myelin sheath, and then this this disease develop multiple is sclerosis. This is a very complicated disease. And this disease has a several phases like there will be an initiation, then there will be a pro-progression. Progression means there is a progression of loss of myelin sheath and then there is a phase of non-progression. So, suddenly it will stop and then there will be a relapse after some time again this will relapse.

So, basically the interferon which is used in this disease it has been reported that when the disease in relapse phase at that time, the loss of myelin sheath was significantly reduced when we treat the human with interferon. So, basically multiple sclerosis is treated by interferon beta. This is a another type of type I interferon.

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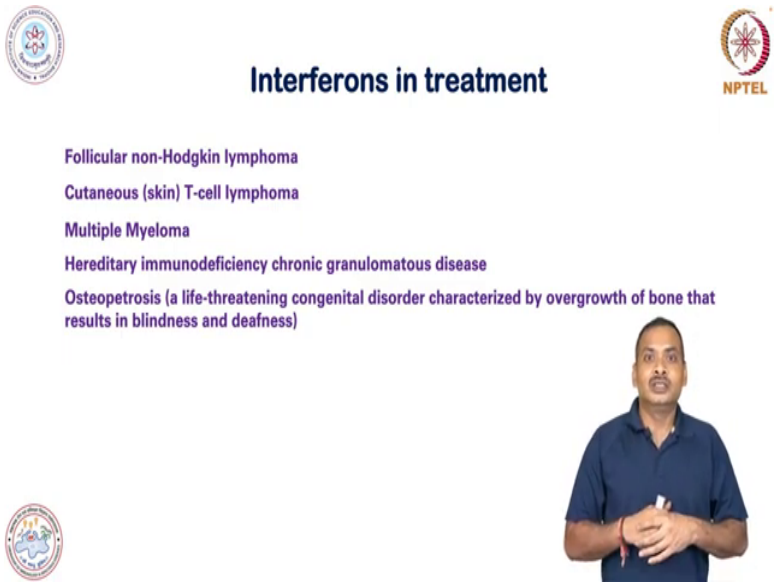

Now, I will talk about the interferon gamma. There are several cases or several diseases which is treated by interferon gamma. One is that follicular non-hodgkin lymphoma, this is again a cancer. There is a cutaneous or skin T cell lymphoma. This is also treated by interferon gamma. And multiple myeloma so, this is also treated by interferon gamma. And if you see these three diseases are cancer.

So, interferon gamma is a widely used in treatment of these cancers. It is also used in treatment of some congenital disease which I have discussed in a great length in previous session when I have discussed about immune cell, neutrophils, I have discussed in great length about chronic granulomatous disease CGD. So, the CGD is basically a deficiency of a function of NADPH oxidase due to some mutation.

So, this CGD is basically those individual they are not able to produce sufficient amount of reactive oxygen or nitrogen species. And there is a test if you remember, there is a NBT test. So, this test generally, they are not those individual cells cannot change, the colour of which is initially the colour of the reagent is colourless. And if you add this enzyme, NADPH oxidase then this will turn to the blue colour.

But in case of CGD patient this does not turn to the blue colour or they do not turn to that intense blue colour. So, this is a kind of diagnostic thing and I have also explained that there is a sum or other way to manage this disease. One is direct approach, direct approaches. Basically, these individuals the CGD patients are basically they develop recurrent infections, like some pseudomonas infection, staphylococcus infection, some fungal infections such as candida infection.

So, these individuals are not able to clear those infection because of a deficiency in the function of reactive oxygen or nitrogen mediated killing of these microbes. So, the way to treat is either do some transplantation bone marrow transplantation another way is you treat these individual with loads of antibiotic which is not recommended not so good or in worse scenario, if there is a there is a big wound and all those things.

Then there is a surgical approach you just clean ~~those abscess~~those abscesses and all those things. And there is a cytokine mediated therapy that is treatment with interferon gamma. So, interferon, gamma therapy significantly reduce the hospitalization of these ~~pediatric~~paediatric patients. So, this is quite effective. Maybe this interferon when we treat the individual with interferon then they somehow activate the macrophages and neutrophils

So, in that way they are able to clear the pathogen. Another which is a quite rare disease this is osteopetrosis. Please remember this is a osteopetrosis it is not osteoporosis, there is a big difference between osteopetrosis and osteoporosis. So, this disease osteopetrosis is also treated by the interferon gamma. This is also very unique disease or very dangerous kind of disease. It is a life-threatening congenital disorder and it is characterized by overgrowth of bone.

So, there is a overgrowth of bone and that result to the blindness, deafness and this, if you see little carefully if there is an overgrowth of bone, long bones or other bones then, what will happen you can think of? It will result to the narrowing of bone marrow cavity. The cavity will be reduced and when cavity will be reduced what will be the most affected? The blood of individual will be most affected.

There will be no sufficient number of embryonic stem cell which makes the red blood cells which makes lymphocytes or various kind of white blood cells. So, all those things will be

compromised so, when there will be a less RBC that will result to the anemia. And when there will be less white blood cell then individual will be prone to the various infection. So, this is all these situations are treated by interferon, gamma and clinician got a good amount of success.

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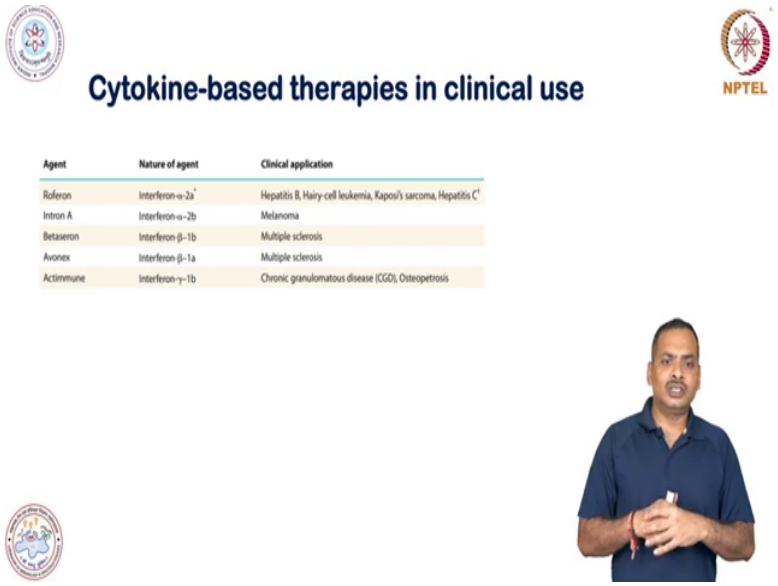

So, now, I will just summarize this cytokine or interferon based therapy. There is a Rhoferron. This is basically interferon alpha 2A, and this is used for the treatment of hepatitis B. Here is a leukemia, kaposi sarcoma and hepatitis C infection. Here just I want to give a again a note that type I interferon is basically consists of interferon, apha and beta and in human there are thirteen subtypes of interferon alpha and only one type of interferon, beta.

So, the another molecule name which is synthesized is interferon A this is basically interferon alpha 2B and it is used for the treatment of melanoma and there is a beta-seron. This is interferon beta 1A which is basically used for multiple sclerosis. EAvonex, this is interferon beta 1A which is used for the treatment of again multiple sclerosis. Active immune this is interferon gamma 1B this is used for the treatment of CGD, chronic granulomatous disease and osteopetrosis.

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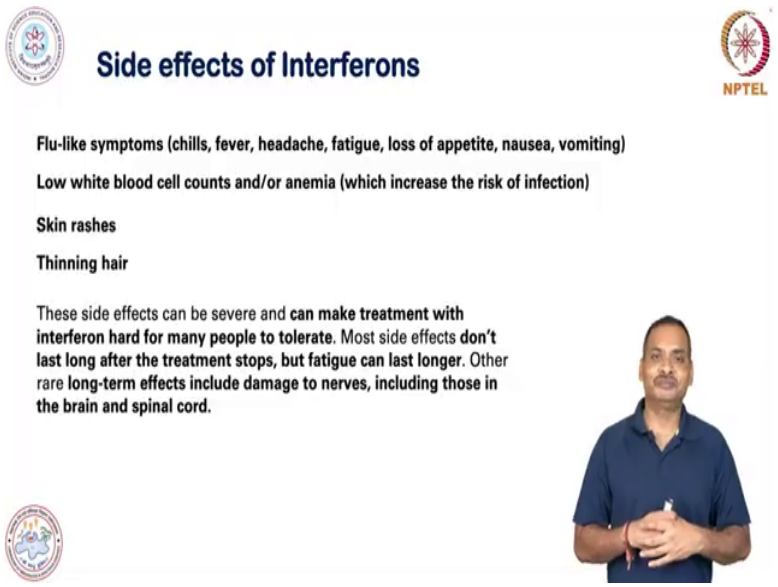

Now, these therapies are also associated with one or other side effects. So, let me elaborate about that. So, the side effects are when we treat with this individual with these interferons, they show some flu like symptom like chill, fever, headache, fatigue, loss of appetite, nausea and nausea and vomiting is basically same its both are written so, just there is there should be no confusion. So, all these are the short-term side effect.

But there could be some long-term side effects or there will be some more problem like significant reduction of white blood cells, anemia, which increases the risk of infection. So, when WBCs will reduce then there is a the individual is much more vulnerable or susceptible to the infection. There could be a skin rashes, thinning hair and there could be a some more side effects, as it is shown in this slide that can basically some sometime people may tolerate.

Many people tolerate this interferon therapy and most side effect do not last long after treatment stop but fatigue can last longer. And other rare long-term effect include damage of nerve, neurons including those in brain and spinal cord. So, there is a possibility that it will develop some multiple sclerosis like a side effect. I am not the right person to say with great confidence because I am not clinician and I am a fundamental immunologist.

So, maybe these not that much severe like multiple sclerosis but maybe some very low grade of this damage to the neuron and spinal cord. So, with this I will stop here and in next session I will talk about other inflammatory cytokine which is used in therapy and basically in several situations we damp these cytokines. So, I will talk all those things in another session or next session. Thank you.