Subtitles and transcriptions

Subtitles and transcriptions are available for selected materials for purpose of helping users understand the contents of the educational sessions.

Uncertain words have been indicated with ?? before and after the part. Parts that could not be understood at all have been indicated as [Audio Not Clear].

Every effort has been made to faithfully reproduce the audio of the sessions as recorded. However, no responsibility is accepted for mistakes or omissions. ESO does not endorse any opinions expressed in the presentations.

Transfusion medicine in pediatric oncology

Dr Witt: Yeah, thank you very much for the introduction, my name is Volker Witt, I'm from the St. Anna Children's Hospital in Vienna, and I have the honour to tell you something about paediatric haematology and oncology transfusion medicine. So, we are dealing with blood. Blood is a special liquid. It contains different cells, erythrocytes, that's the reason why it's red, white blood cells, and platelets, and this is swimming in plasma. The white blood cells are differentiated in different kinds of neutrophilic cells, and there are very important lymphocytes. So, we are now dealing with transfusion medicine in paediatric oncology. Let's go a little bit back to the history to understand what transfusion medicine is offering, and how it looks like, and how it thinks. We can divide some areas in the history of transfusion medicine; before we knew that there is circulation, after we knew that mankind has a blood circulation in the body, and then the knowledge which came when we saw that there is a serology, that there are blood groups. So, when we go really back to history, you can see here a young man who was decapitated because the Pope has an illness on his feet, and so the blood went in this bath to make the illness of the Pope better. The young man died and the Pope died, so, that was not very successful transfusion medicine. William Harvey was the man who gave us not only the idea of a circulation, he found out there is a circulation. And this led to the fact that circles can be conjuncted. And so, in animals and from animals to men, they tried to make transfusions. Mostly in the case, we think, in wartime, but that was not the only reason. It was very often women under delivery, when they bled, and they tried to bring the red blood cells via a lamb into the woman. And as you can see, after lamb blood transfusion, there was the second-step from man to woman transfusion. What was together the common sense, it was not very successful. And even to know that you can take the blood into bottles and you can avoid that it's coagulating by citrate, and you can warm it up, as you can see here, and then transfuse it, the most important thing was that Karl Landsteiner found this sudoku. He found out that if you take the plasma and the red blood cells, you can make this kind of sudoku, this is original sudoku he made with his assistant doctors. And he found out that some of them, the plasma was coagulating erythrocytes from one assistant, and some were not. And so, he found out at the end of the day there are blood groups A, B, and O, and AB. Now, coming to the transfusion. Transfusion, as we all know, should be compatible. So, patients with a blood group A need to have A or O. That is due to the fact that A has anti B, and O has anti A and anti B, but in compatible packed RBCs, the plasma is not anymore in. So, we can take O cells for A, B and AB and O. So, this is a universe donor. The same for plasma is the opposite round. Then, AB is the universal donor for plasmas. When we are thinking about transfusion need, we have to have in mind that we are living in an area where we try to transfuse as less as possible. This has nothing to do with paediatric oncology. It's very important to understand that the best transfusion is the transfusion you don't need. The blood management is very, very important. So, before you give erythrocytes, think about ferro, think about vitamin B12, and folic acid, to bring the production of erythrocytes in the patient up. This is something we cannot do in paediatric oncology patients, because we do everything that they don't produce erythrocytes. Then, we have to look when there

are bleeding risks, not only seeing them bleeding from the mucosa, there might be also patients having ulcers in the gastrointestinal tract. So, if we have the suspicion that the patient has that, we have to care about that to minimise the need for erythrocyte transfusion as much as possible. So, we have to care about the reason. And we have to think the oxygen transport capacity to the tissue, to see the maximum, the best haemoglobin and grammes per decilitre is roughly before 12 grams per decilitre. The oxygen transport capacity rises up until here, and then it comes down, and the blood viscosity goes up. What we do in general is, this is the normal range where we are living. What we in paediatric haematology and oncology do, we do this point, and take it on the other side, and you can see here is 8 grams per decilitre. Having 8 grams per decilitre, the oxygen transport to the tissue is roughly the same as you would have 16. It's better with 10 or 12, that's for sure, but 8 should be enough to bring it up. In many countries now, due to the lack of resources, and the lack of donors for donating back overseas, we go down to 7, this is even enough. When we have more complicated situation, and this comes much more often than we think because every 50 young adults in 20 years will be a survivor of a severe disease of childhood, and many of them may be transplanted or after chemotherapy. So, we have to care about what's about stem cell transplanted patients. There we have to think about the donor and the recipient, and whether there is an incompatibility, a major, a minor, or a directional. That means is the blood group the reason, or is it the alloantibody which is the reason, or is it in both directions? So, we have also the table I'll show you for the simple transfusion. The recipient is O, donor is A, so in that phase 1, the recipient blood group before until transplantation. After transplantation, we go to O, and you see that plasma is going the correct alloantibody, should not when the donor A, there should be no anti A in it. In the phase 3, when the blood group changed from O to A, then we can take the donor blood group, and this is here written for all combinations. We are facing another thing in the world, now we have patients from all over the world. As an example, just to understand what is the problem, I took out not an oncological disease, but a haematological disease we all know, and this is sickle cell disease. We have an historical migration from that area to Europe many, many, many years since the case, not only in the last two decades. So, these patients are coming, and they have differences in blood groups, and that's very important to know. Sickle cell disease, I think you know, they are sickling the cells when they have stress, and so they have crisis and then they have to be transfused. The same is true when a sickle cell disease patient has a malignant disease, or a heterozygous patient with sickle cell disease has a malignant disease, then, he has to be correctly transfused. To show you a case which is important to understand what I want to say to you is, we had a female patient, homozygous sickle cell disease, no family donor. And after a while, she was symptomatic, she has pain crisis, and we saw that she has a stenosis of the arterial cerebri media. And so, we start a red cell exchange to bring her back, and you can see here, the bad thing, the stenosis in the vessels. After this chronic red cell exchange, she has no stroke symptoms, and she was well, and the symptoms went back. You can see here is the result after times RCE, the stenosis went away. But we have to think how we managed that, because we had used red cell exchange, that means for every session, at least eight to nine contacts with different donors. So, it was a red cell exchange. And we performed with apheresis machines, they have programmes for this, so it's a huge amount of packed RBCs. And what is the danger? The danger is alloimmunization. Alloimmunization to our blood groups. And as you can see, that patients with thalassemia and other haemoglobin parties have high levels of alloimmunizations. But the same is true for patients coming from that area to us, and are treated for malignant disease. They have the same genetic blood group types as the sickle cell disease patient. So, what I want to say is, if we are matching what we do in thalassaemic patients, for example, we can reduce the more we match the frequency of alloimmunization. So, if you want it comes from 20 to 14, if we have 28 antigens, it went down to 7%. So, we thought about that, and what we did is we make a database for our blood donors and then, we match not only 20, we match 67 blood groups by genotyping. And nowadays, this is the state of 2012, now we have 55-000 donors, and could you reduce the observed immunisation rate to two? What I want to say with that is if we have patients from that area, they have different types of blood groups than we have here, what they have often is rare in our donor groups, so we have to really type our donors even for Duffy, for example Duffy O is in Africa, Duffy A and B is mainly in Europe. So, if it comes a Duffy O from Africa, he gets alloimmunized in Duffy A and B, and it's very

hard to find then compatible blood support for these patients. So, what we learned from that session is, when we have patients from different areas in the world or with different underlying diseases, we have to think a little bit more about blood groups and optimal matching to avoid one of the most risky things, alloimmunization. Because if you have alloimmunized against more than two or three antigens, it's very hard to find any comparable and packed obviously in Europe for these patients. So, we don't use only the bedside test, sometimes in the bedsides we see this, this is A, and this is B, so it's ectogenetic in A and not in B, so it's blood group A. And the question is, the patient, this is the packed obviously and this is for example the patient. And the question if you see that, I give you the hint, this is a patient with a hyperbilirubinemia. So, if we go back and we see yellow and blue gives us green, so if you make bedside test, be aware that there could be a change also in colour. And now I want to change issue. We talked about erythrocytes transfusion, the risk of alloimmunization in certain types of patients. And now, I want to go to an area which is very, very, there are not many data about that, but it's used in many countries and some hospitals for patients with aplasia, when they are neutropenic and they have bacterial infections, we need to have granulocytes to fight against these bacteria. And this is especially in patients with oncological diseases risk, for severe sepsis and for severe problems with this patient, especially with pseudomonas aeruginosa infections in the urinary tract or the anal tract when there are mutilating diseases, so the surgeon has to take away parts of the parts of the vulva or the penis when there is an infection. So, in our hospital and then some other hospitals we decided to give in aplasia granulocyte transfusions. And the question is, how it could be? And this is part of the transfusion medicine for sure. So, patients receive from donors which are ABO compatible, or if not, then the product is done erythrocyte depleted. They get the granulocytes. To have enough granulocytes and to make it reachable by arthritis which is done from the peripheral blood of the donor, we need to stimulate the donor with either GCSF or dexamethasone, to have enough granulocytes in the peripheral blood so we can make a product, then, either erythrocyte or plasma depleted or as a full concentrate after irradiation, it's given back to the patient then. And to give you an example, here is the layer where the granulocytes are, and this is very important to make the machines taking only these kinds of cells. But if that does not work. You see there are granulocytes and there are lymphocytes in this layer. So, therefore it's very important to have an irradiation if you use granulocytes. To show you what happens when you give granulocytes to a patient, here are data from a patient in our hospital. It's a very long time ago, but we documented it very well because it was a girl and the donor was the father. And she had an infection after autologous stem cell transplantation, and she got granulocyte concentrates from the father in a highly amount with 1.8 x 10 to the 6 granulocytes per kg body weight. And you can see here, the product we give to the recipient, and there is a high amount of granulocytes, but there are also MNCs, that means monocytes and lymphocytes in it. So, what happened to the patient? This is the curve of granulocytes we gave here, the granulocyte concentrate, and you can see that the patient rose, this is the blue line with the granulocytes, and he at least engrafted then. And you see here this is the peak from the granulocyte. It comes up and it rested some days and then it went down. And these are the granulocytes from the patient. So, when we gave the farthest granulocytes, she engrafted> So, the granulocytes gave the signal, and make the way free for an engraftment of the patient. This is what we see really often when we have aplastic patients that one or two granulocytes are leading to an engraftment of the patient after long time aplasia. Not every time but sometimes. The question is, how long are they in the patient? You see that these are hours, there is a phase of where it remains on the patient, and then because they are irradiated, there's an elimination up to zero, so it goes away. The MNC, the same curve, here are the transfused one, and here are the patient's MNCs, and you can see even there was an engraftment after giving that. And the elimination curve was similar due to the fact that they are irradiated, they went away after 84 hours. And after a long day we asked ourselves, are all cells now from the father, or are there still some cells from the father? No, they are no cells from the father, they are all females. So, it was 100% of the patient after 50 days, again the autologous state. You see that the elimination time was roughly 60 hours for granulocytes, 80 hours for MNCs and lymphocytes. And so, what we asked ourselves in this case was, the patient had an CMV infection and was CMV negative before, and the father was CMV positive. This was not an allotransplantation, this was granulocyte irradiated, and given to the patient with a

severe sepsis. And what we found is that the patient had afterwards, IgG positivity for CMV and this was not transfused by IgG. And we looked for the lymphocyte and we could see that CD free cells, and a case that were for a longer time in the patient by these transfusions. And we proposed that there might be a function of these cells even when they are transfused. Years after that we could show that really cells have still a function, are able to initialise an immune function. So, granulocyte transfusion, and these are data from 2009. So, older ones, we have now three times given survey about our activities, and as you can see, we give granulocytes infusion very often, GCSF from family donors and prednisone or Dexamethasone stimulated from unrelated donors, and mostly in allogenic transplantation but also in chemotherapy and it's especially in pseudomonas aerignosa it's very helpful to avoid mutilating surgery for these patients when they have these ulcers on the skin and there's a good risk to tear up for this patient. The survival was also well, there was no controlled trial we did, but there was very good survival of the patient transfused, but not for the patient with multiple organs failure. So, what we decided giving granulocytes needs to be given not in the severest patient but in patients who are in aplasia, neutropenia and when we think it's lasting more than five days, that there will be no engrafting per se, and before they're very ill, they should be given then the outcome is very nice. This is the same for different kinds of pathogens, showing that there is a good survival rate even for fungus, but not so much for viral infection when it's the leading course of the infection. Other centres had also these kinds of data, so they had the same as we have shown. At least there are no randomised control studies for granulocyte transfusion, but I think especially in paediatric transfusion medicine, it's a very, very nice thing because you have mostly adult donors with high levels of granulocytes they can donate for small children. So, we have even high numbers of granulocyte, possibly they can be transfused to the patient. Another thing is, blood is full of pathogens. And this is the last chapter I want to make with you, and we have an immersion risk of new pathogens we don't know. And the good thing was that SARS, MERS and COVID 19 were not transmitted by blood. It's not so true for MERS, but for SARS and COVID 19. But there are even new viruses like Usutu Virus, Bornavirus and even new viruses. So, we have to be aware that blood is not only healthy, it's also the reason for infection. When the donor has an infection and is not symptomatic. The next thing is, there could be not only viruses in, there could also bacteria in, especially in platelet concentrates because they are stored in room temperature. So, we want to avoid a vessel like this with blood cells and pathogens, this is what we want to avoid. The question is, every time what should we do to avoid it, and to tell you a story about Vienna, Vienna as an endemic region for West Nile virus, but it's only a few one, and there is a pathogen inactivation possibility, and it's very easy to perform because you take your product in the transfusion medicine, it's done now for platelet concentrates, and these platelet concentrates you give hematoxylin, you're making UVA illumination, and for some of you it sounds like extracorporeal photo freezes, it's much more very similar. It's integrating with all DNA and RNA, so there is no pathogen without DNA and RNA if we don't take the prions. So, every pathogen non-prion is docked, and there's a cross-link, and then the pathogen is dying before you can't trans use it. That is the reason because pathogen activation is so good for our patients because they are aplastic, they have not in normal immune system, and we need to help them not to get more infection than they get from their gut and other reasons. One point is also, if you use pathogen activation, because it destroys everything which contains DNA and RNA, you don't have to irradiate anymore your blood products. So, what we decided in our hospital, and in Switzerland, it's the whole country, that there is pathogen inactivated platelet concentrates only now for the patient. And what is seen in Switzerland and that is wonderful, notice that it works, these platelets are working like normal platelets, and on the other hand there are no bacterial infection sepsis from platelet concentrates, because one out of 2000 transfusion makes an sepsis, and this is also true for paediatric patients. And you can die from that infection, and it's very serious complication of transfusion and you can avoid it with pathogen inactivated concentrates. Now it's 18:46 and I think we have half an hour. I had the possibility to give you a short journey through some points of transfusion medicine in paediatric oncology, and I hope I could share many questions you have with you and thank you for your attention.

Prof Buser: Thank you very much, Volker, for this very interesting presentation as always. To the audience, if you have questions, please, leave them in the question-and-answer box, write them there so that I can ask them to Dr Witt. So far there are no questions in the Q&A section, so, I would like to start. Volker, you were mentioning in the beginning that you have to transfuse your red blood cells ABO compatible. Can you tell us more about the choice for platelet components, the ABO blood group you select for your paediatric patients?

Dr Witt: Yeah, that's a very, very interesting question because there is no conformity around the world. There are two possibilities to choose, strongly compatible, that means the same blood group, or compatible, that means you have to allow the minor incompatibility. So, this is what we try to do. So, someone with blood group A gets A or AB, but if there is no AB and no A, we give also some low anti A tighter B platelet concentrates. This is due to the fact that platelet concentrates are not any more plasma and platelets as many may think about it, it's platelets in plasma and in additive solutions. So, the amount of plasma is lower, so, even the amount of alloantibodies is lower. So, we, meanwhile, don't look really for the blood group anymore. We try to make it compatible, but if the resources are very, very low, then we look only for the alloantibody, it has alloantibody tighter that is low. That is our policy.

Prof Buser: Thank you very much. We come to the next question that I would have, and that concerns the irradiation of blood components in paediatric oncology. Can you advise us when and what, and can you also maybe touch upon briefly on the new drugs, immune modulations, or immunotherapies that are on the scene now? When do you irradiate blood components for your vulnerable patients?

Dr Witt: There was a development during the last 20 years, not in Austria, but before I came to Austria. There were policies like, if you have more than 1000 leukocytes or lymphocytes, you don't have to irradiate because it's not anymore needed because you have filtration step in the production of the packed obviously and so, it's filtrated blood, so, the amount of lymphocytes is very, very, very, very low, which is true, but we made it really very pragmatic. That means every patient who has the chance of immunosuppression gets irradiated products. One reason is to make it simple for the doctors and for the nurses. And the second is to avoid mistakes. So, it's nothing better than giving a non-irradiated product in a department where you have 20 patients, and 10 should have, because they have more than 1500 leukocytes, un-irradiated products, and the other half of the patients get irradiated to mix that up. And I think, and even the development a patient under therapy, he changed always his number of leukocytes. So, we skipped that. So, every patient with a malignant disease, every patient with an immunosuppressive therapy, every patient with a sort of immunodeficiency per se, gets irradiated products. And especially, of the new cell product therapies, this is the CAR T-cell for example, they get lymphodepletion before they get the CAR T-cells. So, we decided to give them irradiated products only, for red blood cells. And in platelet transfusion it's very simple because every product is luco-depleted because it's pathogen inactivated. And so, that's our policy to make it very simple. So, we have only haemoglobinopathies in the haematology departments who get non-irradiated blood products.

Prof Buser: Thank you very much. A question is, can you tell us more about transfusion thresholds in paediatric oncology patients, for red blood cells and for platelet transfusions, please?

Dr Witt: Yeah, this is something I thought to bring it in the lecture, but I think it's much better to discuss it because, I gave you the example of the oxygen delivery for the tissue and the content of haemoglobin, this nice curve. And what we know is that for longer time, less than 8 grams per decilitre is not good for the organs. So, there could be damage to the organs when it's lasting more than six months. The level of haemoglobin less than 8 grams per decilitre. Must not, but could. So, we have to have in mind that a threshold should be pragmatic, it should take our situation with the resources into account. So, if we have full storage and stocks, it might be easy to take as much as we like. But if you remember this curve, there was the blue curve underlying, which was the viscosity. And the viscosity is increasing. And many of our patients have cardiac circulatory compromise during treatments either due to infection or due to cardiomyopathies or whatever. And so, I think we should transfuse our patients low haemoglobin level and high oxygen delivery

to the tissue. And that means for red blood cells, a level between 7 and 8 is good as a trigger. The literature about that is not very, very, very strict. And I think that's due to the fact that the resources, stocks are not full. So, we have the problem that donors are getting older and older and we are missing younger donors to donate blood. In platelet transfusion, I think the thresholds are very good documented. So, normally, prophylactic should be under 10 g. per litre performed. And then due to the fact if there is a surgery or a surgery in central nervous system, then it's 50 to 80. And I never understood correctly this level of 20 to 30 for sepsis. Because in our IPICU, they are bleeding with 20 and they are bleeding with 30, so you have to increase the platelets a little bit more until they are not bleeding. And I think the most important thing is to use what we have. We have more and more the possibility also in non-emergency departments to use thromboelastography to look what is needed for the patient, is it platelets, is it plasma, is it factor concentrate, it's fibrinogen concentrates? So, that is the threshold we should develop in the next five years, not anymore in number but a good function. And the thromboelastography is a very good and helpful to go this way.

Prof Buser: Thank you very much. And then, the last question would be, what is your opinion or what do you advise for how to choose the blood component for your patients regarding CMV? Do you advise to transfuse CMV serology-tested negative blood components or is it not necessary anymore?

Dr Witt: To tell you the truth, I'm not really sure, because it depends on what kind of test, you're using for CMV PCR. At least, it seems to be that luco reduction is a very good factor and a very good method to avoid CMV infections in your patients. So, CMV serology might be not anymore needed. On the other hand, there is a minimal, minimal risk that even these products have still very low amount of CMV. The amount is such low that it might be that there is no amount of viruses that leads to an infection. But to avoid really every CMV negative donors are at least the best, but the practise tells me, it seems to be enough to make luco reduction, even I'm not sure personally and I'm a little bit afraid about not testing and just looking just for only luco reduction. But at the end of the day, it's enough.

Prof Buser: Thank you, there is one question now in the question section regarding, tumours, the threshold for both platelets and red cells should be different? And what do you do while on the radiotherapy? And I do not understand what SNC tumours mean, the abbreviation of SNC, I don't follow. Please doctor, always if you could specify that. But the question is does it change anything if you are on radiotherapy?

Dr Witt: At the moment that's very, very important. Under radiotherapy, this is something I didn't mention, sorry for that. There is a correlation between the haemoglobin content and the success of irradiation. I think the studies are not very, very good, so, the in-vitro data are much more convincing than the huge, they are not huge, that's the point, data from paediatric patients. But it makes sense if you have all free molecules to be done, then you need oxygen. Otherwise, when this is one of the mechanism, radiotherapy works, then you need to have enough oxygen in the tissue. So, it makes sense that, for example, in our hospital when they have irradiation, some of the colleagues' transfusion is up to nine, but it's not fixed in our hospital, but it's recommended by some protocols to have higher amounts of haemoglobin. I think it would be so important to test this really in a prospective randomised controlled study. But I'm not convinced that this issue is so important for the community of the paediatric oncologists that it will be performed.

Prof Buser: Okay, thank you very much. Unfortunately, it's now seven o'clock and we have to close this session. The question by Dr Alvis, whether it's also another threshold for central nervous system tumours, Dr Witt will respond later on via another channel. So, with this, I would like to propose to close this session and thank all the participants for the participation and we'll would like to show this next slide for the next e-ESO session on the 26th of October. I wish you a wonderful evening altogether. Thank you very much Volker for this wonderful talk and for the lecture.