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Myelodysplastic syndrome / JMML in childhood

Prof Hasle: Thank you very much for the introduction and thank you to the participants for joining this session on myelodysplastic syndrome and JMML in childhood. Dr Tania Masmas will have an eye on the chat and question facilities, and you're welcome to ask questions during the session. And Tania Masmas will intervene and ask them to me when appropriate. So, during this presentation, I will first discuss MDS that is divided into refractory cytopenia of childhood, and MDS with excess of blast. And then, I will discuss juvenile myelomonocytic leukemia, JMML, with a focus on the different genetic subtypes. We have learned over the last years more and more about the overlap between inherited bone marrow failures and genetic syndromes, and MDS in general. And it will be discussed within the part on MDS, and JMML as an integrated part. Much of the data I present today are based on the cooperation within the European Working Group on MDS. The Working Group was founded back in the 90's. Our current protocol from 2006 has included about 1,200 patients with MDS. Most of them refractory cytopenia of childhood, and almost 400 patients with JMML, and 200 patients with therapy-related MDS. The study data center is placed in Freiburg, in Germany, and there are national coordinators and morphology board within the group. So, I'm thankful for the group and all the participants, and contributors for the data that they have provided, making advances in MDS and JMML possible. To diagnose MDS may be a challenge. They often present with a hypocellular bone marrow, and the presenting features may mimic an infection, in which you may also see dysplasia. So, first, you should be sure that this is not just any infection, and there should be some duration of the cytopenia. And often, we need repeated bone marrow examination. Apart from infection, the main differential diagnoses is severe aplastic anemia, and inherited bone marrow failure. The differentiation is difficult, but first of all, you need to be aware of the possibility of MDS, and you need expertise. So, central reference pathology is essential. MDS is a clonal disorder, a myeloid malignancy, and the characteristics are the excess growth advances of the clonal cells, the disturbed differentiation, and the increase in apoptosis. It means that the malignant cells have retained some differentiation, but it's not complete. And then, there's this increased likelihood of apoptosis so, many of the cells die within the bone marrow. So, in contrast to acute leukemia where the bone marrow is often full of immature blast, then, there are only few blasts in the bone marrow of MDS, but most of the cells belong to the malignant clone. There is this overlap between the refractory cytopenia in childhood often being hypocellular, severe aplastic anemia, and inherited bone marrow failure syndromes. And treatment is different since in aplastic anemia, immunosuppressive therapy is often successful, and it may be in some cases of hypocellular refractory cytopenia as well. The predisposing conditions involve many different genetic pathways. One of them being the defect in DNA repair, as seen in Fanconi anemia. Some involve telomere biology with involvement of TERT or TERC genes, like in this character, this is congenital. Some involve ribosomes like in Diamond-Blackfan and Shwachman-Diamond syndrome. And some involve transcription factors like the GATA2. This table shows some of the predisposing conditions for MDS and AML in children. Fanconi anemia is associated with more than 50% lifetime likelihood to develop MDS or AML. For

dyskeratosis congenita the lifetime risk is only 5%, but again, for Shwachman-Diamond and for severe congenital neutropenia, it's about one third of the patients who will develop MDS or AML. In Blackfan-Diamond syndrome, it is unusual to have a malignant transformation. Precise estimates are not available, but it is definitely low, below 5%. There are some cases of familial thrombocytopenia, like the germline RUNX1 mutation that is associated with a significant risk of MDS and AML, although, precise estimates are not available. All the conditions that I mentioned here belong either to conditions where you find pancytopenia, or some with monocytopenia. Then, there are some where there may not be any cytopenia associated before MDS develop. We know that individuals with Trisomy 8 mosaicism have an increased risk of MDS and AML. And those with GATA2 may have normal blood counts for several years, until MDS develop, and the same for SAMD9 and SAMD9L. And then, there may be many more conditions that we don't know of yet. Some of the conditions mentioned here in the bottom, they were only discovered recently. To diagnose MDS in the patients with inherited bone marrow failure may be difficult because in inherited bone marrow failure, you have cytopenia and often myelodysplasia. So, for diagnosis of MDS, you need a chain in a condition with monocytopenia to pancytopenia, or a bone marrow that is changing from being hypocellular to hypercellular, or the demonstration of clonal abnormalities. Although, there are some like the inversion 7, that may be seen in Shwachman-Diamond syndrome, and is not a marker of transformation to MDS. And then, of course, if there is an increase in blast to more than 5%, it would qualify for a diagnosis of MDS. So, there are some minimal diagnostic criteria for diagnosing MDS. You should have at least two of these four criteria unexplained, prolonged cytopenia, bilineage, dysplasia, cytogenetic abnormalities on increase in blast. And then, the recurrent AML cytogenetic aberrations should be excluded, as well as Fanconi anemia, especially, in those presenting with hypoplastic refractory cytopenia. There is a new WHO classification of pediatric malignancies to be published later this year. It will build on the previous WHO's classification mainly based on adults. And it will, unchanged, include refractory cytopenia of childhood, and MDS with excess of blast. Although, advanced MDS and RAEBT, will not be part of the classification anymore. And it will also be new that myeloid neoplasms with germline predisposition would be discussed in separate chapters, and the most common being those with GATA2 deficiency, accounting for about 15% of pediatric MDS. And those with SAMD9, or SAMD9L, accounting for about 8% of pediatric MDS. And these two syndromes account for about half of those with monosomy 7. It is important to remember then when we have identified new genes, where pathogenic variants may be involved, then, not all variants are pathogenic. And it's important to check in databases, or at the EWOG-MDS conferences, whether an identified variant is believed to be pathogenic. The most common type of refractory cytopenia in childhood is the refractory cytopenia. And they present with leucopenia, or low normal white-cell count. Leukocytosis is not seen in MDS. There is neutropenia and often anemia, but more commonly, you see an increased MCV. And then, there's a moderately increased fetal hemoglobin, and from cytopenia. For the diagnosis, a bone marrow Trephine is essential because that will show the disturbed architecture, and recognize some dysplastic features typical of refractory cytopenia of childhood. In the picture here, at the right, you see a typical case of aplastic anemia, where the bone marrow is completely empty. All the spaces are filled with fat cells and virtually no hematocrit tissue. Whereas, in refractory cytopenia, most of the bone marrow is as hypoplastic as in SAA, but there are some clusters with hematopoiesis and if you look more closely at these, you may appreciate dysplastic features. So, there's this pattern of hematopoiesis that is typical of refractory cytopenia. The fact that it is patchy means that there is a caveat when you do the bone marrow biopsy. Because, as seen in this cartoon, you may have a sample from here with virtually no hematopoiesis because it's out here and up here, and out here. And this is not representative of what's going on in the bone marrow. So, you need a long, representative and better even to take two biopsies to have a bigger chance to recognize any disturbed architecture in the bone marrow. Treatment of MDS depends very much of the subtype. If it is refractory cytopenia with hypoplasia, immune suppressive therapy may be used, but for all others it will be stem cell transplantation. There may be some reduced intensity conditioning for refractory cytopenia, but for advanced MDS, myeloablative conditioning is needed. The immunosuppressive therapy is like in aplastic anemia with ATG cyclosporine and G-CSF if the neutrophil is very low. If you treat with ICT, you need to be

patient because you can see here after six months only 6% are in CR, but more than half have a positive response. And if you watch for longer follow-up, then complete remission is here found in one-third of the patients. Here you can see the failure-free survival is a little bit more than 50% after three years. So, some will not respond, some may relapse, but the salvage-rate is high by transplanting after refractory, or relapse of the disease. So, this is the recommended treatment approach from EWOG-MDS, those with sub-genetic abnormalities should go directly to transplant. If there are no transfusion dependency you watch and wait; in case of transfusion dependency, you look for a family donor. In case you find it, you go directly to transplant. If not, you may try immunosuppressive therapy. And in case of no response or relapse, you go to match unrelated transplant donor. I mentioned GATA2 deficiency that is common in pediatric MDS, accounting for 7% of all MDS, but in advanced MDS, it is much more common. And in monosomy 7 it's even more common. So, in those patients with monosomy 7, one third of them had a GATA2 mutation. And they are older, the medium age was 12 years compared to 4 years in those without GATA2 mutation. And you can see here, the proportion of GATA2 mutation increases with age. So, for the teenagers, 72% had a GATA2 mutation, among those with monosomy 7. Trisomy 8 may also be found in patients with GATA2 mutations. Here you can see 16% of those with MDS and trisomy 8 had a GATA2 mutation. When we look at the outcome for patients with GATA2 mutation, then it is similar to those without GATA2 mutation. Here you see the outcome for refractory cytopenia, and for advanced MDS comparing GATA2 with non GATA2, and you can see the overlap in survival figures. And even within monosomy 7, you see a similar survival outcome with and without GATA2. So, in summary, GATA2 is a common predisposing factor and it's found in 7% of all primary MDS, but apparently not in secondary MDS. And most of them have monosomy 7 and they have a high-risk for progression to advanced MDS, and they should not be treated with immunosuppressive therapy. It's important to tissue-type and plan for transplant, and the best before they progress. I just want to mention the most recently discovered significant constitutional predisposition, the SAMD9, or the SAMD9L, two genetic variants that both results in MDS, especially in younger children, and often with monosomy 7. These patients look like a standard MDS patient, but some of them undergo spontaneous regression where the individual can repair the genetic defect. And this is what happened when they lost the monosomy 7 where SAMD9L is located and then, they can make a uniparental disomy later with healthy chromosome 7 and then cytopenia disappear. But for many, the cytopenia and MDS persist and transplant is needed. So, this busy slide is for studying later on, but just to emphasizing that both GATA2 deficiency and SAMD9L syndromes have a lot of associated abnormalities. So, this was my last slide about MDS. Are there any questions about MDS, so far?

Dr Masmas: There's no questions in the panel, but I have a question.

Prof Hasle: Yes, please.

Dr Masmas: Could you talk just shortly on the issue of somatic versus germline mutation in MDS?

Prof Hasle: Yes.

Dr Masmas: Would have a significance and also, do you test all your cytopenic patients for predisposing genetic findings?

Prof Hasle: I think today it is important to test for GATA2 because it is so common, especially in teenagers, and those with monosomy 7. And these patients will need stem cell transplantation, and if there are siblings, they may have the same mutation and they should not be used as donor. So, it is important to exclude. The good news is that if you do a transplant with a related, but unaffected donor, or with an unrelated donor, the outcome is as good as if you had no predisposition.

Dr Masmas: Yeah. What about the other predisposition genes?

Prof Hasle: Well, with SAMD9 and SAMD9L, and monosomy 7 in a young child, like one or two years of age, you may watch and wait for some time to see if the abnormality will regress spontaneously as has been seen in several cases. But if the disease progresses, you will need a bone marrow transplant. So, you should prepare for that as well.

Dr Masmas: Yes, thank you.

Prof Hasle: Okay, I will continue with the JMML at the series where we have learned a lot over the last year, since almost 100 years ago since the first description, and back in the 60s and 70s, it was called first Philadelphia negative CML, and then CMML. But JMML term was used in the late 90s, and has been used since. We have learned about genetic mutations that I will tell about and most lately about different methylation patterns in these patients. It is a disease of the young, mostly boys, and you can see here that most of the patients present with below two years of age. And they often present with hepato and splenomegaly and with leukocytosis with monocytosis. There may also be skin infiltration in a number of these patients. The diagnostic criteria have been suggested by EWOG-MDS where splenomegaly is mandatory, but it should be recognized that some patients will develop splenomegaly only a few months after presentations. They have monocytosis and you should exclude acute leukemia by a blast below 20%. Then, the diagnosis is confirmed by the somatic mutations in PTPN11, NRAS, or KRAS, or with a clinical diagnosis NF1, or with the detection of a CBL mutation. For those few without genetic abnormalities, you need to look for other genetic abnormalities increased in fetal hemoglobin, or myeloid precursors in the peripheral blood. We have known for a long time that RAS mutation is seen in about 25%, and in about 10% you can make a clinical diagnosis of NF1. Both RAS and NF1 is involved in the RAS signaling pathway. We learned some 20 years ago that Noonan syndrome is often explained by a mutation in the PTPN11 coding for SHP2 involved in the same RAS signaling pathway. With Noonan syndrome, that is well-described by these features, you may see a JMML like disease during infancy that may regress spontaneously. And as I mentioned, it has been documented that about half of the patients have a germline PTPN11 mutation explaining the Noonan syndrome. And after this discovery of PTPN11 and the JMML like disease in Noonan, it was tested whether somatic PTPN mutation were present in JMML and it was indeed in one third of the patients. So, when you see an infant with Noonan syndrome, there may be this transient myeloproliferative disorder. We're sampling very much JMML, but it is polyclonal, but the patients may be very ill, and they may benefit from some cytoreduction. But in most cases, it is transient, and it's very seldom that such genetic abnormalities are acquired, but they need to be followed carefully. Another syndrome that was described now about 10 years ago is the CBL mutation. They may present with JMML at around one year of age. They do not present with monosomy 7. They have some characteristic facial features. And what is characteristic about the JMML is that although they have all the clinical characteristics, it may remain stable and improve without therapy over time. For other cases, you may need some therapy. Some patients present with very high white cell count. It may be over 100 with infiltrations in the lungs and pulmonary problems. There may be a very large spleen and significant thrombocytopenia, and there may be a benefit from 6 mercaptopurine and cytarabine, that was shown long ago. More recently, we have some data that Azacytidine may also be successful in reducing the disease burden in these patients, and bridging them to transplant. Splenectomy, despite of a very large spleen does not seem to be of any benefit. So, for most of the patients, transplant is indicated. Here you can see the overall survival of 64% and in event-free survival of 52, and most failures are due to relapse. So, about one third of the patients will relapse. The conditioning regimen has been BU/FLU/MEL based, or TBI, but several studies have shown that with TBI, the outcome is inferior. So, BU/FLU/MEL is the recommended conditioning in Europe. The relapse rate may depend on the genetic subtype being especially high with somatic PTPN11, or with NF1. But there are some patients who have been top list as long-term survivors without transplantation, about 10%. And these will present the patients with CBL mutation, or NRAS. And all these observations lead to this recommendation about therapy, where you look at the different genetic aberrations and whether it's germline or somatic. In case of germline PTPN11, Noonan syndrome, it is uncommon, but they can be observed. Whereas, those with somatic mutation, they

need a transplant, all of them. The same with those with KRAS. For NRAS, there may be about half of them who may do well without a transplant. And those who have the largest chance of remaining well, are those with low fetal hemoglobin and high platelet count. All those with NF1 should be transplanted; whereas, those with CBL mutations should be observed. Those with mutation negative, so, without any of these, we don't know too much about them, but they do not regress, and they would need transplantation. We have learned over the last years that the methylation pattern may be significant predictor of outcome. Here you can see how at high and intermediate, and low methylation groups, and they are not equally distributed among the genotype. So, there are some overlap shown here that PTPN11, for instance, and NF1 is most common here among the high methylation group with the high-risk of relapse. So, in summary, JMML patients is a heterogeneous group and some will just benefit from observation, but some will have emergency situations with respiratory problems because of the high white cell count, and large liver. And will need immediate tumor reduction, and most of the patients will need transplantation, but we need to describe the genetic abnormalities before we can make a decision on transplantation. NF1 can be recognized by the clinical features and you don't need to do the genetic testing. Azacytidine seems promising in getting some control over the disease, and may even improve the outcome after transplantation, but it cannot cure the disease in itself. And relapse is still common after transplantation. It may be reduced by restrictive graft versus host prophylaxis. So, that was my last slide. So, I thank you all for your attention and I would welcome any questions you may have.

Dr Masmas: Yeah, I would also encourage the participants to ask questions in the chat. And by the way, Henrik, can I ask a question?

Prof Hasle: Yes, please.

Dr Masmas: Currently, which JMML patient would you treat with Azacytidine before transplantation?

Prof Hasle: Well, those patients where we know that observation is an option, so, those with Noonan's syndrome, or with CBL, and those with NRAS without any significant cytopenia, they may just be observed. But for all other where there is an indication for transplant, I would start therapy with Azacytidine because it seems to improve the general condition. It may improve cytopenia, and may reduce splenomegaly. So, it may prepare the patient for more smooth transplantation. And I would treat, but with three courses and then, transplant if everything is ready for that, or give a few more courses, if necessary, waiting for a donor.

Dr Masmas: Yeah, yeah, that was my last question. Yeah, good. So, I don't have any other questions in the chat, or in the Q & A. Can I ask a question related to the Myelodysplastic session in the start, about the follow-up of patients with RUNX1 mutation, germline mutations with a little bit of thrombocytopenia and maybe a mild, or moderate infection tendency? How would you follow-up these patients, children?

Prof Hasle: It's a difficult question because we don't know exactly what is the risk of developing MDS. We know that some have lived with moderate thrombocytopenia a long life without any other problems than easy bruisings. But we also know that a significant, although, we don't know exactly how many of these family members may develop MDS. Probably, the early diagnosis is not so important for these patients. So, it may not be indicated to have very frequent CPC's, or bone marrows in these patients. The most important is to have a baseline so, you know the patient, you describe the peripheral bloods, and at least to do a one bone marrow, and then plan follow-up if there are any changes. And important to inform the patient, the families that if they observe anything differently to report, and we repeat the blood counts to see if anything has changed. And then, maybe, there is an indication for a repeated bone marrow examination.

Dr Masmas: Yeah. Would you test siblings through children where you have found RUNX1, or when would you test them?

Prof Hasle: Well, it should be discussed with the parents. If there is no easy bruisings in the siblings, then it's a... There's a good chance that do not have the variant, but maybe difficult to decide on the clinical presentation alone. And if there's a lot of worry in the family and they would like to know if their child is at risk, it may be good to test so they know what the situation is. And in case there is a variant in a healthy sibling, they know that they should be more alert in case of symptoms. And come to you and to have a full workup. And they can be more relaxed if the mutation is not found. So, I think it's an individual decision with families, but for a mutation like RUNX1, I think there's no mandatory pressure on the families to have testing done in children.

Dr Masmas: I just want to see if there's any questions, no. So, my last question then is in, also, like in the MDS area about the telomere diseases. How would you follow-up these patients if they just have a slightly affected peripheral hematology?

Prof Hasle: Yes, these patients are a challenge because they may have other organ involvement. Transplant may be more risky because of pulmonary problems, or other organ problems. And the ideal way of transplanting them has not been established. So, it should very much be individualized depending on the problems they have. I would say that for these patients, there may be a more imperative need to follow on a regular basis their blood counts, and maybe also liver status and pulmonary function. To avoid that they deteriorate slowly, and that would make a transplant much more dangerous for them.

Dr Masmas: Yeah. Thank you, Henrik. I might... I don't have any further questions.

Prof Hasle: Okay, so maybe it's time to conclude the session.

Dr Masmas: Close the session, yeah, I think it'll...

Prof Hasle: So, thank you, everyone. And thank you Tania for...

Dr Masmas: Yeah, thank you.

Prof Hasle: Leading the discussion.

Dr Masmas: Thank you, Professor and thank you to all of you out there.