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Hodgkin's disease in childhood and adolescence (held in collaboration with SIOPe)

Dr Beishuizen: I will discuss tonight about Hodgkin disease in childhood and adolescence and in the next slide you see the contents. So we will discuss the incidence of classical Hodgkin's lymphoma and non-classical Hodgkin's lymphoma, discuss the etiology, symptoms, diagnostic procedures, staging, treatments, and then chemotherapy and radiotherapy, the prognosis, and also toxicity early and late, and when there is time I would like to tell you something about the new agents we're already using in Hodgkin's disease in childhood and adolescence. First, we start about pediatric malignancy in the Netherlands. As you can see in this pie, there are a lot of malignancies also treated in the Netherlands. This is a pie from the Dutch Childhood Oncology Group from 2013 to 2018. You can see indicated by the arrow that your Hodgkin's lymphoma are 5% of cases, of malignancies, in the Netherlands. And all the non-Hodgkin lymphomas, so Burkitt's and non-Burkitt's, are 6%. So nearly half of all lymphoma patients are Hodgkin's lymphoma patients. And as you all know, Sir Thomas Hodgkin has given his name to this disease and he was the first one to describe the disease. And as you can see, the incidence nowadays is more or less five to seven per one million per year. In the younger patients, the male female ratio is five to one and the other patients is one to one. As you can see in the figure in the middle, there is a bimodal age distribution of Hodgkin's lymphoma with a rise in Hodgkin's lymphoma between 15 and 30 and also a rise after 70. In the right side of the slide you can see some predisposing factors, so it's a relation in immunodeficiency, or inherited, or acquired. And also you can see there's a relation with Epstein-Barr virus and infection, but also Hodgkin's disease is known as a second malignancy after chemo and radiotherapy, and I'll come back to that later of course. Important to know is that the WHO classification in 2016 recognizes two main groups, so that's the Nodular lymphocyte predominant Hodgkin lymphoma, also typed non-classical Hodgkin lymphoma. And you have the classical Hodgkin lymphoma, which is the largest group and has four types: nodular sclerosis and mixed cellularity, more or less the highest groups; and the lymphocyte predominant and lymphocyte depleted Hodgkin lymphoma. On the next slide, you can see the summary of the nodular lymphocyte predominant Hodgkin lymphoma. On the right side, a typical histology preparation and with the large in yellow circle, the popcorn cells, which you can see. It's a rare disease and a predominantly localized disease in stage I and II, with a male female ratio of three to one, and the age distribution is between 15 and 35 years. The immunohistochemistry is positive for CD20 and that's a real difference with the classical Hodgkin lymphoma. CD45, EMA, and negative for CD15 and CD30 which are markers we see more in Hodgkin's lymphoma. Molecularly, you can see BCL6 expression and the treatment is also different because it's very low malignant disease, so, after total resection, you can wait and see. If it's not possible to resect the lymph nodes, then we give them three courses of cyclophosphamide, vinblastine, and prednisolone. In the case of relapse, and that's occurring in 30% of cases, classical Hodgkin lymphoma treatment is recommended, including rituximab, because of the CD20 positive staining.

Dr Attarbaschi: Sorry, Auke for interrupting you.

Dr Beishuizen: No, it's okay.

Dr Attarbaschi: Do you see any role for a second surgery? So, if you perform a subtotal resection, let's say off a cervical lymph node area, and the diagnosis is nodular lymphocyte predominant Hodgkin lymphoma, do you see a role for a second surgery if it is not mutilating the patient?

Dr Beishuizen: Yeah, that's a very good remark on the issue. I think there is a role for a second operation, if that's possible, because sometimes you remove a lymph node and then you have the diagnosis, then always we go back to the patient and discuss with the radiologists and the surgeons, if it's possible to remove maybe another lymph node, or maybe two lymph nodes, because when you have removed all the lymph nodes, you don't have to give them treatment. And that's sometimes what we do. So I think there's a real possibility, yes.

Dr Attarbaschi: Thanks for your answer.

Dr Beishuizen: Okay, so next part. I will discuss the clinical presentation, diagnostics you need, and also staging. In clinical presentation, what you nearly always see are enlarged lymph nodes, and especially in the neck region. And the aspect is a sort of bunch of grapes. It's a typical phenomenon you can see when you look at the patient and also when you feel the lymph nodes in the neck regions. The other most important part of the region where you can find Hodgkin's disease is the mediastinal mass and especially in the anterior mediastinal mass. Often you find patients who are dyspnoeic, have pleural effusions, sometimes vena cava superior syndrome, with enlarged veins in the neck regions, and also some orthopnoea. Very important are B-symptoms, and I've written them down. It means that you ask for drenching night sweats and drenching is very important, so sometimes people have night sweats when the weather is warm, but they have to change their clothes or bedclothes, and then you say, "Okay, it's drenching night sweats." Sometimes, they have unexplained fever or weight loss and that means more than 10% in six months. And on the right side, you see a typical picture with what's also very important, the change of the trachea to the right side in this case, so that means that the tumor is pushing the trachea to the right side. And that means that it will be difficult to give that patient anaesthesia. In differential diagnosis, especially when you have in the neck region only lymph nodes, possibilities are, which we show on the right side, on the left side sorry, typical lymph nodes, which can also be something else. And you see on this side the slides which we saw the typical lymphocytes, with a lot of cytoplasm, and you can see that it's an EBV infection, which is, especially in adolescents but also in younger children, a typical infection you can see with enlarged lymph nodes and also possibly with enlarged spleen or liver and a sore throat. Another option is, in case you see on the left side also, a girl with enlarged neck with also some bleeding and some staining of bluish and it's a typical case of atypical mycobacteriosis. On the right-side upper part, you can see enlarged lymph node, but also redness and sore and also a warm aspect and that's a nice picture of bacterial lymphadenopathy. And on the lower right side, you can see a mastoiditis typical case, with enlarged lymph nodes low in the neck region, and that's bacterial mastoiditis. So these you can find also as a differential diagnosis because, as you know, a large part of the enlarged lymph nodes in children are not caused by malignancy but due to an infection. For diagnostics, you need, of course, a biopsy and that's what I'm showing you in the left lower part. There are four options: fine needle aspiration, fine needle biopsy, incision biopsy, and excision biopsy. And of course, we all prefer the excision biopsy but, and that's why I put it between brackets. The fine needle aspiration in children is not the way to diagnose lymph nodes of a lymphoma or a malignancy. So you always need to do at least a fine needle biopsy, but I prefer an incision or an excision biopsy. You can do some laboratory diagnostics, so blood count and smear, too, in the differential diagnosis. ESR is very important, uric acid, LDH, and nowadays you also have tumor markers, especially known in Hodgkin, and that is TARC and I'll come back to that later. On the right side you see a typical morphology in an H-E staining with a Reed-Sternberg cell with two large nuclei and also some typical nucleoli. And on the bottom side, you also see a very nice picture of a Reed-Sternberg cell. When you

have done the biopsy, it's typical that, and especially when you look at non-Hodgkin lymphoma, you see a lot of the same cells, especially in Burkitt lymphoma, but in Hodgkin it's different. And if you look at in the middle, you see a picture made, and you see it's published by Steidl in Journal of Clinical Oncology. And you see that you have the typical Hodgkin or Reed-Sternberg cell, but a lot of other cells in the microenvironment. And on the left, you'll see that the HRS cells, or Hodgkin Reed-Sternberg cells, and compose 0.1 to 10% of cells in the lymphoma tissue. Those are malignant. It has a B-cell origin but no B-cell characteristics, such as CD20, but we have CD30 and CD15. And that is the difference between nodular pyogranuloma, or a non-classical Hodgkin lymphoma, and a classical Hodgkin lymphoma. And when you look at the microenvironment on the right side, you'll see that it consists of activated T-cells, tumor-associated macrophages, eosinophils, fibroblasts, a lot of other cells, which are important for sustaining survival and proliferation of those HRS cells. And those HRS cells produce cyto and chemokines to maintain the inflammatory environment. And then TARC you can see coming back and it's also mentioned in this picture. So the Hodgkin HRS cells are in the middle and you see a lot of other cells influenced by the Hodgkin cells and influence the Hodgkin cell themselves. And sometimes those chemokines or lymphokines can give you serum biomarker, which results from the active crosstalk between the HRS cells in the microenvironment, and it could be a marker for presence of lymphoma, and I will come back to that later in this talk. When we look at staging, the radiology is very important. Of course, you can do a lot with ultrasound, but sometimes you have to measure the lymph nodes or the masses and then ultrasound is not enough. On the other hand, sometimes you can see with the ultrasound lesions in the spleen or liver, which are difficult to see by MRI or FDG-Pet-scan. On the middle you see a typical x-ray of the thorax with a large mediastinum and you see it's in the frontal part and the anterior part of the mediastinum.

Dr Attarbaschi: Auke, sorry for interrupting again. There's a question in the chat. I think it fits very relatively to this slide, asking what is the definition of bulky disease in our current European protocol?

Dr Beishuizen: Yeah, it's defined, good question, It's defined by more than 200 millilitres volume, then we say it's bulky disease. But it means not to define all the lymph nodes apart from each other, you need to have a sort of combination with all lymph nodes together, and then you can say that it's bulky disease, about more than 200 millilitres of volume.

Dr Attarbaschi: Thank you.

Dr Beishuizen: Okay, so in the middle lower part, you see a typical CT scan picture and you can see that the trachea on the left side, the head bronchus of the left side, is smaller than on the left side, so the tumor is giving troubles with breathing in this case with this patient. In this part you see an MRI and you see here a picture of a patient with an enlarged bulb on his head and it appeared to be Hodgkin's diseases, coming from the bone and also pushing the brain a little bit. The patient had no complaints, by the way, unless the tumor on his head. And on the right side you see a picture of that same patient which has more, a lot of lesions on the FDG-Pet-scan in his bone also. So on the left side, the ultrasound, we need to do that for the spleen or liver, the x-ray thorax, you want to know if the patient is at risk. We prefer to do a CT-scan and an MRI scan or an FDG-Pet-scan as staging. When you have done the staging in Hodgkin's disease, we look at Ann Arbor staging, and always with the Cotswolds-modified Ann Arbor staging of the Hodgkin lymphoma. And we recognize four stages. The first one, stage I is involvement of a single lymph node region or lymphoid structure, for instance the spleen. Stage II is involvement of two or more lymph node region and then on the same side of the diaphragm. Stage III has shown involvement of lymph node regions on both sides of the diaphragm. And stage IV says that there are involvement of extra-nodal sites, so in the bone, in the liver, or in the lung, for instance. Also are important the B-symptoms I discussed earlier and also the bulky disease is mentioned in our hands in European protocols, we say more than 200 millilitres. The Hodgkin's disease risk stratifications, the parameters used for this risk grouping are tumor mass as reflected by stage of disease, tumor mass as reflected by bulky disease. You can also have extra lymphatic disease that can be stage IV lung, liver, or bone or an E-lesion, and that means that there is growth of the tumor into the region outside

the lymph node and then you call that an E-lesion. So that is different from a stage IV. Also important are the ESR and B-symptoms. There are two state of the art treatment strategies in Hodgkin's disease, and that's the EuroNet paediatric Hodgkin lymphoma combined-modality therapy or the COG, the Children's Oncology Group, combined-modality therapy. Okay, I'm not sure what this, but I'll go back. Then I would like, I'm not sure if there are some questions.

Dr Attarbaschi: At the moment there's no question in the chat, thank you.

Dr Beishuizen: Okay, then I will discuss the treatment development is done in the Hodgkin disease and then I will focus on the chemotherapy, the radiotherapy.

Dr Attarbaschi: Sorry, Auke, there came in one question concerning what you have mentioned before. Someone is asking whether we still consider performing bone marrow aspiration and biopsy in staging of Hodgkin's disease?

Dr Beishuizen: Thank you very much for this important question. Of course, normally, we do it because we want to know if there is Hodgkin's disease in the bone marrow, but due to the fact that we have the FDG-Pet-scan nowadays, it has shown several times and published in the literature that you can see by the FDG-Pet-scan that there is bone marrow or bone involvement, so at the moment we are not doing regularly the bone marrow aspirations or bone marrow biopsies, trephine biopsies, anymore.

Dr Attarbaschi: I can add that historically we did not perform bone marrow punctures until stage IIa, but in all stages of path and, as Auke said, since we have MRI and PET, we use the combination of these two modalities to assess the bone marrow.

Dr Beishuizen: Okay, then I would like to discuss with you the therapy development in Hodgkin's disease and, as I can show on the next slide, at least in Europe, the therapy development in Germany was very important. They have shown with several treatment protocols, which is shown on the left side, with the DAL Hodgkin's disease 78 started until the GPOH Hodgkin's disease 2002. These are studies done in Germany, and probably also in Austria, and those protocols are very important because they had combined modality therapy, and that means chemotherapy and radiotherapy, but were also risk-adapted therapies. Also they tried to reduce the invasive diagnostic and also adaptation of chemotherapy or adaptation of radiotherapy, that means radio treatment field size adaptation, dose reduction, and also avoidance of radiotherapy. And as is shown, on the bottom side of the table, you can see that EuroNet Paediatric Hodgkin lymphoma group has done the C1 protocol and nowadays the C2, which is also nearly finished because it will be closed at the end of this year. And here you see, as shown on the left side, the DAL Hodgkin disease 82 protocol. This was done in three treatment groups and that was based on disease extension and this is shown here, so treatment group one, treatment group two, and treatment group three. And this is also done nowadays when we look at the current Hodgkin protocols we use. Each group received two times OPPA courses and radiotherapy and they showed an EFS of 99% in treatment group one, 96% in treatment group two, and 90% in treatment group three. So that was, at that time, the golden standard and nowadays these results are still great. And you see when you look at the overall survival of the different treatment protocols, they were very, very good, although already early in the 80 and late 70 years. The radiotherapy development in Germany and Europe, also shown on this slide, in 1978 done was total nodal radiation. Then, the mantle field radiation treatment was done and, since the 1990s, was involved field radiotherapy, and nowadays we do reduce involved field radiotherapy, or involved site or involved node radiotherapy. So very much, and very important results, and differences in treatments were done. The other thing which is important to mention, coming before my next slide, is that also the early response assessment by FDG-PET appeared to be very important. And, as is shown by different groups and different publications, when you look at the FDG-PET scanning after two chemotherapy cycles, you see that the PET negative patients doing very well and the PET positive patients, after two courses, do very bad. So also a very important finding which is used nowadays in the current protocols, and that is shown on the next slide, here you see EuroNet-PHL-C1 protocol, which is based on the

GPOH Hodgkin's disease 2002 protocol, which already looked for OEPA courses and COPDac courses with radiotherapy as a pilot for the C1, and you can see that what is done in that protocol that treatment group one uses two OEPA courses and after an evaluation by FDG-PET scanning, the patient is given radiotherapy or no radiotherapy. And in that protocol also, a randomization was done and it was randomized between COPDac with dacarbazine and COPP with procarbazine, as is shown here. And as we all know, procarbazine is a very important drug for the treatment in Hodgkin's disease, but it's also a very big disadvantage. And that means that the biggest disadvantage is in fact that it gives fertility problems. So in C1, it is discussed quickly randomized in treatment group two and three, between COPDac and COPP, as it is shown, I think it's on the... There's an explanation how you can see evaluation is important, so this is a patient treated by these two OEPA courses and at diagnosis you see there is a lot of tumor in the lung and in the mediastinum, also in the neck region, but also in the bone region, as you can see here. And you see that after two OEPA courses, which has vincristine, etoposides, prednisolone, and anthracycline, you can see that the patient, that FDG-Pet-scan, is negative after two courses and this patient does not need radiation after the treatment, after chemotherapy treatment of six courses, because this was stage IV disease.

Dr Attarbaschi: Auke, there's another question at chat concerning this. Someone's asking if CT alone could give us the same information as PET-CT?

Dr Beishuizen: No, I don't think so because with the CT, it's more especially also in bony disease, it's sometimes not easy to see that there is bony disease, and yeah, I think it's not enough, and also for E-lesions or lesions in the spleen are more difficult to see with the CT-scan alone and then you need also to have the FDG-PET-scan. So to use this as a evaluation after two OEPA courses and say if radiotherapy can be omitted or not, I think you need an FDG-Pet scanning and the CT is not enough.

Dr Attarbaschi: Thank you, I can also add from experience in Austria, from the GPOH 2002 trial, we just performed CT and MRI at the end of the therapy to decide whether the patients should receive irradiation or not, and our results showed that CT or MRI for evaluation treatment response is not that good, as it is with PET-CT or PET-MRI.

Dr Beishuizen: Okay, thank you, Andishe. So the results of EuroNet's PHL-C1 protocol are shown on this slide and on the left side you see the overall survival, which is doing very well, and also the event free survival is 88%. And then you see also on the middle side, the differences between the COPP arm and the COPDac arm are more or less the same, so there is no significant difference between those two arms, suggesting that the COPDac arm can be used as the standard arm of the new protocol. And also, the EFS by radiotherapy is no different between the two arms. So this protocol shows, then, that you can do a protocol in Europe with a large group of patients and with as good results as done earlier. How is the therapy development worldwide? And that is compared with the COG and the St. Jude, and you all see that the overall survival of those patients in Hodgkin's disease in that five to ten years is very good, it means more than 90% of survival. Are there questions?

Dr Attarbaschi: At the moment, there are no questions.

Dr Beishuizen: Okay, then I will go on. I would like to discuss with you the therapy development in Hodgkin's disease because also the late effects which are found and then I will emphasize the fertility, heart failure, and second malignancies are important to take into account when you develop new treatment protocols. And when we look at fertility problems, I already discussed with you the procarbazine, which is known for its fertility problems and I can show you here is just an example of a few patients which we analysed our self, and the patients received MOPP courses, with the procarbazine next to oncovin and prednisolone, and mustard gas, mustard combination, and what you see is that when they received procarbazine, shown by the plus, you see that only four of 17 patients had no problems with fertility, but more than half had no sperm at all. And when we compared it with the patients who did not receive procarbazine, all patients had normozoospermia. As you all know, the cyclophosphamide can also give problems with fertility, and

especially radiotherapy on gonads are also very important. And when we look at heart failure, you see on the left side a publication where it's mentioned that the cumulative incidence 40 years after Hodgkin lymphoma disease, about heart failure is more than 40% and a very important part is the mediastinal radiotherapy, but also anthracyclines doing, and that you can see on the right side of the picture, give a very big rise of the cumulative incidence of congestive heart failure. On the third slide about this topic, you see the second malignancies, and on the left side you see what kind of second malignancies you can find after Hodgkin's disease treatment, and the chance for second malignancies in Hodgkin's disease is more than 5% after 20 years after treatment and 25% 30 years after treatment. And you can see that the largest part of second malignancies is breast cancer. And when we look at the patients who have a second malignancy, then you see the original diagnosis is, in 1/3 of patients, Hodgkin's disease, and the most important risk factor appeared to be radiotherapy. So you can imagine that when we develop treatment that radiotherapy is something you want to omit in the treatment of Hodgkin's disease, although it's a very important part of the treatment in Hodgkin's disease. And that is what we did with our C2 protocol. So we had the COPDac arm as our standard treatment and we want to reduce the amount of radiotherapy, so what we did is that, in patients with treatment level two, or treatment group two, and treatment level three, when we add two courses next to the OEPA courses of evaluation. So when patients are evaluated and should receive radiotherapy, because there was still disease after FDG-PET scanning, after two courses. In case the patients were randomized for the DECOPDac arm, and that means that doxorubicin and etoposides were added to the COPDac arm, to the COPDac course. Then you can do a second evaluation, and in case the second evaluation shows no disease anymore, then those patients, who were treated in this arm, don't need radiation anymore. And so with this protocol, we tried to diminish the radiation treatment for the patients with Hodgkin disease. For survival, as we all know, Hodgkin lymphoma do very well and nearly 100% survival and after, as you can see here, one, three, and five years survival, the survival is 95%, so what do we need more than what we are already doing? But, of course, what I've shown you earlier, there are a lot of second late effects, of heart failure, fertility problems, and also second malignancies, so it would be great to have new drugs with which we can causing less problems in our patients for late effects. Are there questions at this time before I go on?

Dr Attarbaschi: There's one question in chat, but this will fit much better to your next part of the talk on new therapies and just to inform you, you have ten minutes left for the session.

Dr Beishuizen: Okay, so that would be enough, I think. What I would like to do in the last part of the talk is to guide you through some new strategies in Hodgkin's disease, and not only on the treatment but also on diagnostics. And on the next slide, you see the TARC, I already mentioned earlier, and the TARC stands for thymus and activation-regulated chemokine and TARC is known also as a diagnostic marker. It's produced by Hodgkin cells and some, in the body also some other cells, sometimes T-cells or thymocytes. But there are done some studies by a Dutch guy, Plattel, and he shows that when you look for the TARC levels in Hodgkin's disease, they all are very high in most part of the patients. And you can see after one cycle of treatment that nearly all have lower levels of TARC, or nearly are gone. And especially at mid-treatment or after treatment, most patients have normal values of TARC. But sometimes you see that one patient still has TARC in his serum or in his plasma, and especially those patients in early stage have a relapse. And the same was shown in advance stage disease, where you show with two patients, also relapsed, and they still had TARC at a high level after or during treatment. So it seems to me that serial TARC levels may be a predictive or prognostic biomarker for ongoing Hodgkin's disease during and after treatment in adults. And we did ourselves a study in which we compared control patients, so no patients with Hodgkin's disease, and it showed that the level of TARC is low. And when you see in 47 patients who shows Hodgkin patients that TARC was high, it means that you can use TARC as a diagnostic marker in pediatric Hodgkin's disease. I must say that it's not, it's not the only important thing to mention because sometimes you can find TARC in other diseases, especially when they have skin diseases, sometimes dermatitis then also you can see elevation of TARC. So you must be aware that it's not only Hodgkin's disease where you can find TARC enlargement in serum. So when we look at the

new strategies in Hodgkin treatment, and I will show you and discuss with you two possibilities. And I will discuss also those two possibilities in studies done in children. On the left side, you see the tumor cell and on the right side, the T-cell, and there is a possibility to use an antibody drug conjugate and we'll come to that later. Or what is also possible and is done in studies, is to use a PD-1 or PD-L1 inhibitor. And first I will discuss the ADC, which is used and also studied in children, and that's an antibody drug conjugate which is called Brentuximab Vedotin and this is an anti CD30 monoclonal antibody linked to MMAE, monomethyl auristatin E, and that's a Vincristine analogue, and it is shown in the upper part of the slide on the right side. So this is the monoclonal antibody and it's linked to, with a linker to the monomethyl auristatin E. And what is done is that the drug recognizes CD30, it will go in the cell and then in the lysosome the linker will be cut and then the drug will get free in the cell and will give the problems for the tumor cell, which will then die. And we did a study in pediatrics, not only in Hodgkin lymphoma but also in anaplastic large-cell lymphoma, and it was a phase 1/2 study published in the Lancet Haematology by Locatelli and some other European and American pediatric oncologists. And what was done was that we had 36 patients, relapsed refractory patients, 19 Hodgkin patients and 17 ALCL patients, which we could show that the recommended phase two dose was 1.8 milligram per kilogram every three weeks for the Brentuximab Vedotin and it shows an overall response rate of 47% in mono treatment in refractory or relapsed Hodgkin's patients, so very, very good results, with toxicity that is doable in those patient groups, as you can see. Then the next strategy I would like to discuss is the immune checkpoint inhibitors such as Nivolumab or Pembrolizumab and, as you all know, there is a very important part of the killing of cells is done by the T-cells, and due to the PD-L1 PD-1 blockage, the T-cell does not kill the tumor cell anymore. And by inhibiting those PD-L1 PD-1 block, the T-cell has the possibility to recognize the tumor cell again. And that is shown in the next slide, and that is the Checkmate 744 phase I/II trial, which shows that we did a response-adapted therapy with Nivolumab and Brentuximab Vedotin in children and adolescents, and this is published now in several abstracts and different meetings, last few years. And it shows a CMR of 89% and an overall response rate of 98%, so in relapse refractor Hodgkin patients, below 18 years, we have very good results with the combination of PD-L1 blocker, inhibitor, nivolumab PD-1 inhibitor and brentuximab Vedotin.

Dr Attarbaschi: Okay, sorry, could you explain what you mean with CMR?

Dr Beishuizen: Yeah, it's Complete Metabolic Response, I'm sorry, yes, it's a Complete Metabolic Response checked by FDG-PET and it was shown that was in 89% complete metabolic response after four courses of Brentuximab Vedotin with Nivolumab. So very, very good results. Okay, so in summary Hodgkin's disease in children and adolescence, so it has a very variable duration of pre-diagnostic symptoms, a high degree of B-symptoms, but very less degree of tumor lysis syndrome. The most common sites of involvement are the lymph nodes above the diaphragm, and then the neck region, and also the mediastinal mass. The most important drugs known are shown on the left side, so the Vincristine, Prednisolone, Alkylating drugs such as cyclophosphamide, ifosfamide, pro and dacarbazine, anthracyclines are important, etoposides, and also methchloramine and bleomycin, but the last two are not that many used anymore. The most important prognostic factors are stage of disease, Ann Arbor, B-symptoms, bulky disease, above 200 millilitres, which was mentioned earlier, extra-lymphatic disease, E-lesions or bone marrow, liver, or bone disease, ESR above 30 millimetres an hour is an important factor, and also TARC can be used as diagnostic marker. Resistant and relapsed disease I did not mention, but has also a very good prognosis and was also shown by the slide before this one with the combination of Nivolumab and Brentuximab Vedotin. So Nowadays, Brentuximab Vedotin and nivolumab are very important drugs which can be used also in Hodgkin's disease and gives less toxic late effects probably, although we don't know that, especially for Nivolumab and Brentuximab Vedotin. Okay, last slide, questions?

Dr Attarbaschi: Thank you, Auke, for this very nice overview and clear messages concerning Hodgkin's disease in children and adolescents. When I look into the chat there is one question there for a long time,

and the colleague is asking whether you are aware of any elementary factors, such as food colorants or flavours, in the etiology of lymphoma or Hodgkin's lymphoma?

Dr Beishuizen: Yeah, that's difficult to answer, I guess. I'm not aware of it. I have no experience, really, about patients eating special foods and getting Hodgkin or something like that. So no, I cannot answer that question properly, I'm sorry.

Dr Attarbaschi: Me either, I'm also not aware of any studies showing this type of association. Yes, when I look into the chat, there is no further question but one very nice comment from Peru. Someone is saying, Auke, that you gave a very clear and helpful presentation. I think this is what we would like to achieve by these webinars and we are very thankful to you that you took the time to give this session, although I know that you are very, very busy with patients' care and scientific work. So thank you very much.

Dr Beishuizen: Thank you, Andishe. For the nice words also from Peru. It was a pleasure for me to do and I hope to see and, when it's possible, to give more talks about this important disease.

Dr Attarbaschi: Thank you. I wish all a very good evening or morning, wherever you are living. So goodbye from my side.

Dr Beishuizen: Okay, thank you very much.

Dr Attarbaschi: Ciao.

Dr Beishuizen: Ciao.