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International Guidelines on Follow-Up and Survivorship

Hello, my name is Andreas Engert. I am Professor of Internal Medicine, Hematology, and Oncology in Cologne, Germany, and I am chairman of the German Hodgkin Study Group. Today, I am in hot Milano, Italy, and I am here at the EHA conference, a large international conference for hematology, and we have seen many interesting aspects on Hodgkin's and other diseases here at this conference. I want to talk to you about the treatment of patients with Hodgkin lymphoma and diagnostics and followup.

So, for the diagnostics, it is important that you clearly define the stage of these patients. You know that the Ann Arbor classification is used, stages 1 to 4 and then A or B if these patients have B symptoms and depending on this classification, patients then are allocated to early favorable that is stages 1 and 2 without any risk factors or the unfavorable stages 1 and 2 with risk factors, and these risk factors are rather similar between groups and countries and advanced stages, so patients in stage 3 and 4 and selected 2B is usually with a large mediastinal mass or external disease. PET can be used in the staging procedure. CT scan still is the mainstay of treatment. What is important certainly is that you counsel these patients for fertility issues because many of these patients are very young, and they will all receive chemotherapy so it is important for you as a doctor, certainly also extremely important for the patient to know about this problem, to know about the risk of infertility certainly depending on the number and choice of chemotherapy but that is an important issue. Once you have done that, you allocated your patient, and you have got the appropriate diagnosis from your pathologist and eventually even the reference pathology and experienced pathologist to confirm Hodgkin's, then you allocate patients to their appropriate risk group.

In the early favorable, we recommend 2 cycles of ABVD followed by 20 Gy of involved-field radiation that is based on our HD10 trial that was published in the New England Journal in 2010. Others do just chemotherapy mainly in the U.S. and Canada and some other countries that is response-adapted treatment, so usually 4 cycles of ABVD are being given or eventually 6 depending on the response. Early unfavorable patients also receive ABVD that is usually 4 cycles in these patients, 6 cycles have been shown to not improve outcome here, 4 cycles followed by radiation therapy. It is 30-Gy involved field in these patients and 20 Gy like in early favorable, 30 Gy in early unfavorable. We ran a trial termed HD14 published in the JCO a few years ago where we increased toxicity and

efficacy by introducing BEACOPP escalated, so 2 cycles of BEACOPP escalated were followed by 2 cycles of ABVD and then followed by 30-Gy involved-field radiation. This led to a significantly better tumor control; however after 7 years even the overall survival was not different, so it is standard in our hands by definition, but worldwide standard I still think should be 4 cycles of ABVD followed by 30-Gy involved field or eventually more chemotherapy if you want to do this. However, there is one caveat. Patients having significant tumor left in early stages might not respond that well overall. This was shown for instance by a shared analysis with the Canadian group, Ralph Meyer's data also published in the New England Journal. Some of these patients have not received any radiotherapy at all, and we looked in this shared analysis at particular risk factors, and it turned out that patients who had residual disease measured by CT scan had a much higher risk of relapse if they just continued on chemotherapy.

Advanced-stage patients, there is also a discussion between centers in Europe and the US about the use of BEACOPP escalated, so we are using 6 cycles of BEACOPP escalated in these patients followed by radiation in patients who have residual tumor of 2.5 cm or more, and our PET positive shows a PET-guided radiation and we cut down the number of patients receiving radiation with this approach to 11%. Overall, 6 cycles of BEACOPP escalated followed by radiation in some of these patients results in an enormous improvement in tumor control that is more than 90% at 5 years and overall survival of more than 95% also at 5 years. However, ABVD is still being used in many countries. It is a little bit less effective. It is also less toxic compared to BEACOPP escalated, so future trials will incorporate a new drug, antibody drug conjugate, brentuximab vedotin, to either increase efficacy of ABVD or an ABVD variant. It is AVD without bleomycin or reduced toxicity with BEACOPP escalated. These are ongoing trials, and we will have to see what the results will be in the future. If patients relapse then they would receive 2 cycles of chemotherapy such as DHAP or ICE and go to transplant. If they do not respond to the initial chemotherapy, they should be treated with a non-cross-resistant regimen such IGEF gemcitabine-containing regimen and then go to transplant because transplant is the best chance for these patients for a long-term cure. If patients relapse after high dose, then brentuximab vedotin is registered for treatment of these patients. Up to 16 cycles can be given in 3-week intervals, but you should see if these patients respond because if they do not, then it is not necessary to continue for 16 cycles, so typically PET-CT scan is done after 4 cycles to look for response at that stage and patients are then followed up, so generally speaking followup of these patients is less well defined than the treatment part, so we usually do a CT scan after 3 months after the end of treatment and the only patients who have residual disease, measurable disease have a second CT scan after 1 year. Those who are in remission do not, and we follow these patients more clinically in laboratory. What you should certainly take care of or consider is the risk of secondary malignancies in these patients that is leukemia as

major risk within 5 years, non-Hodgkin lymphoma in 5 to 10 years, and solid tumors thereafter. Certainly, also, patients might consult you for issue such fatigue or infertility, and that is an important question you should also address for these patients.