Managing Hodgkin Lymphoma

**Discrimination of Unfavorable Risk Group Has Significant Impact on Early Stage HL Treatment Outcome**

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Hello everybody, it is a pleasure to be here in Lugano. Reporting from this meeting, my name is Peter Borchmann. I am the scientific secretary of the German Hodgkin Lymphoma Study Group, and I will present data on the discrimination of an early unfavorable risk group that has a significant impact on treatment outcome in early stage Hodgkin lymphoma. There are three different or even more different definitions of what early stage Hodgkin lymphoma actually means. We have our own classification system on the left side of the slide. The German Hodgkin's Lymphoma Study Group classification system discriminates between large mediastinal mass, ESR above 50 or more than 30 if B symptoms are present, more than three nodal areas involved, or more than one or equal to the one extranodal lesion. So if one of these risk factors is present, then patients would not be early favorable risk group patients any longer. They would be assigned to the early unfavorable risk group. These risk factors differ little bit for example with EORTC. Here, we also have a large mediastinal mass as a risk factor, but it is a bit larger with a ratio of 0.35, more than third in our system. The ESR is the same but they use more equal to four nodal areas involved, and they have H as disease independent factor within that classification system. So, patients, for example being older than 50 years, they are assigned to the early unfavorable risk group independent of their tumor status. Again, the NCCN classification system is very different. They have the bulky disease definition which does not exist. As a risk factor with more than 10 cm, they have ESR independent of the symptoms, and then they have the B symptoms separately. So, this is slightly different from the staging systems used in Europe. And the question is whether or not these different classification systems discriminate in between early favorable patients and early unfavorable patients, or if these patients exist at all nowadays since we have very active first-line treatment regimens.

The treatment today is still guided by these classification systems. These systems vary as I have shown before between the study groups, and if we really need this staging or classification risk factor systems, we do not know. So we wanted to compare the different systems from us, from the EORTC, and from the NCCN. We wanted to have a closer look which of the risk factors within these classification systems are significant for

the outcome of our patients in the modern treatment era. You have to know that these systems all come from a time when early stage Hodgkin lymphoma was treated with radiotherapy only and results with combined modality treatment today are much better. So it might well be that these systems are not valid any longer. We have a chance to have a closer look at this very important questions within our HT10 and 11 trials in which HT10 was for early favorable patients, HT11 for early unfavorable. But in both studies, we had a common treatment arm with four cycles of ABVD, followed either by 30 or 20 Gray involved field radiotherapy. So we have all the different patients, if early favorable or unfavorable, treated the same way with combined modality treatment. There were more than 1,000 patients in these trials and 173 were qualified for this analysis, 483 in the HT10 trial and 624 in the HT11 trial. It is a large number of patients in which we could investigate this clinically important question. The age was as expected. The median age was rather low. We are dealing with young patients, 33 years, slight majority being men, and obviously half of the patients having received 30 Gray and the other half 20 Gray involved-field radiotherapy. The median observation time was long with 18 months for progression-free survival and more than 19 months for overall survival. Within this observation period, 8% of all patients, which is 90 patients, had failure with the primary endpoint progression-free survival, so they relapsed from the disease, and 3% of these patients actually died. The question is, is this discrimination between early favorable and unfavorable patients reasonable? Is it still valid in the modern treatment era of combined modality treatment with respect to PFS and overall survival?

Looking at the German Hodgkin Lymphoma Study Group definition, you see, although all these patients had been treated the same way, in yellow, the upper curve, there is some progression-free survival at 5 years of 95.8% as compared to 86.4% with the early unfavorable group, so there is a difference of more than 9% in progression-free survival. Even in the era of combined modality treatment, this risk factor staging system still discriminates in between favorable and a more unfavorable group, and the difference is meaningful with more than 9%. The same is true actually for the other staging system. You see the EORTC definition and you see the difference might be slightly less pronounced of 6.7%, but still there is this difference; you can see it easily. And the same is true for the NCCN definition where the difference is 8.6%. So overall, all the three different systems discriminate in between favorable and unfavorable risk patients. What is the sensitivity and specificity of these different systems? In other words, how many patients with an event had been classified as unfavorable? If you looking at the sensitivity, you will see the sensitivity is high in all systems, 84%, 79%, and 83%. It has a high sensitivity, so most patients who had a failure and had relapsed were classified as unfavorable. On the other hand, the specificity is really poor, which means, in other words and this is true for all systems, that many many patients had been classified as

unfavorable, although they had no event, so it is about 50% of all patients. But to be on the safer side, you have to take those into account. We then did univariate analysis of the risk factors because obviously we were using different risk factors and it might well be that some of them are useful and others are not so. We took the chance to investigate these questions. We added most factors from the three-staging systems and other candidate risk factors such as stage 2 or 1, the presence of bulky disease of more than 5 cm in diameter, male gender, and other factors from the International Prognostic Score. We found in the end that models of high sensitivity, so not missing relapsing patients include risk factors indicating either large tumor burden which, I think, is self-explaining, so a large mediastinal mass or more than three or four lymph node areas involved. Those are highly indicative of having higher risk for relapse. On the other hand, high tumor activity. The erythrocyte sedimentation rate also indicates this higher risk of relapsing for early stage patients. Within our definition in a multi-varied logistic regression model, only large mediastinal mass and the three or more nodal areas remain significant. These factors indicate a large tumor burden, and they have slightly different observations, but actually it is not that important. It is important that these risk factors indicating a large tumor mass, they are predictive of a somewhat poorer prognosis. Within the EORTC definition, it is the same. You can see here, its large mediastinal mass with the high odds ratio and also more or equal to four nodal areas and exactly the same result. It is very important on this slide though that H, a factor derived from the patient and not from the tumor, actually does not play a role at all, which is very important because otherwise you would say a patient with stage 1A without risk factors but 55 years of age would have to be treated as unfavorable. So this patient would need more chemotherapy and more radiotherapy although he is older and would not really better tolerate more treatment, so you can forget about this risk factor in early stage disease. It is an important finding therefore.

Actually, the same is true for the American NCCN system where you also can see the number of nodal areas involved and their presence or absence of bulky disease. So parameters for tumor burden are the most important prognostic factors. Are these factors also important for overall survival? Because this may be an even more important endpoint in early stage disease than progression-free survival. And we had a closer look to this question an in univariate analysis there was similar risk factors profiled involving tumor size, ESR involved areas, and extranodal involvement, and then of course because it is overall survival, age. We have many patients in this trial being like 75 years of age, and we do not discriminate in between dying of Hodgkin lymphoma or of any other reasons. Having a closer look at the different staging systems and the overall survival you see the difference is not as large obviously as with the PFS, but it still exists and the hazard ratio does not include the one, so it is highly

significant also. This is true for the German Classification System. It is true for the EORTC definition, and it is also true for the NCCN definition.

The better PFS difference translates into a novel survival difference in the score. To summarize, this is the first and large analysis evaluating the impact of the risk groups, and risk factors and outcomes in the modern combined modality treatment area without the treatment bias because all patients had been treated exactly the same way, and all three different staging definitions selected a higher risk group out of the early stage patients with a significant impact both on PFS and overall survival. They all have a high sensitivity but a poorer specificity. Models of high sensitivity include risk factors like large tumor burden, large mediastinal mass, or bulky disease, or numbers of lymph nodes involved, or a high tumor activity as indicated by the ESR.

To conclude, improvement of these different systems might only be achieved by detection of more and highly specific risk factors. We do not have these risk factors yet. We are trying to adapt treatment and to reduce the burden of treatment by introducing response adapted treatment, for example, by PET, but this is completely different from the baseline staging definition where you do not have a response of treatment. You do not know what is going on after you have initiated treatment. You have to decide whether you go for early unfavorable or favorable. In this situation, there are so far no other risk factors that would be better than those indicating tumor burden, and those are important. They are not only important for the progression-free survival but also for the overall survival, and so we conclude that it is still reasonable still today to discriminate in between unfavorable and favorable risk groups in early stage Hodgkin lymphoma in the modern combined modality treatment era. I would like to thank to Helen Görgen, our statistician, who did all this work on this data and Beate Klimm who is a co-author for this poster. Thank you very much for your attention.