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Trends in Survival in HL: The Effect of Better Management

It is a real pleasure to be here today. My name is Magnus Björkholm. I am working at Karolinska Hospital in Stockholm, and the topic today is trends in survival in Hodgkin lymphoma - the effect of better management. I will have to give some kind of background, what has happened with treatment during the last 50 years.

So, it was early known that the anatomical extent of the disease was related to outcome, so staging principles have been introduced, the Ann Arbor staging classification in 1971, and that was an improvement because we were also including computerized tomography, and today, we have PET-CTs to help us out, but initially it was related to or based upon lymphangiographs and exploratory laparotomy with splenectomy. Radiotherapy, the first patient was treated back in 1902, but from late 1960s, we had curative treatment for localized Hodgkin lymphoma patients, and during the 1960s, MOPP was introduced, that is for dry chemotherapy. Before that, we had only arsenic and radiotherapy for advanced Hodgkin lymphoma. The chemo combination ABVD came during the mid 1970s, and the German Hodgkin Lymphoma Study Group introduced BEACOPP chemotherapy during recent years. We also had the introduction of risk stratification, so patients with early Hodgkin lymphoma or early stage Hodgkin lymphoma were divided into favorable and unfavorable disorders or diseases, and we also had the International Prognostic Scores – seven variable scores which could discriminate between patients with a dismal outcome and patients with a good outcome from a survival point of view. Also during the last three decades, combined modality treatment has shown to be superior to radiotherapy alone in patients with more localized Hodgkin lymphoma, and of course during all this time supportive care has improved everything from blood transfusions to antibiotics, etc.

So if you look at the side effects of the treatment given during the 1960s, 1970s, and maybe also 1980s, we could see in grade series that 70% of patients were cured, but within the first 10 years of the diagnosis, the large majority of deaths appearing was related to the Hodgkin lymphoma itself, but afterwards the excess death rate is more or less totally related to second malignancies, to cardiac complications, infectious disorders, etc. So, if you look at large series of patients, you could see that after 10 years very few cases of Hodgkin lymphoma tumor death appears. So, the risk for solid

cancer is two to five times increased, and cancers are appearing on most irradiated sites. Acute leukemia following alkylators gives 50- to 70-fold increased risk for leukemia, acute myeloid leukemia being the dominating second cancer. Also, cardiac and pulmonary disorders continue to increase after 10 to 15 years from diagnosis. Importantly, patients who develop second cancers following Hodgkin lymphoma also have a less good prognosis compared to patients with the primary cancer without having Hodgkin lymphoma before. This is true for breast cancer, it is true for gastrointestinal cancer, it is also true for non-small cell lung cancer and acute myeloid leukemias and myelodysplastic syndromes. So, with this background, I would like you to know about the outcome, and I need to present some methods to be able to measure this on a population-based way. So, in Sweden, the Stockholm Hodgkin Lymphoma Group was founded back in 1973 and the Swedish Hodgkin Lymphoma Group in the mid-1980s, and we published national recommendations in the mid-1980s. We also had the Swedish Cancer Registry which was founded or started in 1958, and by 1973, the coverage was very good for diagnosis like Hodgkin lymphoma. So, clinical studies due to various selection processes mainly excluding older patients do not give a true picture of progress. It has certain shortcomings, and this is a good basis than for population-based studies. So, before novel and less toxic therapy, the largest potential to improve survival and quality of life in patients with Hodgkin lymphoma was to reduce treatment-related excess morbidity/mortality. The objectives of this study was to evaluate progress over the years and also try to look into the future and also find potential interventions.

Then, I have to explain the term relative survival. Relative survival ratio is the observed survival in a patient group divided by expected survival of a comparable matched group from the entire population. So we have been matching our patients sort of with geography, with sex, with age, and calendar year of diagnosis. Relative survival provides a measure of excess mortality associated with disease and the study. Relative survival-based population data estimates the same quantity as you are familiar with, that is cause-specific or disease-specific survival. Transient survival might be influenced by changes in diagnostics and characteristics of the disease, but we have been comparing calendar periods 1973-1979 with the more recent calendar periods, and the stage distribution appears to be quite similar and also the presence of B-symptoms, there is a slight increase of nodular sclerosis histopathology. So the normal thing is to do a cohort analysis when estimating relative survival, that is to look at patients diagnosed 1980-1985 and in the year 2000 to see what has happened with these patients. Period analysis is another way to attack this problem. It provides very good predictions of the prognosis of newly diagnosed patients. It sort of highlights temporal trends in which patient survival sooner than cohort methods which describe the past.

The data I am going to present is based on some 7,000 patients diagnosed with Hodgkin lymphoma in the period 1973-1979, and there are three main findings I think. Firstly, the relative survival has improved in all age groups over the years, and it has been most pronounced in the age group 51-65 years. There is also a plateau in relative survival in patients below 65 years of age during the last calendar period, and we could define this like a statistical cure because there is no observed excess mortality up to certain years compared to the general population, so that sort of indicates reduction in long-term treatment-related mortality. We can see that the 10-year relative survival analysis in patients below 35 years of age was above 0.95, and for older patients, it is only 0.44 for patients 66-80, and it is even worse in patients 81+. So there are also other studies comparing relative survival between countries like Germany and the United States that have recently been published, and it seems that the data are very close to our data coming from Germany, but US patients overall seem to have somewhat lower relative survival, in particular in younger patients and men. So what is the clinical relevance of the information and what did we learn? The resultant effect of different improvements in the management of Hodgkin lymphoma patients have contributed to these positive findings. More can of course be done in particular for elderly patients, and I think I have a list that could really contribute to the success where the rather sophisticated statical methods we have also been trying to look into the future. If we look at the 20-year accrued probability of death as a result of excess Hodgkin lymphoma deaths and other courses, for example for males in Sweden at the age diagnosed at the age 60 years, a very high proportion died of Hodgkin lymphoma or its complications in 1973. But it has sort of drastically decreased, so patients diagnosed in 2003, they have a very low probability of excess death up to the year 2023. At the same time, death rates from other causes is of course increasing with time, and that will still be some excess lymphoma or Hodgkin lymphoma treatment-related deaths in the coming decades. We have also looked at the observed and extrapolated excess deaths in cardiovascular disorders, and what we can see is that this type over course of death will decrease in patients diagnosed in the year 2000, much less in comparison to previous calender periods.

If we look upon the possibilities to improve outcomes for the coming decades, there are a number of aspects and some of them have already been started. So a continuous follow up of patients treated with old treatment is important, and there are national programs in Holland, Sweden and many other countries for patients given extended radiotherapy and also mock chemotherapy. PET-CT is a very valuable tool for staging and restaging Hodgkin lymphoma, but we also need to better define the predictive role of entering PET-CT investigations. We can also explore the possibility to identify patients not responding, for instance to ABVD chemotherapy by biological studies like circulating biomarkers, gene expression profiling, tumor infiltrate, etc. And of course to identify the

optimal use of brentuximab vedotin, which has shown fantastic response rate in refractory Hodgkin lymphoma patients. Proton therapy is a new way to give radiation which could really, really reduce the amount of radiation given to healthy tissue surrounding the tumor. Collaboration between study groups, we need more and more patients, so that is another important issue. And of course, to explore and develop new drugs, targeted therapy, less toxic treatment.

So what is the clinical relevance of the information given today? What did we learn? Well, the resultant effect of different improvements in the management of Hodgkin lymphoma patients have contributed to these positive findings, but of course, more can be done, in particular for elderly patients. Well-defined programs for follow up of patients treated in earlier eras, and also to prevent modified cardiovascular disease, second cancer, etc., and having the start of cancer survivorship programs. So, the key message is, I think you would like to have from this presentation is that we are doing better, but there is a lot to be improved, especially in older patients. We show that here that novel treatment strategies needing to reduce long-term toxicity, here I think it is especially fascinating with the development of brentuximab vedotin in various phases of the disease, and of course arrange for follow up of patients and recruit patients for clinical and other studies that will help us to improve the outcome for the next generation of patients. So, thank you very much for your attention.