Managing Hodgkin Lymphoma

Radiation Therapy As Part of the Standard Therapy for Stage 1 and 2 Hodgkin Lymphoma

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Hello, my name is Mary Gospodarowicz. I am medical director of Princess Margaret Cancer Center in Toronto, and I am reporting today live from the 12th International Conference in Malignant Lymphoma being held in Lugano, Switzerland. I would like to spend the next few minutes giving you an overview of my presentation today which is a debate on the topic of whether radiation therapy should be part of the standard approach to the management of stage 1 and 2 Hodgkin lymphoma. This is a very controversial topic. I will be debating with Professor Tim Illidge from Manchester, and I will take the side stating that no indeed, radiation therapy should not be the standard part of the management of stage 1 and 2 Hodgkin lymphoma. To tell you why I believe that, it is probably good to go back and go through the history of the development of management of localized Hodgkin lymphoma. So, radiation therapy was the first proven curative treatment of Hodgkin lymphoma. It was proven in 1950s that patients could be cured, usually patients with localized disease. In 1960s, MOPP chemotherapy was developed, and this was the first curative systemic treatment. Although the results were fabulous, there was a price for the treatment. Radiation therapy, we know, can cause second cancers. MOPP however, in a number of patients, resulted in acute leukemia and about 5% of patients developed acute leukemia and died within 5 years of treatment. So the name of the game in 1970s to 1980s was to avoid chemotherapy and optimize the use of radiation. With the involved field, radiation failure rate was high, so there was a move to extend field radiation which improved the outcomes, and then in patients who were even higher risk to combine radiotherapy with chemotherapy. So, in 1980s, majority of patients with stage 1 and 2 Hodgkin lymphoma were cured, but we have found out that the long-term survival was far less than that. In fact, the disease-specific survival was in order of 95%, but the long-term survival was somewhere between 70% and 80% percent in a very young group of patients who were not supposed to die young. The studies have reviewed that most of the patients died of causes other than Hodgkin and mostly of late effects of treatment, second cancers, infections, or cardiac disease. And the large cooperative study was done to show that. So, in 1990, we knew that the major challenge in early stage Hodgkin lymphoma was to improve the overall survival by eliminating death of other causes that occurred later after the treatment. So, we embarked in Canada on a perspective randomized trial trying to eliminate radiotherapy, and what it allowed us to do was the development of ABVD chemotherapy which was very effective, was proven to

be far more effective than MOPP chemotherapy, did not cause infertility, and it did not cause leukemia. So, although the treatment had its acute toxicity and there were concerns of cardiac toxicity, overall it was a very good chemotherapy. So we chose to randomize patients with early stage Hodgkin lymphoma to what was then our standard approach with use of extended-field radiotherapy or in high-risk patients combined short chemotherapy with extended-field radiotherapy versus ABVD alone. We always wanted to go for long-term survival. The trial was ahead of its time. We had great problems accruing patients because of the belief that patients needed to receive radiotherapy. However, over the next decade, we completed the accrual, and the first report of this trial was published in 2005, at which point we showed that a very high proportion of patients treated with ABVD alone were failure free. However combined modality therapy of radiation and chemotherapy resulted in fewer failures and the difference was 13% failure rate versus 6% failure rate. However, there was no evidence in the overall survival. We then followed the patients to the expected endpoint of the trial, and last year we reported the longer term results with a median followup of over 11 years. This analysis proved that the hypothesis we had in the beginning was indeed right because in the updated report, the overall survival of patients treated with ABVD alone was much better, statistically significantly better than the survival of patients treated with combined modality therapy. Now the trial has been criticized because we no longer use extended-field radiation, but the benefit of this trial is in the randomized setting to show how well patients do with chemotherapy alone. In the meantime, many many groups have been doing trials trying to lower the total treatment burden by reducing radiotherapy fields and limiting the number of courses of chemotherapy. In fact, the German Hodgkin Study Group said what is now considered in many centers as standard treatment in very favorable groups of patients giving just two courses of ABVD and to integrate to involve field radiotherapy in somewhat high-risk patients, four courses of ABVD with 30 Gray of radiation therapy. So, it is possible that the reduction in the dose and field of radiotherapy will result in a lower rate of late effects, second cancers, and better long-term survival. However, I still have concerns because while we were doing the study HD6, we also engaged a number of population-based cohort studies and case control and case cohort studies looking at the risk of second malignancies in patients treated for Hodgkin. Using huge cohorts of patients and population-based data, we can demonstrate increased risk of second malignancy with doses of radiotherapy as low as 4 Gray and certainly higher risk of second malignancies with dose of 20 Gray which is what is being used right now. The patients who are particularly at risk are young women who are at risk of secondary breast cancer. With the amount of radiotherapy, that risk was as high as 30% at 30 years; that means that women who are treated in their 20s would have 30% risk of developing breast cancer by the age of 50. I think we can do better than that, and we do not know to what extent the reduced dose and field of radiotherapy will reduce this risk. Our modeling studies suggest that they will reduce the risk significantly to a much lower risk; however, it

will be still higher than the general population. The current attitude and the current focus for this debate is to debate of whether to use radiotherapy or not use radiotherapy in Hodgkin lymphoma in early stage.

I would like to remind you that radiotherapy is the most effective single agent for Hodgkin's disease. The local control is 100%, and in patients who have insufficient response to chemotherapy, radiation cures Hodgkin's disease. So rather than focusing in a dichotomous situation whether to always use radiotherapy or never use radiotherapy, I think that I would recommend that we personalize treatment, and there is lot of evidence that patients, who have a low-risk early stage disease who respond very well to chemotherapy do not need radiation and can avoid radiation. There is also a lot of information that patients who have insufficient response to chemotherapy, when given radiation, can be cured and can also enjoy long-term survival. Therefore, on the population basis, we can afford a number of patients treatment without placing them at risk of second malignancies while maintaining the cure rate in other patients. So the debate needs to change from that asking whether one should ever use radiotherapy or not to the debate in which exact situations radiotherapy should be used to benefit the patients the most.

I want to thank you for joining us for this session reported live from the 12th International Conference of Malignant Lymphoma in Lugano, Switzerland. Please be sure to stay logged on and view additional highlights from this conference. Thank you very much.

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