Managing Hodgkin Lymphoma

Role of Radiation Therapy in the Treatment of Hodgkin Lymphoma

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Hello, my name is Tim Illidge. I work at the University of Manchester in the United Kingdom. I am reporting live from the 12th International Conference on Malignant Lymphoma being held in Lugano, Switzerland. I would like to take the opportunity to provide you with a brief overview of what I presented in my controversy session, and the title was "Radiotherapy Remains the Standard Component of Treatment in Early Stage Hodgkin Lymphoma."[1] Over the last 30 to 40 years, the standard approach in management of Hodgkin lymphoma has been to use radiotherapy, which is a highly effective treatment in the treatment of Hodgkin lymphoma, relapse occurs outside of the radiation field, so quickly combined modality became the standard of care. And through large randomized studies, in particular led by the German study Hodgkin group, the standard of care has became two cycles of ABVD and a modest 20-Gray radiotherapy.[2] With those excellent results from 1,370 patients with a median follow up of 7.5 years, the overall survival was 95% and the failure from a treatment failure at 86%. That has become the current standard for patients with early stage favorable Hodgkin lymphoma. What has brought into question is whether radiotherapy should continue to remain a component of the treatment is the late effects that are seen with radiation treatment. This largely relates to very large fields of radiotherapy that are now outdated and that are no longer used, and dosage of radiotherapy that are no longer used. And what brought this to the fall in particular was the study published by the Canadian group, the HD6 study, which showed a survival advantage for patients that received chemotherapy alone, four to six cycles of ABVD versus subtotal nodal irradiation and two cycles of ABVD.[3] It is important when we look at this study to remember when the study was first reported with a median follow up of just 4 years that there was no difference in survival. However, with longer follow up, an improved survival was seen in the patients that got chemotherapy. If, however, we dig a little deeper and look at those deaths, we see there were just 20 deaths in the combined modality arm and 12 in the chemotherapy arm, so relatively small numbers of deaths in a study that was incompletely accrued. In particular, in the radiotherapy deaths, we find that there were five so-called others, which include Alzheimer disease, drowning, and

suicide. While statistically correct to put these patients in that group, medically, it is not related to the radiotherapy alone. If we take away those five patients, we see that there is no longer a survival difference. One of the major proponents for looking at the data on chemotherapy is to say that actually the patients that have got chemotherapy alone really did very well and that we can treat patients with four to six cycles of ABVD and not have any radiotherapy alone. Personally that is not evidence which is based on randomized trials that are done against modern combined-modality treatment that includes two ABVD and small-field radiotherapy with just 20 Gray. So we have no modern randomized-controlled data to suggest that we should move to chemotherapy alone. Furthermore, when we are asking this question regarding four to six cycles of chemotherapy, it is important to remember the cardiac toxicity of increasing doses of Adriamycin and in particular the bleomycin lung injury that is seen in older patients in particular, and we see very much from the German Study Hodgkin Group and recent publications that bleomycin lung injury remains an underreported and very significant problem. So when we look at the benefit and risk analysis of chemotherapy versus combined-modality treatments, it is important that we have a very balanced view about that and that we should really only move towards chemotherapy alone strategies when we have strong, large, well-conducted robust randomized clinical trials. We do not have that for chemotherapy alone versus the combined-modality approach.

The other area which is becoming increasingly interesting and important is the use of FDG-PET as an imaging biomarker to try and predict which patients require radiotherapy. In other words, if after two or three cycles of ABVD, the patient achieves a PET-negative response, then they could be spared radiotherapy, and there have been enormous international efforts to try and achieve this goal in selecting patients that can be treated without radiotherapy. The UK NCRI group presented their data after the American Society of Hematology last year.[4] What we showed was that there was a 25% PET-positive rate after three cycles of ABVD, so actually quite a high positive rate. A very conservative definition of a PET negative was made, and when we looked at the analysis, if we did a protocol analysis, what we saw was a 7% difference between the arm that resided the combined-modality treatment with radiotherapy and the treatment arm of chemotherapy alone. So, in other words, about 10% of the patients who were PET negative relapsed after the chemotherapy alone. It looks like FDG-PET may be able to predict for some patients that are going to do very, very well with chemotherapy alone. However, at the moment, it seems really rather premature to move to this way of treating patients based on the Deauville score of FDG-PET. Furthermore, when look at the EORTC H10 study, we see that study failed to be able to use FDG-PET as an imaging biomarker to predict which patients could be spared

radiotherapy, and the independent data monitoring committee closed that study early and made all of the arms have radiotherapy because they were concerned of the relapse rate within the patients that received chemotherapy alone.[5]

So, in summary, we have large numbers of patients in well-conducted randomized clinical trials which demonstrate that 20-Gray radiotherapy with two cycles of ABVD remains the standard of care for our patients. There is currently a lack of randomized evidence which suggests that chemotherapy alone is the right choice for patients, and this is too premature to move to FDG-PET adjusted strategies, although this offers great promise for the future, and there is no doubt in the future we will be more able with confidence to select patients using FDG-PET that can go on and receive just chemotherapy alone and be spared radiotherapy. Thank you for joining us in this session, and I hope that you have found it useful and informative.

References

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