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Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Radiation in Early-Stage Hodgkin Lymphoma

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H&O What is the history of using radiation therapy in the treatment of classic Hodgkin lymphoma?

RM There is a long and successful history of using radiation treatment, which dates back to the beginning of the twentieth century. The use of radiation therapy to shrink Hodgkin lymphoma was a major medical breakthrough. The potential to cure Hodgkin lymphoma became apparent in the 1950s and 1960s, with accurate staging and a better understanding of the extent of the disease. Radiation emerged as the standard mechanism of managing patients, which resulted in cure rates in the 40–50% range. However, the extent of the radiation field was quite wide. Patients received radiation to the upper body, torso, and groin.

As time passed, it became evident that the use of radiation therapy, while successful, was associated with late effects. Patients successfully treated with radiation therapy were at risk of developing heart disease and other forms of cancer at an increased rate when compared with control populations. As Hodgkin lymphoma is typically a disease of young people and associated with potentials for cure, the health of patients 20 or 25 years later is a real issue. During the 1970s and 1980s, a number of strategies were tested to both increase the cure rate of the disease and to reduce the risks of late effects. These strategies included combining chemotherapy with radiation. As success in combining chemotherapy with radiation became evident, it was possible to reduce the size of the radiation fields and the radiation doses with the goal of reducing the risk of late effects that would occur 10–20 years later. In the 1990s, these strategies were fully incorporated so that standard chemotherapy and reduced amounts of radiation were given to patients with limited-stage disease. Another strategy that emerged was eliminating radiation from the management of patients with limited-stage disease. As a result, over the past 10 years, 2 main treatment options have become apparent. The first is 2–4 months of chemotherapy with radiation that is limited to the disease site. The other option is giving chemotherapy alone. I will discuss the pros and cons of these 2 approaches in a later section. With new imaging techniques such as positron emission tomography (PET) scanning, current research is evaluating whether one can administer initial chemotherapy and see how well it has worked according to the results of the PET scan, and then determine the potential role of radiation treatment.

H&O Are there any areas where the use of radiation alone has shown promising results?

RM There is an important role for radiation in patients with Hodgkin lymphoma as it is an effective technique for shrinking and eliminating the disease. An important role of radiation includes its use for patients who do not have widespread Hodgkin lymphoma, but instead have disease that is associated with a large, bulky mass. In many patients, such bulky disease will be located in the mediastinum. Optimum treatment for these patients includes combining chemotherapy and radiation treatment. Another important role of radiation treatment is for patients in whom chemotherapy has not been successful in eradicating the disease or in whom the Hodgkin lymphoma has come back after treatment that included chemotherapy only.

A controversial topic is how to manage patients with lymphocyte predominant Hodgkin lymphoma. Because it

is a relatively uncommon disease, the opportunity to conduct definitive clinical trials is more limited and thus we do not have the same experience of comparing outcomes associated with different approaches. Radiation treatment can be an important component in treating these patients.

H&O What are the current treatment approaches for patients with early-stage Hodgkin lymphoma?

RM First, it is important to define what is meant by early stage. I would categorize this as patients with stage I and IIA disease, excluding patients with B symptoms and patients with bulky disease. It is rare for a Hodgkin lymphoma patient to have stage I or II disease that is confined to the abdomen and I would not include these patients in the category of early-stage disease. Thus, early-stage disease includes patients with stage I or IIA, nonbulky, non–intra-abdominal disease. My approach for these patients would be to give 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), and then restage their disease using physical examination plus computed tomography (CT) and PET scans. If the results of those tests are favorable and the patient appears to have achieved a remission, I would give 2 more cycles of ABVD to a total of 4, at which point I would consider the treatment complete. If the tests are not favorable after the 2 months and the patient does not show a remission, I would give an additional cycle of ABVD, and I would arrange for the patient to receive radiation treatment.

H&O What was the rationale behind your trial on ABVD alone versus radiation-based therapy in limited-stage Hodgkin lymphoma?

RM This a complicated question that involves aspects of both Hodgkin lymphoma and how clinical trials are performed. The long-term outcomes of patients with Hodgkin lymphoma are determined by how well the disease is controlled, while minimizing the risk of late effects, such as heart disease and second cancers that can occur as a result of radiation. The dilemma one faces is that those late effects do not become apparent for 12–15 years. In younger patients, it will take even longer. Thus, you are stuck in a catch-22, where you would like to know the 12-, 15-, and 20-year outcomes of today's treatment, but obviously, this is not possible. Most trials of Hodgkin lymphoma focus on how well treatment strategies control the disease over the first 3–5 years. Although that is important, it fails to address the issues associated with outcomes in the second and third decades following treatment.

The design of our trial began in the early 1990s and the trial commenced in 1994. In this study, patients with nonbulky stage I or IIA disease were randomized to receive ABVD alone or radiation-based treatment. We used a risk-categorization schema to stratify patients into favorable and unfavorable cohorts. For the control arm, patients in the favorable-risk cohort received subtotal nodal irradiation (STNI) alone, whereas the unfavorable-risk cohort received 2 cycles of ABVD followed by STNI. The experimental arm therapy was the same for both risk groups, and included 4–6 cycles of ABVD, with the number of cycles dependent on the rapidity of response documented by CT.

H&O What were the overall findings?

RM Unlike most trials, where the outcome being assessed is disease control at 3–5 years, our major outcome was 12-year overall survival, and therein lies the dilemma. It took longer than we hoped to accrue patients—we finished accrual in 2001. We reported the results of the disease control at 5 years in 2003, and that was published in 2005. In the last 15 months, we reported the final outcome of the 12-year overall survival. What we found was that the use of radiation did improve disease control. The disease control at 12 years was 92% for those patients who received radiation, compared with 87% for patients who received chemotherapy alone. Therefore, using radiation improved the disease control by about 5%. The second finding was that 87% of patients were cured with chemotherapy alone. I think that represents a landmark of how successful chemotherapy can be. In contrast, the overall survival at 12 years was 94% among patients who received chemotherapy alone versus 87% among patients who received radiation. Radiation helped control the disease, but people lived longer when treated with chemotherapy because there were fewer late effects. The findings were important, as they showed how well patients can do with chemotherapy alone, and secondly, that while the degree of disease control is an important factor, it is not the only factor to consider when evaluating longer-term survival, as one also has to account for the long-term effects associated with radiation. Thus, survival in our trial was better in patients who received chemotherapy alone.

H&O What concerns does this trial raise?

RM The limitation and the criticism of our trial is that our results were obtained with the radiation therapy of that time, which was STNI. This has not been used for at least the last 12 years. Instead, much smaller radiation fields are now prescribed. We would fully expect that there will be fewer late effects with the current use of these smaller radiation fields, but also anticipate that risks will remain. As a result, we are left with the conundrum as to which

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of today's 2 strategies will be superior in the long term. What we would like to know is the long-term outcomes of today's treatments, but that is not yet possible.

H&O What are some areas of ongoing research?

RM I think that the most immediate priority is to place into context the role of PET scanning and how helpful PET scanning can be in determining treatment options. The second priority is to better understand the biology of Hodgkin lymphoma and the genetic determinants that make up an individual's disease, because not all patients are the same. If we understood the biology at a more personal level for each patient, it may help to better direct therapy. A third avenue includes new types of drugs that are being used to treat Hodgkin lymphoma. These include agents that are antibody-based and use immune strategies to attack the disease. Finally, there are ongoing advances in new types of radiation treatment, where the beams of radiation can become more focused on the areas where the Hodgkin lymphoma exists and attempt to achieve benefits while reducing radiation to the surrounding tissues.

H&O What are the biggest remaining challenges?

RM I think one of the biggest challenges is the conundrum I have described, where what is really important for these patients is their long-term outcomes. There will always be this issue of wanting to understand the long-term outcomes associated with today's treatments. By the time we understand the long-term outcomes of today's treatments, a decade or more will have passed and there will be advances, which will result in another generation of questions. Thus, we will constantly have this tension of trying to take what we have learned from understanding the long-term outcomes and place it into the context of modern treatment. I think the other challenge that exists is that although Hodgkin lymphoma has exemplified a success in treating patients with cancer, we lack true understanding of how to target treatment against the very specific genetic determinants of the disease. If we could have a better understanding of that biology, there may be more opportunities for better treatment.

Suggested Readings

Meyer RM, Gospodarowicz MK, Connors JM, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *N Engl J Med*. 2012;366:399-408.

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