Treatment for Favorable Localized Hodgkin Lymphoma: the Final Answer Is Awaited

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The likelihood that combined-modality therapy will provide a small progression-free survival advantage is real but not likely to be equated to an overall survival advantage, as it depends on when one looks at the data. The studies to date demonstrate a late fall-off in survival due to one or another toxic effect of radiation.

The article in this issue of ONCOLOGY by Kelsey et al differs very little from a recent publication on the issue of early Hodgkin lymphoma (HL) therapy from radiation oncologists.[1] These have been matched by editorials that question the role of radiation therapy in early HL, especially in nonbulky favorable presentations.[2-7] The argument that extensive radiation fields and doses have both been reduced and thus radiation therapy is less likely to be carcinogenic is well accepted, but most of the publications from the United States, Canada, and Europe have recorded the long-term toxicity of the radiation therapy given 20 or more years ago. The most vulnerable groups are the pediatric and adolescent age groups, in whom long-term cardiac and carcinogenic activity has been carefully recorded.[8,9]

There have not been as many randomized trials with adequate numbers of patients to explore the issue of the need for radiation therapy in nonbulky favorable early HL. The major trial which probably has evoked most of the commentaries, such as that by Kelsey et al, has been the Canadian/Eastern Cooperative Oncology Group (ECOG) HD6 trial, which basically has concluded that in time there did not appear to be a survival advantage for patients in the arm receiving extensive radiation.[10] In two-thirds of the cases, an additional 2 cycles of ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, dacarbazine) were added to the radiation arm. In fact, there was a survival disadvantage with an increased mortality due to more likely radiation toxicity. One can accept that subtotal nodal radiation is no longer used and thus most, if not all, radiation oncologists accept this fact. However, the important result of the H6 data is the fact that the chemotherapy-alone arm had a 12-year failure-free survival rate of 86%, with a superior 12-year survival for patients treated with chemotherapy alone. Radford, in a recent article, noted that these results were equivalent to those of the German Hodgkin Study Group (GHSG) HD10 trial, in which treatments consisting of 2 cycles of ABVD and 20 Gy of radiation to the involved field was shown to be optimal.[5]

Almost every randomized trial noted in the report by Kelsey et al showed an advantage to adding radiation therapy to whatever chemotherapy was used. The same was noted in the H6 trial as well. Depending on the center, the differences vary from 5% to 8%. However, the true meaning of the trials cited in the Kelsey article needs to be elucidated. Most are not relevant to current therapeutic challenges and needs. The European Organisation for Research and Treatment of Cancer (EORTC) trial (Noordijk et al) will remain an abstract, given that the chemotherapy-alone regimen, EBVP (epirubicin, bleomycin, vinblastine, and prednisone), was shown to be equivalent to a much-reduced-dose version of ABVD and thus only proves that inadequate chemotherapy needs the addition of radiation therapy.[11] The Picardi et al trial was limited to patients with bulky disease who received a unique regimen, VEBEP (vinblastine, etoposide, bleomycin, epirubicin, prednisone), for PET-negative status and then were randomized to radiation or follow-up; thus it cannot be compared against the effectiveness of ABVD in favorable (nonbulky arm) early HL in the H6 trial.[12] The Aviles trial was designed for bulky disease as well.[13] That leaves only four trials, including the H6 trial, completely published in the last 12 years that evaluated ABVD alone. In none was there a survival advantage because of effective salvage treatment, but the progression-free survival (PFS) advantage was eliminated by later fatal complications in the radiation arm. Even the longer follow-up in the GHSG HD10 trial (2 cycles of ABVD followed by only 20 Gy of radiation therapy) found 14 patients with second cancers among 299 patients treated.[14] It is important to remember that the toxic complications of higher doses used in the past occurred progressively over time (20 to 40 years). There is no objective evidence that 20 Gy is safe to the cardiac area, especially since most patients
have mediastinal involvement and would require radiation therapy to the chest. One study in pediatric HL suggested that even doses of 15 Gy to 25 Gy were associated with a 17% incidence of second cancers.[15,16] The issue of the long-term toxicity of an anthracycline such as doxorubicin or epirubicin given alone has not been addressed completely. These agents appear to have been associated with rare subclinical cardiac toxicity in long-term survivors of childhood cancer.[17] The toxic potential of these agents should be assessed in the absence of radiation therapy. There have been few studies in adults of very-long-term cardiac toxicity in patients treated with ABVD. Several studies of patients with diffuse large-cell lymphoma treated with anthracycline-containing regimens at a median age of 55 did show some increased cardiac toxicity.[18] However, another study of similar patients from a French trial had 1 of 141 patients developing congestive heart failure in a 5-year follow-up. It should be noted that these patients were on the average 20 years older than the usual age at presentation of HL.[17]

The status of management of early HL is actually in flux. Current trials employ PET scanning to assess the effectiveness of chemotherapy, particularly in early favorable disease. Therapeutic decisions are often made on the basis of interim PET results. Very recent data from the UK Lymphoma Group (RAPID, a randomized trial presented at the 2012 annual meeting of the American Society for Hematology) have shown that a negative PET scan after 3 cycles of ABVD alone is associated with an outcome equivalent to that of the cohort in which involved-field radiation therapy (IFRT) is added; these results provide further evidence that patients with early favorable HL can be spared radiation therapy in the circumstance of a PET-negative response to chemotherapy. The likelihood that combined-modality therapy will provide a small PFS advantage is real but not likely to be equated to an overall survival (OS) advantage, as it depends on when one looks at the data. The studies to date demonstrate a late fall-off in survival due to one or another toxic effect of radiation. Currently, the uncertainty regarding benefit is better encoded in the title of a 1991 article by Dr. Richard Hoppe: ‘Early-Stage Hodgkin’s Disease: a Choice of Treatments or a Treatment of Choice?’[19] Eventually there could be dramatic changes in the prospects for patients who have early HL with favorable presentations. The new agent brentuximab vedotin (Adcetris), an immunotoxin, has shown a remarkable effectiveness even in drug-resistant patients. It is being evaluated now combined with chemotherapy, with this regimen being compared to the classic ABVD regimen. It is possible that some of the more troublesome aspects of ABVD can be changed, especially eliminating bleomycin. Chemotherapy alone may become more effective and, in a sense, may yield outcomes equal to or exceeding what is now seen with combined-modality treatments. The conclusions cited by Kelsey et al are only presumptive when the prior data cited are critically analyzed. A total of 4 cycles of chemotherapy and limited radiation therapy (36 Gy) are more commonly used, which is certainly likely to result in long-term toxic problems. For example, Brusamolino et al showed that 22% of patients treated with chemotherapy and adjuvant radiotherapy had cardiac toxicity or second tumors by 15 years.[20] Clinicians need to review these factors prior to determining a treatment plan for a new patient with early favorable disease.

In conclusion, what do we know today based on the evidence from clinical trials of early favorable HL?

- PFS will be enhanced in the range of 5% to 8% with combined-modality therapy.
- OS will not be improved by combined-modality therapy.
- Long-term radiation toxicity is assured in patients receiving the standard or reduced dose of radiotherapy, on the order of 20% with late effects at 20 years.
- The toxicity of this therapy comprises cardiac toxicity as well as second tumors.
- Chemotherapy alone can produce at least 80% to 85% or more PFS, but the number of cycles less than 6 is still subject to investigation. The RAPID trial used 3 cycles of therapy.
- There may be cardiac toxicity from anthracycline use alone, but Canadian studies suggest that cardiac hospitalizations are not increased.[21]
- The combination of radiation and anthracyclines has the highest risk of complicating toxicities.
- Patients with bulky disease may require radiation therapy unless risk-adapted studies with PET scanning can show otherwise in clinical trials.
- Further advances in systemic therapy with a new immunotoxin may enhance a durable PFS, but that awaits further clinical investigation.
- The risk of second solid tumors in pediatric HL is substantially reduced if radiation is eliminated.[22]

Financial Disclosure: Dr. Canellos serves on Celgene’s Business Advisory Committee.
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