Limited-Stage Hodgkin Lymphoma: Managing Uncertainty

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In 1991, an editorial written by Hoppe1 was published in Journal of Clinical Oncology that discussed uncertainties associated with optimum management of patients with early-stage Hodgkin lymphoma; the editorial was entitled “A Choice of Treatments or a Treatment of Choice?” The editorial addressed the role of staging laparotomy to define patient-specific treatment, whether preferred management was with radiation therapy and/or chemotherapy and, within these choices, the details of the radiation treatment prescriptions and chemotherapy regimens. Considerable new evidence has been obtained since Hoppe’s 1991 editorial, and cure rates with initial therapy have improved from his descriptions of 75% to almost 90%.2,3 However, debates continue about fundamental management choices, including the role of radiation therapy and whether determinants exist that permit patient-specific decisions.4

In the article that accompanies this editorial, Raemaekers et al5 provide further insights into managing these patients. Their report illustrates the complexities associated with designing clinical trials that are hoped to bring about clarity and consensus to unresolved areas, and how caution is required if one is anticipating that new landmark evidence will emerge and lead to uniform agreement. Instead, practitioners should expect that until transformational new therapies become available, new findings will provide important incremental knowledge, but that management decisions for individual patients will continue to be associated with degrees of uncertainty about which treatment will lead to the patient’s best outcome.

Raemaekers et al6 describe results of two randomized controlled trials (RCTs) that each test the predictive properties of positron emission tomography (PET) performed part way through a planned course of therapy.7 The first trial, referred to as Hodgkin 10 Favorable (H10F), includes patients with stage I to II Hodgkin lymphoma who have no defined risk factors; the second trial, Hodgkin 10 Unfavorable (H10U), includes patients with stage I to II disease associated with a risk factor, defined as patient age of 50 years or older, more than three nodal areas of disease, bulky mediastinal disease, and/or an adverse combination of B symptoms and/or an increased erythrocyte sedimentation rate. Patients assigned to the experimental arms of each trial who had a favorable midtreatment PET result received less treatment than those allocated to control arm therapy; in contrast to control arm patients, these experimental arm patients did not receive radiation therapy. Patients in the experimental arm with an unfavorable midtreatment PET result received more treatment than control arm patients: in addition to receiving the same radiation therapy as control arm patients, experimental arm patients also received additional cycles of chemotherapy with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, whereas control arm patients received additional cycles of doxorubicin, bleomycin, dacarbazine, and vinblastine (ABVD).7

Central to the design of both H10 trials is that midtreatment PET was performed in a symmetric manner for both experimental and control populations. Images were interpreted through an independent adjudication process by experts who were unaware of the randomized treatment assignment. Rather than designing each trial to report a single comparison of outcomes of all randomly assigned patients, symmetric PET testing with independent review led investigators to plan analyses of each trial, first as comparisons of patients in control and experimental arms with favorable midtreatment PET results, and second as comparisons of patients in control and experimental arms with unfavorable midtreatment PET results. In this report, Raemaekers et al5 describe results of H10F and H10U interim analyses comparing outcomes of patients who had favorable midtreatment PET results. Using the primary end point of progression-free survival (PFS), both analyses were designed to evaluate noninferiority of the experimental arm therapies (ie, no radiation therapy). Each interim analysis demonstrated that the null hypotheses of inferiority of experimental arm therapy would not be rejected and, thus, the conduct of both trials was altered so that all future patients would receive radiation therapy.

The H10 trials are a major accomplishment; their importance rests with the primary findings of radiation treatment being associated with superior 1-year PFS of 5.1% in H10F (100% v 94.9%) and 2.6% in H10U (97.3% v 94.7%).3 An opportunity for multiple critiques is likely to lead to ongoing debates: for example, the H10U population is defined by a patient-related factor (age) and multiple disease-related factors (bulky disease, more disseminated disease), and the importance of a radiation therapy research question to these varied populations is debatable; the trial design has the intervention associated with the research question occurring more than 2 months after random assignment, which creates risks of compliance, cointerventions, and contamination; the specifics of PET timing and interpretation will require synthesis with other trials evaluating PET; the trial includes involved nodal radiation therapy, for which long-term disease control has not been evaluated in an RCT and which is potentially associated with issues of generalizability, including quality control8,9, the analysis
plan is not linked directly to random assignment but instead is determined by the postrandomization PET evaluation; conclusions of interim analyses were based on a small number of events and are thus potentially unstable; and the difficult decisions around continued trial conduct may restrict eventual abilities to address the primary research question. This said, the trial is a monumental undertaking, and we can anticipate that the main conclusions are correct. The important issue is to determine the implications of these results in informing current management.

Three main factors contribute to difficulties in achieving consensus about the best management option for patients with limited-stage Hodgkin lymphoma. First, durable complete control of the cancer is possible for the vast majority of patients. Second, patients with Hodgkin lymphoma are younger than most patients with cancer; the median age of patients in most trials is 35 to 38 years—2,3—the median age of patients in the H10 trials was 31 years.5 Third, treatment used to achieve cancer control, especially radiation therapy, is associated with risks of adverse late effects, which include second cancers and cardiovascular disease.9 For patients with limited-stage disease, these risks contribute to the combination of second cancers and cardiovascular disease being a more common cause of mortality than Hodgkin lymphoma. This observation becomes apparent even within the first decade of follow-up after treatment,4,10 with recognition that late-effect risks will continue to increase through the second and third decades of follow-up.5,11 Thus, with complete control of cancer in a young population who would otherwise be relatively free of comorbidities affecting survival, the knowledge that treatment can contribute to potentially fatal comorbidities becomes a major consideration in determining optimum therapy.

These three factors have important ramifications for clinical trial design. Historically, the paradigm for improving the outcomes of patients with cancer has involved demonstrations of so-called treatment activity, usually measured by antitumor responses, followed by time-dependent measures of a continued response and thus cancer control (eg, PFS)12,13; longer durations of cancer control are expected to be associated with extended periods of survival. The relationship linking duration of disease control with survival has led to use of measures such as PFS as end points within clinical trials. The rationale for using PFS stems from expected intrinsic patient benefits associated with achieving a state of cancer control, feasibility of measurement, ability to meet statistical requirements of observing a sufficient number of events within acceptable time periods that permit trial analysis and relevant reporting and, importantly, expected surrogacy as a proxy measure for overall survival. However, for patients with limited-stage Hodgkin lymphoma, failure of disease-control end points to serve as proxy for overall survival exists, as is perhaps best exemplified by the NCIC Clinical Trials Group–Eastern Cooperative Oncology Group (NCIC CTG–ECOG) HD.6 trial.3 Although this trial is associated with considerable debate, fracturing of the linkage between the disease-control end point and overall survival was clearly evident with the hazard ratios (HRs) associated with these comparisons being reciprocals. Compared with the control group, which was randomly assigned to receive treatment that included radiation therapy, freedom from disease progression (FFPD) was inferior in the experimental group, which was randomly assigned to receive ABVD alone (HR, 1.91; 12-year FFPD, 87% v 92%), whereas overall survival was superior with ABVD alone (HR, 0.50; 12-year survival, 94% v 87%). These results create a dilemma for interpreting RCTs involving patients with limited-stage Hodgkin lymphoma if the interventions compared might be associated with differential risks of late effects. Because disease-control end points are not reliable in predicting overall survival, it can be argued that overall survival should be directly evaluated. To capture the risks of late effects on survival, median follow-up of patients needs to extend, at a minimum, into the second decade after treatment. Given that the median follow-up of H10 patients described in the current report by Raemaekers et al is 1.1 years,7 reliable reporting of overall survival is at least a decade away.

Three other RCTs will inform decisions about response-adapted therapy on the basis of midtreatment PET. Preliminary results of the United Kingdom RAPID trial have been published in abstract form.14 In this trial, patients with nonbulky stage I to IIA disease received three cycles of ABVD followed by PET. Those with an adjudicated favorable result were randomly assigned to receive involved-field radiation or no additional therapy. With a median follow-up of 3.8 years, the respective 3-year PFS results were 93.8% versus 90.7%, with the difference of 3.1% associated with 95% CIs of −1.4% to 10.7%; the upper limit of 10.7% exceeded the prespecified noninferiority boundary of 7%. Respective 3-year overall survivals in an intent-to-treat analysis were 92.2% and 98.3%; given the noninferiority design, these survival results cannot be considered robust and require the context of a per-protocol analysis. Despite failing to meet the prespecified PFS noninferiority boundary, the authors concluded that radiation therapy is unnecessary for those with a favorable PET result. The discrepancy between the clinical and statistical conclusions exemplifies the conundrum associated with management decisions that involve trade-offs that balance margins of difference in disease control and perceived risks of radiation-related late effects.

The other two trials are the German Hodgkin Study Group (GHSG) HD16 and HD17 trials.15 In HD16, patients resembling those enrolled onto the H10F trial receive two cycles of ABVD followed by PET. In HD17, patients resembling those of H10U receive two cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, followed by two cycles of ABVD followed by PET. In both trials, those with a favorable PET result are randomly assigned to receive involved-field radiation or no further therapy; the primary end points are PFS. On the basis of evidence to date, especially for HD16, one anticipates that PFS will again be superior with radiation therapy. Synthesis of the H10, United Kingdom RAPID, and GHSG HD16 and HD17 trials will assist in understanding the relevance of response-adapted approaches in determining the role of radiation therapy in different patient populations and how to integrate the specifics of PET timing and interpretation and the optimum number of chemotherapy cycles into a management plan. A limitation of all four trials is that each has a primary end point of PFS reported after brief follow-up: this end point is now known to be an unreliable surrogate for longer-term overall survival. Viewed from a different perspective, all four trials are driven by desires to reduce treatment because of the implications of late effects on survival, yet the primary end points do not measure either late effects or overall survival.

Three additional pieces of evidence help inform today’s decision making. First, we know that radiation fields can be reduced from the outdated subtotal nodal field used in the NCIC CTG–ECOG HD.6 trial to the much smaller involved field. This reduction clearly reduces risks of late effects, although potentially important risks seem to remain.11,16,17 Second, in a nonrandomized, individual-patient comparison of patients mutually eligible for the GHSG HD10 and NCIC
CTG–ECOG HD.6 trials, those not achieving a remission after two cycles of chemotherapy had clinically important superior outcomes when treatment included radiation\(^1\); thus, no matter what specifics of evaluation are used to guide response-adapted management, those with an unfavorable evaluation should receive radiation therapy.\(^3\)

Third, the NCIC CTG–ECOG HD.6 trial, which provides the foundational RCT evidence for use of chemotherapy alone, excluded patients with bulky disease.\(^3\) Until clearer evidence is provided, standard management of these patients should include radiation therapy.

The NCIC CTG–ECOG HD.6 trial results have been interpreted as providing justification for treatment of patients with stage I to IIA nonbulky Hodgkin lymphoma with chemotherapy alone.\(^4\) In the important subset analysis of that trial, 12-year FFPD was inferior by 8% (86% v 94), yet 12-year overall survival was superior (92% v 81%).\(^3\)

This magnitude of trade-off framed the justification to use ABVD alone, especially with the added knowledge that outcomes with chemotherapy alone were even more favorable in the 39% of patients treated with ABVD alone who achieved a remission state on the basis of computerized tomographic re-evaluation after two cycles of treatment (12-year FFPD and overall survival, 94% and 98%, respectively). The H10 and RAPID trials suggest that with midtreatment PET, at least 75% of patients can now be considered in this favorable group and that these patients’ incremental PFS benefit with radiation therapy is likely to be no more than 5%. The benefits of not receiving radiation therapy are that within the first decade of follow-up, no differences in overall survival are expected, and in the longer term, fewer late effects may be associated with superior survival. What is now crucial to the management of these patients is careful presentation and discussion of these treatment options by physicians from multiple disciplines, acknowledgment that uncertainties and trade-offs exist, and that a choice of treatments continues to be available.

**AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**
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