In “The Case for Combined-Modality Therapy for Limited-Stage Hodgkin’s Disease,” [1] authors Hill-Kayser, Plastaras, Tochner, and Glatstein provide a detailed, instructive, and informative discussion of the insights into the management of Hodgkin’s lymphoma that can be derived from the recently published National Cancer Institute of Canada Clinical Trials Group (NCIC CTG)/Eastern Cooperative Oncology Group (ECOG) Hodgkin’s Disease.6 (HD.6) study comparing radiation-based treatment with chemotherapy alone for limited-stage Hodgkin’s lymphoma [2]. Unfortunately, much of their discussion focuses on the control arm when the study’s real value, that is, what is most relevant for the management of patients in 2012, lies in what was achieved in the experimental arm. To understand the most important lessons learned from the HD.6 study, attention should dwell on the remarkably good outcomes that followed initial treatment with chemotherapy alone—the best outcomes ever reported for limited-stage Hodgkin’s lymphoma.

The experimental arm of the HD.6 study called for patients with limited-stage Hodgkin’s lymphoma (stages IA or IIA and low bulk [≤10 cm], excluding highly favorable stage IA nodular sclerosing or lymphocyte predominant subtypes) to be treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) alone [3]). ABVD was chosen because it was the most effective, well-tolerated, multiagent chemotherapy regimen for Hodgkin’s lymphoma available in the early 1990s when the HD.6 trial was designed [4]. This selection of chemotherapy regimen has stood the test of time, and ABVD is still the widely acknowledged chemotherapy of choice for limited-stage Hodgkin’s lymphoma in 2012. With a median follow-up duration >11 years, the estimated 12-year overall survival rate for patients assigned to the experimental ABVD alone arm of the HD.6 trial was 94%. No other trial examining treatment strategies for limited-stage Hodgkin’s lymphoma has ever reported better results. The most appropriate benchmark is the German Hodgkin Study Group (GHSG) HD10 study [5], which showed that brief ABVD (either two or four cycles) plus involved-field radiation (either 20 Gy or 30 Gy), for a more favorable subset of patients with limited-stage Hodgkin’s lymphoma than was enrolled in the NCIC CTG/ECOG HD.6 study, produced a 95% overall survival rate at 8 years. Thus, the strategy of ABVD alone, as given in the HD.6 study, matched or exceeded the strategy of combined-modality treatment when one focuses on the most clinically relevant outcome, the overall survival rate. Hill-Kayser and her colleagues are correct in noting that the control arm of the HD.6 study, which employed wide-field radiation, is outmoded and has appropriately been abandoned. However, that observation is irrelevant. The HD.6 study demonstrated not that inclusion of radiation in the primary treatment of limited-stage Hodgkin’s lymphoma is bad, but that it is unnecessary.

When comparing two different treatment approaches for an imminently curable disease such as Hodgkin’s lymphoma, it is important to consider the full picture, including the effectiveness of primary treatment, secondary treatment, and toxicity. As shown in Figure 1, the primary treatment outcome, which is best characterized by such endpoints as the progression-free survival interval or time to progression, may not be the most appropriate measure of the overall strategy. If reliably curative secondary treatment is available, as is true for Hodgkin’s lymphoma, then one must measure the relative merits of primary treatment using outcomes that reflect overall treatment, such as the overall survival time or freedom from second treatment failure rate. In the case of limited-stage Hodgkin’s lymphoma,
the valid comparison is between strategy A, primary treatment with ABVD alone followed by secondary treatment for a small minority of patients who relapse, and strategy B, combined-modality treatment followed by secondary treatment for a small minority of patients who relapse. Obviously, if strategy B is ultimately followed by a better long-term overall survival rate, even when secondary treatment has been factored in, strategy B should be chosen. However, if the long-term survival rates are equivalent after strategy A and strategy B, the choice between them must rest on other considerations, most notably long-term toxicity. Even if the primary treatment employed in strategy A is somewhat less effective than that used in strategy B, as long as the ultimate outcomes, reflecting the added contribution of secondary treatment, are the same, strategy A is more desirable if it is less toxic because strategy B visits the toxicity on all patients, whereas it is avoided by most patients following the plan in strategy A.

The most helpful way to view the lessons learned from the HD.6 study is to focus on the overall goal of treatment—achieving the best overall survival outcome with the least overall risk for toxicity to the patient, especially the least long-term, irreversible toxicity. The NCIC CTG/ECOG HD.6 [2] and GHSG HD10 [5] studies provide a rich dataset for such an assessment. Both studies showed that ~95% of patients with limited-stage Hodgkin’s lymphoma are cured when modern treatment approaches are employed. Additionally, most patients are cured by their primary treatment—ABVD alone following the HD.6 strategy and ABVD followed by radiation using the HD10 approach. A small minority of patients relapse and require secondary treatment, but ultimately the large majority of patients are cured. However, on their way to being cured, patients are exposed to very different risks for potential late toxicity following these different initial treatments. The HD.6 ABVD alone approach exposes very few patients to radiation because the use of radiation is confined to relapse treatment, if it is used at all. The combined-modality approach exposes every patient to radiation. Because the ultimate cure rates with both approaches are the same, ~95%, almost all patients managed with combined-modality treatment are unnecessarily exposed to radiation. Hill-Kayser and colleagues correctly claim that involved-field radiation in 2012 is much different and very likely much less toxic than extended-field radiation as given in the 1990s. However, it is also unarguable that any exposure to a therapeutic dose of ionizing radiation must carry some risk. Indeed, although it is plausible that current radiation techniques, with their smaller fields, lower doses, and more sophisticated dosimetry, inherently cause less tissue damage and confer a lower risk for inducing second neoplasms, it is as yet unclear how much less damage and how much lower a risk for a second cancer can be expected. One must ask, however, why any additional risk should be visited on the patient when doing so carries no clear benefit. Stated differently, radiation should be added to ABVD chemotherapy for all patients with limited-stage Hodgkin’s lymphoma if and only if the addition produces a clearly superior survival outcome, which has never been demonstrated.

One recommendation made by Hill-Kayser and her colleagues deserves to be firmly restated and emphasized. The management of all lymphomas, including limited-stage Hodgkin’s lymphoma, should be provided by a multidisciplinary team. Only in such a collaborative environment can the subtleties and nuances of treatment design be fully appreciated and, in addition, such teamwork facilitates clinical and translational research. Identification of chemotherapy alone as the most desirable primary treatment for patients with limited-stage Hodgkin’s lymphoma, the most valid conclusion to draw from the
HD.6 study, should not be viewed as the final answer. It is highly likely that some patients with limited-stage disease would do better with combined-modality treatment or even novel treatments that have not yet reached the clinic. The challenge is identifying these subgroups and treatments. Rather than arguing that all or no patients should be offered radiation, we should be vigorously attempting to determine who benefits by current treatment strategies and who does not. Three promising strategies to improve outcomes have emerged in recent years. Determination of biologic markers that reliably predict treatment resistance, such as microenvironmental infiltration by tumor-associated macrophages [6] and expression of specific cytokines or cytokine receptors [7], may permit the identification of patients who can be spared or should be given radiation. Alternatively, functional imaging assessment with such techniques as fluorodeoxyglucose positron emission tomography during treatment [8] may pick out those for whom chemotherapy alone will be inadequate and who, therefore, should have their treatment switched from chemotherapy to radiation. Finally, the addition of novel, potent therapeutic agents such as brentuximab vedotin may improve on the already very good results achieved in the treatment of Hodgkin’s lymphoma of all stages [9].

The publication of the HD.6 study is a landmark in the management of Hodgkin’s lymphoma. Its findings provide clinicians with the evidence needed to craft the primary treatment of limited-stage Hodgkin’s lymphoma in such a way that the likelihood for cure is maximized and long-term toxicity minimized. Patients treated initially with ABVD alone can be reassured that they are being offered a strategy that provides the best chance for cure combined with the least likelihood of a major late toxicity. Investigators should now move on to discover better ways to identify subsets of patients with less favorable prognoses and novel treatment approaches that are even more effective while continuing to minimize the burden of lifelong toxicity for our patients.

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