Limited-Stage Hodgkin Lymphoma: Optimal Chemotherapy and the Role of Radiotherapy

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OVERVIEW

Approximately 90% of patients with early-stage Hodgkin lymphoma (HL) will be cured with first-line therapy. Chemotherapy alone or combined-modality therapy are both acceptable standard treatment options for nonbulky early-stage HL. Combined-modality therapy is associated with more serious late effects and, in at least one study, showed inferior survival rates compared with chemotherapy alone. Modern radiotherapy fields and doses are likely to result in fewer complications, but given the common involvement of the mediastinum in HL, complete avoidance of the heart, lungs, and breasts in the radiotherapy field is unlikely. In patients receiving chemotherapy alone, four to six cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD), with fewer cycles being given to those with an early complete remission, is recommended. Three cycles of ABVD may be adequate in those with an early negative PET, but these results have been published only in abstract form. Current standards for combined-modality therapy include two cycles of ABVD and 20 Gy of involved field radiotherapy in those with a favorable risk profile and four cycles of ABVD plus 30 Gy for unfavorable HL in early-stage patients. Standard of care for bulky early-stage HL remains combined-modality therapy. Whether an interim PET will allow selection of patients with nonbulky HL who will benefit most from consolidative radiotherapy is still under investigation.

The question of whether chemotherapy alone or combined-modality therapy (CMT) represents the optimal approach for early-stage classical HL has been debated for more than two decades, including most recently at the 2012 annual meeting of the American Society of Hematology.1 Current guidelines and recommendations continue to support either approach in the treatment of nonbulky early-stage HL.2 The recent publication of the 12-year follow-up of a randomized trial of ABVD alone compared with radiation-based therapy in limited-stage HL showed for the first time a survival advantage in the chemotherapy-alone arm, despite an inferior progression-free survival (PFS), and has rekindled the debate.3 In addition, the recently presented preliminary results of the phase III United Kingdom RAPID and European Organisation for Research and Treatment of Cancer (EORTC) H10 trials evaluating chemotherapy alone compared with CMT provide important new data for consideration.4,5

Balancing efficacy with long-term toxicity in early-stage HL has proven to be an extraordinary challenge, primarily related to the significant delay of more than 10 years, and in many cases 30 years, between HL therapy and its associated complications. Evaluating alterations in therapy requires decades of follow-up to determine whether new approaches have indeed accomplished the goal of decreased long-term toxicity. Dissecting the late effects of chemotherapy compared with radiation when a large percentage of patients receive both modalities presents an additional hurdle. Finally, currently undefined potential host factors in patients with HL, such as subtle immune deficiencies or genetic susceptibilities to cancer, continue to represent potential explanations for at least a portion of the second malignancies. Despite these obstacles, continued discussion regarding optimal therapy of early-stage HL is warranted as additional phase III data becomes available.

LATE COMPLICATIONS OF THERAPY

Central to the discussion of chemotherapy alone compared with CMT is a brief review of the potential serious long-term complications of treatment. Potential late complications of current regimens are difficult to assess, given the modifications of both radiation techniques and chemotherapy agents over time. Abandonment of the MOPP (mechlorethamine, vincristine, procarbazine, prednisone) regimen and alkylating agents in the primary therapy of HL has virtually eliminated the incidence of secondary acute leukemia related to primary therapy, except in those receiving escalated (esc) BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen and alkylating agents in the primary therapy of HL has virtually eliminated the incidence of secondary acute leukemia related to primary therapy, except in those receiving escalated (esc) BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone). Even with the alkylator-dense escBEACOPP regimen, reducing the number of cycles resulted in many fewer cases of acute leukemia.6
The transition from extended field radiotherapy to combined-modality therapy with chemotherapy and involved field radiotherapy (IFRT) in the 1990s was the first step aimed at curbing radiation-related toxicities.\textsuperscript{7,8} Retrospective studies demonstrate a significant reduction in second breast cancers in women treated with mediastinal radiotherapy (RT) compared with mantle RT (hazard ratio [HR] 2.7, 95% CI: 1.1 to 6.9), and a breast in patients receiving IFRT compared with extended field radiotherapy (p = 0.04).\textsuperscript{9,10} In a population-based study of second cancers occurring up to 30 years after treatment in HL survivors, women treated in their twenties had the highest relative risk compared with an age matched control population (24.3% vs. 4.5% at 30 years).\textsuperscript{11} Of concern, there was no difference in the incidence of solid tumors in patients treated between 1970 to 1984 and 1985 to 1996, despite the likelihood that patients received more limited doses and fields of RT in the second era. In addition, the relative risk of second solid cancers was also increased after chemotherapy alone, perhaps associated with the increased risk of lung and bladder cancers associated with alkylating agents. A British national cohort study of 5,002 women treated with RT for HL reported a standardized incidence ratio of 5 for breast cancer risk and a remarkable standardized incidence ratio of 47 for those treated at age 14.\textsuperscript{12} Risk remained high more than 40 years after treatment. The risk of lung cancer is also substantially increased after both RT and chemotherapy for HL, most commonly in smokers, but not exclusively.\textsuperscript{13} Smoking increases the risk of lung cancer more than 20-fold in HL survivors and appears multiplicative, not additive, in combination with RT.\textsuperscript{14}

Reducing the dose and field of RT and eliminating alkylating agents from primary therapy will likely result in fewer second cancers, but it not clear that there is a “safe and effective” dose of RT.\textsuperscript{15} The German Hodgkin Study Group (GHSG) HD10 and HD11 trials, which compared limited chemotherapy combined with 20 or 30 Gy IFRT in early-stage HL, reported a 3.7% to 4.6% incidence of second malignancy at a median follow-up of 7.5 years with no difference in the incidence of second malignancies or deaths caused by second cancers in those receiving 20 Gy versus 30 Gy.\textsuperscript{16,17}

In addition to second cancers, cardiovascular and cerebrovascular diseases are common causes of premature death in HL survivors. Compared with population-based reference rates, Aleman et al. reported a 2- to 7-fold increased risk of myocardial infarction (MI), angina, congestive heart failure (CHF), and valvular disorders in HL survivors treated with mediastinal RT.\textsuperscript{18} Anthracyclines significantly added to the risk of CHF and valvular disorders with a 25-year cumulative incidence of CHF after mediastinal RT and anthracyclines of 7.9%. Swerdlow et al. found a standardized mortality ratio (SMR) of 2.5 for fatal MI in HL survivors. Risks were independently increased for patients treated with RT, anthracyclines, or vincristine.\textsuperscript{19} Risk was particularly high for patients receiving ABVD chemotherapy (SMR 9.5), including those who received ABVD but no mediastinal RT (SMR 7.8). Hodgson et al. recently showed a significant increase in cardiac-related hospitalizations in patients treated with ABVD alone compared with the general population, with a 10-year risk of cardiac-related hospitalization of 5.5% compared with 2.2% expected in the general population.\textsuperscript{20} After a median follow-up of 14.7 years for 1,279 patients treated with mediastinal RT, the 20-year cumulative incidence of cardiac events was 16%.\textsuperscript{21} Patients treated with neck and mediastinal RT had a 30-year cumulative incidence of stroke or transient ischemic attack of 7%, representing a two- and-a-half-fold increase over a control population.\textsuperscript{22}

When weighing the risks and benefits of various treatment approaches it is critical to take into account the site(s) of disease, patient’s age and gender, family history of cancer and cardiovascular disease, smoking history, and the presence of additional cardiovascular risk factors such as diabetes, hypertension, hypercholesterolemia, and obesity.

**KEY POINTS**

- Chemotherapy alone cures nearly 90% of patients with nonbulky HL, but is associated with a slightly higher relapse rate than combined-modality therapy.
- In the combined-modality approach to early-stage HL, the number of cycles of chemotherapy (two to four) and dose of radiotherapy (20 to 30 Gy) are dictated by the risk stratification group.
- Interim and end-of-treatment PET scans may help guide the decision of when to use radiotherapy.
- Patients with bulky disease should receive combined-modality therapy with four to six cycles of ABVD followed by IFRT.
- Late effects are more common with combined-modality therapy and may result in inferior overall-survival rates compared with chemotherapy alone. Modern radiotherapy techniques are likely to result in fewer long-term complications.

**RISK STRATIFICATION**

Comparing results of trials and discussing treatment recommendations for early-stage HL continues to be complicated by the lack of a uniform risk stratification system (Table 1). Current trials in North America differentiate treatment approaches based only on the presence or absence of bulky disease, with bulk defined as a mediastinal mass ratio (MMR) of more than 1/3 or a lymph node mass larger than 10 cm. The GHSG defines an unfavorable presentation as having any one of the following characteristics: an extranodal site of disease, patient’s age and gender, family history of cancer and cardiovascular disease, smoking history, and the presence of additional cardiovascular risk factors such as diabetes, hypertension, hypercholesterolemia, and obesity.
studies with comparable characteristics may provide more accurate comparisons. Ideally, a universal prognostic index should be developed and incorporated into all early-stage trials.

NONBULKY, EARLY-STAGE HODGKIN LYMPHOMA

Approximately 60% of patients with newly diagnosed HL will have stage I or II disease and the vast majority will be classified as nonbulky. Given the excellent prognosis of early-stage nonbulky HL, efforts to minimize therapy in HL have focused primarily on this group. The standard of care options for both CMT and chemotherapy alone, as well as the ongoing studies that may influence future treatment recommendations, are discussed below.

The objective of the GHSG HD10 and HD11 trials was to minimize the dose and field of RT, as well as the number of cycles of chemotherapy, but not to eliminate RT entirely. Results of these studies represent the current standard of care for CMT in early-stage HL. HD10, for patients with a “favorable” presentation by GHSG criteria, randomly assigned 1,370 patients to one of four groups: four cycles of ABVD plus 30 Gy IFRT; four cycles of ABVD plus 20 Gy IFRT; two cycles of ABVD plus 30 Gy IFRT; or two cycles ABVD plus 20 Gy RT. In this favorable subset, two cycles of ABVD plus 20 Gy of IFRT was equivalent to all other approaches and was associated with a 5-year freedom from treatment failure of 91% and overall survival (OS) of 97%. Patients with unfavorable results were enrolled on the HD11 trial (1,395 patients) and were randomly assigned to one of four groups: four cycles of ABVD plus 30 Gy IFRT; four cycles of ABVD plus 20 Gy IFRT; four cycles of standard BEACOPP plus 30 Gy IFRT; or four cycles of standard BEACOPP plus 20 Gy IFRT. Outcomes were superior for those receiving 30 Gy compared to 20 Gy, but the use of standard dose BEACOPP did not improve outcomes. At 5 years, the freedom from treatment failure was 85% and OS 95% for patients treated with four cycles of ABVD plus 30 Gy. Importantly and often misunderstood in the general oncology community, the number of cycles of ABVD (two vs. four) and the dose of RT (20 Gy vs. 30 Gy) should reflect the appropriate GHSG risk stratification.

In an effort to determine whether the use of chemotherapy alone resulted in a survival disadvantage for patients with early-stage HL, the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and Eastern Cooperative Oncology Group (ECOG) conducted a study (HD.6) of 405 patients with nonbulky stage I-IIA HL comparing ABVD alone with subtotal nodal irradiation (STNI), with or without ABVD. All patients in the ABVD-alone arm received four to six cycles of ABVD depending on computed tomography (CT) response following cycle two. In patients assigned to STNI, those with an unfavorable risk profile (Table 1) received two cycles of ABVD plus STNI, and those with a favorable risk profile received STNI alone. The 12-year PFS was 87% in the chemotherapy-alone arm compared with 92% in the RT arm (p = 0.05), but the 12-year OS favored the patients receiving ABVD alone; 94% compared with 87% (p = 0.04). In the ABVD-alone arm, there were 12 deaths (six caused by HL, four caused by second cancers, and two caused by cardiac events). In the RT arm, there were 24 deaths (four caused by HL, 10 caused by second cancers, two caused by cardiac events, three related to infection, and five from other causes). Importantly, 12-year follow-up does not yet reflect the striking increase in second malignancies and cardiovascular disease that begins approximately 15 to 20 years after initial therapy with extended field RT, raising the concern that the survival curves will continue to separate with longer follow-up. Applicability of results of the CMT arm are limited by the use of STNI, an outdated approach that likely holds significantly increased risk of late toxicity compared with modern limited-RT fields. However, two important end points of this study are still highly relevant to current therapy. First, this study represents the largest prospective series of nonbulky, early-stage HL patients treated with ABVD alone providing a reliable estimate of long-term PFS with this approach. Second, this study helps addresses the number of cycles of chemotherapy for patients treated with ABVD alone. All patients were assessed by CT following two cycles of chemotherapy for patients treated with ABVD alone.
ABVD. Sixty-nine of 196 (35%) patients treated with ABVD alone achieved complete response (CR) after two cycles. For patients who achieved CR by CT after two cycles, the 5-year PFS was 95% compared with 81% for patients who did not achieve CR after two cycles (Fig. 1). This data suggests that for patients with limited-stage, nonbulky HL who achieve a CR by CT after two cycles of ABVD, a total of four cycles is adequate.

In an attempt to more precisely compare HD.6 with HD10 and HD11 because of differences in eligibility, staging, end points, and follow-up duration, investigators performed an individual patient-data comparison of the ABVD-alone arm of HD.6 with the two cycles of ABVD plus 20 Gy IFRT arm of HD10 and the four cycles of ABVD plus 30 Gy IFRT arm of HD11. Patients were included in this analysis if eligible for HD.6 with the two cycles of ABVD plus 20 Gy IFRT arm of HD10 because of differences in eligibility, staging, end points treated with CMT (Table 2). For patients achieving a CR by CT after two cycles of ABVD, there was no improvement in outcome with RT. However, in patients who did not achieve a CR by CT after two cycles of ABVD, RT appears to improve PFS. At 8-years follow-up, there were 17 deaths (4.2%) in the 406 HD10/HD11 patients (five from HL and 12 from other causes) and nine (4.9%) in the 182 HD.6 patients (four from HL and five from other causes).

Several large European and North American trials are now evaluating interim PET-directed therapy in patients with early-stage HL, with the goal of minimizing chemotherapy cycles as well as avoiding or limiting RT. In the United Kingdom RAPID trial, patients with nonbulky stage I-IIA HL received three cycles of ABVD followed by a PET/CT. Patients with a negative scan (PET-) were randomized to IFRT or observation. All patients with a positive interim PET (PET+) scan received one additional cycle of ABVD and IFRT. Scans were considered “positive” if the London Deauville visual score was 3 or higher. 602 patients were randomly assigned: 33% were stage I and 67% were stage II; 68% were favorable by GHSG criteria and 63% were favorable by EORTC criteria. 75% of patients (420/565) had a negative interim PET and were randomly assigned to IFRT (209 patients) or observation (211 patients). At a median follow-up of 48.6 months from randomization, PET+ patients (145/565) had an excellent 3-year PFS of 85.9% and OS of 93.9%. PET- patients randomly assigned to observation had a 3-year PFS of 90.7% compared with 94.5% for those randomly assigned to IFRT (CI: −10.7% to 1.4%) and 3-year OS rates of 99.5% versus 97%, respectively. 25 of 209 PET- patients assigned to IFRT did not receive the RT. For PET- patients, the 3-year PFS for the 184/209 patients who received IFRT according to protocol assignment was 97% compared with 90.7% for those randomized to observation (p = 0.03). Of the seven deaths in the IFRT arm, five occurred in patients who never received RT. Universal application of these trial results will require strict adherence to the London Deauville criteria used in the trial. Outcomes for PET- patients treated with three cycles of ABVD with or without RT were excellent, but because of the lower limit of the confidence interval of −10.7%, the trial does not rule out an advantage in PFS with the use of IFRT. Importantly, even the PET+ patients had an excellent outcome when treated with four cycles of ABVD and IFRT, arguing against altering chemotherapy regimens on the basis of the interim PET.

Interim analysis of the phase III H10 (EORTC/LYSA/FIL) trial, which accrued 1,137 patients with newly diagnosed stage I or II classical HL, were recently presented. Patients were randomly assigned to PET-directed or standard therapy with modest variations in the schema for favorable compared to unfavorable patients by EORTC criteria (Fig. 2). All patients received two cycles of ABVD followed by a PET scan. In the PET-directed group, patients with a negative interim PET (PET-) received from two to four more cycles of ABVD whereas patients with a positive interim PET (PET+) received two cycles of escalated BEACOPP and 30 Gy INRT (involved node RT). Patients on the standard arm received from one to two more cycles of ABVD and 30 Gy INRT re-

![FIG 1. Freedom from disease progression for patients achieving CR/CRu after two cycles of ABVD compared with those who did not achieve CR/CRu after two cycles. Copyright 2012, N Engl J Med. Reprinted with permission.](image-url)
Pet positive patients received two cycles of escBEACOPP.

Favorable

Randomize

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Unfavorable

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FIG 2. Schema for H10 Trial (EORTC/LYSA/FIL).

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; LYSA, Lymphoma Study Association; FIL, Fondazione Italiana Linfomi; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; PET, 18FDG-positron emission tomography; INRT, involved node radiotherapy; escBEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone.

Regardless of the interim PET scan result. In the favorable arms (444 patients), the 1-year PFS was 100% in the RT group compared with 94.5% in the PET-negative patients not receiving RT; ten patients relapsed (one in the standard arm and nine in the PET-directed arm). In the unfavorable arms (693 patients), the 1-year PFS was 97.3% in the RT group compared with 94.7% (no RT); 23 patients relapsed (seven in the standard arm and 16 in the PET-directed arm). On the basis of the study stopping rules, this study was discontinued early because of the difference in relapse rates between the consolidative RT and observation arms. The question remains whether these small differences in PFS in favor of RT warrant the use of even limited RT in all patients without a proven survival benefit.

Two additional studies may provide additional insight into the number of cycles of chemotherapy needed in those who achieve an early CR by PET/CT and are treated with chemotherapy only. First, the ongoing GHSG HD16 trial, which includes only patients with favorable stage I-II HL according to the GHSG criteria, randomly assigns patients to standard therapy with two cycles of ABVD and 20 Gy IFRT compared with an experimental arm, in which patients are stratified by interim PET following two cycles of ABVD: PET-positive patients receive 20 Gy IFRT while PET-negative patients receive no further treatment. The second study, CALGB 50604, recently completed accrual with enrollment at 162 patients with nonbulky stage I-II HL. All patients received two cycles of ABVD followed by an interim PET/CT scan. PET negative patients received two more cycles of ABVD while PET positive patients received two cycles of escBEACOPP plus IFRT.

BULKY, EARLY-STAGE HODGKIN LYMPHOMA

The standard treatment for bulky early-stage HL outside the setting of a clinical trial remains CMT in most countries. Unfortunately, bulky mediastinal disease is most common in young women, the very population in which mediastinal RT holds the highest risk secondary to RT-induced breast cancers. Given the lower incidence of bulky HL, conducting randomized trials to evaluate the role of RT may not be feasible. Patients with bulky disease are represented in the unfavorable GHSG and EORTC early-stage studies, but will likely represent too small a group to perform subset analyses. The recent intergroup trial E2496 included 268 patients with stage I/II bulky HL of 854 total patients; patients were randomly assigned to ABVD or Stanford V.27 Patients on the ABVD arm with bulky mediastinal disease received from six to eight cycles of ABVD and modified IFRT (36 Gy) while patients on the Stanford V arm received modified IFRT (36 Gy) to sites larger than 5 cm in maximum transverse dimension at diagnosis plus spleen if involved on CT. For bulky patients on both arms, the 5-year failure-free survival and OS were 82% and 94%, respectively, with no difference between arms. Trials investigating the elimination or reduction of RT in this patient population should be compared with this data.

There is scant data regarding PET-directed therapy in limited-stage, bulky HL. A Canadian study of patients with residual abnormalities on CT scan after treatment used end of chemotherapy PET scans to guide consolidative RT.28 Patients with positive end of chemotherapy PET scans received consolidative RT but patients with negative end of chemotherapy PET scans received no further therapy. There was no difference in 3-year time to progression between the patients with bulky disease and those without bulky disease (86% vs. 91%, p = 0.71). Patients (160) in an Italian study of radiotherapy compared with observation for bulky disease (defined as at least 5 cm, median size 9 cm) and a negative end of chemotherapy PET showed an increase in relapses at 40 months in the patients who did not receive RT (14% vs. 4%).29

CONCLUSION

Chemotherapy alone cures 85% to 90% of patients with nonbulky HL with long-term survival rates of close to 95% expected. Preliminary results of the RAPID and EORTC H10 studies show that CMT results in a 4% to 6% improvement in 5-year PFS on average of patients with nonbulky early-stage HL may be associated with improved survivals caused by fewer late effects. Efforts to decrease dose and fields of RT will likely result in fewer longer-term complications; however, because mediastinal nodes are involved in the majority of patients with HL, most patients will continue to have at
least modest exposure to the heart, lungs, and breasts regardless of efforts to administer only involved field or even involved nodal RT. For all patients with initial bulky disease or those with nonbulky disease but a positive early or end of treatment PET, consolidative RT (30 Gy) is indicated.

The optimal number of cycles of ABVD chemotherapy in the combined modality setting is from two to four depending on the GHSG risk group. As few as three cycles may be adequate when using chemotherapy only, if an early interim PET is negative, however this data has not yet been published. Outside the setting of a clinical trial, from four to six cycles of ABVD is appropriate. There is no clear role for more intensive chemotherapy such as BEACOPP in the initial treatment of early-stage HL. Whether all or part of the bleomycin doses can be safely eliminated from the ABVD regimen is under study in the setting of advanced stage HL, as well as in early-stage disease in the setting of CMT. Hopefully, limiting the number of cycles of ABVD will result in less late cardiac complications. The addition of new agents such as brentuximab vedotin into first-line therapy may result in higher cure rates with fewer complications when compared with ABVD or CMT.

Disclosures of Potential Conflicts of Interest

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References


