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Balancing Risks and Benefits of Therapy for Patients with Favorable-Risk Limited-Stage Hodgkin Lymphoma: The Role of ABVD Chemotherapy Alone

Dr. Annette E. Hay, MB, ChB, MRCP, FRCPath and

Clinical Fellow, NCIC Clinical Trials Group, Queen's University, 10 Stuart Street, Kingston, Ontario, Canada, K7L 3N6, Phone: 613-533-6430, Fax: 613-533-2411

Ralph M. Meyer Dr., MD

President, Juravinski Hospital and Cancer Centre, Regional Vice President, Cancer Care Ontario, 711 Concession Street, Hamilton, Ontario, Canada, L8V 1C3, Phone 905-387-9711 (extension 63001), Fax: 905-575-6323

Annette E. Hay: AHay@ctg.queensu.ca; Ralph M. Meyer: Ralph.Meyer@jcc.hhsc.ca

SYNOPSIS

More than 85% of patients with non-bulky stage IA-IIA Hodgkin lymphoma will obtain long-term disease control. However, as long-term survival is dependent on both disease control and avoidance of late toxic effects associated with the treatment received, the initial choice of treatment can be associated with trade-offs that balance optimum disease control with avoidance of these late-effect risks. Previous radiation therapy paradigms that used wide-field target volumes were the major treatment modality associated with late-effects, which include risks of second cancers and cardiovascular disease. Current treatment options include combining involved-field radiation (IFRT) with chemotherapy consisting of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) as combined modality therapy (CMT), which provides optimum long-term disease control for 90–95% of patients but continues to be associated with risks of radiation therapy-related late-effects, and ABVD as a single modality, which is associated with risks of disease recurrence that are 5–7% greater than that observed with CMT, but avoids the late-effect risks associated with radiation therapy. Recent data suggest that positron emission tomography (PET) can be used to assist in assessing the risk-benefit proportions of these therapies at an individual patient level. As more than two decades of follow-up can be required to understand the magnitude of late-effect risks, health professionals and patients will continuously face the dilemma of making treatment decisions without the benefit of completely understanding the risk-benefit balances associated with how current treatments will affect all outcomes of interest in the decades to come. Optimum management of these patients therefore requires careful multidisciplinary evaluation and communication strategies that account for patient preferences.

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Correspondence to: Ralph M. Meyer, Dr., Ralph.Meyer@jcc.hhsc.ca.

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Keywords

Hodgkin lymphoma; Chemotherapy; Combined modality therapy; Radiation therapy; Review

INTRODUCTION

Current controversies in managing patients with Hodgkin lymphoma are a result of uncertainties in balancing the best measures to eradicate the disease while minimizing the risks of long-term adverse effects that are associated with available therapies. For patients with localized Hodgkin lymphoma and favorable risk features, debates relate to the relative merits of treatment with ABVD chemotherapy alone versus combining fewer cycles of this treatment with localized radiation therapy (RT); for those with advanced disease, debates center around use of ABVD versus bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone and procarbazine (BEACOPP). Common to both debates is realization that most clinical trials that inform today's practices do not directly address the morbidities and mortality that become apparent in the second and third decades post treatment and that currently available data about these long-term outcomes relate to previous treatment strategies that are now outdated.

Reviews describing these debates benefit from placing current perspectives onto a background of prior accomplishments in managing patients with Hodgkin lymphoma. Early in the 20th century the diagnosis was fatal to all but a few with accessible, localized tumors where radical surgical excision afforded freedom from disease^{1, 2}. Pioneers in radiation therapy discovered means to control localized disease^{3, 45}, over time observing fewer relapses with increasing radiation fields, leading to adoption of extended-field irradiation encompassing the mantle field (axillary, mediastinal and axillary nodes), spleen and para-aortic region^{6, 7}. Simultaneously, chemotherapy evolved from single-agent nitrogen mustard⁸ to combinations resulting in the possibility of cure, even for those with advanced disease⁹. Cure rates increased with co-administration of radiation and chemotherapy, termed combined modality therapy (CMT)¹⁰. By the turn of the millennium long-term disease control was observed in 80% – 90% of those with favorable limited-stage Hodgkin lymphoma treated with CMT and many reports described cure rates of greater than 90%^{10–12}. With long-term follow-up of young survivors, there was increasing recognition of the problem of late treatment-related toxicities resulting in premature death, despite cure of Hodgkin lymphoma¹³. Over recent decades, strategies attempting to reduce late effects while maintaining or improving disease control in newly diagnosed patients have included adoption of ABVD as the standard chemotherapy regimen because it is more effective than historical regimens and is not associated with the risks of leukemogenesis or gonadal toxicity¹⁴, reduction of radiation from extended to involved fields¹¹, abbreviation of the number of cycles of chemotherapy as part of CMT¹⁵ and omission of radiation therapy by utilizing ABVD chemotherapy alone^{16–18}.

The objective of this review is to describe the rationale and context of a treatment decision to use chemotherapy alone as treatment for patients with stage IA-IIA non-bulky Hodgkin lymphoma and builds upon evidence presented in a recent review¹⁹. As described in that review, a focus of the current debate about treatment options has been the reporting of the final results of the NCIC Clinical Trials Group (NCIC CTG) - Eastern Cooperative Oncology Group (ECOG) HD.6 trial, in which patients with stage IA-IIA non-bulky Hodgkin lymphoma were randomized to receive 4–6 cycles of ABVD alone (the choice of 4 vs. 6 cycles was based upon disease control assessment after two treatment cycles) or subtotal nodal radiation, given as a single modality to patients less than 40 years who had no more than three nodal sites of disease and an erythrocyte sedimentation rate (ESR) of less

than 50, or combined with two cycles of ABVD for patients not satisfying these three qualifying criteria¹⁶. The main results of this trial were that chemotherapy alone was associated with superior 12-year overall survival (94% vs. 87%; hazard ratio [HR] = 0.50, 95% confidence interval [CI], 0.25 to 0.99; P = 0.04) but inferior disease control as assessed by 12-year freedom from disease progression (87% vs. 92%; HR = 1.91, 95% CI, 0.99 to 3.69; P = 0.05). Superior overall survival with ABVD alone was because fewer deaths attributed to causes other than Hodgkin lymphoma were observed.

PATIENT POPULATION and CURRENT GUIDELINES

Several bodies have used various approaches to consider evidence and reach consensus to produce practice guideline recommendations intended to assist those managing patients with favorable-risk, limited-stage Hodgkin lymphoma^{20–23} (Table 1). While some details differ, these bodies have generally defined this population as those with stage IA-IIA non-bulky disease. Added factors used by some have included the number of nodal sites or areas, ESR and, less commonly in selected patients, B symptoms. Our discussion will be based on a population that includes all those with stage IA-IIA, non-bulky disease excepting those rare patients with these features who also have intra-abdominal disease. We have chosen these parameters because they were used as eligibility criteria in the NCIC CTG - ECOG HD.6 trial^{16, 24}.

Allowing for slight differences in population definition, recommendations from all four guideline bodies include use of CMT with 2–4 cycles of ABVD and IFRT with 20–30 Gy (variations within these ranges depend on patient specifics). In addition, one body, the National Comprehensive Cancer Network (NCCN), also includes 4–6 cycles of ABVD alone as an acceptable alternative, but assigns this recommendation a lower level of evidence (Level 2A). Of these four guidelines, only the NCCN guidelines included consideration of the final analysis of the HD.6 trial, which was published in 2012 and reports 12-year outcomes¹⁶. The other three bodies published their recommendations prior to 2012 and considered the initial HD.6 results, which were published in 2005 and described 5-year outcomes²⁴; in comparison with the final reporting of that trial; these earlier results demonstrated similar superiority of radiation-based therapy with respect to disease control with no differences in overall survival detected. Among guideline developers who do not recommend ABVD alone as a treatment option, reasons cited include the preliminary nature of the report describing 5-year outcomes, inferior disease control outcomes associated with this therapy, the outdated nature of subtotal nodal RT received by HD.6 control arm patients, and the expectation that current use of IFRT will be associated with a reduced risk of adverse late treatment effects.

COMPONENTS OF THE DECISION-MAKING PROCESS

Outcome Measures and Surrogates

While overall survival coupled with health-related quality of life are likely the outcome measures of most importance to patients, clinical trials testing treatment strategies for populations with stage IA-IIA non-bulky Hodgkin lymphoma usually prioritize endpoints that measure disease control. The reasons for using these endpoints include the historical observation that disease control was a reasonable surrogate for overall survival and that earlier availability of robust disease-control data facilitated timely reporting. However, recent data demonstrate that progressive disease accounts for a minority of deaths in patients with stage IA-IIA non-bulky Hodgkin lymphoma, even when median follow-ups are less than a decade (and thus do yet account for the additional late-effects mortality rates that will be observed in the second and third decades that follow treatment)^{15–17}. Therefore, while common, use of disease-control surrogate outcomes obtained with less than a decade of

follow-up is associated with substantial risks if intended to be a proxy for long-term survival.

Compounding this generic limitation is the need for clarity around the problems associated with specific disease-control endpoints. For instance, a recommended endpoint is time to progression (TTP)²⁵. In calculating TTP, events contributing to this composite endpoint include the first of progressive Hodgkin lymphoma or death from Hodgkin lymphoma. The endpoint thus fails to capture deaths attributed to causes other than progressive Hodgkin lymphoma. Furthermore, given that stage IA-IIA non-bulky Hodgkin lymphoma is not associated with a sufficient disease burden to directly affect survival unless preceded by disease progression, all events associated with this endpoint will be due to disease progression²⁶. As most deaths in this population are unassociated with disease progression, TTP is not, nor can it be expected to be, an accurate surrogate for overall survival.

Another surrogate endpoint is progression-free survival (PFS), which is also a composite in that events include the first of progressive Hodgkin lymphoma or death from any cause. This endpoint thus has the potential to account for deaths attributed to late-treatment effects provided that the reporting of the clinical trial includes a duration of follow-up that is sufficient to span the time period when late-effects occur, and that the number (and thus relative proportion) of types of events (i.e., progressive disease vs. death from any cause) that comprise this composite are provided²⁶⁻²⁹. Without such clarity, PFS has also been shown to be an unreliable proxy for long-term overall survival^{16, 17, 26}.

Practitioners and policy makers need to recognize the important differences that exist between debates around use of disease-control endpoints as surrogates for overall survival in trials testing therapies for patients with metastatic carcinoma versus those evaluating patients with stage IA-IIA non-bulky Hodgkin lymphoma. In the former, any lack of surrogacy likely emphasizes the extreme precision of disease progression measurement associated with principles of conducting explanatory clinical trials³⁰, especially within the context of limited survival durations; this limitation may be exaggerated when subsequent lines of therapy provide transient benefits. In contrast, for patients with stage IA-IIA non-bulky Hodgkin lymphoma, lack of surrogacy relates to deaths from causes other than progressive disease – an observation that is further compounded by knowledge that some of these deaths are related to the therapy received. Thus, the outcomes of interest that are associated with treatment policy determinations for these patients are associated with a unique paradigm that is distinct from considerations used for most other cancers: long-term overall survival is the outcome of greatest importance, data for this endpoint are largely unavailable for today's purported new therapeutic advances, and reliable proxy outcome measures that might facilitate estimates of the relative long-term survivals associated with today's competing options do not exist. Finally, contributing to current dilemmas about outcome measures is the lack of published quality of life data from trials that compare CMT and ABVD alone approaches to management. Evaluations of this endpoint, both during and following treatment may assist in determining patient preferences.

Therapy that includes Radiation

The background and rationale for choosing CMT that includes modern radiation treatment practices is detailed in a companion article³¹. Recognizing that the options of CMT and ABVD alone are associated with relative risks and benefits, and trade-offs thus exist, we recognize several parameters that require consideration when choosing an overall treatment policy and implementing this policy in individual patients.

First, adverse late-effects associated with wide-field radiation strategies such as subtotal nodal and extended-field RT are well documented³². Examples include a population-based

cancer registry study that includes 32,591 patients and identified significantly increased risks for all solid tumors; whereas chemotherapy alone resulted in an observed to expected (O/E) ratio of 1.7, the ratio for patients receiving RT was 4.4 when follow-up was 20–24 years post-diagnosis. Associations were observed between RT and risks for esophageal, gastric, rectal, female breast, bladder, thyroid and bone/connective tissue malignancies³³. That these risks exist with outdated RT strategies is well accepted and includes recognition that risks increase through at least the second and third decades of follow-up. The outcomes of HD.6 control arm patients, who received subtotal nodal RT, are consistent with these data. With a median follow-up of 4.2 years, there were 10 second cancers and 12 cardiac events in the 203 patients allocated to receive RT-containing therapy²⁴, whereas with a median follow-up of 11.3 years, there were 23 and 26 events observed, respectively¹⁶.

Second, we recognize that when compared with outdated RT, modern RT includes reduced doses and smaller target volumes and will be associated with reduced risks of late-effects³². However, the magnitude of reduction remains uncertain and likely remains important. For instance, observations from the German Hodgkin Study Group (GHSG) HD8 trial, which randomly allocated patients to receive CMT that included EFRT or IFRT observed that with a median follow-up of 4.6 years, 24 of 532 (4.5%) patients assigned to EFRT and 15 of 532 (2.8%) assigned to IFRT had developed secondary malignancies³⁴; with a median follow-up of 11 years, the incidence of second malignancies had increased to 58 (10.9%) and 45 (8.5%) events respectively³⁵. While cardiac events were not tracked, the incidence of deaths attributed to cardiac causes showed a similar trend: at a median of 4.6 years, there were 5 and 7 cardiac deaths in the EFRT and IFRT groups, respectively, whereas with a median follow-up of 11 years, there were 15 and 12 such deaths. Thus, while risks will be reduced with IFRT as compared with EFRT, important risks of late-effects appear to remain with IFRT especially when one considers that the data upon which this concern is based do not yet include follow-ups well into the second decade post-treatment.

Third, we have previously reported our speculation that that risks of late-effects first become apparent in older patients^{19, 26}. We base this premise on the apparent increased risks of both death and of non-fatal second cancers and cardiac events observed in patients allocated to receive RT in the HD.6 trial who were assigned to the unfavorable-risk cohort, a determination that included older age as a criterion¹⁶, and the observation that excess absolute risks of second cancers increases with attained age following treatment for Hodgkin lymphoma³⁶. This premise is further suggested by outcomes observed in an individual-patient cross-trial comparison of patients assigned to ABVD alone in HD.6 with patients assigned to the preferred arms of the GHSG HD10/11 trials; more deaths without prior progression of Hodgkin lymphoma were observed in older patients²⁶. If true, our supposition would mean that patients younger than 40 years at diagnosis will require follow-up well into the second, if not third, decade post-therapy before risks of adverse late-effects can be understood.

Excellent outcomes have been achieved with CMT strategies tested in the GHSG HD10 trial (8-year freedom from treatment failure of 86% with two cycles of ABVD and 20 Gy IFRT)¹⁵ and the European Organization for Research and Treatment of Cancer (EORTC) H8F trial (10-year event-free survival of 93% with three cycles of MOPP-ABV and 36–40 Gy IFRT)¹¹. These results establish a baseline for comparing new strategies that include involved nodal (INRT)³⁷ and involved site (ISRT)³⁸ radiation. However, while results from these two trials inform current recommendations, neither report includes median follow-up into the beginning of the second decade, let alone into the third decade post-treatment, and median ages were 38.7 and 30 years, respectively – meaning that extended follow-up is needed to better understand the risks of late-effects in younger patients. The relative merits of CMT strategies incorporating INRT and ISRT will require similar scrutiny with long-

term follow-up of comparative data evaluating disease control and occurrence of late-effects; given the time frames required, reports with such details are more than a decade away.

Therapy with Chemotherapy Alone

Systematic evaluations of a strategy to treat patients with stage IA-IIA, non-bulky Hodgkin lymphoma with chemotherapy alone should only consider trials that test optimum chemotherapy (i.e., ABVD). Thus, previous trials evaluating regimens such as MOPP (or its equivalents)¹⁴, epirubicin, vinblastine, etoposide (EVE)³⁹, and epirubicin, bleomycin, vinblastine and prednisone (EBVP)⁴⁰ do not provide data that contribute to current decision-making. Similarly, a 2011 Cochrane review does not assist policy determination because this analysis included three such trials; the other two trials included did test ABVD but evaluated populations that included patients with stage III and bulky disease⁴¹.

We have previously summarized the specifics and context of randomized trials comparing chemotherapy alone with strategies that include RT for patients with limited-stage Hodgkin lymphoma^{19, 42}. One of these reports described results of a MEDLINE search using PubMed from January 2002 to February 2007 and a review of abstracts from the American Society of Hematology (ASH) and American Society of Clinical Oncology (ASCO) annual meetings from 2002 to 2006. This search identified three RCTs testing ABVD alone in previously untreated adult patients with limited-stage Hodgkin lymphoma⁴². One of these trials was the initial report of HD.6²⁴, one was a single institution comparison of ABVD with CMT in patients with stage I-II A or B and stage IIIA disease⁴³ and one was a subset analysis of a larger trial evaluating patients with all stages of Hodgkin lymphoma⁴⁴. None of the trials detected differences in overall survival and only the HD.6 trial had sufficient power to detect differences in disease control, which favored the group receiving RT. The premise that ABVD alone is associated with disease control that is approximately 7% worse than CMT approaches comes from these data.

We repeated this PubMed search in May 2013 using the MESH term 'Hodgkin' and the limiting terms 'randomized controlled trials' and 'meta-analysis' to identify publications since February 2007; 231 citations were identified and reviewed. After excluding articles that were not phase III randomized controlled trials or meta-analyses testing ABVD-based chemotherapy alone as initial therapy for patients with non-bulky stage IA-IIA Hodgkin lymphoma, three publications remained. These included the above-described final analysis of HD.6¹⁶, a meta-analysis⁴¹, and a pediatric study testing COPP/ABV therapy alone⁴⁵. Furthermore, we reviewed ASH abstracts from 2007 to 2012 and identified two additional RCTs; the United Kingdom National Cancer Research Institute (NCRI) RAPID¹⁷ and EORTC-led H10¹⁸ trials, which both tested response-adapted strategies using positron emission tomography (PET).

We have previously provided our interpretation of the important conclusions associated with HD.6 data¹⁹. First, superior 12-year overall survival (94% vs. 87%) was observed with ABVD alone and this difference was due to more deaths in the RT arm from causes other than progressive Hodgkin lymphoma or early treatment complication; that these results are contributed to by use of an outdated RT strategy is recognized. Second, the 12-year outcomes of patients assigned to ABVD alone, overall survival of 94% and freedom from disease progression of 87%, are considered to be excellent and comparable to those reported in randomized trials testing CMT that includes IFRT. Third, the observation that the risk of disease progression with chemotherapy alone was almost twice that associated with treatment that includes RT (HR = 1.91) while the risk of death was reduced by half (HR = 0.5) refutes use of disease control measures as an accurate proxy for overall survival in this patient population. Finally, among patients in the ABVD alone cohort who were evaluable

for response after two treatment cycles (90% of patients), those with a complete or unconfirmed complete remission (CR/CRu) had superior 12-year disease control (94% vs. 81%; HR = 0.28; P = 0.02) and a trend to superior 12-year overall survival (98% vs. 92%; HR = 0.17; P = 0.06) when compared with those not achieving a CR/CRu status; these data provide a basis of support to test response-adapted therapy using PET.

The UK RAPID and EORTC-led H10 trials have been reported in preliminary abstract form and provide insights about PET-directed response-adapted therapy and comparisons of chemotherapy alone with CMT. Using a non-inferiority design, the RAPID trial enrolled 602 patients with stage IA-IIA non-bulky Hodgkin lymphoma between 2003 and 2010¹⁷. All received three cycles of ABVD followed by centrally-reviewed PET. Those with a scan deemed to be consistent with potential persisting disease received a fourth cycle of ABVD and IFRT. Those with negative scan were randomized to receive IFRT and no further treatment. Of the 426 patients with a negative scan (75% of those accrued), 420 were randomized and included in an intent-to-treat analysis that demonstrated 3-year PFSs of 90.7% among those receiving ABVD alone and 93.8% among those randomized to receive IFRT. This difference of -2.9% was associated with 95% confidence intervals of -10.7% and +1.4% and thus exceeded the pre-specified non-inferiority boundary of -7%. The 3-yr overall survivals were 99.5% among those allocated to ABVD alone and 97% among those allocated to IFRT. The authors concluded that patients with a negative PET scan after three cycles of ABVD do not require IFRT, chemotherapy alone reduces treatment time and costs, and improves tolerability while removing the burden of early and late radiation-associated toxicities¹⁷. Given the non-inferiority design, subsequent reporting will need to include the results of a per-protocol analysis.

The H10¹⁸ trial began accruing patients ages 15 to 70 with newly diagnosed supra-diaphragmatic stage I-II classic Hodgkin lymphoma in 2006 – we confine our synopsis to the favorable risk population who were identified as having fewer than four nodal areas of disease with no areas of bulky disease, ages less than 50 years, and ESR less than 30 with B symptoms or less than 50 without B symptoms (the H10F trial). All patients underwent PET after two cycles of ABVD; patients randomized to a control arm received three cycles of ABVD and 30 Gy INRT without consideration of PET results whereas those in the experimental arm received PET-directed therapy. Experimental arm patients with negative PET scan received two additional cycles of ABVD (total of four cycles) and those with a positive scan received two cycles of escalated-dose BEACOPP and 30 Gy INRT. Of 444 patients, 381 (86%) were deemed to be PET negative; the 1-year PFS outcomes were 94.9% with ABVD alone and 100% with CMT (HR 9.36, 95% CI 2.45, 35.73). These findings led an independent Data Safety Monitoring Committee to recommend that the trial be halted, including with an explanation that the *a priori* null hypothesis for non-inferiority would not be rejected.

While determination of practice policies requires results from properly designed and executed randomized controlled trials, non-randomized comparisons may contribute additional context and allow for hypothesis generation. The NCIC CTG and GHSG have thus conducted an individual-patient cross trial comparison²⁶ evaluating 588 patients that would have been mutually eligible for the HD.6 trial and either the GHSG HD10¹⁵ or HD11 trial⁴⁶ (Table 2, Figure 1). The 8-year TTP was superior and PFS trended toward superiority in the GHSG cohort, who were assigned to CMT. No differences in 8-year overall survival were apparent (95% in both cohorts). With a median follow-up of 11.2 years, 10 deaths were observed in 182 patients in the HD.6 cohort, 5 from Hodgkin lymphoma or immediate treatment toxicity and 5 from other causes; with a median follow up of 7.6 years, 19 deaths were observed in 406 patients in the GHSG cohort, 7 from Hodgkin lymphoma or immediate treatment toxicity and 12 from other causes. All TTP events were due to disease

progression. Of the 27 PFS events in HD.6, 23 were due to disease progression and four were deaths without prior disease progression; of the 38 PFS events in the GHSG cohorts, 25 were due to disease progression and 13 were deaths without prior disease progression. A subset analysis of those eligible for HD10 suggested disease control benefits associated with CMT may be limited to those not achieving CR/CRu, as assessed by physical examination and CT scanning. Among those assessed as achieving a CR/CRu after 2 cycles of ABVD; the respective 8-year TTP and overall survivals were 95% and 100% in the HD.6 cohort and 93% and 96% in the HD10 cohort. In contrast, among those assessed as not achieving a CR/CRu after 2 cycles of ABVD; the respective 8-year TTP and overall survivals were 78% and 91% in the HD.6 cohort and 92% and 95% in the HD10 cohort.

In Table 3, we summarize the relevant parameters associated with these comparative reports evaluating response-adapted therapy. Important differences include the randomized and non-randomized designs, the median durations of follow-up, the patient populations included, the timing of response assessment, the modality for assessing response and the determinants for a positive or negative result. These variations likely explain the major differences in the proportions of patients deemed to have achieved a CR state at the specific evaluation time point with values of 40% in the HD.6 trial, 62% in the HD10 trial, 75% in the RAPID trial and 86% in the H10F trial. Across these reports, there are considerable differences of the benchmark time point used for endpoint comparison (PFS assessed at 1, 3, and 8 years) and the durations of median follow-up. However, allowing for these differences, use of response-adapted strategies appears to have the potential to narrow the gap in PFS differences between ABVD alone and CMT approaches observed with non-response-adapted strategies from 7% to less than 5%. Based on these data and previous results observed with evaluations of non-response-adapted strategies, it appears highly unlikely that overall survival will be inferior with ABVD alone used according to a response-adapted strategy; given uncertainties associated with the frequency of late-effects that may be observed during the second and third decades of follow-up of patients treated with CMT that incorporates modern RT strategies, the potential for superior overall survival using a strategy of ABVD alone is very plausible. Necessary parameters for long-term overall survival to be superior with ABVD alone include accounting for late-effects associated with an increased use of second-line therapy that is likely to be required in up to 5% of patients and assurances that with long-term follow-up more frequent late disease recurrence is not observed.

It is essential to note that these data do not include patients with bulky disease. Furthermore, these data either directly support, or are consistent with, a recommendation that patients who do not enter a CR/CRu status with mid-treatment evaluation should receive radiation therapy.

THE PRESENT AND FUTURE

Based on the above data, we recommend that new patients with stage IA-IIA non-bulky Hodgkin lymphoma be presented with the option to receive treatment with a strategy that has as its intent therapy with ABVD alone. The advantages of this strategy include high expectations of disease control, avoidance of radiation-related late-effects and, based on high-quality data, expectations of at least comparable overall survival. This strategy should be implemented according to a response-adapted paradigm with mid-treatment evaluation of disease response using PET. We recognize that this strategy is shaped by the HD.6 trial, which evaluated outdated RT technology, the preliminary nature of the data associated with the RAPID and H10F trials and the non-randomized design of the HD.6 – HD10/11 comparison. We also recognize that there are remaining uncertainties about the optimum timing of mid-treatment evaluation (e.g., after two vs. after three treatment cycles) and the

specifics associated with determining PET positivity versus negativity. Long-term disease control with initial therapy according to this strategy may be inferior to a CMT strategy, but we expect the margin of inferiority to be less than 5% and that this risk will be compensated by avoidance of late-effects that are attributed to RT. In discussing this option with patients, careful presentation of a CMT option is also required and these options are best presented through multidisciplinary collaborations that include a hematologist or medical oncologist and a radiation oncologist.

We expect that future advances will include refinements in identifying patient populations through use of predictive biomarkers⁴⁷ with potential candidates including 3-dimensional telomere signatures⁴⁸ macrophage-like genetic signatures of Hodgkin Reed Sternberg cells⁴⁹ and plasma Epstein Barr Virus DNA levels⁵⁰. Refinements in response assessment will also include these laboratory-based biomarkers and applications of new imaging technologies (e.g. new PET ligands) that include understandings of optimum timing and standardization of response assessment. We expect that RT technologies will continue to evolve so that disease control can be maximized while treatment to normal structures is minimized^{51, 52} and that new systemic therapies that include targeted agents, such as brentuximab⁵³, will provide new options to current therapies. These future opportunities will require high-quality clinical trials and multidisciplinary collaboration and must account for a fundamental paradigm associated with this patient population, which is the importance of long-term outcomes and our limitations in appreciating all details of how these are affected by today's treatment choices.

Reference List

1. Gall EA. The surgical treatment of malignant lymphoma. *Annals of Surgery*. 1943 Jan 12; 118(6): 1064–70. [PubMed: 17858327]
2. Pack GT, Molander DW. The Surgical Treatment of Hodgkin's Disease. *Cancer Research*. 1966 Jun 1; 26(6 Part 1):1254–63. [PubMed: 5947349]
3. Gilbert R, Babaianta L. Notre methode de roentgentherapie da la lymphogranulomatose (Hodgkin): Resultats eloignes. *Acta Radiologica*. 1931 Dec 31; 12(6):523–9.
4. Peters V. A study of survivals in Hodgkin's disease treated radiologically. *Am J Roentgenol Radium Ther*. 1950; 63:299–311.
5. Kaplan HS. The radical radiotherapy of regionally localized Hodgkin's disease. *Radiology*. 1962; (78):553–61. [PubMed: 14453744]
6. Carde P, Burgers JM, Henry-Amar M, et al. Clinical stages I and II Hodgkin's disease: a specifically tailored therapy according to prognostic factors. *Journal of Clinical Oncology*. 1988 Feb 1; 6(2): 239–52. [PubMed: 2578012]
7. Tubiana M, Henry-Amar M, Hayat M, et al. The EORTC treatment of early stages of hodgkin's disease: The role of radiotherapy. *International Journal of Radiation Oncology*Biophysics*. 1984 Feb; 10(2):197–210.
8. WILL DAMESHEK, LOUI WEISFUSE, TOBI STEIN. Nitrogen mustard in Hodgkin's Disease: Analysis of fifty consecutive cases. *Blood*. 1949 Apr 1; 4(4):338–79. [PubMed: 18116112]
9. DEVITA JR, SERPICK AA, Carbone PP. Combination Chemotherapy in the Treatment of Advanced Hodgkin's Disease. *Annals of Internal Medicine*. 1970 Dec 1; 73(6):881–95. [PubMed: 5525541]
10. Engert A, Franklin J, Eich HT, et al. Two Cycles of Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine Plus Extended-Field Radiotherapy Is Superior to Radiotherapy Alone in Early Favorable Hodgkin's Lymphoma: Final Results of the GHSG HD7 Trial. *Journal of Clinical Oncology*. 2007 Aug 10; 25(23):3495–502. [PubMed: 17606976]
11. Ferme C, Eghbali H, Meerwaldt JH, et al. Chemotherapy plus Involved-Field Radiation in Early-Stage Hodgkin's Disease. *N Engl J Med*. 2007 Nov 8; 357(19):1916–27. [PubMed: 17989384]

12. Press OW, LeBlanc M, Lichter AS, et al. Phase III Randomized Intergroup Trial of Subtotal Lymphoid Irradiation Versus Doxorubicin, Vinblastine, and Subtotal Lymphoid Irradiation for Stage IA to IIA Hodgkin's Disease. *Journal of Clinical Oncology*. 2001 Nov 15; 19(22):4238–44. [PubMed: 11709567]
13. Henry-Amar, M.; Aeppli, DM.; Anderson, J. Long term survival and study of causes of death. In: Somers, R.; Henry-Amar, M.; Meerwaldt, JK.; Carde, P., editors. *Treatment strategy in Hodgkin's disease*. London: John Libbey and co; 1990. p. 381-418.
14. Carde P, Hagenbeek A, Hayat M, et al. Clinical staging versus laparotomy and combined modality with MOPP versus ABVD in early-stage Hodgkin's disease: the H6 twin randomized trials from the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Group. *Journal of Clinical Oncology*. 1993 Nov 1; 11(11):2258–72. [PubMed: 7693881]
15. Engert A, Plutschow A, Eich HT, et al. Reduced Treatment Intensity in Patients with Early-Stage Hodgkin's Lymphoma. *N Engl J Med*. 2010 Aug 11; 363(7):640–52. [PubMed: 20818855]
16. Meyer RM, Gospodarowicz MK, Connors JM, et al. ABVD Alone versus Radiation-Based Therapy in Limited-Stage Hodgkin's Lymphoma. *N Engl J Med*. 2011 Dec 11; 366(5):399–408. [PubMed: 22149921]
17. Radford J, Barrington S, Counsell N, et al. Involved Field Radiotherapy Versus No Further Treatment in Patients with Clinical Stages IA and IIA Hodgkin Lymphoma and a 'Negative' PET Scan After 3 Cycles ABVD. Results of the UK NCRI RAPID Trial. *ASH Annual Meeting Abstracts*. 2012 Nov 16.120(21):547.
18. Andre MP, Reman O, Federico M, et al. Interim Analysis of the Randomized EORTC/Lysa/Fil Intergroup H10 Trial On Early PET-Scan Driven Treatment Adaptation in Stage I/II Hodgkin Lymphoma. *ASH Annual Meeting Abstracts*. 2012 Nov 16.120(21):549.
19. Meyer RM, Hoppe RT. Point/counterpoint: early-stage Hodgkin lymphoma and the role of radiation therapy. *Blood*. 2012 Nov 29; 120(23):4488–95. [PubMed: 22821764]
20. NCCN Clinical Practice Guidelines in Oncology: Hodgkin Lymphoma. National Comprehensive Cancer Network; 2013. (Version 2) Available at: URL: www.nccn.org
21. Eichenauer DA, Engert A, Dreyling M. On behalf of the ESMO Guidelines Working Group. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2011 Sep 1; 22(suppl 6):vi55–vi58. [PubMed: 21908505]
22. Brusamolino E, Bacigalupo A, Barosi G, et al. Classical Hodgkins lymphoma in adults: guidelines of the Italian Society of Hematology, the Italian Society of Experimental Hematology, and the Italian Group for Bone Marrow Transplantation on initial work-up, management, and follow-up. *Haematologica*. 2009 Apr 1; 94(4):550–65. [PubMed: 19278966]
23. Das, P.; Ng, A.; Constine, LS., et al. ACR Appropriateness Criteria; Hodgkin's lymphoma - favorable prognosis stage I and II. American College of Radiology. 2008. Available at: URL: <http://www.guideline.gov/content.aspx?id=32633&search=hodgkin+lymphoma>
24. Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized Comparison of ABVD Chemotherapy With a Strategy That Includes Radiation Therapy in Patients With Limited-Stage Hodgkin's Lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. *Journal of Clinical Oncology*. 2005 Jul 20; 23(21):4634–42. [PubMed: 15837968]
25. Cheson BD, Pfistner B, Juweid ME, et al. Revised Response Criteria for Malignant Lymphoma. *Journal of Clinical Oncology*. 2007 Feb 10; 25(5):579–86. [PubMed: 17242396]
26. Hay AE, Klimm B, Chen BE, et al. An Individual Patient-Data Comparison of Combined-Modality Therapy and ABVD Alone for Patients with Limited-Stage Hodgkin Lymphoma. *Annals of Oncology*. 2013 in press.
27. Wu L, Cook RJ. Misspecification of Cox regression models with composite endpoints. *Statist Med*. 2012 Dec 10; 31(28):3545–62.
28. Pfirrmann M, Hochhaus A, Lauseker M, Saussele S, Hehlmann R, Hasford J. Recommendations to meet statistical challenges arising from endpoints beyond overall survival in clinical trials on chronic myeloid leukemia. *Leukemia*. 2011 Sep; 25(9):1433–8. [PubMed: 21597465]

29. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin G. Composite outcomes in randomized trials: Greater precision but with greater uncertainty? *JAMA: The Journal of the American Medical Association*. 2003 May 21; 289(19):2554–9. [PubMed: 12759327]
30. Meyer RM. Contrasting Explanatory and Pragmatic Randomized Controlled Trials in Oncology. *American Society of Clinical Oncology Annual Meeting Book*. 2011:31.
31. Andre MP. TO BE CONFIRMED. *Hematology/Oncology Clinics of North America*. 2013 (in press).
32. Hodgson DC. Late Effects in the Era of Modern Therapy for Hodgkin Lymphoma. *ASH Education Program Book*. 2011 Dec 10; 2011(1):323–9.
33. Dores GM, Metayer C, Curtis RE, et al. Second Malignant Neoplasms Among Long-Term Survivors of Hodgkin's Disease: A Population-Based Evaluation Over 25 Years. *Journal of Clinical Oncology*. 2002 Aug 15; 20(16):3484–94. [PubMed: 12177110]
34. Engert A, Schiller P, Josting A, et al. Involved-Field Radiotherapy Is Equally Effective and Less Toxic Compared With Extended-Field Radiotherapy After Four Cycles of Chemotherapy in Patients With Early-Stage Unfavorable Hodgkin's Lymphoma: Results of the HD8 Trial of the German Hodgkin's Lymphoma Study Group. *Journal of Clinical Oncology*. 2003 Oct 1; 21(19):3601–8. [PubMed: 12913100]
35. Sasse S, Klimm B, Goergen H, et al. Comparing long-term toxicity and efficacy of combined modality treatment including extended- or involved-field radiotherapy in early-stage Hodgkin's lymphoma. *Annals of Oncology*. 2012 Nov 1; 23(11):2953–9. [PubMed: 22767583]
36. Hodgson DC, Gilbert ES, Dores GM, et al. Long-Term Solid Cancer Risk Among 5-Year Survivors of Hodgkin's Lymphoma. *Journal of Clinical Oncology*. 2007 Apr 20; 25(12):1489–97. [PubMed: 17372278]
37. Campbell BA, Voss N, Pickles T, et al. Involved-Nodal Radiation Therapy As a Component of Combination Therapy for Limited-Stage Hodgkin's Lymphoma: A Question of Field Size. *Journal of Clinical Oncology*. 2008 Nov 10; 26(32):5170–4. [PubMed: 18838714]
38. Specht L, Yahalom J, Illidge T, et al. Modern Radiation Therapy for Hodgkin Lymphoma: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group (ILROG). *International Journal of Radiation Oncology*Biophysics*. 2013 (in press).
39. Pavone V, Ricardi U, Luminari S, et al. ABVD plus radiotherapy versus EVE plus radiotherapy in unfavorable stage IA and IIA Hodgkin's lymphoma: results from an Intergruppo Italiano Linfomi randomized study. *Annals of Oncology*. 2008 Apr 1; 19(4):763–8. [PubMed: 18180244]
40. Noordijk EM, Carde P, Dupouy N, et al. Combined-Modality Therapy for Clinical Stage I or II Hodgkin's Lymphoma: Long-Term Results of the European Organisation for Research and Treatment of Cancer H7 Randomized Controlled Trials. *Journal of Clinical Oncology*. 2006 Jul 1; 24(19):3128–35. [PubMed: 16754934]
41. Herbst C, Rehan F, Skoetz N, et al. Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma. *Cochrane Database Syst Rev*. 2011
42. Meyer, RM. Selected management issues of patients with Hodgkin Lymphoma. In: Crowther, MA.; Ginsberg, J.; Schunemann, HJ.; Meyer, RM.; Lottenbert, R., editors. *Evidence-Based Hematology*. 1. Wiley-Blackwell; 2008. p. 365-71.
43. Straus DJ, Portlock CS, Qin J, et al. Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. *Blood*. 2004 Dec 1; 104(12):3483–9. [PubMed: 15315964]
44. Laskar S, Gupta T, Vimal S, et al. Consolidation Radiation After Complete Remission in Hodgkin's Disease Following Six Cycles of Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine Chemotherapy: Is There a Need? *Journal of Clinical Oncology*. 2004 Jan 1; 22(1):62–8. [PubMed: 14657226]
45. Wolden SL, Chen L, Kelly KM, et al. Long-Term Results of CCG 5942: A Randomized Comparison of Chemotherapy With and Without Radiotherapy for Children With Hodgkin's Lymphoma: A Report From the Children's Oncology Group. *Journal of Clinical Oncology*. 2012 Sep 10; 30(26):3174–80. [PubMed: 22649136]

46. Eich HT, Diehl V, Goergen H, et al. Intensified Chemotherapy and Dose-Reduced Involved-Field Radiotherapy in Patients With Early Unfavorable Hodgkin's Lymphoma: Final Analysis of the German Hodgkin Study Group HD11 Trial. *Journal of Clinical Oncology*. 2010 Sep 20; 28(27): 4199–206. [PubMed: 20713848]
47. Meyer RM. EBV DNA: a Hodgkin lymphoma biomarker? *Blood*. 2013 May 2; 121(18):3541–2. [PubMed: 23640993]
48. Knecht H, Kongruttanachok N, Sawan B, et al. Three-dimensional telomere signatures of Hodgkin- and Reed-Sternberg cells at diagnosis identify patients with poor response to conventional chemotherapy. *Translational Oncology*. 2012; 5(4):269–77. [PubMed: 22937179]
49. Steidl C, Diepstra A, Lee T, et al. Gene expression profiling of microdissected Hodgkin Reed-Sternberg cells correlates with treatment outcome in classical Hodgkin lymphoma. *Blood*. 2012 Oct 25; 120(17):3530–40. [PubMed: 22955918]
50. Kanakry JA, et al. Plasma Epstein-Barr virus DNA predicts outcome in advanced Hodgkin lymphoma: correlative analysis from a large North American co-operative group trial. *Blood*. 2013; 121(18):3547–53. [PubMed: 23386127]
51. Hoppe BS, Flampouri S, Su Z, et al. Effective Dose Reduction to Cardiac Structures Using Protons Compared With 3DCRT and IMRT in Mediastinal Hodgkin Lymphoma. *International Journal of Radiation Oncology*Biophysics*. 2012 Oct 1; 84(2):449–55.
52. Fiandra CF, Filippi AR, FAU-Catuzzo P, Catuzzo PF, et al. Different IMRT solutions vs. 3D-conformal radiotherapy in early stage Hodgkin's Lymphoma: dosimetric comparison and clinical considerations. *Radiation Oncology*. 2012 (1748–717X (Electronic)).
53. Younes A, Gopal AK, Smith SE, et al. Results of a Pivotal Phase II Study of Brentuximab Vedotin for Patients With Relapsed or Refractory Hodgkin's Lymphoma. *Journal of Clinical Oncology*. 2012 Jun 20; 30(18):2183–9. [PubMed: 22454421]

KEY POINTS

- More than 80% of patients with stage IA-IIA non-bulky Hodgkin lymphoma are cured with ABVD chemotherapy alone.
- Death following a diagnosis of Hodgkin lymphoma is more commonly due to factors unrelated to disease progression and includes treatment-related adverse late-effects.
- Follow-up into the third decade following treatment is required to properly assess overall survival following radiation therapy.
- Refinement of early response assessment using PET-CT scans assists individualizing therapy, including defining those who may benefit most from combined modality therapy.

Figure 1. Comparison of eligibility for GHSG HD10 and HD11 and NCIC CTG-ECOG HD.6 clinical trials

Abbreviations: NCIC CTG: NCIC Clinical Trials Group

ECOG: Eastern Cooperative Oncology Group

GHSG: German Hodgkin Study Group

ABVD: Doxorubicin, bleomycin, vinblastine and dacarbazine

IFRT: Involved-field radiation therapy

Table 1

Current treatment guidelines for patients with stage I–II Hodgkin Lymphoma

Guideline Body	Patient population	Recommended therapy
National Comprehensive Cancer Network, 2013 ²⁰	Stage IA–IIA favorable disease: <i>no mediastinal bulk, peripheral disease < 10 cm, ESR < 50, < 3 sites of disease</i>	<ul style="list-style-type: none"> • Combined modality therapy (2–4 ABVD + ISRT) (Category 1) OR • Stanford V x 8 weeks (Category 2A) OR • ABVD alone (Category 2A)
European Society for Medical Oncology, 2011 ²¹	Stage IA–IIA without risk factors: <i>GHSg - large mediastinal mass, extranodal disease, elevated ESR, < 3 nodal areas; EORTC/GELA - large mediastinal mass, age < 50, elevated ESR, < 4 nodal areas</i>	<ul style="list-style-type: none"> • 2 cycles of ABVD + 20 Gy IFRT (Grade A recommendation)
Italian Society of Haematology, 2009 ²²	Stage I–II favorable disease: <i>EORTC - < 3 nodal involved areas, age < 50 years, and M/T ratio < 0.33, and ESR < 50 without B symptoms, or ESR < 30, with B symptoms.</i>	<ul style="list-style-type: none"> • 3 to 4 courses of ABVD + 30 Gy IFRT (Grade A recommendation) OR • 2 ABVD + 20 Gy IFRT in clinical trial setting (Grade B recommendation)
American College of Radiology, 2008 ²³	Stage I–II favorable disease: <i>According to GHSg or EORTC criteria above</i>	<ul style="list-style-type: none"> • Combined modality therapy (2–4 cycles of ABVD + 20 to 30 Gy IFRT)

Abbreviations: ABVD – doxorubicin, bleomycin, vinblastine, dacarbazine

EORTC – European Organisation for Research and Treatment of Cancer

ESR – erythrocyte sedimentation rate

GELA – Groupe D-Etude des Lymphomes de l'adulte

GHSg – German Hodgkin Study Group

IFRT – involved field radiation therapy

ISRT – involved site radiation therapy

M/T – mediastinum/thorax

Table 2

Cross-trial comparison demonstrating events contributing to clinical trial endpoints at 8 years of follow-up, in 588 patients with stage IA-IIA favorable risk Hodgkin lymphoma²⁶

GHSG HD10/11 ABVD + IFRT N=406	NCIC CTG-ECOG HD.6 ABVD alone N=182	Hazard ratio (95% Confidence Intervals)
Time to progression		
Composite endpoint where event is first of progression or death from Hodgkin lymphoma		
93% <i>All 25 events were disease progression</i>	87% <i>All 23 events were disease progression</i>	0.44 (0.24, 0.78)
Progression free survival		
Composite endpoint where event is first of progression or death from any cause		
89% <i>25 events were disease progression 13 events were death without prior progression</i>	86% <i>23 events were disease progression 4 events were death without prior progression</i>	0.71 (0.42, 1.18)
Overall survival		
Event is death from any cause		
95% <i>19 events</i>	95% <i>10 events</i>	1.09 (0.49, 2.40)

Abbreviations: GHSG: German Hodgkin Study Group

NCIC CTG: NCIC Clinical Trials Group

ABVD: doxorubicin, bleomycin, vinblastine and dacarbazine

IFRT: Involved-field radiation therapy

Outcomes of comparative reports testing response-adapted strategies in patients with stage IA-IIA non-bulky Hodgkin lymphoma

Table 3

	Type of study	Response assessment	CR rate	Point estimate	PFS of patient achieving early CR (%)		Overall survival of patients achieving early CR (%)	
					ABVD alone	CMT	ABVD alone	CMT
RAPID (UK)	Randomized controlled trial	Negative PET after 3 ABVD	75%	3-yr	90.7	93.8	99.5	97
EORTC-led HI0F	Randomized controlled trial	Negative PET after 2 ABVD	86%	1-yr	94.9	100	100	100
NCIC CTG-ECOG HD.6 and GHSG HD10	Non-randomized cohort comparison	Negative CT after 2 ABVD	40% (HD.6) 62% (HD10)	8-yr	95	93	100	96

Abbreviations: EORTC: European Organization for Research and Treatment of Cancer

NCIC CTG: NCIC Clinical Trials Group

ECOG: Eastern Cooperative Oncology Group

GHSG: German Hodgkin Study Group

PET: Positron emission tomography

CT: Computerized tomographic scanning

CR: Complete response

PFS: Progression-free survival

ABVD: Doxorubicin, bleomycin, vinblastine and dacarbazine