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An individual patient-data comparison of combined modality therapy and ABVD alone for patients with limited-stage Hodgkin lymphoma

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Background: Treatment options for patients with nonbulky stage IA–IIA Hodgkin lymphoma include combined modality therapy (CMT) using doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) plus involved-field radiation therapy (IFRT), and chemotherapy with ABVD alone. There are no mature randomized data comparing ABVD with CMT using modern radiation techniques.

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Patients and methods: Using German Hodgkin Study Group HD10/HD11 and NCIC Clinical Trials Group HD.6 databases, we identified 588 patients who met mutually inclusive eligibility criteria from the preferred arms of HD10 or 11 ($n = 406$) and HD.6 ($n = 182$). We evaluated time to progression (TTP), progression-free (PFS) and overall survival, including in three predefined exploratory subset analyses.

Results: With median follow-up of 91 (HD10/11) and 134 (HD.6) months, respective 8-year outcomes were for TTP, 93% versus 87% [hazard ratio (HR) 0.44, 95% confidence interval (CI) 0.24–0.78]; for PFS, 89% versus 86% (HR 0.71, 95% CI 0.42–1.18) and for overall survival, 95% versus 95% (HR 1.09, 95% CI 0.49–2.40). In the exploratory subset analysis including HD10 eligible patients who achieved complete response (CR) or unconfirmed complete response (CRu) after two cycles of ABVD, 8-year PFS was 87% (HD10) versus 95% (HD.6) (HR 2.8; 95% CI 0.64–12.5) and overall survival 96% versus 100%. In contrast, among those without CR/CRu after two cycles of ABVD, 8-year PFS was 88% versus 74% (HR 0.35; 95% CI 0.16–0.79) and overall survival 95% versus 91%, respectively (HR 0.42; 95% CI 0.12–1.44).

Conclusions: In patients with nonbulky stage IA–IIA Hodgkin lymphoma, CMT provides better disease control than ABVD alone, especially among those not achieving complete response after two cycles of ABVD. Within the follow-up duration evaluated, overall survivals were similar. Longer follow-up is required to understand the implications of radiation and chemotherapy-related late effects.

Clinical trials: The trials included in this analysis were registered at ClinicalTrials.gov: HD10 - NCT00265018, HD11 - NCT00264953, HD.6 - NCT00002561.

Key words: Hodgkin lymphoma, chemotherapy, combined modality therapy, radiation therapy, progression-free survival, clinical trial

introduction

There is considerable debate about optimum management of patients with nonbulky stage IA and IIA Hodgkin lymphoma [1]. One practice guideline recommends a single option of combined modality therapy (CMT) consisting of two to four cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) plus involved-field radiation therapy (IFRT) [2]; another includes ABVD alone as an acceptable alternative [3]. Three randomized, controlled trials (RCTs) contribute to these recommendations [4–6]. The German Hodgkin Study Group (GHSG) evaluated CMT in two RCTs that included patients with favorable (HD10) [4] and unfavorable (HD11) [5] limited-stage disease. Based on disease control at median follow-up of 91 months, results of HD10 demonstrated that two cycles of ABVD plus 20 Gy IFRT was noninferior to CMT that included four cycles of ABVD and 30 Gy IFRT. In HD11, four cycles of ABVD and 30 Gy IFRT remained standard treatment, when neither noninferiority of four cycles of ABVD and 20 Gy IFRT, nor superiority of CMT that included standard doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP) followed by 30 Gy IFRT were observed. The strategy of ABVD alone was tested in the NCIC Clinical Trials Group (NCIC CTG)–Eastern Cooperative Oncology Group (ECOG) HD.6 trial [6, 7]; with a median follow-up of 11.3 years, those allocated to four to six cycles of ABVD alone experienced superior overall survival in comparison with patients receiving treatment that included subtotal nodal radiation therapy (STNRT) [6]. This was attributed to observing fewer deaths from causes unrelated to progressive Hodgkin lymphoma. Because STNRT represents outdated therapy, there is a desire to understand how results of the HD.6 ABVD-alone cohort might compare with those achieved using modern CMT. Comparing outcomes of HD10/11 and HD.6 is complicated by differences in eligibility, end points and follow-up durations. We conducted this exploratory study describing outcomes of mutually inclusive patients from these three RCTs to help inform the current debate and to

generate hypotheses that assist formulating future research directions.

methods

This NCIC CTG-GHSG collaborative analysis utilized anonymized individual patient data. All patients provided written informed consent at trial entry. Approvals from research ethics boards (REBs) were obtained from all treatment centers. Both Groups obtained updated REB approvals for this project.

Potentially eligible patients had previously untreated nonbulky stage IA–IIA Hodgkin lymphoma and were randomized to receive two cycles of ABVD and 20 Gy IFRT (HD10), four cycles of ABVD and 30 Gy IFRT (HD11) or four to six cycles of ABVD alone (HD.6). Patients were required to be eligible for HD.6 and either HD10 or HD11, as determined by baseline characteristics at the time of original study entry. Eligible patients from HD.6 with extranodal involvement, an erythrocyte sedimentation rate (ESR) of 50 or greater, or three or more nodal areas of Hodgkin lymphoma were assigned to the HD11 subset, others were assigned to HD10. Computer programming was utilized to map anatomic distribution of disease to nodal areas (GHSG) and disease sites (NCIC CTG). Response after two cycles of ABVD was collated for HD10 and HD.6 patients (response was not assessed after two cycles in HD11). Response assessments were carried out using CT scanning; no assessments included positron emission tomographic (PET) scanning.

Outcomes were defined using Revised Response Criteria for Malignant Lymphoma [8]. Patients meeting mutually inclusive eligibility criteria were grouped into two cohorts: those randomized to CMT on HD10/11 and to ABVD only on HD.6. As our analysis would be underpowered for definitive conclusions, no prespecified hypothesis was defined, no *P*-values are reported and all comparisons are considered exploratory. Cox models stratified by propensity score were used to obtain hazard ratios (HR) and 95% confidence intervals (CI) for time to progression (TTP), progression-free survival (PFS) and overall survival, and are expressed as outcomes of HD10 and/or HD11 relative to HD.6. Prespecified exploratory subset analyses were eligibility for HD10 versus HD11, favorable versus unfavorable risk according to HD.6 criteria and complete response or unconfirmed complete response (CR/CRu) versus no CR/CRu after two cycles of ABVD among those eligible for both HD10 and HD.6. Complete methodological

Table 1. Outcome measures and end point events of 588 patients with nonbulky stage I–IIA Hodgkin lymphoma

End point	GHSB HD10/11 (n = 406)	NCIC CTG HD.6 (n = 182)	HR	95% CI
8-year TTP ^a	93%	87%	0.44	0.24, 0.78
Total events	25	23		
PD events	25	23		
Survival events	0	0		
8-year PFS ^b	89%	86%	0.71	0.42, 1.18
Total events	38	27		
PD events ^c	25	23		
Survival events	13	4		
8-year OS	95%	95%	1.09	0.49, 2.40
Survival events	19	10		

^aTime to progression (TTP) was measured from date of randomization to the first of date of PD or death attributed to progressive Hodgkin lymphoma.

^bProgression-free survival (PFS) was measured from date of randomization to the first of date of progressive disease (PD event) or death (survival event) from any cause.

^cFor six patients in each cohort, PD was later followed by death; only the PD event is captured in PFS. These deaths were not necessarily attributed to Hodgkin lymphoma.

GHSB, German Hodgkin Study Group; NCIC CTG, NCIC Clinical Trials Group; HR, hazard ratio; CI, confidence intervals; OS, overall survival.

details are provided in the supplementary Appendix, available at *Annals of Oncology* online.

results

Of 655 eligible patients allocated to the selected arms of HD10 and HD11, 406 (62%) were eligible for HD.6; 254 of 299 (85%) from HD10 and 152 of 356 (43%) from HD11. The most common reasons for ineligibility were B symptoms and large mediastinal mass. Of 196 eligible HD.6 patients randomized to ABVD alone, 182 (93%) are included; 110 eligible for HD10 and 71 eligible for HD11. One patient was unassigned as the ESR was unavailable. Stage IA lymphocyte predominant disease and reduced creatinine clearance accounted for ineligibility for HD10/11 (supplementary Appendix, available at *Annals of Oncology* online). Baseline characteristics of mutually eligible patients are provided in the on-line appendix (supplementary Appendix, available at *Annals of Oncology* online). Median age was 35 years and balanced between cohorts. A greater proportion of HD.6 patients had nodular sclerosing histology and stage IA disease. Median follow-up durations were 92 months for HD10, 91 months for HD11 and 134 months for HD.6.

The TTP was superior for GHSB patients with 8-year estimates of 93% versus 87% (HR 0.44; 95% CI 0.24–0.78). All TTP events in both cohorts were due to progressive disease. The 8-year PFS was 89% for GHSB HD10/11 patients allocated to two to four cycles of ABVD followed by IFRT and 86% for NCIC CTG HD.6 patients allocated to four to six cycles of ABVD alone (HR 0.71; 95% CI 0.42–1.18). The nature of the PFS events is shown in Table 1. The 8-year overall

survival estimates were 95% in both cohorts (HR 1.09; 95% CI 0.49–2.40).

Among 364 patients mutually eligible for HD10, respective 8-year GHSB and NCIC CTG outcomes for TTP were 93% and 85% (HR 0.43, 95% CI 0.22–0.85), for PFS were 87% and 82% (HR 0.58; 95% CI 0.32–1.05) and for overall survival were 96% and 94% (HR 0.65, 95% CI 0.25–1.72) (supplementary Appendix, available at *Annals of Oncology* online). Discrepant outcomes were suggested according to CR/CRu status after two cycles of ABVD. Among the 202 patients achieving a CR/CRu after two treatment cycles, the 8-year PFS of GHSB patients was 87% and among NCIC CTG patients was 95% (HR 2.83; 95% CI 0.64–12.49). The 8-year overall survivals were 96% and 100%, respectively. In contrast, among the 162 not achieving a CR/CRu status, continuation with IFRT instead of ABVD improved 8-year PFS (88% versus 74%; HR 0.35, 95% CI 0.16–0.79), respective 8-year overall survivals were 95% and 91% (HR 0.42; 95% CI 0.12–1.44). For the 223 patients mutually eligible for HD11, the 8-year TTPs were 94% (GHSB) and 91% (NCIC CTG) (HR 0.60, 95% CI 0.21–1.73), the 8-year PFS for both cohorts was 91% (HR 1.15; 95% CI 0.45–2.97), and overall survivals were 95% and 97% (HR 2.03; 95% CI 0.53–7.79).

Among 162 patients defined as having favorable-risk disease according to HD.6 protocol criteria, the respective 8-year TTPs of GHSB and NCIC CTG cohorts were 92% and 91% (HR 0.72; 95% CI 0.25–2.12), PFSs were 92% and 91% (HR 0.77; 95% CI 0.26–2.3) and overall survivals were 99% and 98% (HR 0.51; 95% CI 0.03–8.07). For those meeting HD.6 unfavorable-risk criteria, respective 8-year TTPs were 94% and 86% (HR 0.40; 95% CI 0.20–0.80), PFSs were 87% and 84% (HR 0.71; 95% CI 0.40–1.28) and 8-year overall survivals were 94% versus 94% (HR 1.10, 95% CI 0.48–2.54).

Among 406 GHSB patients with median follow-up of 91 months, there were 19 deaths with 7 attributed to Hodgkin lymphoma or immediate treatment toxicity and 12 to other causes. Among 182 NCIC CTG patients with median follow-up of 134 months, there have been 10 deaths; 5 were attributed to Hodgkin lymphoma or immediate treatment toxicity and 5 to other causes. Additional tables and figures are presented in the supplementary Appendix, available at *Annals of Oncology* online.

discussion

Long-term outcomes of patients with nonbulky stage IA–IIA Hodgkin lymphoma require treatment strategies that balance establishing complete disease control while reducing the risk of late treatment effects. Clinical trials of the past two decades have demonstrated that CMT including IFRT is as effective and has fewer late treatment effects [9] when compared with CMT that includes STNRT [10]. Thus, CMT that includes IFRT currently represents a standard of care, with a recognized limitation that comparisons of large patient numbers followed after initial treatment into the second decade and beyond have not yet been reported. While the incidence and severity of late treatment effects including secondary malignancies and cardiovascular disease attributable to IFRT is less than with more extensive radiation therapy, the magnitude of this reduction and the importance of remaining risks are uncertain. Recent innovations in radiation therapy include involved involved-site

radiation therapy (ISRT) which is considered an alternative to IFRT according to the 2013 National Comprehensive Cancer Network guidelines [11], involved-node radiation therapy [12] (INRT), which has been adopted by some institutions and by the European Organisation for Research and Treatment of Cancer in its H10 trial [13], conformal radiation [14] and proton therapy [15]. Each of these strategies represents a potential advancement in balancing disease control with the risk of late treatment effects, but to date, there are no publications of RCTs comparing these strategies or of follow-up into the period during which late-effects become evident.

The NCIC CTG-ECOG HD.6 trial demonstrated that four to six cycles of ABVD alone is associated with long-term disease control in 87% of patients. This magnitude of disease control was 5% worse than observed in patients treated with a strategy that included STNRT and 8% worse in a subset analysis that included patients assigned to CMT that included STNRT. However, overall survival was superior because there were fewer deaths from other causes. While recognizing that these relative outcomes cannot be directly generalized to CMT that includes IFRT, the results have led to treatment with ABVD alone also being considered a standard care alternative. Limitations associated with ABVD alone include the increased risk of disease recurrence, late-effect risks associated with subsequent lines of therapy and the potential for anthracycline-induced cardiotoxicity [16].

This analysis informs, but does not resolve, ongoing debates. Our data are consistent with previous observations that long-term disease control is superior with CMT. This is best demonstrated by TTP, an end point that in our combined populations was always due to progressive disease. Our analysis supports previous data that suggest CMT is associated with 8-year TTP superiority of the magnitude of 6% (93% versus 87%). Our data also suggest that overall survival within the first decade of follow-up is unlikely to differ between these two treatment options as 8-year estimates were of 95% for both cohorts.

Observations from our predefined subset analysis show striking differences in disease-control outcomes of patients eligible for HD10 according to CR/CRu status assessed by CT scan and physical examination after two cycles of ABVD, leading us to conclude that patients not achieving a CR/CRu at this time point should receive CMT; the 8-year TTP with ABVD alone was inferior to CMT (92% versus 78%). In contrast, the excellent 8-year outcomes of patients assigned to ABVD alone who achieved a CR/CRu status after two cycles of ABVD (TTP of 95%; overall survival of 100%) support treatment with ABVD alone. This strategy of response-adapted therapy now includes the ability to incorporate PET scanning into the decision-making process. Preliminary results of two RCTs testing interim PET scanning are now available. Radford [17] has reported outcomes of 420 patients with a negative PET scan after three cycles of ABVD: among those receiving no further therapy, the 3-year PFS was 90.7% in comparison with 93.8% among those randomized to receive IFRT. The 3-year overall survivals were 99.5% among those allocated to no further therapy and 97% among those allocated to IFRT. The authors concluded that IFRT was unnecessary for patients with a negative PET scan after three cycles of ABVD. In contrast, Andre has reported results of an RCT involving 382 favorable risk patients

comparing CMT that includes three cycles of ABVD and INRT with a PET-directed, response-adapted approach; after two cycles of ABVD those with a negative PET scan receive two further cycles of ABVD and no radiation treatment. The 1-year PFS outcomes in the PET negative cohort were 94.9% with ABVD alone versus 100% with additional INRT, which led to a recommendation by the data safety monitoring committee of the trial to halt accrual to this arm. It is not expected that either of these trials will be able to report overall survival outcomes of the duration we report in this analysis for at least 5 years. Additional data will come from the GHSG HD16 and HD17 trials, which also compare nonrisk-adaptive CMT approaches with a PET-directed, response-adapted strategy.

Our study has important limitations. Although data were prospectively collected within the conduct of RCTs, our analyses are retrospective and biases due to imbalances of baseline patient characteristics, co-interventions, end point measurement and frequencies and nature of follow-up likely exist. Our analyses have limited statistical power. The median follow-up durations of the two cohorts differed by 42 months, with even the 134-month median follow-up of the HD.6 cohort being insufficient for detailed understandings of late-effect risks.

Our analyses, while exploratory, help generate hypotheses for future research. The populations considered were assembled according to two risk-stratification schema, which include disease and patient-related factors. The HD10 and HD11 cohorts differ by disease-related factors only. As HD.6 eligibility criteria excluded those with bulky disease and B symptoms, the remaining eligibility differences between HD10 and HD11 were the presence of extranodal disease, number of nodal areas of disease and ESR elevation. Recognizing that GHSG patients entered on to HD11 received more cycles of chemotherapy than those entered on to HD10, our data do not show obvious prognostic differences between either the GHSG or NCIC CTG-ECOG populations according to their eligibility for HD10 and HD11. Overall survivals were similar among those eligible for HD10 when compared with HD11 in both the GHSG and NCIC CTG cohorts and among those eligible for HD11, TTP did not appear to differ between the GHSG and NCIC CTG-ECOG cohorts. In fact, among the NCIC CTG cohort, TTP appeared to be worse in those eligible for HD10 (supplementary Appendix, available at *Annals of Oncology* online), a findings that may be due to imbalances of other factors between these risk groups such as age, or other baseline characteristics. Still, exploration of this finding might consider whether a select proportion of patients with fewer nodal sites may harbor disease that is more biologically aggressive. In contrast, the risk-stratification schema used in HD.6 included a patient factor, age, in addition to disease-related factors. Using this schema, inferior survival of unfavorable-risk patients is suggested in both the GHSG and NCIC CTG cohorts. Among the combined favorable cohorts there were two deaths, both attributed to progressive Hodgkin lymphoma. In contrast among the combined unfavorable cohorts there were 25 deaths with 16 attributed to causes other than progressive Hodgkin lymphoma. These findings are consistent with previous observations that older age is associated with poorer survival [18] through a relation with an increased risk of deaths from causes other than progressive Hodgkin lymphoma and invite evaluation of

whether risks of late treatment effects are observed after a briefer period of follow-up in older patients [1]. Better understandings of the factors associated with the hypotheses generated by these data might provide insights into whether either of the two treatment strategies tested have a potential for differential benefit for a specific population.

Our analyses demonstrate potential limitations of end points used in clinical trials evaluating patients with lymphoproliferative disorders. Patients with stage IA-IIA nonbulky Hodgkin lymphoma typically do not have systemic illness and, compared with patients who have metastatic carcinoma or fulminant lymphoma, are highly unlikely to die directly due to lymphoma unless there is prior progressive disease. In our analysis, all 48 TTP events were due to progressive disease. In contrast, PFS has features of a composite end point, as progressive disease and death from any cause are included, with deaths attributed to treatment-related late-effects or unrelated causes. Reporting of outcomes associated with the individual end points included within a composite has been recommended, as each may be associated with distinct weighting when considered from different perspectives [19]. While our analysis is limited by its nonrandomized design associated with potential for bias and has limited statistical power, the data suggest that differences in the proportions of individual end points that constitute the composite can occur.

In conclusion, our exploratory analyses align with other data showing that for patients with nonbulky stage IA-IIA Hodgkin lymphoma, CMT including IFRT improves long-term disease control compared with ABVD alone. This appears to be so especially among patients with fewer pretreatment anatomical areas of Hodgkin lymphoma who do not enter a CR/CRu status after two cycles of ABVD. To date, no differences in overall survival are detected. Longer follow-up of trials evaluating treatment options for these patients is needed to properly assess that end point.

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disclosure

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