INTRODUCTION

Over the last 40 years, major advances have been achieved in the treatment of patients with advanced Hodgkin lymphoma (HL). Since its introduction in 1975, the combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) has become a standard of care for these patients. After six to eight cycles of this regimen, approximately 70% of these patients can be cured, and 50% of those who experience relapse or progression of disease can be treated with salvage therapies, including high-dose therapy followed by stem-cell rescue (SCT). However, in the 1980s, several groups began to develop novel combinations in an attempt to improve cure rates for the disease by increasing...
the activity of initial therapy, thereby reducing the need for salvage treatments. Initially, investigators tested a sequential combination of ABVD and MOPP (melphalan, vincristine, procarbazine, and prednisone) or more complex regimens that included several additional active drugs.4-6 More importantly, investigators of the German Hodgkin Study Group (GHSG) developed the BEACOPP regimen, consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, which was administered at escalated or standard doses.6,7

The BEACOPP regimen, particularly when administered at escalated doses (e-BEACOPP), was associated with better response rates and higher efficacy compared with hybrid regimens when used to treat advanced HL. These results have prompted several investigators to adopt it as the new standard for advanced HL, although many physicians have been reluctant to abandon ABVD, as a result of its high activity, its excellent tolerability, and the relative absence of major early and late complications of therapy.

Investigators recently published the results of four randomized trials comparing ABVD and BEACOPP, and all demonstrated similar findings: comparable survival rates but lower rates of disease progression after treatment with BEACOPP, particularly for patients with high-risk disease.9-12 These studies also demonstrated increased rates of adverse events during and after the administration of BEACOPP compared with those after ABVD, suggesting the need for prolonged survival analysis of these trials.

One of these trials, HD2000, aimed to compare ABVD, BEACOPP, and COPP-EBV-CAD (CEC), the latter of which consists of cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epipodophyllotoxins, vincristine, procarbazine, vinblastine, and bleomycin (a modified version of the original hybrid, MOPP-EBV-CAD)7,8, as initial therapy for advanced HL. We published our initial results in 2009 after a median follow-up of 42 months.9 In this report, we describe the post hoc analysis of mature results of this trial after a median follow-up of 10 years.

PATIENTS AND METHODS

Patients

The HD2000 trial was conducted for previously untreated patients with biopsy-proven classic HL. Patients in this trial had clinical stage IIb, III, or IV disease; were older than 16 years of age; and had no cardiac, pulmonary, hepatic, or renal dysfunctions, unless thought to be directly related to HL. Pregnant or lactating women and patients with prior malignancy, HIV positivity, or Eastern Cooperative Oncology Group (ECOG) performance status greater than 3 were ineligible for the study.

All patients underwent clinical staging according to the Cotswold modifications of the Ann Arbor criteria.12 Bulky disease was defined as a thoracic mass with a diameter ≥ 6 cm or any extramediastinal mass greater than 10 cm in diameter on computed tomography.

This study fully complied with all provisions of the Declaration of Helsinki and was conducted in accordance with Good Clinical Practice rules. All patients provided written informed consent to participate.

Patients were randomly assigned to receive six cycles of ABVD, four cycles of e-BEACOPP followed by two cycles of standard-dose BEACOPP (s-BEACOPP), or six cycles of CEC (Fig 1). Drug doses, time schedules, and study procedures were provided in our previous report.9

At the end of chemotherapy, radiotherapy (RT) was administered to sites of previously defined bulky disease or to slowly or partially responding sites, with recommended doses of 30 to 36 Gy, as defined in the original report.9 Although some underwent positron emission tomography (PET) imaging, response in this trial was assessed by computed tomography alone.

Statistical Methods

The primary end points of this long-term study were progression-free survival (PFS), cumulative incidence of secondary malignancies (considering death as a competing risk), and frequency of late adverse events. Secondary end points were overall survival (OS) and failure-free survival (FFS), to allow comparison with our previously reported results.9 For this analysis, the initial definition of sample size was not applicable; the analysis was conducted as a post hoc long-term observational study of patients enrolled in the HD2000 trial. All participants in this study were included in this intention-to-treat analysis, and only those with major violations of inclusion criteria were not considered evaluable.

PFS was defined as the time from the date of diagnosis to the date of last observation, progression, relapse, or death resulting from any cause. OS was computed from the date of diagnosis to the date of last follow-up or death resulting from any cause. FFS was calculated from the date of diagnosis to the date of last follow-up or one of the following events: response other than complete remission (CR), relapse, or death resulting from any cause.

Survival curves were calculated using the Kaplan-Meier estimates, and statistical comparison between curves was performed using the log-rank test.15 Effect size was reported as a hazard ratio (HR) with a 95% CI and estimated using the Cox proportional hazards (PH) regression method, adjusted by the international prognostic score of Hasenclever.15,16 The proportionality of the hazard risk was graphically checked using the scaled Schoenfeld residuals method.17 The risk of secondary malignancies was reported as a cumulative incidence function, with death as a competing risk, using the Gooley method18; comparisons between curves were performed using the Gray test. Toxicity was evaluated using standard ECOG criteria.19

Continuous variables were reported as medians and categorical variables as frequencies (absolute and percentage). Comparisons between categorical variables were examined using the χ² or Fisher exact test, and continuous variables were analyzed by means of the Kruskal-Wallis test. All reported tests were two sided, and any P value < .05 was considered to indicate moderate strength of evidence against the null hypothesis. P values were not adjusted for multiple comparisons. The analysis was performed according to the intention-to-treat approach, except for studies involving second malignancies and late adverse events, which were analyzed according to actual therapy received.

RESULTS

From April 2000 to June 2007, 307 patients were registered in this study; 12 were subsequently excluded: four in the ABVD arm (missing data, n = 3; lost to follow-up, n = 1), four in the BEACOPP arm (revised histology, n = 1; not compliant, n = 1; missing data, n = 2), and four in the CEC arm (missing data, n = 3; lost to follow-up, n = 1). On the basis of intention to treat, 99, 98, and 98 patients were randomly assigned to receive ABVD, BEACOPP, or CEC, respectively (Fig 1).

The main characteristics of the 295 eligible and assessable patients, along with treatment details and dose-intensity of therapy, were described in the original report.9 RT was administered in 46%, 44%, and 43% of patients randomly assigned to ABVD, BEACOPP, or CEC, respectively (P = .871). At the end of all therapy, including RT, the CR rate was 84% with ABVD, 91% with BEACOPP, and 83% with CEC.

The median follow-up for the entire group of patients was 120 months (range, 4 to 169 months). Overall, 80 PFS events were
Long-Term Follow-Up of Randomized HD2000 Trial for Advanced HL

Patients recruited (N = 307)

- ABVD (n = 103)
  - Excluded (n = 2)
    - Revised histology (n = 1)
    - Not compliant (n = 1)
  - Eligible (n = 101)
    - Missing data (n = 3)
    - Lost to follow-up (n = 1)
  - In analysis (n = 99)
    - Full course (n = 90)
    - Partial course (n = 9)

- BEACOPP (n = 102)
  - Excluded (n = 0)
  - Eligible (n = 100)
    - Missing data (n = 2)
    - Lost to follow-up (n = 1)
  - In analysis (n = 98)
    - Full course (n = 88)
    - Partial course (n = 10)

- CEC (n = 102)
  - Excluded (n = 0)
  - Eligible (n = 102)
    - Missing data (n = 3)
    - Lost to follow-up (n = 1)
  - In analysis (n = 98)
    - Full course (n = 86)
    - Partial course (n = 12)

Fig 1. CONSORT diagram. Treatment allocation and number of patients included in the analysis. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CEC, cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin.

Table 1. Events and Causes of Death Recorded at Last Follow-Up by Treatment Arm

<table>
<thead>
<tr>
<th>Event or Cause of Death</th>
<th>ABVD (n = 99)</th>
<th>BEACOPP (n = 98)</th>
<th>CEC (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event (PFS)</td>
<td>Early Update</td>
<td>Total</td>
<td>Early Update</td>
</tr>
<tr>
<td>Progression</td>
<td>12</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Relapse</td>
<td>14</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Death resulting from any cause</td>
<td>—</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression</td>
<td>7</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First line</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Second line</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Second malignancy</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Unknown</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>5</td>
<td>13</td>
</tr>
</tbody>
</table>

NOTE: Early indicates data recorded by Federico et al9 in 2009; update indicates data recorded at last follow-up in 2014. Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CEC, cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin; PFS, progression-free survival.

recorded (24 progressions, 43 relapses, and 13 deaths resulting from any cause), including an additional 21 episodes compared with the initial report (13 relapses and eight deaths [seven resulting from second malignancies and one resulting from toxicity of salvage treatment]). By therapy arm, five, 11, and five new events occurred in the ABVD, BEACOPP, and CEC arms, respectively (Table 1). Among patients experiencing relapse, no significant deviation from the planned dose-intensity of the assigned therapy was observed (data not shown).

Ten-year PFS rates were 69% (95% CI, 58% to 77%), 75% (95% CI, 64% to 83%), and 76% (95% CI, 66% to 84%) for patients randomly assigned to ABVD, BEACOPP, or CEC, respectively (Fig 2). The HR for PFS adjusted for International Prognostic Score (0 to 2 versus 3 to 7) for BEACOPP versus ABVD was 0.73 (95% CI, 0.42 to 1.24); it was 0.72 (95% CI, 0.42 to 1.24) for CEC versus ABVD.

The HR of BEACOPP versus ABVD lacked the proportionality of risk that was missed after approximately 30 months of follow-up. BEACOPP was associated with a 52% risk reduction compared with ABVD (HR, 0.48; 95% CI, 0.25 to 0.93) during the first 30 months of observation, whereas in subsequent follow-up, a non-negligible rate of events (six deaths) was observed only in the
BEACOPP arm (HR, 1.70; 95% CI, 0.72 to 4.02) when compared with ABVD (zero events; Table 2; Fig 3).

With regard to the analysis of FFS, 41 patients did not achieve CR, 43 developed relapses, and seven died as a result of causes unrelated to lymphoma. Ten-year FFS results were 65% (95% CI, 54% to 73%), 73% (95% CI, 62% to 81%), and 71% (95% CI, 61% to 79%) for ABVD, BEACOPP, and CEC, respectively (Fig 2). For FFS, the HR between BEACOPP and ABVD did not follow the proportionality of risk with changing time after 30 months of follow-up (data not shown).

In the group of 84 patients who did not achieve CR or experienced progressive or relapsed HL, salvage data were available for 73 (87%). Among them, three (4%) died before salvage therapy could begin, 26 (36%) received conventional chemotherapy, 40 (55%) underwent SCT, and four (5%) were treated with RT alone. Among the patients for whom induction therapy failed, 15 (two with refractory disease and 13 after relapse), 12 (one with refractory disease and 11 after relapse), and 13 (three with refractory disease and 10 after relapse) were treated with SCT in the ABVD, BEACOPP, and CEC arms, respectively.

With updated follow-up, 42 deaths were recorded: 24 resulting from lymphoma progression, two resulting from toxicity of initial therapy, seven resulting from toxicity of salvage therapy, and eight resulting from second malignancies; in one patient, the cause of death was unknown. Compared with those reported in 2009, eight additional deaths occurred as a result of lymphoma progression and seven as a result of second malignancies (Table 1). The distribution of deaths attributable to HL by randomized arm was 11 with ABVD, five with BEACOPP, and eight with CEC (P = .022). At 10 years of follow-up, no significant differences emerged among the three arms in terms of OS results: 85% (95% CI, 75% to 91%) with ABVD, 84% (95% CI, 74% to 90%) with BEACOPP, and 86% (95% CI, 77% to 92%) with CEC (P = .892; Fig 2).

Analysis of second malignancies was based on the actual treatment. Sixteen patients received chemotherapy that was different from that originally intended, because of physician or patient choice: one patient randomly assigned to ABVD received CEC, nine patients randomly assigned to BEACOPP received ABVD, and six patients randomly assigned to CEC received ABVD. Thirteen second malignancies occurred in this trial: one after ABVD, six after BEACOPP, and six after CEC treatment (Table 3). All second malignancies but one were diagnosed in patients in CR, and eight resulted in death (seven of these eight patients were in first CR). Five of 13 had received RT as part of their initial treatment. Three of these developed a solid tumor within or close to an irradiated field (lung cancer and pleural sarcoma after treatment with BEACOPP and irradiation of the mediastinum; thyroid carcinoma after ABVD and irradiation of the mediastinum). The median time from the end of treatment for HL and diagnosis of second malignancy was 90 months (range, 4 to 153 months). The second malignancy crude rate was 5.0 × 1,000 person-years (95% CI, 2.9 to 8.7), and the overall 10-year cumulative incidence rate was 4.2% (95% CI, 2.1% to 8.8%). The cumulative incidence rates at 10 years after ABVD, BEACOPP, and CEC were 0.9% (95% CI, 0.1% to 4.5%), 6.6% (95% CI, 2.4% to 13.9%), and 3.9% (95% CI, 1.5% to 8.4%), respectively.

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In this report, we provide a 10-year follow-up analysis of the HD2000 trial, which compared six cycles of ABVD, four cycles of e-BEACOPP followed by two of s-BEACOPP, and six cycles of CEC as initial treatment for patients with advanced HL. Ten-year PFS results were 69%, 75%, and 76% (P = .027) for ABVD, BEACOPP, and CEC arms, respectively; corresponding 10-year OS results were 85%, 84%, and 86% (P = .892). In comparison with our prior analysis, we have confirmed better control of disease with BEACOPP compared with that observed following ABVD; however, this benefit was counterbalanced by a statistically higher rate of late major events after BEACOPP, particularly second malignancies, which resulted in patients’ death, a finding that was also observed for patients who had received CEC.

The OS results in this trial with BEACOPP are similar to those reported in an analysis of the GHSG HD9 study, in which 86% of patients who received e-BEACOPP were still alive at 10 years. The cumulative risk of second malignancies in that study was 6.5%, similar to that observed in our trial. However, the risk of second malignancies after ABVD in our study was low, resulting in OS rates similar to those reported after BEACOPP. Both the sequential COPP-ABVD arm in the HD9 trial and the CEC regimen in the HD2000 trial were associated with rates of second malignancies that were similar to those associated with BEACOPP, possibly because of the high doses of alkylating agents in these regimens. Forty-five percent of our patients received consolidative RT. This may also have contributed to an increased risk of development of second malignancies in our trial, although the number of patients receiving RT was similar among the three study arms.

Recently, Skoetz et al from the GHSG reported results of a meta-analysis comparing BEACOPP and ABVD; in that study, there was a 10% OS benefit favoring BEACOPP. However, these results were reported after only 5 years of follow-up, and 10-year results may be needed to clarify this improvement in risk of death after the more intensive regimen.

The value of long-term analysis after treatment of patients has been confirmed by investigators of the NCIC Clinical Trials Group/ECOG HD6 trial. Although patients in that study had limited-stage HL and received therapy possibly considered outdated in the modern era, better early control of HL with more intensive therapy did not translate into a survival advantage, because of late events unrelated to the disease.

To put the results of our study into proper context, we acknowledge the limitations of our study, which was not powered to demonstrate differences in terms of OS. However, aside from strict statistical considerations, we believe the differences in results with these regimens after prolonged observation time are relevant from a clinical point of view. So far, only the HD9 and HD2000 trials have provided 10-year survival data on advanced HL. Mature follow-up results of other, larger randomized trials comparing ABVD and BEACOPP should be strongly encouraged to confirm these observations.

For the time being, we suggest that BEACOPP is an option for treatment of advanced HL, but it should not be considered the standard for all patients, because 70% of these patients may be cured with ABVD and limited RT. Moreover, considering the young age of patients with HL and the long-term toxicity of BEACOPP found in our study, a careful assessment of the risk–benefit ratio of the initial treatment choice is warranted. Although the International Prognostic Score for HL is commonly used to assess the risk of disease progression in trials for HL, the value of this prognostic index as a method of choosing therapy for advanced HL has not yet been validated. Moreover, PET has been suggested as a strong prognostic factor when used to assess early response during ABVD treatment.

Table 3. Secondary Malignancies by Treatment Arm

<table>
<thead>
<tr>
<th>Second Malignancy</th>
<th>ABVD (n = 113)</th>
<th>BEACOPP (n = 89)</th>
<th>CEC (n = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder carcinoma</td>
<td>—</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>Lung carcinoma</td>
<td>—</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Thyroid carcinoma</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>—</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Pleural sarcoma</td>
<td>—</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Follicular lymphoma (grade 3a)</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma (T cell)</td>
<td>—</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>—</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CEC, cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblistine, and bleomycin.
have been conducted investigating the role of early PET as a decisional tool, and early data have confirmed the value of this approach to treatment management.25–27 In most of these studies, ABVD was chosen as initial treatment, and early positive PET findings were used to identify patients at high risk of progression, who were then shifted to more-intense chemotherapy regimens, including BEACOPP or high-dose chemotherapy and SCT. In these studies, patients with negative early PET findings subsequently received modified versions of ABVD, with the aim of further reducing the risks of both acute and late toxicities. Such response-adapted approaches may be appropriate treatment strategies, although they have yet to be included in standard management of advanced HL.

Finally, promising agents have been developed that seem highly active in therapy for relapsed HL. The immunoonjugate anti-CD30 antibody brentuximab vedotin has been recently approved for treatment of relapsed refractory HL and, combined with AVD, is currently being compared with ABVD in a randomized trial for the initial therapy of advanced disease.28,29 In another trial conducted by the GHSG, brentuximab vedotin is being used to create a targeted BEACOPP variant that could result in a regimen that is equally effective but less toxic than e-BEACOPP (ClinicalTrials.gov identifier, NCT01569204). More recently, two drugs targeting programmed death 1, namely nivolumab and pembrolizumab, also demonstrated promising activity in patients with relapsed or refractory disease, and their use in HL will be developed.30,31

In conclusion, mature follow-up results of the HD2000 trial demonstrated excellent outcomes for patients with advanced HL, which were achieved with either ABVD or BEACOPP, although these combinations have different activity and toxicity profiles. With the availability of PET for the early assessment of patient risk and of new drugs characterized by high response rates and favorable safety profiles, we believe it is time to move from the “old fight” between ABVD and BEACOPP to the development of an integrated and more personalized approach for each patient.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Long-Term Results of the HD2000 Trial Comparing ABVD Versus BEACOPP Versus COPP-EBV-CAD in Untreated Patients With Advanced Hodgkin Lymphoma: A Study by Fondazione Italiana Linfomi

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Honoraria: Pfizer
Consulting or Advisory Role: Roche, Celgene, TEVA Pharmaceuticals Industries
Travel, Accommodations, Expenses: Takeda Pharmaceuticals, Celgene

Paolo G. Gobbi
No relationship to disclose

Nicola Cascavilla
No relationship to disclose

Caterina Mammi
No relationship to disclose

Fiorella Ilariucci
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Caterina Stelitano
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Maurizio Musso
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Luca Baldini
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Honoraria: Novartis

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Consulting or Advisory Role: Roche, Amgen

Giuseppe Polimeno
No relationship to disclose

Potito Rosario Scalzulli
No relationship to disclose

Angela Ferrari
No relationship to disclose

Luigi Marcheselli
No relationship to disclose

Massimo Federico
No relationship to disclose
Acknowledgment

We thank Fredrick B. Hagemeister, MD, for his valuable support in reviewing the manuscript. This work is dedicated to the memory of Matteo Dell'Olio, MD.

Appendix

<table>
<thead>
<tr>
<th>Table A1. Late Nononcologic Adverse Events by Treatment Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
</tr>
<tr>
<td>Cardiopathy</td>
</tr>
<tr>
<td>Femoral head necrosis</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
</tr>
<tr>
<td>Epilepsy</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>Parathyroid adenoma</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CEC, cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin.