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ORIGINAL REPORT

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ABVD Compared With BEACOPP Compared With CEC for the Initial Treatment of Patients With Advanced Hodgkin's Lymphoma: Results From the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial

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ABSTRACT

Purpose
To compare doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) versus bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) versus cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxirubicin, vincristine, procarbazine, vinblastine, and bleomycin (COPPEBVCAD; CEC) for advanced Hodgkin's lymphoma (HL).

Patients and Methods
Three hundred seven patients with advanced HL (stage IIB, III, and IV) were randomly assigned to receive six courses of ABVD, four escalated plus two standard courses of BEACOPP, or six courses of CEC, plus a limited radiation therapy program.

Results
After a median follow-up of 41 months, BEACOPP resulted in a superior progression-free survival (PFS), with a significant reduction in risk of progression (hazard ratio [HR] = 0.50) compared with ABVD. No differences between BEACOPP and CEC, or CEC and ABVD were observed. The 5-year PFS was 68% (95% CI, 56% to 78%), 81% (95% CI, 70% to 89%), and 78% (95% CI, 68% to 86%), for ABVD, BEACOPP, and CEC, respectively (BEACOPP *v* ABVD, $P = .038$; CEC *v* ABVD and BEACOPP *v* CEC, P = not significant [NS]). The 5-year overall survival was 84% (95% CI, 69% to 92%), 92% (95% CI, 84% to 96%), and 91% (95% CI, 81% to 96%) for ABVD, BEACOPP, and CEC, respectively (P = NS). BEACOPP and CEC resulted in higher rates of grade 3-4 neutropenia than ABVD ($P = .016$); BEACOPP was associated with higher rates of severe infections than ABVD and CEC ($P = .003$).

Conclusion
As adopted in this study BEACOPP is associated with a significantly improved PFS compared with ABVD, with a predictable higher acute toxicity.

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INTRODUCTION

Hodgkin's lymphoma (HL) is one of the most treatable adult cancers, with long-term cure rates of higher than 80% achieved even in patients with advanced disease.[1,2]

The combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is currently considered the standard of care for HL worldwide.[3] In order to improve ABVD, other regimens, including Stanford V; mechlorethamine, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, and doxorubicin (MOPPEBVCAD); etoposide, vinblastine, and doxorubicin (EVA); etoposide, epirubicin, bleomycin, cyclophosphamide, and prednisolone (VEBEP); and chlorambucil, vinblastine, procarbazine, doxorubicin, bleomycin, vincristine, and etoposide (ChlVPP/ABVVP) have been proposed. However, none of them have so far demonstrated a clear superiority over ABVD.[4-9] In 1990, the German Hodgkin Study Group (GHSG) developed a dose-escalated and accelerated combined modality regimen consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), plus radiation therapy (RT).

The HD9 trial compared cyclophosphamide, vincristine, procarbazine, and prednisone, plus doxorubicin, bleomycin, vinblastine, and dacarbazine (COPP/ABVD) with standard-dose BEACOPP (std-BEACOPP) and escalated-dose BEACOPP (esc-BEACOPP). The trial demonstrated the superiority of esc-BEACOPP, both in terms of failure-free survival (FFS) and overall survival (OS).[10]

Concern about the toxicity of BEACOPP has been raised, however, and further trials designed to identify a therapy with the best risk-to-benefit ratio have been initiated by several cooperative groups, and some of them are currently ongoing.

In 2000, the Gruppo Italiano per lo Studio dei Linfomi started the HD2000 trial, which compared ABVD, BEACOPP, and cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxirubicin, vincristine, procarbazine, vinblastine, and bleomycin (COPPEBVCAD [CEC]), in combination with a limited RT program delivered according to the criteria of bulky disease and/or response. In our this report, we present the results of this prospective, randomized, multicenter trial that accrued a total of 307 patients.

PATIENTS AND METHODS

The trial was conducted in compliance with the Declaration of Helsinki, was accepted by the appropriate research ethics committee, and required each patient to give written informed consent before registration and random assignment.

Previously untreated patients older than 16 years, with a histologically confirmed diagnosis of classical HL, clinical stage IIB, III, or IV disease, and Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 3 were eligible.

Patients were staged according to Cotswolds criteria,[11] with the exception of bulky disease definition. For study purposes, bulky disease was defined as a thoracic mass of at least 6 cm in diameter, or any extramediastinal mass larger than 10 cm in diameter on a computed tomography (CT) scan.

Patients were randomly assigned to receive six courses of ABVD, four escalated plus two standard courses of BEACOPP, or six courses of CEC. Patients with less than partial response after the first three cycles of chemotherapy were taken off study. Randomization was stratified by stage (IIB *v* III *v* IV). Drug doses and administration schedules for each regimen are presented in Table 1. Growth factors were not allowed routinely but used at physician discretion.

At the end of chemotherapy, RT was scheduled for sites of previous bulky disease or on slowly or partially responding sites. The recommended total doses were 30 to 36 Gy with a boost of 6 additional Gy to persisting disease sites. Disease status was assessed by CT scan. For patients investigated also by fluorine-18 2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) imaging, response was assessed on the basis of CT scan alone.

The study was initially designed to compare myelotoxicity referred to leukopenia of CEC and BEACOPP regimens with respect to that of ABVD, taken as standard arm. Sample size was calculated considering an event probabilities of 11%, 51%, and 90% for ABVD, CEC, and BEACOPP, respectively. With a two-sided $\alpha = .05$ and power of 80% (error type II = .2), 75 patients were required, 25 in each arm, to test the hypothesis by means of χ^2 test. Once, in the first 18 months, Gruppo Italiano per lo Studio dei Linfomi centers became familiar with BEACOPP, the protocol was amended and BEACOPP and CEC regimens were tested against ABVD primarily in terms of FFS. FFS was defined from the date of study entry to the last follow-up, or to one of the following events: any response other than complete remission (CR) at the end of therapy (chemotherapy ± RT), progression, relapse, or death from any cause. Additional outcome measures were progression-free survival (PFS), response rates, OS, relapse-free survival (RFS), and toxicity. PFS was measured from the date of study entry to the last follow-up, or to one of the following events: death from any cause, disease progression during treatment, or relapse. OS was defined from the date of study entry to the date of last observation or death from any cause; RFS was defined for complete responders from the date of therapy completion to the date of the last observation or relapse. Quality of response was defined according to Costwolds criteria. For study purposes we identified slow responders as those patients without initial bulky disease and still residual masses at the end of chemotherapy.

Table 1. Drug Doses and Time Schedules of the Three Chemotherapy Regimens

Drug	Dose (mg/m^2)	Route	Days
ABVD, every 28 days			
Doxorubicin	25	IV	1, 15
Bleomycin	10	IV	1, 15
Vinblastine	6	IV	1, 15
Dacarbazine	375	IV	1, 15
CEC, every 28 days			
Cyclophosphamide	650	IV	1, cycles 1, 3 and 5 only
Lomustine	100	PO	1, cycles 2, 4 and 6 only
Vindesine	3	IV	1
Melphalan	6	PO	1-3
Prednisone	40	PO	1-14
Epidoxorubicin	40	IV	8
Vincristine	1.4 (2 maximum)	IV	8
Procarbazine	100	PO	8-14
Vinblastine	6	IV	15
Bleomycin	10	IV	15
BEACOPP, every 21 days			
Bleomycin	10	IV	8
Etoposide	200 (E)−100 (S)	IV	1-3
Doxorubicin	35 (E)−25 (S)	IV	1
Cyclophosphamide	1,250 (E)−650 (S)	IV	1
Vincristine	1.4 (2 maximum)	IV	8
Procarbazine	100	PO	1-7
Prednisone	40	PO	1-14
G-CSF	300-μg total	SC	8+ (until neutrophils $> 0.5/\mu$L)

Abbreviations: E, escalated; S, standard; G-CSF, granulocyte colony-stimulating factor; IV, intravenously; PO, orally; SC, subcutaneously.

Toxicity was measured according to the standard ECOG criteria.[12] The dose intensity of each drug and each regimen was calculated according to the criteria reported by Hryniuk[13] and using examples and suggestions furnished by DeVita et al.[14] The International Prognostic Score (IPS) was calculated according to the method of Hasenclever and Diehl.[15] All statistical analyses were accomplished using Stata Statistical Software, release 8.2 (Stata Corp, College Station, TX).

The sample size was calculated with the following assumptions: one-sided 5% significance test (α error = .05) controlled by multiple comparisons (Tukey, Ciminera, and Heyse procedure),[16] with a three-arm trial; power of 80% (β error = .2), with 4 years of uniform recruitment and 2 years of follow-up; hazard ratio (HR) of 0.4 for FFS in the experimental arms, assuming 5-year FFS of 65% for ABVD as reference. As a result, 282 patients were required (94 in each arm), with 62 expected events. After randomization a 10% drop out rate was expected, thus a cohort of about 310 patients was necessary to test the hypothesis.

We used one-sided test in consideration of the expected superiority of BEACOPP and CEC, in term of FFS[6,17] in comparison with the historical knowledge about ABVD chemotherapy regimen.[2]

Enrollment was halted in June 2007 when 307 patients from 33 centers had been enrolled.

All analyses were conducted according to the intention-to-treat (ITT) principle, with the proviso that patients for whom an exclusion criterion was

discovered after random assignment would be considered to be ineligible; patients who had insufficient follow-up information to determine treatment outcome were also excluded from analysis.[18] Only in the analysis of the FFS rate the level of statistical significance was set at a one-sided $P < .05$ and the reported P value in tables and figures was adjusted for multiple comparisons, because the trial was powered and monitored on the basis of FFS. In all other analyses, the level of statistical significance was set at a two-sided $P < .05$.

Survival curves were calculated using Kaplan-Meier estimates,[19] and statistical comparisons between curves were made using the log-rank test. Comparisons between curves that had been adjusted by potentially confounding factors were obtained using the Cox proportional hazard regression method.[20] The proportionality of hazard was checked graphically by means of scaled Schoenfeld residuals.[21] The χ^2 test, Fisher's exact test, and Kruskal-Wallis test were used to compare variables.[22]

RESULTS

Between April 2000 and June 2007, 103, 102, and 102 patients were randomly allocated to ABVD, BEACOPP, and CEC treatment arms, respectively. Two patients were subsequently excluded—one due to a withdrawn consent and one for revised histology (non-Hodgkin's lymphoma). Thus, 305 were analyzed according to ITT (Fig 1). As of December 2007, 10 patients were excluded because of lack of data. Baseline characteristics of our patients, including demographics, clinical features, and treatment details, are presented in Table 2.

Outcomes

At the end of chemotherapy, CR rates were similar among the three arms: 70% (95% CI, 60% to 79%), 81% (95% CI, 73% to 86%), and 69% (95% CI, 60% to 79%) for patients treated with ABVD, BEACOPP, and CEC, respectively ($P = .130$). After RT, the resulting CR rates were 84% (95% CI, 76% to 91%), 91% (95% CI, 85% to 97%), and 83% (95% CI, 75% to 90%) for ABVD, BEACOPP, and CEC, respectively ($P = .207$).

After a median follow-up of 41 months (range, 4 to 91 months), 73 failures were recorded, including nine early failures, 33 incomplete responses, 30 relapses, and one death in CR. A total of 59 patients developed progressive disease, including 24 progressions, 30 relapses, and five deaths (three deaths during treatment, one death at the end of chemotherapy, and one death in CR). Progression occurred in 12, two, and 10 patients in ABVD, BEACOPP, and CEC arms, respectively. Relapse occurred in 14, eight, and eight patients treated with ABVD, BEACOPP, and CEC, respectively. As salvage therapy 26 patients (45%) received high-dose therapy and autologous peripheral blood stem-cell transplant. Overall, 23 patients died: eight in the ABVD, eight in the BEACOPP, and seven in the CEC arm. Of these, 15 patients died as a result of lymphoma progression or recurrence; other causes of death were recorded as complications of first-line treatment

Table 2. Patient Characteristics and Treatment Details in the Three Treatment Arms

Characteristic	% ABVD (n = 99)	% BEACOPP (n = 98)	% CEC (n = 98)
Median age, years	32	29	33
≥ 45 years	18	17	26
Male sex	43	60	56
Pathology subtype			
Lymphocyte rich	2	5	2
Nodular sclerosis	81	84	81
Mixed cellularity	11	7	15
Lymphocyte depletion	2	5	2
Unclassified	1	1	1
Clinical stage			
IIB	33	31	29
IIIA	27	21	21
IIIB	17	25	24
IVA	13	6	10
IVB	9	16	16
Bulky disease	31	37	37
International Prognostic Score*			
0-1	41	28	26
2-3	47	54	59
4-7	11	18	15
0-2	70	57	56
3-7	30	43	44
Median delivered dose intensity	0.90	0.83	0.84
Radiation therapy	46	44	43
RT delivered dose, Gy			
Median	36	36	36
Range	30-43	30-41	30-40
Interval CT/RT, weeks			
Median	5	6	7
Range	2-12	3-12	2-14

NOTE. Because of rounding, percentages may not total 100.
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; CEC, cyclophosphamide, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine; RT, radiation therapy; CT, chemotherapy.
*Data were available for 284 patients (93%).

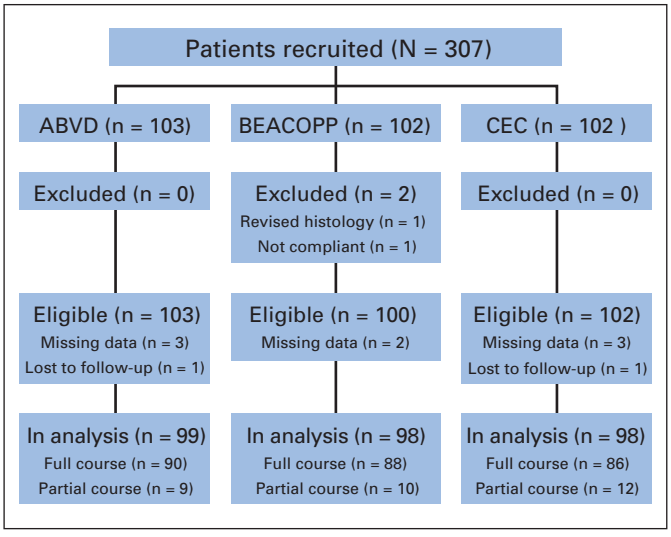

Fig 1. Treatment allocation and number of patients included in the analysis, according to the CONSORT statement.[18] After random assignment, two patients were considered ineligible and were excluded. Patients were included in the analysis according to the intention-to-treat principle. Ten patients were excluded because there was a lack of data on their therapy or follow-up. Thirty-one patients did not receive all six scheduled cycles of chemotherapy (nine patients in doxorubicin, bleomycin, vinblastine and dacarbazine [ABVD], 10 patients in bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone [BEACOPP], and 12 patients in cyclophosphamide, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine [COPPEBVCAD/CEC]).

in two patients, myelodysplastic syndrome in one patient, complications of salvage treatment in two patients, cardiorespiratory disease in two patients, and hepatic dysfunction during follow-up in one patient. There were two fatal acute treatment-related events, both in the BEACOPP arm.

The estimated 5-year FFS, PFS, RFS, and OS rates are shown in Figure 2 and summarized in Table 3.

Finally, four second malignancies were recorded: one thyroid cancer (27 months after the end of ABVD treatment), one Kaposi's sarcoma (69 months after the end of BEACOPP treatment), and one myelodysplastic syndrome, and one follicular lymphoma (4 and 10 months after the end of CEC treatment, respectively).

Multivariate analysis of study end points was performed to analyze the role of confounding factors. The better results obtained with BEACOPP in terms of FFS did not change when the therapy was adjusted by IPS (IPS ≥ 3 *v* 0 to 2). A PFS analysis adjusted for IPS showed a HR of 0.46 (95% CI, 0.24 to 0.88) associated with BEACOPP, with a risk reduction of progression of 54% in comparison with the ABVD treatment. As shown in Figure 3, the magnitude of BEACOPP and CEC over ABVD was more evident in patients with high IPS (IPS, 3 to 7).

Toxicity

Hematologic and nonhematologic toxicities are summarized in Table 4. BEACOPP and CEC resulted in higher rates of grade 3-4 neutropenia (54% and 48%) compared with ABVD (34%; $P = .016$). BEACOPP was associated with higher rates of severe infections (14%) compared with ABVD (2%) and CEC (4%; $P = .003$). Frequency of grade 3-4 anemia was higher with BEACOPP and CEC (16% and 15%) than for ABVD (5%; $P = .038$). Nonhematologic toxicity was

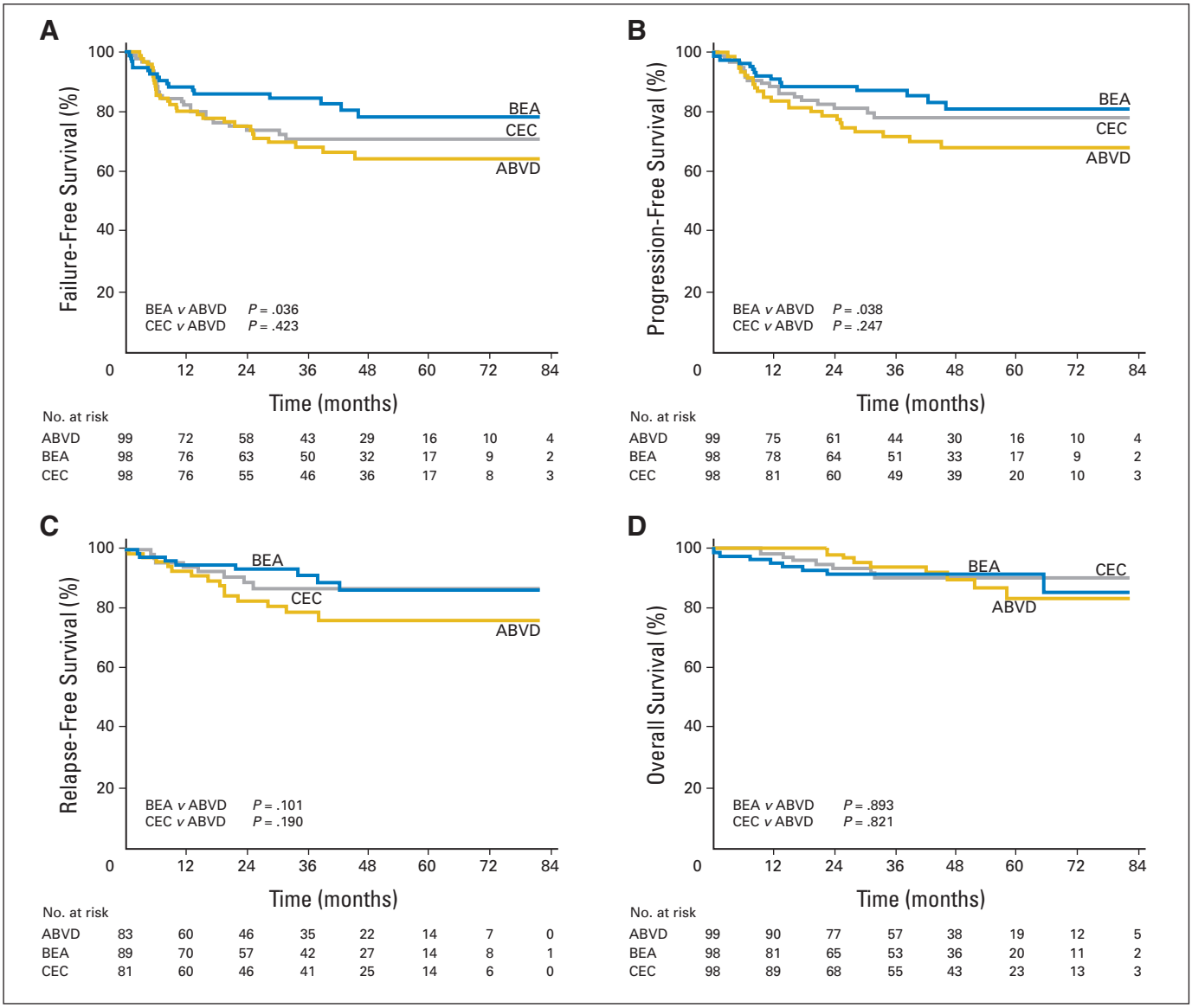

Fig 2. Kaplan-Meier analysis of the probability of the failure-free survival, progression-free survival, relapse-free survival, and overall survival according to intention to treat. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEA, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; CEC, cyclophosphamide, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine.

Table 3. Estimates of the FFS, PFS, RFS, and OS at 5 Years According to Treatment Arm

Variable	ABVD (n = 99) Estimate	ABVD (n = 99) 95% CI	BEACOPP (n = 98) Estimate	BEACOPP (n = 98) 95% CI	CEC (n = 98) Estimate	CEC (n = 98) 95% CI	*P*
FFS	65	53 to 74	78	67 to 86	71	60 to 79	
BEACOPP *v* ABVD							.036*
CEC *v* ABVD							.423*
BEACOPP *v* CEC							.132*
PFS	68	56 to 78	81	70 to 89	78	68 to 86	
BEACOPP *v* ABVD							.038†
CEC *v* ABVD							.247†
BEACOPP *v* CEC							.378†
RFS	76	63 to 86	86	74 to 93	87	75 to 93	
BEACOPP *v* ABVD							.101†
CEC *v* ABVD							.190†
OS	84	69 to 92	92	84 to 96	91	81 to 96	
BEACOPP *v* ABVD							.893†
CEC *v* ABVD							.821†

Abbreviations: FFS, failure-free survival; PFS, progression-free survival; RFS, relapse-free survival; OS, overall survival; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; CEC, cyclophosphamide, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine.
*One-sided log-rank test adjusted *P* value.
†Two-sided log-rank test.

similarly moderate in all three arms. Only CEC showed a higher frequency of grade 3-4 neurotoxic events (6%) than ABVD and BEACOPP (0% and 1%, respectively; $P = .013$).

BEACOPP and CEC chemotherapies had to be discontinued in six patients due to viral infection (n = 1), Candidiasis (n = 1) and hepatic dysfunction (n = 1) in BEACOPP arm, and recurrent pulmonary infection (n = 1), deep venous thrombosis (n = 1), and severe prolonged neutropenia (n = 1) in CEC arm.

DISCUSSION

The HD2000 trial compared ABVD with BEACOPP and CEC as initial treatment of advanced HL. After a median follow-up of more than 3 years, BEACOPP was associated with a better PFS when compared with ABVD. The superiority of BEACOPP was not modified when therapy was adjusted by IPS. No statistically significant difference was observed between BEACOPP and CEC, or between CEC and ABVD. Differences in terms of PFS did not translate into differences in OS.

The question of which chemotherapy regimen should be offered to patients with advanced HL has been investigated in several trials. In the late 1990s, when the HD2000 trial was defined, the most promising data came from the HD9 trial.[10] The most recent analysis, with a median follow-up of 112 months, confirmed their initial results and demonstrated superior FFS and OS for patients treated with esc-BEACOPP.[23] The clinical benefit of esc-BEACOPP can be estimated into a survival benefit in at least 10% of patients with the poorest prognosis,[24] although it should be compared with the higher

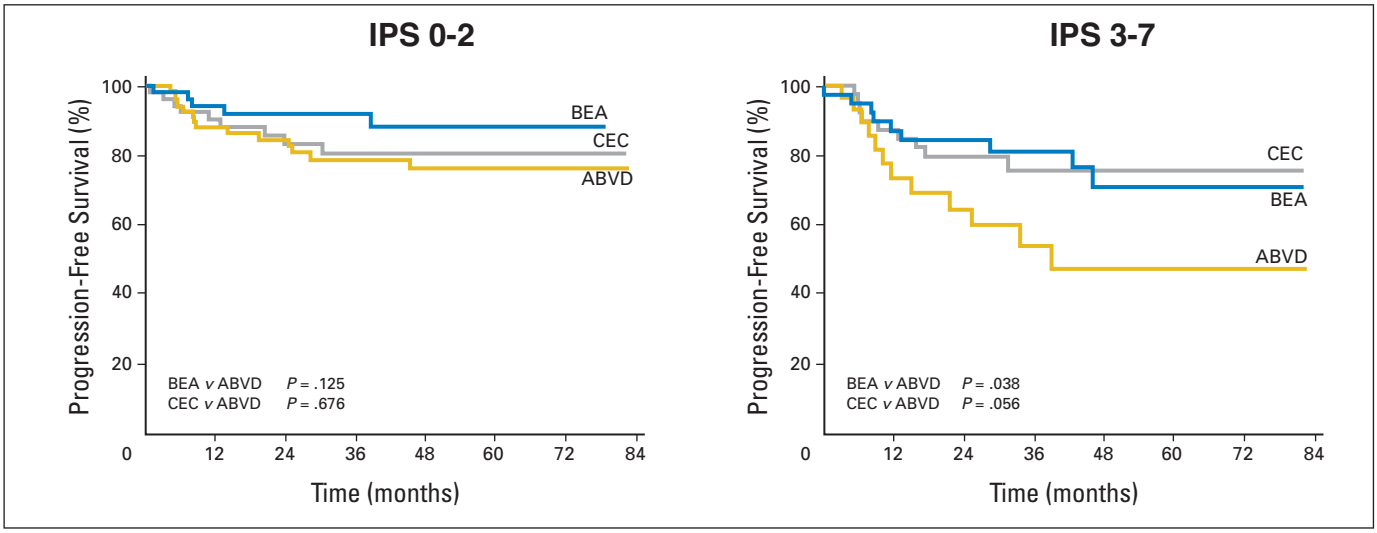

Fig 3. Kaplan-Meier analysis of the progression-free survival according to intention to treat stratified by International Prognostic Score (IPS). ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; BEA, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; CEC, cyclophosphamide, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin and vindesine.

Table 4. Acute Adverse Effects of Chemotherapy

Grade 3-4 Adverse Effect	%			
	ABVD	BEACOPP	CEC	*P*
Hematologic toxicity				
Anemia	5	16	15	.038
Leukopenia	22	57	47	< .001
Neutropenia	34	54	48	.016
Thrombocytopenia	3	22	17	< .001
Infections	2	14	4	.003
Nonhematologic toxicity				
Neurologic, sensory	0	1	6	.013
Nausea/vomiting	13	8	5	.145
Mucositis	1	4	3	.327
Alopecia	31	29	34	.766
Pain	0	3	1	.082
Constipation	2	1	3	.703

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

risk of hematologic toxicity and with increased overall toxicity including 3% treatment-related mortality, and infertility in almost all patients.

Although smaller than the HD9, HD2000 trial offers some piece of information on BEACOPP value for advanced HL. This study in fact addresses the efficacy of BEACOPP outside the GHSG, and compares BEACOPP with ABVD. When this trial was initially designed, the clinical activity of BEACOPP was known to be impressive but its toxicity was a main concern, and the principal aim of our study was to assess marrow damage by studying apoptosis of CD34-positive mononuclear cells and this will be the subject of a separate report. Concerns about toxicity prompted us to adopt a less intensive BEACOPP schedule. The number of cycles was reduced from eight to six, and patients were switched to std-BEACOPP after four initial courses of the escalated regimen.

Based on our results, we can conclude that the adoption of such a modified schedule did not substantially affect the efficacy of BEACOPP. In particular, we observed a CR rate of 91%, that compares favorably with the 96% of 8 courses of esc-BEACOPP. Similarly, patients treated with BEACOPP in our trial achieved a 5-year FFS rate of 78% that is between the 75% and 85% 5-year freedom from treatment failure rate observed for std- and esc-BEACOPP,[10] respectively.

In this study, the efficacy of ABVD was broadly similar to published data[25,26] in terms of response and outcome. However, patients treated with ABVD in this trial had a 65% 5-year FFS, whereas it was 78% for the ABVD arm in a previous Italian study.[27] There is no clear reason for this difference, as patients from the two studies were comparable in terms of IPS and dose intensity. However, some imbalance in terms of bulky disease was observed, which is a likely explanation for the poorer outcome of the HD2000 patients treated with ABVD.

Although patients treated with ABVD showed a higher risk of disease progression and relapse, no differences in terms of OS emerged, partly due to the efficacy of salvage treatments adopted. This finding differs from the results of the GHSG HD9 trial that showed a statistically significant difference in survival of esc-BEACOPP compared with COPP-ABVD. The HD2000 and HD9 trials however cannot be fully compared because the smaller sample size of our trial and its limited power for observing survival differences.

Together with ABVD and BEACOPP, we also tested the efficacy of the CEC hybrid regimen. The choice of including this arm was based on the results of the previous trial in which we compared ABVD, Stanford V, and MOPPEBVCAD regimens.[27] Differing from our previous evaluation, the current CEC regimen was slightly modified by substituting mechlorethamine with cyclophosphamide. This change was due to the unavailability of mechlorethamine and to the supposedly similar efficacy of equivalent doses of a different alkylator. The results obtained with CEC in terms of response and survival are intermediate between those obtained after ABVD and BEACOPP. The absence of differences confirms the results of our previous trials,[5,6,27] however small differences could not have been shown due to the limited number of patients.

As far as treatment-related toxicity is concerned, patients treated with BEACOPP had more frequent severe events, both in terms of neutropenia and infections. However, the incidence of fatal treatment-related effects was less than 2%, slightly lower than the originally reported incidence in the HD9 trial. Overall, the adoption of a modified, less intensive schedule, made BEACOPP apparently safer than originally reported, suggesting that the addition of two cycles to the six courses of intensive chemotherapy may only increase the associated toxicity and probably not have any impact on patients' outcome. So far, no case of secondary acute leukemia has been observed among our patients treated with BEACOPP, with only one case of MDS observed in the CEC arm. We believe this finding confirms the validity of our initial choice of using a less intensive schedule.

HD2000 trial raises the question of whether, in the choice of initial treatment of patients with advanced HL, it is better to accept the high costs of intensive regimens like BEACOPP or to choose a more manageable but less active regimen, such as ABVD, reserving more toxic treatments for progressing/relapsed patients. Although our results demonstrate a superiority of BEACOPP, before drawing definite conclusions, we suggest waiting for the results coming from two trials conducted by the Intergruppo Italiano Linfomi and the European Organisation for the Research and Treatment of Cancer, both focused on the comparison between BEACOPP and ABVD.

Although BEACOPP may be superior to ABVD, mostly for patients with unfavorable advanced HL, it is still clinically mandatory to try to avoid unnecessary toxicity for those in the best prognostic group. At present, a response to treatment is considered to be the most important single prognostic factor for the individual patient, and FDG-PET imaging is emerging as a powerful tool for an early assessment of response. Several studies have investigated the role of FDG-PET imaging in HL response assessments.[28,29] A recent analysis of 260 patients with advanced HL, who were treated with ABVD, and RT if indicated, and then evaluated using FDG-PET after two courses of ABVD (FDG-PET-2), showed a 2-year PFS rate of 12.8% and 95%, for patients with FDG-PET-2–positive and –negative scans, respectively ($P < .0001$).[30] Thus, it should be possible to identify those patients with a suboptimal response to initial therapy by using FDG-PET imaging. Response-adapted therapy, aiming to achieve high cure rates with minimal acute and delayed toxicity, is currently therefore a concrete possibility.

In conclusion, as adopted in this study, BEACOPP results in a better PFS compared with ABVD, particularly in patients with a high IPS, with worst toxicity profile. However, our results must face with the hypothesis of a potential benefit from response adapted therapy,

based on early assessment of response with FDG-PET. This hypothesis is currently investigated by several ongoing trials whose results will probably allow us to deliver BEACOPP only to patients not achieving an early response with ABVD. This would avoid an unnecessary acute and delayed toxicity in those patients with a very low risk of treatment failure.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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