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ORIGINAL REPORT

Dose Intensity of Chemotherapy in Patients With Relapsed Hodgkin's Lymphoma

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ABSTRACT

Purpose
High-dose chemotherapy (HDCT) followed by autologous stem-cell transplantation (PBSCT) has become the standard treatment for patients with relapsed Hodgkin's lymphoma (HL). The intensity of treatment needed is unclear. This European intergroup study evaluated the impact of sequential high-dose chemotherapy (SHDCT) before myeloablative therapy.

Patients and Methods
Patients with histologically confirmed, relapsed HL were treated with two cycles of dexamethasone, cytarabine, and cisplatin, and those without disease progression were randomly assigned. In the standard arm (A), patients received myeloablative therapy with carmustine, BEAM (carmustine, etoposide, cytarabine, and melphalan) followed by PBSCT. Patients in the experimental arm (B) also received sequential cyclophosphamide, methotrexate, and etoposide in high-doses before BEAM. Freedom from treatment failure (FFTF) was the primary end point. Remission rates, overall survival (OS), and toxicity of treatment were secondary end points.

Results
From a total of 284 patients included, 241 responding patients were randomly assigned after two cycles of dexamethasone, cytarabine, and cisplatinum. Patients treated in arm B had longer treatment duration and experienced more toxicity and protocol violations ($P < .05$). Mortality was similar in both arms (20% and 18%). With a median observation time of 42 months, there was no significant difference in terms of FFTF ($P = .56$) and OS ($P = .82$) between arms. FFTF at 3 years was 62% (95% CI, 56% to 68%) and OS was 80% (95% CI, 75% to 85%). Patients with stage IV, early relapse, multiple relapse, anemia, or B symptoms had a higher risk of recurrence ($P < .001$).

Conclusion
Compared with conventional high-dose chemotherapy, additional SHDCT is associated with more adverse effects and does not improve the prognosis of patients with relapsed HL.

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INTRODUCTION

Combination chemotherapy cures approximately 80% of patients with Hodgkin's lymphoma (HL), but those experiencing treatment failure have a poorer prognosis.[1] High-dose chemotherapy (HDCT) followed by autologous stem-cell transplantation (PBSCT) has become standard of care in these patients as demonstrated in randomized trials.[2,3] Variables affecting outcome in patients with relapsed HL undergoing HDCT include chemotherapy sensitivity to conventional salvage treatment, remission status before HDCT, and duration of first remission.[4-8] Randomized clinical studies demonstrated a relationship between intensity of chemotherapy and tumor response in this disease.[3,9] Since sequential HDCT (SHDCT) indicated promising results in a number of clinical studies,[10-16] the German Hodgkin Study Group (GHSG) evaluated a SHDCT regimen in a prior phase II study demonstrating that this was safe and effective in patients with relapsed and refractory HL.[17]

In this study, we thus sought to compare the efficacy, safety, and adverse event profile of a standard HDCT with that of a combined SHDCT-HDCT program in patients with histologically confirmed relapsed HL.

PATIENTS AND METHODS

Study Design and Patients

The HDR2 (Randomized Trial of BEAM Plus PBSCT Versus Single-Agent High-Dose Therapy Followed by BEAM Plus PBSCT in Patients With Relapsed Hodgkin's Disease) study protocol was approved by the GHSG steering group and by the ethics committees of participating centers. This was a randomized, prospective, multicenter intergroup phase III study conducted by the GHSG, European Organisation for the Research and Treatment of Cancer Lymphoma Group, European Bone Marrow Transplantation Group, and the Spanish Grup per l'Estudi dels Limfomes de Catalunya i Balears (GELCAB) in which 95 European centers participated (Appendix).

Patients with histologically confirmed early and late relapsed HL, as well as patients with multiple relapses and no prior HDCT were enrolled. Diagnosis of relapsed HL was made by the local pathologist and then centrally confirmed by a group of reference pathologists. After written informed consent, patients were registered at the GHSG central trial office.

In line with the definition of our and other cooperative groups, early first relapse was defined as prior response lasting 3 to 12 months and late relapses as CR lasting more than 12 months.[15-18] Patients were eligible if they were 18 to 60 years of age, had an Eastern Cooperative Oncology Group performance status ≤ 2, and had received primary multiagent chemotherapy such as cyclophosphamide, vincristine, procarbazine, and prednisone/doxorubicin, bleomycin, and vinblastine/doxorubicin, bleomycin, vinblastine, and dacarbazine/mechlorethamine, vincristine, procarbazine, and prednisone/bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), or comparable regimen with or without radiotherapy (RT).

Patients were excluded if they had a concurrent malignancy other than basal-cell carcinoma of the skin or cervical intraepithelial neoplasia, unstable angina, congestive heart failure (higher than New York Heart Association II), poorly controlled diabetes, chronic pulmonary disease, cerebral disorders, coronary angioplasty or myocardial infarction within the past 6 months. Other exclusion criteria were active infection, HIV positivity, creatinine clearance lower than 60 mL/min, pregnant or lactating women, and concurrent treatment with investigational drugs.

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. An international review board was established and the study was registered as NCT00025636. Interim analyses were performed by an independent statistician and reviewed by an independent data and safety monitoring committee.

Random Assignment and Masking

After response to dexamethasone, cytarabine, and cisplatinum (DHAP), patients were centrally randomly assigned in the GHSG central trial office and the participating centers were informed without masking. As the duration of therapy in the intensified arm B was longer and a delay of potential RT in arm A would have compromised efficacy, placebo application and similar masking procedures would have been unethical. Random assignment was stratified with respect to center, type of relapse (early, late or multiple), stage at relapse, and age.

Study Treatment

Patients received two courses of DHAP (dexamethasone 40 mg intravenously [IV] days 1 to 4; cytarabine $2 \times 2{,}000$ mg/m^2 IV over 3 hours, day 2, twice per day; cisplatinum 100 mg/m^2 continuous IV over 24 hours, day 1) followed by 10 μg/kg of daily granulocyte colony-stimulating factor (G-CSF; lenograstim) until the end of peripheral blood stem cell (PBSC) aphereses. Stem cell aphereses started when CD34$^+$ cells reached more than 10/μL in the peripheral blood. The second DHAP cycle followed by 5 μg/kg G-CSF was administered when WBC had recovered to $\geq$ 3,000/μL and platelets to $\geq$ 75,000/μL.

Patients achieving complete response (CR), partial response (PR), or stable disease (SD) after DHAP were randomly assigned between the standard arm (A) or the intensified arm (B). All patients received BEAM (carmustine 300 mg/m^2 IV over 2 hours, day 37; etoposide 2×150 mg/m^2 IV over 30 minutes, days 37 through 40; cytarabine 2×200 mg/m^2 IV over 30 minutes, days 37 through 40; melphalan 140 mg/m^2 IV over 30 minutes, day 37) followed by PBSCT with at least 2×10^6 per kg body weight of CD34$^+$ PBSC on day 42 and G-CSF 5 μg/kg subcutaneously (SC) twice per day from day 41 until WBC $\geq$ 3,000/μL for 3 days.

In arm B, patients were treated with SHDCT consisting of cyclophosphamide (4,000 mg/m^2 IV over 8 hours, day 37) followed by prophylactic uromitexane 4,000 mg/m^2 continuous IV days 37 to 39 and G-CSF 5 μg/kg SC by day 38 until WBC $\geq$ 3,000/μL for 3 days, followed by high-dose methotrexate (8,000 mg/m^2 IV for 6 hours, day 51) with adequate hydration and leucovorin rescue as previously described[17] and vincristine (1.4 mg/m^2, maximum 2 mg, IV day 51) followed by high-dose etoposide (500 mg/m^2 IV for 8 hours, days 58 through 61 with G-CSF 5 μg/kg SC from day 62 until WBC were $\geq$ 3,000/μL for 3 days). After therapy with BEAM (starting on day 80), PBSCs were reinfused and G-CSF administered until hematologic recovery as in arm A. Patients with residual lymphoma ($>$ 1.5 cm on computed tomography scan) at the final evaluation (100 days after BEAM) received 30 Gy involved-field RT.

Assessments

Before inclusion into the study, the extent of disease was assessed by chest x-ray, abdominal ultrasound, computed tomography, and bone marrow biopsy. After two cycles of DHAP, all sites of initial disease manifestation were reassessed by adequate methods. Restaging for the final response evaluation was performed 100 days after PBSCT. Follow-up visits were carried out at 3-month intervals during the first 2 years, then at 6-month intervals, and after 5 years every 12 months.

The main end point for patients who had responded to two courses of DHAP was freedom from treatment failure (FFTF). Treatment failure was defined as death from any cause, recurrence of HL, additional therapy in non-CR, or unknown tumor status. Secondary end points were CR rate 100 days after PBSCT, progression-free survival (PFS), overall survival (OS), WHO grade 3/4 toxicity, and secondary neoplasia. Events for PFS failure were death from any cause and new recurrence of HL.

Statistical Analysis and Role of the Funding Source

We hypothesized a higher efficacy of the intensified arm B compared to the standard arm A. The sample size calculation assumed an FFTF rate of 60% after 2 years in arm A and 80% in arm B. Four interim analyses were conducted and a stopping rule after the restricted procedure with an α error probability of .05 and a statistical power of 0.80 was applied. The final statistical analysis was planned after at least 64 failures requiring a minimum of 200 randomly assigned patients. This final analysis for the main end points was performed according to the intention-to-treat principle with a log-rank test of Kaplan-Meier curves.

A previously developed prognostic score based on time to recurrence, stage at relapse, and anemia[19] was used for prediction of PFS. Early relapse, hemoglobin lower than 10.5 g/dL in women and lower than 12.0 g/dL in men, and stage 3 to 4 disease were summed, one point each to a maximum of three points. In addition, age, sex, B symptoms at relapse, primary treatment protocol, and extranodal involvement were included in Cox regression analysis to predict PFS.

The level of significance was set to $P < .05$ (two sided). All statistical analyses were performed with Statistical Analysis System release 8.02 (SAS Institute, Cary, NC).

The study funding source (German Cancer Aid) was not involved in study design; in the collection, analysis, and interpretation of data; in the writing of the report or decision to submit the manuscript.

RESULTS

Patients and Treatment

From December 2000 to December 2006, 281 patients with relapsed HL were recruited (Fig 1). After treatment with two cycles of DHAP, 241 patients (86%) who did not experience progression or

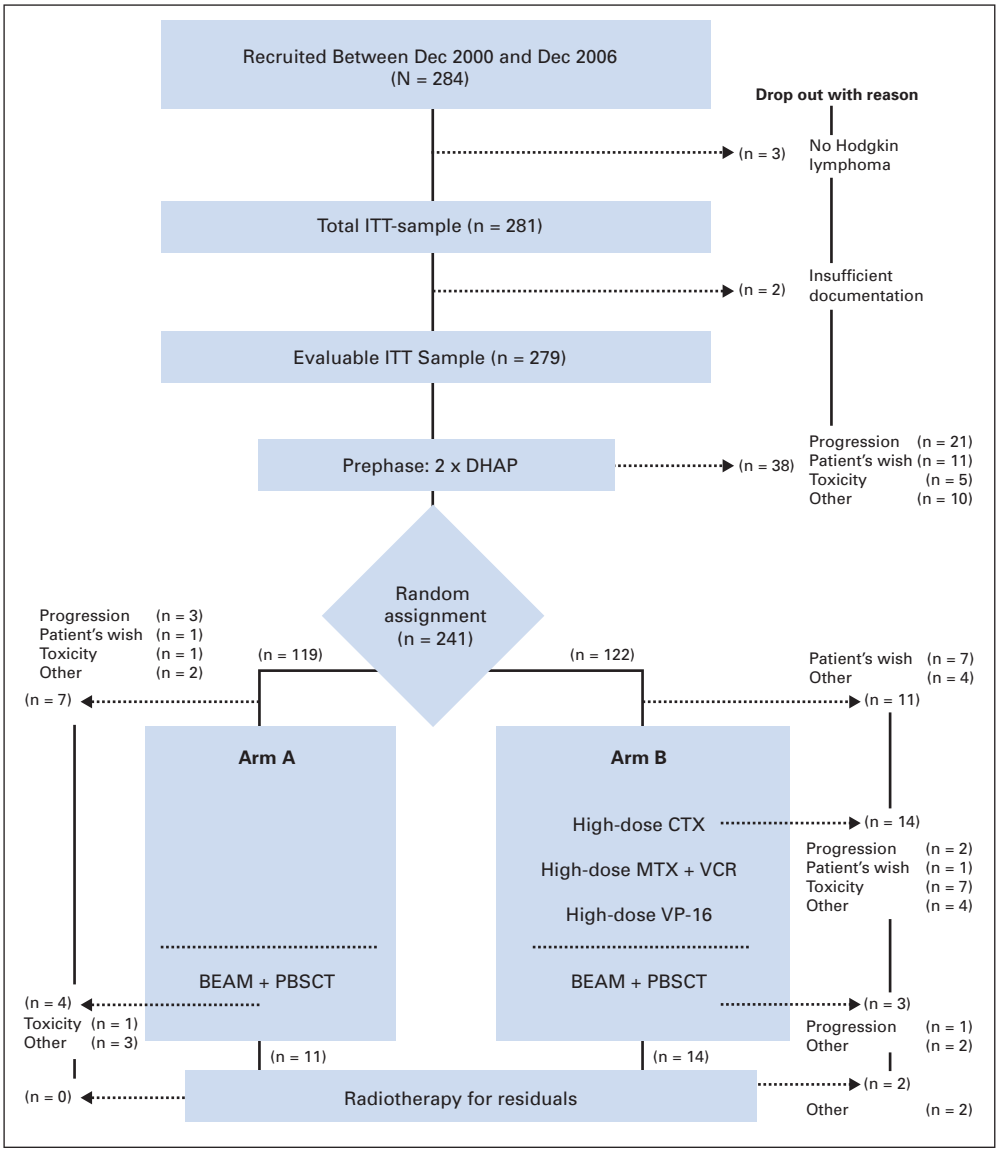

Fig 1. CONSORT diagram showing the flow of participants through each stage of the trial with random assignment after prephase with dexamethasone, cytarabine, and cisplatinum (DHAP). ITT, intention to treat; CTX, cyclophosphamide; MTX, methotrexate; VCR, vincristine; VP-16, etoposide; BEAM, carmustine, etoposide, cytarabine, and melphalan; PBSCT, autologous stem cell transplantation.

other treatment failures were randomly assigned to arms A or B. Arms were well balanced with respect to demographics and baseline characteristics (Table 1). The mean duration of treatment differed significantly between arms: 2.1 months for arm A (median, 1.8; range, 1.2 to 5.5) and 4.0 months for arm B (median, 3.8; range, 1.3 to 10.0). PBSC collection was successful in 99% of 225 patients with documentation of stem cell count. This rate is in line with an earlier report.[19] Compared to the planned dose, the given doses of single drugs ranged between 95% and 100% in arm A and 82% to 98% in arm B. RT of residual lymphoma was applied to 11 patients (9%) in arm A and 14 patients (11%) in arm B. The median total RT dose was 30 Gy in both arms.

Efficacy

After two cycles of DHAP, 68 patients reached CR/CR unconfirmed (CRu; 24%), 129 patients reached PR (46%), and 55 patients reached SD (20%). Of these 252 patients, 11 dropped out for reasons given in Figure 1 and 241 were randomly assigned. Twelve patients had progressive disease (4%) and 15 unknown tumor status (5%).

At the final evaluation, 99 patients in arm A (83%) and 101 in arm B (84%) achieved CR/CRu; seven patients in both arms had a PR (6%). SD was observed in two patients in arm A (2%) and in one patient in arm B (1%). There were 10 patients with progressive disease in both arms (8%). The tumor status after treatment was unknown in one patient in both arms (1%).

The median follow-up for OS was 42 months. At 3 years, rates for OS were 87% and 80% ($P = .816$), PFS rates were 72% and 67% ($P = .505$), FFTF rates were 71% and 65% ($P = .557$) for arms A and B, respectively (Fig 2). The standard arm A was descriptively superior to the experimental arm in all survival measures. Thus, the additional SHDCT chemotherapy in arm B did not improve efficacy and the primary end point was not met. This lack of improvement was also observed in all analyzed subgroups including early or late relapses and patients with different tumor status after DHAP.

Safety and Adverse Event Profile

Nearly all patients developed at least one adverse effect of WHO grade 3/4 (arm A, 96%; arm B, 98%). Overall, more toxicity was

Table 1. Patient Characteristics

Variable	Total		Not Randomly Assignment		Standard Arm A		Intensified Arm B	
	No.	%	No.	%	No.	%	No.	%
No. of patients	279		38		119		122	
Age, years								
Mean	35.3		34.9		35.3		35.4	
SD	10.3		13.1		9.7		10.1	
Sex, female	101	36	17	45	45	38	39	32
Ann Arbor stage								
IA	36	13	2	5	17	14	17	14
IB	5	2	—		3	3	2	2
IIA	73	26	6	16	29	24	38	31
IIB	16	6	3	8	8	7	5	4
IIIA	43	15	7	18	21	18	15	12
IIIB	32	11	7	18	11	9	14	11
IVA	40	14	6	16	17	14	17	14
IVB	33	12	7	18	13	11	13	11
Relapse type								
Early	76	27	15	41	27	23	34	28
Late	157	57	15	41	74	62	68	56
Mult.	44	16	7	19	18	15	19	16
Anemia	55	20	13	34	20	17	22	18
Prior chemotherapy								
COPP/ABVD	144	52	23	61	59	50	62	51
BEACOPP b	12	4	1	3	7	6	4	3
BEACOPP e	31	11	6	16	9	8	16	13
BEACOPP u	40	14	3	8	20	17	17	14
Other	52	19	5	13	24	20	23	19
2-4 cycles	118	42	16	42	51	43	51	42
6 and more	92	33	15	39	36	30	41	34
Unknown	69	25	7	18	32	27	30	25
Prior radiotherapy, yes	178	64	21	55	72	61	85	70

Abbreviations: SD, standard deviation; COPP, cyclophosphamide, vincristine, procarbazine, and prednisone; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; BEACOPP b, BEACOPP basis; BEACOPP e, BEACOPP escalated; BEACOPP u, BEACOPP unspecified.

observed with the intensified arm: 45% of patients in arm A and 88% in arm B had grade 4 toxicity before BEAM and PBSCT (Table 2). The main toxicity was myelosuppression with leukocytopenia and thrombocytopenia occurring in 87% to 93% of patients. Severe mucositis was observed in 57% (arm A) and 67% (arm B) of patients. Other toxicities included infections (33% and 48%), gastrointestinal toxicity (23% and 29%), and pain (18% and 24%).

A total of 60 of 279 patients died in this study (22%). The main reason was Hodgkin's lymphoma occurring in 35 patients (13%): 14 in arm A, 13 in arm B, and eight not randomly assigned. Further causes of death included: toxicity of study treatment in six patients (2%; arm A: two, not randomly assigned: four); toxicity of additional salvage therapy in five patients (2%; arm A: two, arm B: three); infections/sepsis in five patients (2%; arm A: four, arm B: one); unclear in four patients (2%, all arm B); other disease in tow patients (1%; arm A: one, not randomly assigned: one); and secondary neoplasia (arm B), accident (not randomly assigned), and cardiovascular disease (arm A) in one patient each.

Prognostic Factors

Prognostic factors for PFS after relapse were evaluated by univariate Kaplan-Meier analysis and multivariate Cox regression. As stage III patients had a similar risk for PFS failure compared with stage II patients in univariate analysis, the previously established prognostic score[20,21] was slightly modified in that only stage IV (and not stage III) was scored as additional risk factor. Both, multiple relapses and early relapse was scored as risk factor. The resulting prognostic score differentiated four risk groups as shown in Figure 3. Patients with none of these risk factors (n = 117) had a PFS of 81% (95% CI, 72% to 87%) at 3 years. Conversely, almost all patients in the small group of those having three risk factors (n = 14) relapsed or died within 3 years (PFS, 14%; 95% CI, 2% to 37%).

The significance of the three predictors used in the present analysis was confirmed in multivariate Cox regression with proportional hazards (stage 4, hazard ratio [HR], 1.7, 95% CI, 1.0 to 2.7; anemia HR, 1.9, 95% CI, 1.1 to 3.0; early or multiple relapse: HR, 1.7, 95% CI, 1.1 to 2.7). These results showed approximately equal weight of these predictors thus validating the scoring rules applied. Beyond these variables, B symptoms (HR, 1.7, 95% CI, 1.1 to 2.7) and first-line treatment (BEACOPP *v* other regimens, HR, 1.7, 95% CI, 1.0 to 2.7) significantly increased the risk of failure to a similar extent. Age older than 50 years and extranodal involvement showed no additional predictive value ($P = .62$ and $P = .23$). This finding is probably related to the age limit of 60 years in this study.

DISCUSSION

The rationale for the HDR2 trial was to improve treatment results for patients with relapsed HL. After induction treatment with two time-condensed cycles of DHAP, we evaluated the impact of SHDCT in this setting and compared the most frequently used high-dose regimen (BEAM) with a sequential high-dose regimen followed by BEAM. The results demonstrate that SHDCT does not improve outcome, and was associated with more adverse events and toxicity. Prognostic factors identified may be useful to define more homogeneous cohorts of risk groups in patients with relapsed HL for further analyses and to identify patients with poor-risk relapse who need alternative approaches.

There are a number of studies that evaluated HDCT followed by PBSCT in patients with relapsed or refractory HL.[4,12,17,22-28] This strategy has been shown to produce long-term survival in patients with HL, mainly those with chemotherapy-sensitive relapse. Based on the results of two earlier randomized trials, HDCT/PBSCT has become standard treatment for patients with relapsed HL.[2,3] However, the relapse rates of 30% to 50% observed in most trials using single HDCT in HL suggested that this strategy might have little effect on nonproliferative cells. To possibly overcome this problem, SHDCT regimens with proven activity in solid tumors were introduced in the treatment of lymphoproliferative disorders.[10-16] In accordance with the Norton-Simon hypothesis,[29] noncrossresistant drugs in high or ultra-high-doses were given at short time intervals after initial cytoreduction. SHDCT thereby enabled high-doses of cytostatic drugs given over a minimum period of time resulting in dose over time intensification. Examples of SHDCT used to treat patients with relapsed and refractory lymphoma were the studies reported by Gianni et al.[12,13] Their treatment program was based on sequential administration of high-doses of cyclophosphamide, methotrexate, and etoposide, and was followed by total-body irradiation and melphalan.

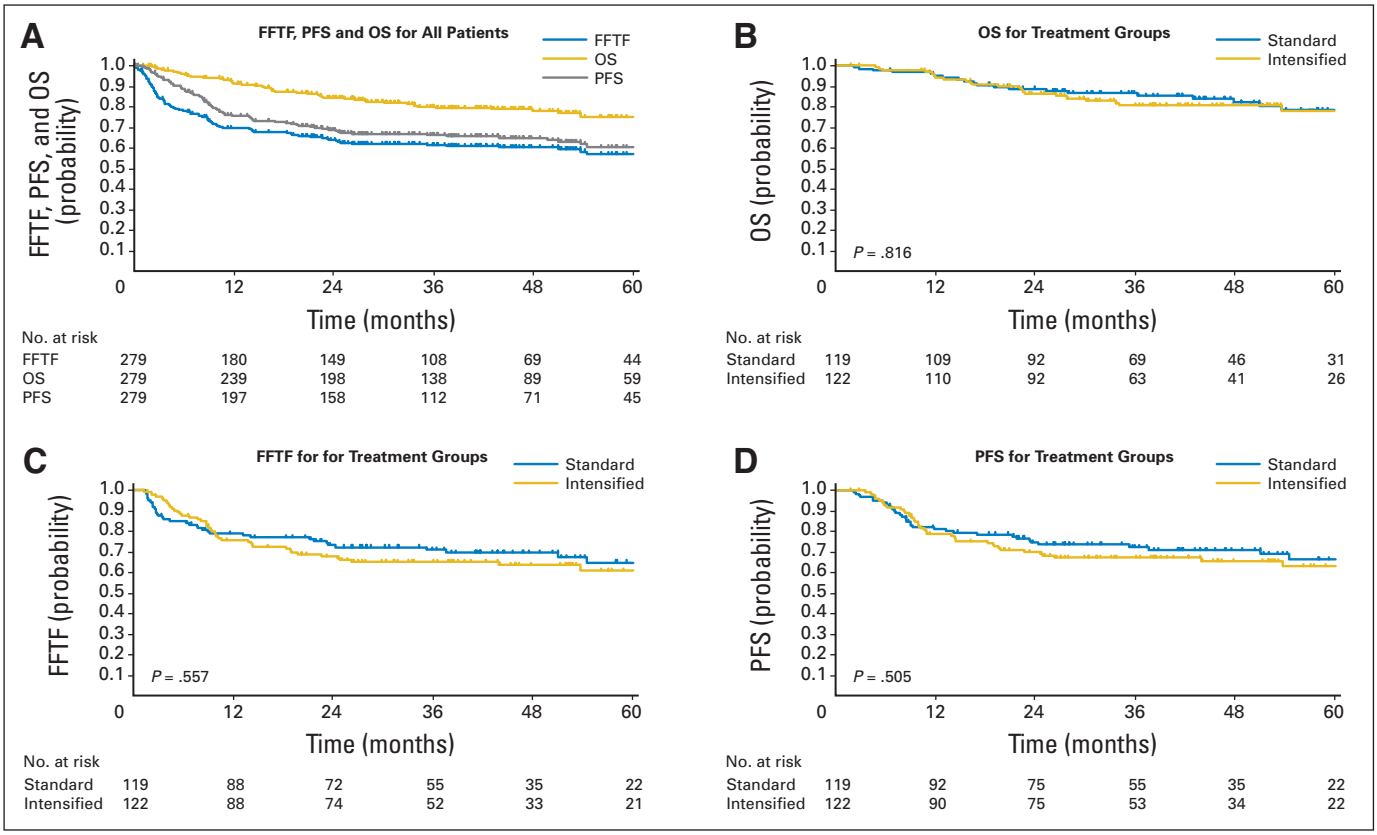

Fig 2. Kaplan-Meier curves from treatment begin to 5 years. (A) Freedom from treatment failure (FFTF), progression-free survival (PFS), and overall survival (OS) for total evaluable intention-to-treat sample. (B) OS of randomly assigned patients in standard arm A and intensified arm B. (C) FFTF in randomly assigned patients of standard arm A and intensified arm B. (D) PFS of randomly assigned patients in standard arm A and intensified arm B.

In an earlier phase II pilot study, the GHSG had established feasibility and safety of a very similiar program and choice of drugs that was followed by BEAM in 102 patients with relapsed and refractory HL.[17] Despite concerns of additive toxicity, this four-step program proved to be well-tolerated in a multicenter setting when given after initial cytoreduction using two cycles of time-condensed DHAP. The rates of CR (72%) and overall response (80%) indicated that this program was effective in relapsed and refractory HL. In addition, patients with both, early and late relapse had a very similiar outcome suggesting that negative prognostic factors could be overcome with further dose intensification.

Table 2. Toxicity

Variable	Total (N =223) No.	%	Standard Arm A (n = 113) No.	%	Intensified Arm B (n = 110) No.	%
WHO grade 3/4 toxicities						
Anemia	136	61	59	52	77	70
Thrombopenia	202	91	100	89	102	93
Leukopenia	196	88	98	87	98	89
Infection	90	40	37	33	53	48
Nausea	90	40	40	35	50	46
Mucositis	138	62	64	57	74	67
Respiratory	18	8	7	6	11	10
Before BEAM WHO grade						
0-2	25	11	21	19	4	4
3	50	23	41	36	9	8
4	148	66	51	45	97	88

Abbreviation: BEAM, carmustine, etoposide, cytarabine, and melphalan.

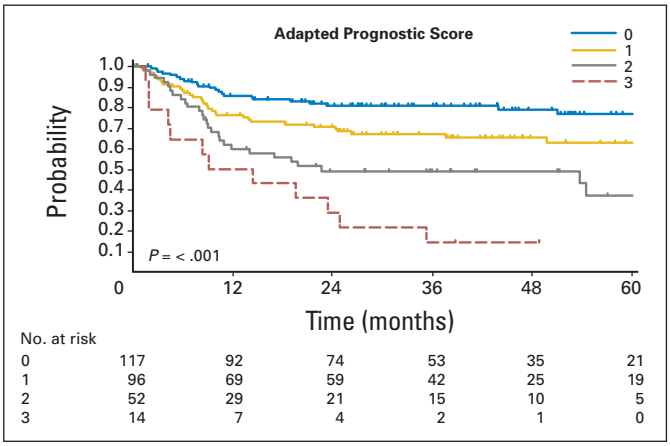

Fig 3. Kaplan-Meier curves of progression-free survival in four groups of patients differentiated with an adapted prognostic score. Presence of stage IV disease, early or multiple relapse, and anemia summed up to a score ranging from 0 to 3.

As a consequence of these challenging results, the GHSG initiated the HDR2 European intergroup study presented here that was conducted together with the European Organisation for the Research and Treatment of Cancer Lymphoma Group Lymphoma Group, European Bone Marrow Transplantation Group, and the Spanish GELCAB. With 284 patients included, this trial is the largest randomized study performed in relapsed HL to our knowledge. Adverse events and mortality were similar to other studies using HDCT.[3-8] Although there were more adverse effects in the intensified arm, this did not translate into higher mortality. Response however, did also not differ between the two treatment modalities (83% and 84% CR/CRu, respectively). With a median follow-up of 42 months, the 3-year OS was 87% (A) and 83% (B) ($P = .816$), PFS was 72% and 67% ($P = .505$), and FFTF was 71% and 65% ($P = .557$). Overall, these results compare very favorably with other reports using HDCT in this setting.[3-8] Some recruitment bias might have contributed to the challenging level of tumor control observed in this study: patients were randomly assigned after the initial two DHAP cycles so that chemotherapy refractory patients did not proceed to HDCT. In contrast, this was a dose-dense program with only 16 days median between the first and second DHAP cycle and 54 days between the first DHAP and the last day of BEAM in the standard arm. Patients with HL have been shown to be particularly responsive to dose-dense treatment.[9] In addition, age restriction (< 60 years), and the exclusion of patients with primary progressive HL or major organ dysfunction in this trial might also have contributed to the low toxicity-related mortality (2%), good overall response, and tumor control.

This study failed to demonstrate superiority of SHDCT. This treatment was more toxic and clearly failed to reach the requested 20% improvement in FFTF at 2 years over the standard arm. As a matter of fact, FFTF was 71% in the standard arm and 65% for arm B where additional SHDCT was given ($P = .557$). There was also no difference between arms for patients with higher risk scores including those with early relapses. Thus, the concept of SHDCT is refuted with our data at least for relapsed HL.

Duration of initial remission and remission status after conventional chemotherapy have been reported as prognostic factors in patients with relapsed HL.[18,20,21] In this study, subgroup analysis for patients suffering from early and late relapse as well as for those with different response after induction therapy showed no advantage for the intensified arm. The prognostic impact of duration of initial remission, anemia, and stage at relapse as described in a prior analysis[30] were confirmed in this trial. A prognostic score based on these variables allowed identifying four groups with different risk for recurrence and death. Furthermore, B symptoms and the primary treatment protocol were also identified as prognostically relevant for PFS in this study. Patients treated with a more intensified primary treatment protocol (BEACOPP) had a 3-year PFS of 58% compared to 72% for those treated with other first-line regimens. It is important to note that this higher risk of PFS failure with BEACOPP was observed in relapsing patients. In first-line therapy, BEACOPP has been shown to be more effective than other regimens and thus results in better prevention of relapse.[9]

In conclusion, we did not observe any advantage of further dose intensification using additional SHDCT in patients with relapsed HL. Based on the data presented here, two cycles of intensified conventional chemotherapy (DHAP) followed by HDCT (BEAM) is an effective and safe treatment for patients with relapsed HL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Data analysis and interpretation: Andreas Josting, Horst Müller, Peter Borchmann, Jan Glossmann, Andreas Engert
Manuscript writing: All authors
Final approval of manuscript: All authors

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