Dexa-BEAM in Patients With Hodgkin's Disease Refractory to Multidrug Chemotherapy Regimens: A Trial of the German Hodgkin's Disease Study Group

By Michael G. Pfreundschuh, Ulrich Rueffer, Bernd Lathan, Norbert Schmitz, Oana Brosteanu, Dirk Hasenclever, Rainer Haas, Hartmut Kirchner, Peter Koch, Rolf Kuse, Markus Loeffler, and Volker Diehl

Purpose: **A prospective phase II study was conducted to evaluate the efficacy of dexamethasone, carmustine, etoposide, cytarabine, and melphalan (Dexa-BEAM) as salvage chemotherapy for patients with Hodgkin's disease.**

Patients and Methods: **Fifty-five patients progressing on or relapsing after eight- or 10-drug chemotherapy (cyclophosphamide, vincristine, procarbazine, and prednisone plus doxorubicin, bleomycin, vinblastine, and dacarbazine [COPP + ABVD] or COPP + ABV + ifosfamide, methotrexate, etoposide, and prednisone [IMEP]) were treated with Dexa-BEAM. Patients who responded after two cycles of Dexa-BEAM either continued treatment for another two to three cycles or received high-dose chemotherapy/autologous bone marrow transplantation (HDCT/ABMT) with cyclophosphamide, etoposide, and carmustine (BCNU) (CVB) as conditioning regimen.**

Results: **Seventeen patients (31%) achieved a complete remission and 16 (29%) a partial remission, resulting in a response rate of 60% (95% confidence interval, 46% to 73%). Progressive disease developed in 18 patients. Toxicity of Dexa-BEAM was acceptable with pronounced, but temporary World Health Organization (WHO) grade III/IV granulocytopenia and thrombocytopenia occurring in more than 90% of all courses. Two patients died of sepsis during granulocytopenia. Three prognostic subgroups could be distinguished: (1) patients progressing on initial chemotherapy, (2) patients relapsing within 12 months, and (3) patients with late relapses. The response rates for these groups were 52%, 60%, and 83%, and the median survival duration 12, 29, and 40+ months, respectively. In a nonrandomized comparison, the survival of patients who responded to two cycles of Dexa-BEAM and had additional cycles of Dexa-BEAM (n = 14) was not different from those responding patients who underwent HDCT/ABMT (n = 19). However, the power to detect a 20% survival difference was only 33% in this comparison.**

Conclusion: **Dexa-BEAM is an effective salvage treatment for patients with Hodgkin's disease who fail to respond to multidrug chemotherapy. Efficacy and toxicity are comparable to HDCT/ABMT and underline the need for prospective randomized trials to define better the role of HDCT with and without ABMT in these patients.**

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THE INTRODUCTION of combination chemotherapy has markedly improved the outcome of patients with advanced Hodgkin's disease.[1] However, 30% to 50% of patients who present with advanced disease experience progressive disease during primary therapy or relapse after achieving remission.[2-4] Except for cases with localized nodal disease, which may be controlled by radiotherapy,[5-7] most patients with relapsing or refractory Hodgkin's disease require second-line chemotherapy and their prognosis is poor. In an effort to improve the results of salvage therapy in these patients, the German Hodgkin's Disease Study Group developed the regimen of lomustine, etoposide vindesine, and dexamethasone (CEVD),[8] which was well tolerated and yielded high response rates. Encouraged by the results of the CEVD protocol, we looked for further improvements by dose-intensification and/or the addition of drugs with known activity in Hodgkin's disease. Carmustine, etoposide, cytarabine, and melphalan have been shown to be active single agents in refractory lymphomas[9,10] and the combination of these agents (BEAM) has been successfully used as a myeloablative regimen before autologous bone marrow transplantation (ABMT) for lymphoma.[11] As a modification of this regimen, the dexamethasone plus BEAM (Dexa-BEAM) regimen was designed to study the feasibility, efficacy, and tolerance of this combination in a setting in which bone marrow support was not necessary. We now report on our experience with the Dexa-BEAM regimen in patients with refractory or relapsing Hodgkin's disease. Our results indicate that Dexa-BEAM is an effective treatment with acceptable toxicity for this group of patients. Moreover, it may serve as a rapid indicator for remaining chemosensitivity in patients for whom ABMT is considered.

From the Klinik I für innerc Medizin der Universitätsklinik Köln, Köln; Med. Klinik & Polyklinik des Saarlandes, Homburg; II. Med. Klinik & Polyklinik der Christian-Albrechts-Universität, Kiel; Med. Universitätsklinik & Polyklinik Heidelberg, Heidelberg; Med. Hochschule Hannover, Hannover; Med. Klinik A der Universitätsklinik Münster, Münster; and Allgemeines Krankenhaus St. Georg, Hamburg, Germany.

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Address reprint requests to Volker Diehl, MD, Hodgkin Studiensekretartiat, Universitätsklinik Köln, Josef-Stelzmann-Str 9, D-50924 Köln, Germany.

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PATIENTS AND METHODS

From January 1988 to December 1990, 55 patients with histologically proven Hodgkin's lymphoma who had failed to respond to cyclophosphamide, vincristine, procarbazine, and prednisone plus doxorubicin, bleomycin, vinblastine, and dacarbazine (COPP + ABVD) or plus ifosfamide, methotrexate, etoposide, and prednisone (COPP + ABV + IMEP) chemotherapy[12,13] were treated with Dexa-BEAM in 19 centers. Patients with an extent of disease not encompassable by radiotherapy were eligible for the Dexa-BEAM protocol under the following conditions: (1) progressive disease under first-line chemotherapy, (2) early first relapse (within 12 months), (3) late first relapse, or (4) second or subsequent relapses after remissions obtained by COPP + ABVD. The patient characteristics are listed in Table 1. Forty-two patients had received both chemotherapy and radiotherapy, of whom four had received chemotherapy after radiotherapy-induced first remission, and 38 had received combined chemoradiotherapy. Of the 42 patients who had received radiotherapy, 23 had been treated below the diaphragm. Twenty-eight patients had failed to respond after one, 22 after two, and five after three chemotherapy programs. The response to initial chemotherapy of the 55 patients had been progressive disease in 21, early relapse in 21, late relapse in 12, and was not defined (progressive disease or early relapse) in one patient.

The Dexa-BEAM regimen consisted of dexamethasone (8 mg every 8 hours orally from days 1 to 10), carmustine (60 mg/m^2 intravenously [IV] on day 2), etoposide (75 mg/m^2 IV from days 4 to 7), cytarabine (100 mg/m^2 IV every 12 hours from days 4 to 7), and melphalan (20 mg/m^2 IV on day 3). Treatment was repeated on day 29. During the period of treatment-induced myelosuppression, oral antimicrobial prophylaxis was performed at the discretion of the participating center, mostly consisting of the combination of trimethoprim-sulfamethoxazole, colistin sulfate, and amphotericin B suspension.

Table 1. Characteristics of Patients Treated With Dexa-BEAM

Total no. entered	55
No. assessable	55
Age, years	
Range	19-53
Median	32
Prior therapy	
CT + RT	42*†
CT	13
Type of initial chemotherapy	
COPP + ABVD or COPP + ABV + IMEP	37
COPP, then ABVD	16
COPP, then ABVD, then IMEP	2
No. of prior chemotherapy programs	
1	28
2	22
3	5
Stage before Dexa-BEAM	
IA	1
IB	2
IIA	2
IIB	6
IIIA	2
IIIB	1
IVA	12
IVB	27
Unknown	2

Abbreviations: CT, chemotherapy; RT, radiotherapy.
*Four patients had initial CT in relapse after RT-induced CR.
†Twenty-three patients also had infradiaphragmatic RT.

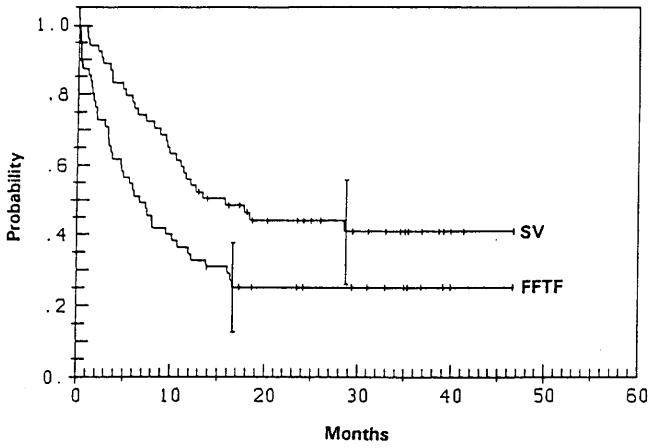

Fig 1. Survival (SV; 31 events) and FFTF (41 events) of 55 patients treated with Dexa-BEAM. Median observation time, 32 months.

Before Dexa-BEAM therapy, extent of disease was assessed by chest x-ray, abdominal sonogram and/or computerized tomography, and bone marrow and liver biopsy. Before each additional cycle of Dexa-BEAM, nodal involvement was assessed by physical examination, chest x-ray, and abdominal sonogram. After the end of Dexa-BEAM therapy, all manifestations of Hodgkin's lymphoma were reassessed by adequate methods, including pathologic restaging for patients who had had bone marrow and/or liver involvement before Dexa-BEAM therapy.

Written informed consent was obtained from all patients. All patients who started therapy were considered assessable for response. Complete response (CR) was defined as the disappearance of all measurable disease for at least 4 weeks after the end of treatment, and partial response (PR) was defined as a more than 50% reduction of the measurable tumor mass for at least 4 weeks and disappearance of systemic symptoms. Death within 6 weeks from the initiation of Dexa-BEAM therapy from causes other than refractory disease was designated as early death.

Patients with chemotherapy-sensitive disease (as indicated by the achievement of a complete or partial remission after two cycles of Dexa-BEAM) were offered subsequent high-dose chemotherapy (HDCT) followed by ABMT. The myeloablative regimen consisted of the CVB regimen:[14] cyclophosphamide 1.5 g/m^2 on days −6 to −3, etoposide 250-400 mg/m^2 on days −6 to −3, and carmustine (BCNU) 300 to 800 mg/m^2; 300 mg of BCNU was administered on day −6 and 800 mg on days −6 to −3 (200 mg/m^2 each day). Responding patients who did not undergo HDCT/ABMT were to receive a total of four cycles of Dexa-BEAM, unless undue toxicities or early relapse occurred. The time to treatment failure and survival of transplanted patients was included in the freedom from treatment failure (FFTF) and survival curves of the entire treatment population (Fig 1).

Survival and FFTF of all patients were determined as time from

Table 2. Results of Dexa-BEAM Therapy

Parameter	No.	%
Patients entered	55	
Assessable	55	100
CR	17	31
PR	16	29
No change	2	4
Progressive disease	18	33
Therapy-related death	2	4

the beginning of Dexa-BEAM therapy to death and failure, respectively, and remission duration from the date of documented remission to relapse. All three end points were evaluated according to the method of Kaplan and Meier.

The design of the Dexa-BEAM protocol was in accordance with the declaration of Helsinki. It was approved by the local institutional review board at the study center, the University of Cologne. Before therapy, written informed consent was obtained from all patients after they had been given advice on the purpose and investigational nature of the study, and informed of potential risks.

RESULTS

The results of therapy are listed in Tables 2 and 3. Of 55 patients, 15 received one cycle, 20 received two cycles, 11 received three cycles, eight received four cycles, and one received five cycles of Dexa-BEAM. Seventeen patients (31%) achieved a CR and 16 (29%) achieved a PR, resulting in an overall response rate of 60% (95% confidence interval, 46% to 73%). Radiotherapy to bulky and/or residual nodal disease was given to eight patients. No change was seen in two patients, and 18 patients had progressive disease. Two patients died of sepsis during Dexa-BEAM–induced myelosuppression.

Twenty-seven patients were treated with Dexa-BEAM because of Hodgkin's lymphoma progressing despite treatment with COPP + ABVD or COPP + ABV + IMEP chemotherapy, respectively. Of those, six (22%) achieved a CR, and eight (30%) a PR, resulting in a response rate of 52%. The respective figures were four of 15 (27%) CRs and five of 15 (33%) PRs for patients

Table 3. Results of Dexa-BEAM Therapy According to Response to Initial Chemotherapy

		Response to Dexa-BEAM					
		CR		PR		PR + CR	
Response to Prior Therapy	n	No.	%	No.	%	No.	%
Progressive disease	27	6	22	8	30	14	52
Early relapse	15	4	27	5	33	9	60
Late relapse	12	7	58	3	25	10	83
Undefined*	1						

*Progressive disease or early relapse.

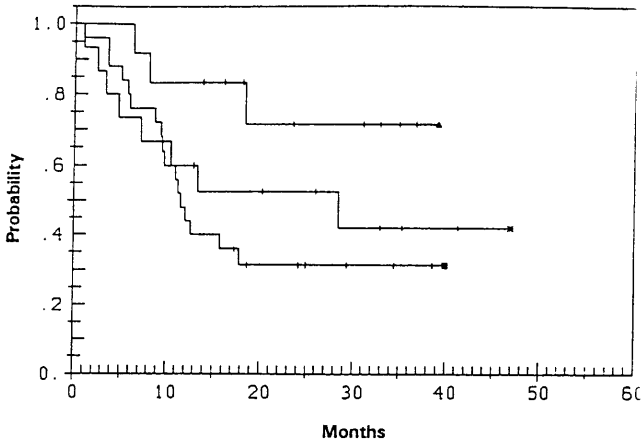

Fig 2. Survival of patients treated with Dexa-BEAM according to response to primary chemotherapy. (▲) Late relapses (12 patients, 3 events); (*) early relapses (15 patients, 8 events); (■) primary progressive disease (27 patients, 19 events).

in early relapse (response rate, 60%) and seven of 12 (58%) CRs and three of 12 (25%) PRs, respectively, in patients with late relapse (response rate, 83%). There was no difference in the response rate between patients who had received monthly alternating or sequential COPP + ABVD or COPP + ABV + IMEP therapy, respectively.

Survival and FFTF curves are shown in Fig 1. The median time to treatment failure was 7 months, and the median survival time was 15 months. When plotted according to the response to primary therapy, survival curves of patients with progressive disease on primary chemotherapy showed a rapid decline, despite a response rate of 52% to Dexa-BEAM (Fig 2). The survival of patients with early and late relapses was significantly better.

Typical for Dexa-BEAM was a rapid response. As listed in Table 4, 27% of all responses were observed after the first and 76% after the second cycle of Dexa-BEAM. Thus, Dexa-BEAM is useful as a rapid indicator for remaining chemotherapy sensitivity, which is generally considered an eligibility criterion for ABMT.

Nineteen of 33 responding patients proceeded to receive HDCT with the CVB regimen followed by ABMT. Responders with and without subsequent HDCT/ABMT were well balanced for response to initial chemotherapy

Table 4. Kinetics of Response to Dexa-BEAM Therapy

Response	Cycle No. 1	Cycle No. 2	Cycle No. 3 to 5
CR + PR			
No.	9	25	33
%	27	76	100

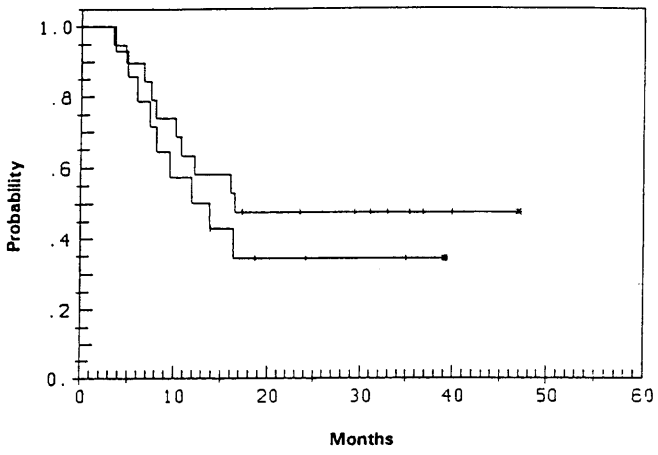

Fig 3. FFTF of 33 patients responding to Dexa-BEAM; (*) 19 patients treated with HDCT/ABMT (10 events); (■) 14 patients who did not have HDCT/ABMT (9 events). Difference is not statistically different ($P = .4$).

and response to Dexa-BEAM (PR *v* CR); however, there was a trend ($P < .053$) for more advanced stage of disease before Dexa-BEAM in patients who continued to receive Dexa-BEAM (stage I to IIIA, two patients; IIIB/IV, 13; one unknown) when compared with patients with HDCT/ABMT (I-IIIA, eight; IIIB/IV, 10; one unknown). Interestingly, the FFTF (Fig 3) and survival curves (Fig 4) of the latter patients and of the 14 responders who did not undergo ABMT were not significantly different after a median observation time of 32 months (Fig 3).

The predominant side effects of Dexa-BEAM were severe myelosuppression, with granulocytopenia less than 500/μL and thrombocytopenia less than 50,000/μL occurring after most treatment cycles (Table 5). The time from the beginning of therapy to the recovery of blood counts above a critical level of greater than 1,000 granulocytes/μL and greater than 50,000 thrombocytes/μL was 12 to 21 days, with a median of 17 days. Hence, severe infections of World Health Organization (WHO) grades III and IV were a major complication after 10% of the Dexa-BEAM courses, with two patients dying to a gram-negative sepsis during granulocytopenia. Transient cardiac arrhythmias and psychosis were observed in 2%. No cumulative toxicities were observed in patients who received three or more cycles of Dexa-BEAM.

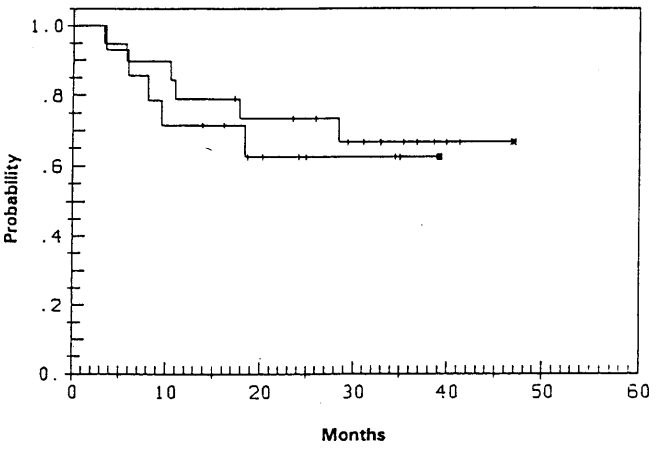

Fig 4. Survival of 33 patients responding to Dexa-BEAM; (*) 19 patients treated with HDCT/ABMT (6 events); (■) 14 responding patients who did not have HDCT/ABMT (5 events). No significant difference between the two groups ($P = .63$). A survival difference of 20% would be detectable with a power of 33%.

Table 5. WHO Grade III/IV Toxicity After Dexa-BEAM Therapy

Toxicity	% of Patients
Granulocytopenia	92
Thrombocytopenia	87
Mucositis	21
Infection	10
Nausea/vomiting	10
Cardiotoxicity	2
Psychosis	2

DISCUSSION

The experience of the German Hodgkin's Disease Study Group with the Dexa-BEAM protocol in patients with relapsed or refractory Hodgkin's disease demonstrates that high response rates to effective third-line therapy can be obtained in a substantial number of patients who have received modern eight-drug (COPP + ABVD) or even 10-drug (COPP + ABV + IMEP) regimens as initial chemotherapy. One advantage of Dexa-BEAM is the rapid response, with 76% percent of all responses becoming apparent after two cycles. This allows for the early identification of patients who are good candidates for HDCT/ABMT.[15] Moreover, as many effective drugs of the Dexa-BEAM protocol are also used in myeloablative regimens before ABMT (eg, the CVB[14] and BEAM[11] protocols), Dexa-BEAM can serve as a reliable test for remaining sensitivity of the neoplastic cells to these drugs.

The toxicity of the Dexa-BEAM regimen is considerable, yet acceptable, keeping in mind that it was designed anticipating pronounced, but temporary myelosuppression. There were no severe bleeding episodes, but two patients died of infectious complications during neutropenia. Other WHO grades III/IV toxicities were rare.

The encouraging results of this study have led to a subsequent placebo-controlled dose-escalation study of Dexa-BEAM with and without the support of the hematopoietic growth factor granulocyte-macrophage colony-

stimulating factor to determine the maximum-tolerated dose of etoposide administered with the Dexa-BEAM protocol. While results of this ongoing study are pending, it is clear that the etoposide dose within the Dexa-BEAM protocol can be at least tripled with acceptable hematologic and extramedullary toxicities. However, it remains to be seen whether this further dose escalation of Dexa-BEAM will improve response rates and survival.

Our results confirm observations made by others[16,17] that patients who are not cured by their initial treatment fall into three groups: those with progressive disease on primary treatment, those with short initial remissions, and those with initial remissions lasting longer than 12 months. Additional risk factors for relapsing patients have been reported, such as age less than 30 years,[18] advanced disease at diagnosis, and B symptoms at relapse.[19] However, due to the small number of patients in the respective subgroups, of these parameters only advanced stage before Dexa-BEAM (IIIB/IV *v* I-IIIA) was associated with a shorter survival duration after Dexa-BEAM.

An observation that has been made with other conventional salvage protocols also applies for Dexa-BEAM: despite their high response rate, remissions are not durable in the majority of patients. This holds especially true for patients with progressive disease under initial combination chemotherapy: even though the majority of them (52%) had a major response to Dexa-BEAM, their survival was poor. It remains to be seen whether this extremely poor prognostic subgroup really benefits from HDCT/ABMT.

Similarly, the treatment approach of choice for patients of the other two prognostic subgroups, ie, those with early and late relapse, remains to be determined. Results obtained with the initial chemotherapy combinations are poor in early relapse and there is a general consensus that more intensive, possibly non–cross-resistant chemotherapy regimens are necessary to obtain a second response, which (according to the policy of many centers) should be consolidated by HDCT/ABMT. In patients who relapse more than 12 months after the end of primary therapy, high second remission rates can be achieved by readministering the initial chemotherapy, and nearly half of these remissions are of prolonged duration.[16,17] However, the eventual cure rate of these patients is only approximately 25%, and quite a few experience second neoplasms, especially acute leukemias.[18] Therefore, non–cross-resistant chemotherapy combinations with low leukemogenic potential are to be preferred in these patients, and HDCT/ABMT can be discussed for responders.

Our results with Dexa-BEAM are superior to those that we observed with the high-dose cytarabine plus mitoxantrone (HAM) protocol[20] in a similar group of patients. In addition to its superior efficacy, Dexa-BEAM proved to be considerably less toxic than HAM in a multicenter setting. As the results of salvage chemotherapy regimens are influenced by prior therapy, disease extent, systemic symptoms, and performance status, it is difficult to compare the various salvage protocols. So far, no salvage regimen has been demonstrated to be clearly superior to others, and the differences between published protocols, such as lomustine, etoposide, and prednimustine (CEP),[21,22] lomustine, etoposide, and methotrexate (CEM),[23] etoposide, vincristine, and doxorubicin (EVA),[24] high-dose cytarabine and dexamethasone (DHAP),[25] methyl-Gag, ifosfamide, methotrexate, and etoposide (MIME),[26,27] methotrexate, vincristine, prednisone, leucovorin, cytosine arabinoside, cyclophosphamide, and etoposide (MOPLACE),[28] prednisone, etoposide, chlorambucil, and lomustine (PECC),[29] and others,[30] probably refer more to differences in toxicities and patient selection than to different efficacy, an experience that we have also made with our consecutive trials of CEVD, HAM, and Dexa-BEAM. The historical comparison between Dexa-BEAM and CEVD suggests that, even in the subgroup of patients with progressive disease under primary combination chemotherapy, the results of the highly dose-intense Dexa-BEAM regimen are not better than those obtained with our previous CEVD protocol, even though none of the CEVD responders had received HDCT/ABMT. Remarkably, two patients who failed to respond after Dexa-BEAM achieved long-lasting remissions with CEVD. Thus, in addition to dose-intensification, other mechanisms might be important for controlling refractory Hodgkin's disease.

The outcome of Dexa-BEAM patients who received HDCT/ABMT is within the range of the results that have been reported by several other transplant teams.[31-33] Interestingly, the FFTF and survival of Dexa-BEAM responders who received HDCT (CVB protocol) followed by ABMT were not significantly different from responders who continued on Dexa-BEAM. This might be even more surprising, as in the latter group not all responders received the planned total of four cycles Dexa-BEAM, mostly because early relapse occurred. As this comparison was not randomized, selection bias cannot be excluded, even though response to initial chemotherapy and CRs to Dexa-BEAM were well balanced between the groups. However, there was a trend that patients who continued on Dexa-BEAM had more advanced disease before Dexa-BEAM. Thus, patients who continued on Dexa-BEAM might have had the poorer prognostic crite-

ria. Even though (due to the low number of patients) only large differences in survival between the two treatment modalities would be detectable (20% difference with a power of 33%), a large survival advantage for patients undergoing HDCT/ABMT does not seem to be likely. Our results are in line with another group that has also not been able to show an improvement in outcome for poor-risk relapsing patients by HDCT/ABMT.[19] While Dexa-BEAM seems to have an efficacy comparable to the one obtained with HDCT/ABMT, its toxicity and fatal complications are also in the range of what has been reported for HDCT/ABMT.[34] Thus, both the efficacy and the toxicity of the Dexa-BEAM regimen in comparison to HDCT/ABMT underline the need for randomized studies to define the role of intensive salvage regimens with and without HDCT/ABMT in the treatment of patients with Hodgkin's disease who are not cured by the initial chemotherapy program. Such randomized trials are the only way to define the optimal timing for HDCT/ABMT[35] and to answer the question if HDCT/ABMT is better treatment or generates better results because healthier patients are treated.[36] A respective trial of the German Hodgkin's Disease Study Group that compares HDCT/ABMT with growth factor–supported dose-escalated Dexa-BEAM in patients with chemotherapy-sensitive relapse from Hodgkin's disease is ongoing.

APPENDIX

The following institutions and persons were involved in this study: Trial coordinator (PI): M. Pfreundschuh (Homburg); Study Secretariat: U. Rueffer, H. Nisters-Backes, B. Lathan; Biometry: O. Brosteanu, D. Hasenclever, M. Loeffler (all in Köln); Participating Clinicians (residence): Dr M. Baldus (Ludwigshafen), Dr Bischoff (Heidelberg), Dr R. Haas (Heidelberg), Professor Dr C. Hauswaldt (Braunschweig), Dr H. Kirchner (Hannover), Dr P. Koch (Münster), Dr Kretschmer (Düsseldorf), Professor Dr R. Kuse (Hamburg), Dr Natt (Sanderbusch), Dr M. Planker (Krefeld), Dr J. Preiß (Saarbrücken), Dr S. Roller (Ulm), Dr G. Schalk (Stuttgart), Dr N. Schmitz (Kiel), Dr C. Tirier (Essen), Dr P. Worst (Mannheim); and Chairman: V. Diehl (Köln).

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