Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial

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Summary

Background High-dose chemotherapy followed by transplantation of autologous haemopoietic stem cells (BEAM-HSCT) is frequently used to treat patients with relapsed Hodgkin's disease. We aimed to compare this treatment with conventional aggressive chemotherapy without stem-cell transplantation (Dexa-BEAM).

Methods 161 patients between 16 and 60 years of age with relapsed Hodgkin's disease were randomly assigned two cycles of Dexa-BEAM (dexamethasone and carmustine, etoposide, cytarabine, and melphalan) and either two further courses of Dexa-BEAM or high-dose BEAM and transplantation of haemopoietic stem cells. Only patients with chemosensitive disease (complete or partial remission after two courses of Dexa-BEAM) proceeded to further treatment. The primary endpoint was freedom from treatment failure for patients with chemosensitive disease. Analysis was per protocol.

Findings 17 patients were excluded from the study after randomisation (ten given Dexa-BEAM and seven given BEAM-HSCT). Median follow-up was 39 months (IQR 3–78). Freedom from treatment failure at 3 years was significantly better for patients given BEAM-HSCT (55%) than for those on Dexa-BEAM (34%; difference –21%, 95% CI –39·87 to –2·13; p=0·019). Overall survival of patients given either treatment did not differ significantly.

Interpretation High-dose BEAM and transplantation of haemopoietic stem cells improves freedom from treatment failure in patients with chemosensitive first relapse of Hodgkin's disease irrespective of length of initial remission.

Lancet 2002; **359:** 2065–71

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Introduction

Patients with advanced Hodgkin's disease have an excellent outlook if treated with modern chemotherapy with or without radiotherapy.[1–3] Patients who relapsed after first-line chemotherapy can achieve further remissions with salvage treatment;[4–7] the chance of cure, however, is limited, and will depend on many prognostic factors, such as length of initial remission, age, type of treatment previously received, presence of B-symptoms (fever, night sweats, weight loss >10% of previous bodyweight), and stage.[8–10] Disease status is the most important factor predicting outcome of patients scheduled to receive high-dose chemotherapy and autologous stem-cell transplantation.[11,12]

What is the optimum type of salvage treatment, and does high-dose chemotherapy have any benefit compared with other forms of salvage treatment, not needing transplantation of haemopoietic stem cells? To address this latter question, we prospectively compared aggressive conventional chemotherapy (Dexa-BEAM) with high-dose chemotherapy and autologous stem-cell transplantation (BEAM-HSCT) in patients with relapsed Hodgkin's disease responding to salvage chemotherapy.

Patients and methods

Patients

Patients 16–60 years of age were eligible for the study if they had received chemotherapy for advanced Hodgkin's disease and had biopsy-proven relapse. We included patients with stage I or II disease at relapse if they presented with additional risk factors (bulky mediastinum, involvement of three or more lymph-node regions, extranodal disease, or erythrocyte sedimentation rate >30 mm), or if they had shown stage III or IV disease early in the course of disease before enrolment. Histological verification of relapse was not mandatory for patients with unequivocal progressive intrathoracic or abdominal disease. Other criteria for eligibility were Karnofsky performance score above 70% and adequate cardiac, pulmonary, renal, and liver function. We excluded patients if they were HIV positive, had infection unresponsive to treatment, or had previously been treated with Dexa-BEAM (dexamethasone and carmustine, etoposide, cytarabine, and melphalan),[6] mini-BEAM,[13] or high-dose chemotherapy.

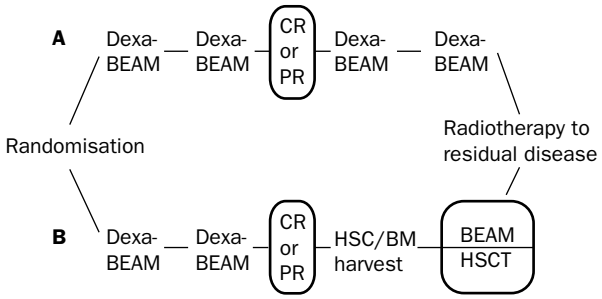


Figure 1: **Study protocol**
Dexa-BEAM=dexamethasone and carmustine, etoposide, cytarabine, and melphalan; CR=complete remission; PR=partial remission; HSC=autologous haemopoietic stem cells; BM=bone marrow; HSCT=haemopoietic stem-cell transplantation.

Staging adhered to guidelines from the German Hodgkin's Lymphoma Study Group (GHSG) and included computed tomography of the thorax and abdomen and bone-marrow biopsy. We defined bulky disease as one node or nodes 5 cm or greater, mediastinum 5 cm or greater, or mediastinal mass one-third or greater of maximum thoracic diameter. Response

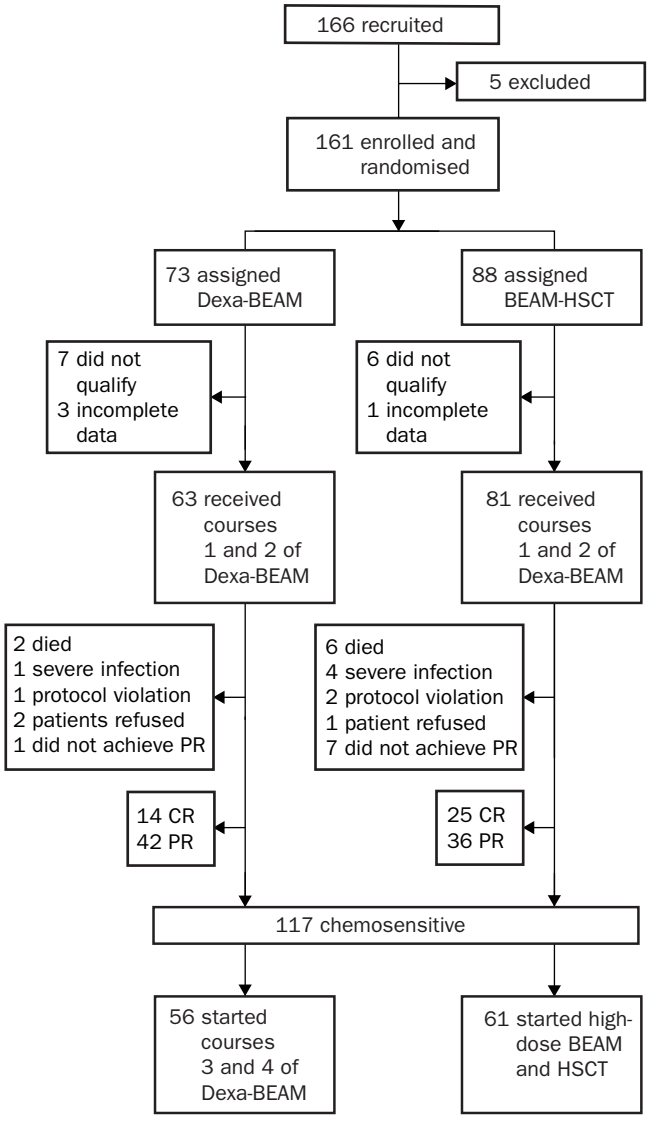


Figure 2: **Trial profile**
CR=complete remission; PR=partial remission.

	Chemosensitive patients		All assessable patients (n=144)
	Dexa-BEAM (n=56)	BEAM-HSCT (n=61)	
Age (years, median [range])	34 (16–55)	30 (21–57)	32 (16–59)
Time from diagnosis to first course of Dexa-BEAM (months, median [range])	20·5 (3–99)	16·3 (3–79)	..
Men	36 (64%)	39 (64%)	94 (65%)
Stage			
IA–IIB	23 (41%)	18 (30%)	47 (33%)
IIIA–IVB	30 (54%)	39 (64%)	89 (62%)
Missing	3 (5%)	4 (7%)	8 (6%)
Sites of lesions			
Above diaphragm	39 (70%)	41 (67%)	97 (67%)
Below diaphragm	30 (54%)	24 (39%)	63 (44%)
Mediastinum	23 (41%)	28 (46%)	64 (44%)
Bone marrow	6 (11%)	10 (16%)	18 (13%)
Other extranodal lesions	18 (32%)	31 (51%)	66 (46%)
Bulky disease	12 (21%)	13 (21%)	30 (21%)
Histology			
NS	28 (50%)	35 (57%)	77 (53%)
MC	17 (30%)	15 (25%)	37 (26%)
LD	1 (2%)	1 (2%)	3 (2%)
LP	3 (5%)	2 (3%)	7 (5%)
Not classified/ not done	7 (13%)	8 (13%)	20 (14%)
Stratum			
Early first relapse	17 (30%)	21 (34%)	51 (35%)
Late first relapse	26 (46%)	29 (48%)	63 (44%)
Multiple relapses	13 (23%)	11 (18%)	30 (21%)

Data are number (%) unless otherwise stated. NS=nodular sclerosis; MC=mixed cellularity; LD=lymphocyte depletion; LP=lymphocyte predominance.

Table 1: **Patients' characteristics at randomisation**

to treatment was defined as: complete remission (no evidence of Hodgkin's disease); unconfirmed complete remission (patient fulfilled criteria for complete remission but had residual lymph-node mass >1·5 cm in diameter that regressed by more than 50% after chemotherapy); partial remission (substantial reduction of all lesions and reduction of large lymph nodes or measurable organ lesions by >50% at the largest diameter; in the case of mediastinal involvement, reduction of the tumour by >25% in the maximum thoracic diameter was needed); or less than partial remission if these criteria were not met. The institutional review board of each participating centre approved the study protocol, and we obtained written informed consent from patients.

Randomisation and stratification

Data managers randomly assigned eligible patients at the GHSG trial office by computer before any therapeutic intervention. Early randomisation was done to allow time

	Dexa-BEAM (n=49)	BEAM-HSCT (n=51)	p
Toxic effect			
Infection	24 (49%)	24 (47%)	0·848
Oral (mucositis)	12 (24%)	19 (37%)	0·168
Gastrointestinal	10 (20%)	7 (14%)	0·374
Pulmonary or respiratory tract	6 (12%)	2 (4%)	0·125
Cardiac	3 (6%)	1 (2%)	0·288
Neurologic	2 (4%)	1 (2%)	0·534
Hepatic	2 (4%)	0	0·145
Renal	1 (2%)	0	0·305

Data are number (%). Grades 3 and 4 toxic effects in accordance with WHO grading system are given.

Table 2: **Severe adverse effects in chemosensitive patients**

	Dexa-BEAM (n=21)	BEAM-HSCT (n=17)
Cause of death		
Hodgkin's disease	14	11
Early treatment-related toxic effect	6	1
Septicaemia after salvage therapy	0	1
Overwhelming post-splenectomy infection	0	1
Fibrosis of lung	0	1
Pneumococcal meningitis and pneumonia	0	1
Secondary leukaemia	0	1

Table 3: **Causes of death in chemosensitive patients at last follow-up**

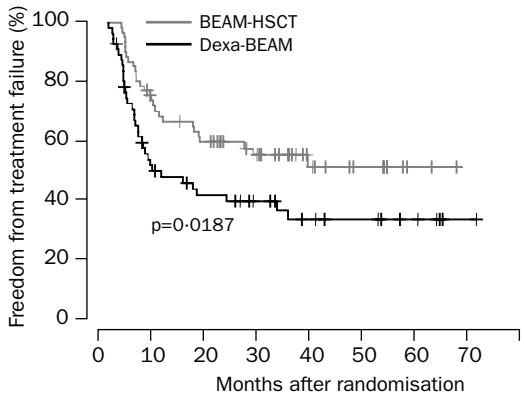
to find a hospital bed and also because we felt that this procedure would increase general acceptance of the study. We used the minimisation method of Pocock[14] for randomisation, to account for type of relapse and participating institution. The types of relapse considered were early and late first relapse and multiple relapses. We substituted dropouts during the first two courses of Dexa-BEAM chemotherapy with the next randomly assigned patient who presented with the same type of relapse. The numbers of randomised patients therefore differ between treatment groups if all patients are considered, but are balanced for the strata of chemosensitive patients.

Patients with early first relapse had initial complete remission of at least 3 months but less than 12 months after first-line chemotherapy. Patients with late first relapse had first remission of more than 12 months; these patients could only be included in the study if their first-line treatment had consisted of seven or eight drugs. Patients with multiple (second or later) relapses were eligible for the study after failure of any first-line or salvage chemotherapy. We measured remission duration from the end of first-line treatment or from the end of salvage therapy for multiple relapses to the date when the most recent relapse was diagnosed.

Treatment

The treatment protocol is shown in figure 1. All patients received two courses of Dexa-BEAM,[6] consisting of dexamethasone (8 mg every 8 h orally, days 1–10), carmustine (60 mg/m^2 intravenously, on day 2), etoposide (250 mg/m^2 intravenously, days 4–7), cytarabine (100 mg/m^2 intravenously every 12 h, days 4–7), and melphalan (20 mg/m^2 intravenously, on day 3). Etoposide was given at a total dose of 1000 mg/m^2 per cycle because preliminary information from a dose-escalation study[15] suggested this dose would be feasible. The total dose of etoposide given with cycles one and two of Dexa-BEAM was reduced to 600 mg/m^2 after 111 patients had been randomly assigned because of toxic effects.

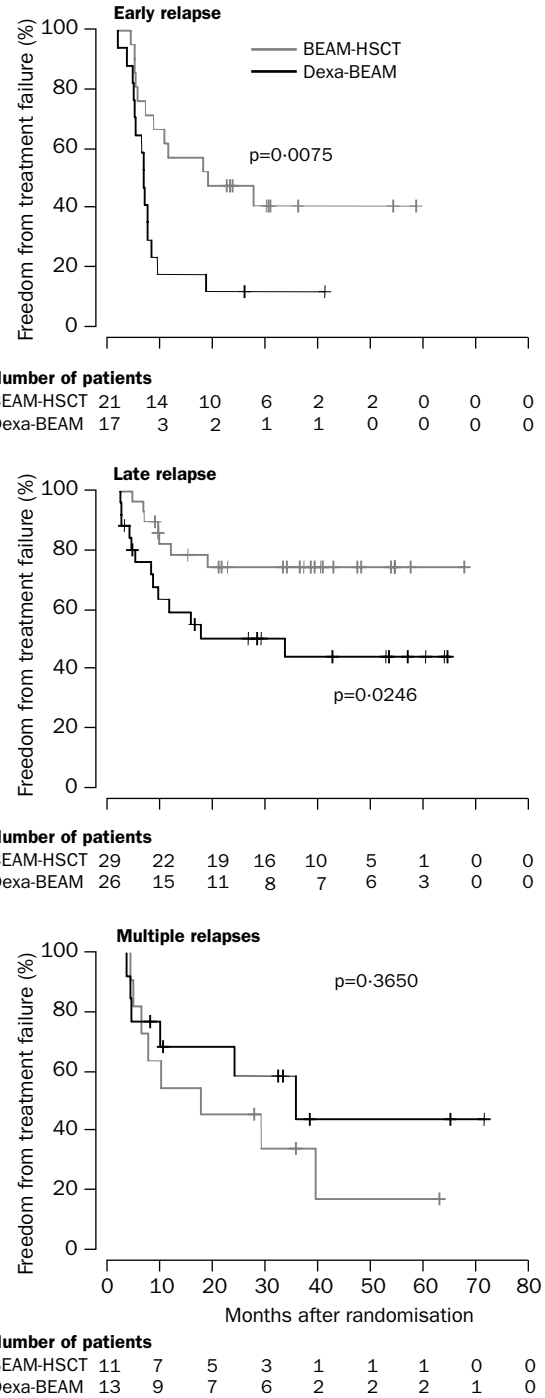
Granulocyte-colony-stimulating factor was given on day 8 of Dexa-BEAM, and was continued until leucocyte recovery or until the last day of stem-cell harvesting if blood-progenitor cells were gathered. Bone-marrow or progenitor cells were harvested after the second course of Dexa-BEAM. Because of difficulties in obtaining sufficient numbers of progenitor cells after two courses of Dexa-BEAM,[16] harvesting of stem cells after the first course of Dexa-BEAM was allowed. Restaging was mandatory for all patients after the second course of Dexa-BEAM. We



Number of patients

BEAM-HSCT	61	43	34	25	13	8	7	0
Dexa-BEAM	56	27	20	15	10	8	5	1

Figure 3: **Freedom from treatment failure for patients with relapsed chemosensitive Hodgkin's disease**



Number of patients

Early relapse									
BEAM-HSCT	21	14	10	6	2	2	0	0	0
Dexa-BEAM	17	3	2	1	1	0	0	0	0
Late relapse									
BEAM-HSCT	29	22	19	16	10	5	1	0	0
Dexa-BEAM	26	15	11	8	7	6	3	0	0
Multiple relapses									
BEAM-HSCT	11	7	5	3	1	1	1	0	0
Dexa-BEAM	13	9	7	6	2	2	2	1	0

Figure 4: **Freedom from treatment failure for patients with early relapse (upper), late relapse (middle), and multiple relapses (lower) of Hodgkin's disease**

	Endpoint	Treatment	Proportion of patients who survived or had FFTF*	Percentage difference (95% CI)	p
All patients with chemosensitive relapse (n=117)	Survival	Dexa-BEAM	65%	–6% (–23·88 to 11·88)	0·331
		BEAM	71%		
	FFTF	Dexa-BEAM	34%	–21% (–39·87 to –2·13)	0·019
		BEAM	55%		
Patients with early relapse (n=38)	Survival	Dexa-BEAM	40%	–3% (–36·85 to 30·85)	0·623
		BEAM	43%		
	FFTF	Dexa-BEAM	12%	–29% (–53·17 to –4·83)	0·008
		BEAM	41%		
Patients with late relapse (n=55)	Survival	Dexa-BEAM	75%	–18% (–38·59 to –2·59)	0·088
		BEAM	93%		
	FFTF	Dexa-BEAM	44%	–31% (–58·20 to –3·80)	0·025
		BEAM	75%		
Patients with multiple relapses (n=24)	Survival	Dexa-BEAM	83%	13% (–21·83 to 47·83)	0·421
		BEAM	70%		
	FFTF	Dexa-BEAM	44%	10% (–34·13 to 54·13)	0·365
		BEAM	34%		

*Estimated from curves, so exact numbers cannot be given.

Table 4: **Overall survival and freedom from treatment failure (FFTF) at 3 years**

excluded patients with bone-marrow biopsy findings positive for Hodgkin's disease at restaging.

Only patients who had complete or partial remission after two courses of Dexa-BEAM continued treatment as per study protocol. These patients are called chemosensitive hereafter.

Chemosensitive patients randomly allocated Dexa-BEAM received the third cycle as soon as restaging showed at least partial remission and haemologic recovery had happened. The fourth cycle of Dexa-BEAM was given after haemologic recovery from cycle three. Patients randomly assigned BEAM-HSCT underwent high-dose chemotherapy followed by transplantation of either autologous bone marrow or peripheral-blood-progenitor cells. BEAM was started 4 weeks after white blood cell count returned to normal after Dexa-BEAM, and consisted of carmustine (300 mg/m^2 intravenously, on day –7), etoposide (150 mg/m^2 intravenously, every 12 h from day –7 to day –4), cytarabine (200 mg/m^2, every 12 h from day –7 to day –4), and melphalan (140 mg/m^2, on day –3). Cryopreserved bone-marrow or peripheral-blood-progenitor cells were infused on day 0 followed by granulocyte-colony-stimulating factor until leucocyte recovery.

Involved-field radiotherapy was recommended for all patients with residual lesions judged to represent active Hodgkin's disease. We did the first restaging 3 months after end of chemotherapy, and this staging was repeated at 6 and 12 months, and every 6 months thereafter.

Statistical analysis

The primary endpoint of our study was freedom from treatment failure in patients with chemosensitive disease. Patients with progressive disease or who did not achieve complete remission 3 months after the end of treatment, those who relapsed after attainment of complete remission for at least 3 months, and patients dying from any cause, were regarded as treatment failures. Secondary endpoints were response rates, complete remission at 3 months after end of treatment, and overall survival. Freedom from treatment failure and overall survival were measured from registration to end of observation or occurrence of an event.

150 chemosensitive patients were needed to have 80% power to detect an improvement of 20% in freedom from treatment failure after 2 years for patients given high-dose chemotherapy if a one-sided type I error of 5% was accepted. The scientific committee decided to stop the study because of low accrual of patients after 117 chemosensitive patients had been recruited.

We compared frequencies with the χ^2 test. We used Bonferroni's method for multiple testing of significance tests of clinical characteristics and toxic effects. We did Kaplan-Meier analyses for the endpoints freedom from treatment failure and overall survival for chemosensitive patients, and did two-sided log-rank tests for comparisons between treatment groups and types of relapse over total observation time. A stratified log-rank test adjusted for types of relapse was also done to establish differences in freedom from treatment failure and overall survival between groups.[14] All p values for Kaplan-Meier analyses refer to log-rank tests.

Role of the funding source

The sponsors had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between February, 1993, and September, 1997, 166 patients from 56 institutions were assessed for recruitment to the study, and five were excluded before randomisation (figure 2). 161 patients were thus randomly allocated. 13 patients (seven given Dexa-BEAM and six given BEAM-HSCT) were not eligible: six had never achieved a complete remission, three had been in complete remission for less than 3 months, three had relapsed with non-Hodgkin lymphoma, and one had been pretreated with Dexa-BEAM. Four patients (three given Dexa-BEAM and one given BEAM-HSCT) had incomplete data. These exclusions left 63 patients in the group assigned Dexa-BEAM and 81 patients in the group assigned BEAM-HSCT. Patients given BEAM-HSCT were slightly younger than those given Dexa-BEAM (table 1). Patients randomly assigned BEAM-HSCT also had a shorter median duration of remission before relapse than those given Dexa-BEAM.

After the first two courses of Dexa-BEAM, 39 patients (27%) had achieved complete remission and 78 (54%) partial remission. 27 patients (19%) did not proceed to further courses of chemotherapy because of failure to achieve complete or partial remission (n=8), protocol violations or refusal of patients (6), death from treatment-related toxic effects (8), and development of serious infections precluding further treatment by protocol (5). Causes of death were septicaemia in five patients, pneumonia, lung abscess, and seizures probably due to cerebral bleeding in one each.

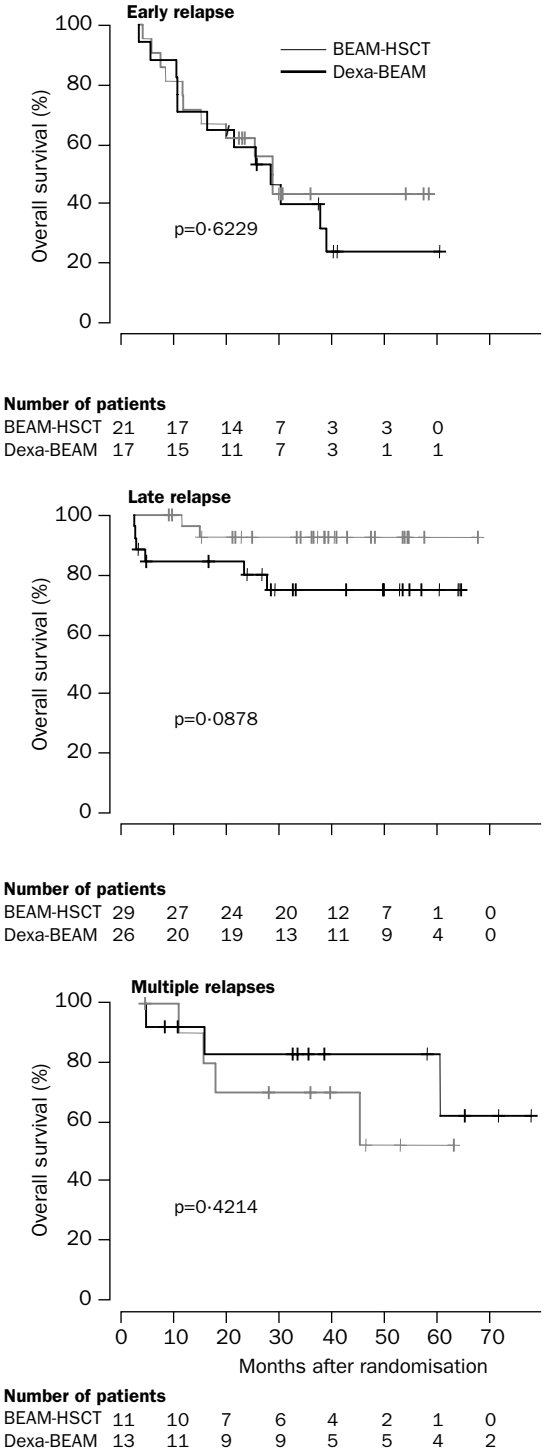


Figure 5: **Overall survival for patients with early relapse (upper), late relapse (middle), and multiple relapses (lower) of Hodgkin's disease**

56 chemosensitive patients started the third course of Dexa-BEAM median 4 weeks (range 2–24) after the second course; 47 (84%) completed all four cycles of Dexa-BEAM. 61 patients started BEAM high-dose chemotherapy followed by autologous transplantation of bone-marrow cells (n=6) or peripheral-blood progenitor cells (50) median 5·5 weeks (3–39) after the second course of Dexa-BEAM. Five patients (8%) did not receive transplantation because of progressive disease (n=2) or if the treating physician made that choice (3). Involved-field radiotherapy was documented in 11 patients (five Dexa-BEAM and six BEAM-HSCT).

3 months after end of treatment, 91 (78%) of 117 patients with chemosensitive disease were in complete or unconfirmed complete remission (39 Dexa-BEAM and 52 BEAM-HSCT, p=0·067). Nine patients (8%) had achieved partial remission (six Dexa-BEAM and three BEAM-HSCT), and 11 (9%) had not responded (six Dexa-BEAM and five BEAM-HSCT). The higher rate of complete remission in patients on BEAM-HSCT than in those on Dexa-BEAM was not associated with better freedom from treatment failure at 3 years (p=0·064). Five patients given Dexa-BEAM died of infectious complications, and one given BEAM-HSCT died. Frequency of toxic effects did not differ significantly between groups (table 2).

At last follow-up (3–78 months after end of treatment), 38 (32%) of 117 patients with chemosensitive relapse of Hodgkin's disease had died (table 3). 64 patients (55%) were alive in complete remission, one (1%) was in partial remission, and eight (7%) were alive with active disease. 32 patients had relapsed. Eight (47%) of 17 patients relapsing after Dexa-BEAM alone received high-dose chemotherapy later in the course of their disease.

At median follow-up of 39 months (3–78), 3-year survival of chemosensitive patients was 68% (95% CI 59–77); thus, median survival was not reached. Survival did not differ significantly between treatment groups (table 4).

Freedom from treatment failure for chemosensitive patients who received BEAM-HSCT was significantly better than for patients treated with Dexa-BEAM (figure 3). Median time to treatment failure was 12 months for Dexa-BEAM but was not reached for BEAM-HSCT patients.

Freedom from treatment failure was significantly better for patients with early or late first relapse if treated with BEAM-HSCT (figure 4). At 3 years, the estimated percentage of failure-free patients with early first relapse given BEAM-HSCT was about four times greater than with Dexa-BEAM (table 4). For patients with late first relapse the failure-free portion at 3 years was a third greater for those given BEAM-HSCT than those given Dexa-BEAM. For patients with multiple relapses, this percentage at 3 years was three-quarters greater for patients treated with Dexa-BEAM than with BEAM-HSCT. Survival differences within strata did not differ significantly (figure 5).

Comparison stratified for type of relapse confirmed the significant difference in favour of BEAM-HSCT for freedom from treatment failure and survival (p=0·010). Overall survival again did not differ significantly (p=0·405).

Discussion

We have shown that patients with first relapse of Hodgkin's disease and tumour sensitive to salvage chemotherapy have significantly better freedom from treatment failure with BEAM-HSCT than after Dexa-BEAM. Overall survival did not differ significantly between treatments.

We noted some imbalances in patients' characteristics, distribution of type of relapse, and rate of complete remission after two cycles of Dexa-BEAM between treatments. These differences were accounted for by stratified Kaplan-Meier analyses, which showed the effect of the type of relapse, but did not show an effect for rate of complete remission after two cycles of Dexa-BEAM.

These findings accord with the results of a small randomised trial by the British National Lymphoma Investigation.[13] About half the patients who failed salvage chemotherapy received high-dose therapy later in the

course of disease. To some extent, therefore, that study and our's also compare early with late high-dose treatment. This, together with the fact that patients with relapsed Hodgkin's disease can achieve multiple remissions with conventional treatment, could explain why freedom from treatment failure, but not overall survival, was better after high-dose chemotherapy in both studies.

Early toxic effects of the conventional treatment chosen by our group was higher than generally seen.[17] Not only did the first two courses of Dexa-BEAM result in eight treatment-related deaths and five life-threatening infections but also cycles three and four given to patients on Dexa-BEAM led to five additional deaths in 56 patients (9%), whereas only one of 61 patients (2%) undergoing BEAM-HSCT died early. A high death rate from toxic effects of salvage chemotherapy was reported by Tourani and colleagues,[7] who treated patients with three cycles of aggressive chemotherapy including carmustine and etoposide. Results of that study and our's show that dose escalation without haemopoietic stem-cell support has its limits, and potential gains in efficacy at some point will be offset by increased toxic effects. We can only speculate whether toxic effects would have been reduced but efficacy preserved had all patients received lower doses of etoposide—the drug that presumably was the main cause of the frequent septic complications seen. We for the first time have shown that high-dose chemotherapy, which is very similar to conventional salvage therapy, gives significantly better results in patients with late compared with early relapse of Hodgkin's disease.

Length of initial remission is an important prognostic factor, and disease characteristics could be more important than the combination of cytotoxic drugs, even if doses at the upper end of the dose range are used.[8,17–19] Patients with multiple relapses did not show any obvious benefit from high-dose chemotherapy. These patients could represent a subtype of Hodgkin's lymphoma, characterised by a chronically relapsing course, which repeatedly responds to various treatment modalities, the modality itself perhaps not being important. The numbers of such patients were small, however, and conclusions are difficult to draw.

We wanted to restrict high-dose chemotherapy and its accompanying risks to patients with chemosensitive disease, because results of many studies have shown that this group of patients has the most favourable prognosis after high-dose chemotherapy.[11,12,20] Patients with disease refractory to salvage chemotherapy have a less favourable outcome after stem-cell transplantation than patients with chemosensitive disease,[21] although a few might still benefit from the procedure.[22]

Up to now, we have noted only one secondary leukaemia in a patient treated with BEAM and stem-cell transplantation. With a median follow-up of 39 months, however, we cannot yet compare incidence and type of secondary cancers seen in patients given or not given high-dose chemotherapy.[23]

High-dose chemotherapy, as we used it, was unable to change the outlook of patients with Hodgkin's disease who relapsed many times, and the results for patients with first relapse must be further improved. Immunotoxins,[24] bispecific antibodies,[25] or infusion of cytotoxic T cells specific for Epstein-Barr virus[26] all merit further study, and could be effective in a setting of minimum residual disease induced by high-dose chemotherapy. Reduction of the unacceptably high transplant-related mortality after allogeneic stem-cell transplantation for Hodgkin's disease might also be possible,[27,28] with conditioning regimens of reduced intensity.[29,30]

We conclude that all patients with Hodgkin's disease at first relapse responding to conventional salvage chemotherapy should be offered high-dose treatment followed by autologous stem-cell transplantation. Close observation of the long-term effects of conventional treatment and high-dose chemotherapy, and continued investigation of new treatment modalities in well-designed prospective trials, will help to improve further the outlook for patients with relapsed Hodgkin's disease.

Contributors

N Schmitz, D Hasenclever, and V Diehl had the original idea and designed the study. B Pfistner did the statistical analyses and interpreted results. M Sextro, M Sieber, and B Koch were responsible for management and quality control of clinical data and patients' follow-up. All authors analysed and interpreted data, wrote the draft report, and approved the final version.

Participating centres

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Conflict of interest statement

None declared.

Acknowledgments

We thank all physicians, nurses, and clerks at the study sites who assisted with the study; and Christel Diener for preparation of the report. The study was supported by Deutsche Krebshilfe and Mildred Scheel Stiftung.

References

1 Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med* 1992; **327:** 1478–84.

2 Horning SJ, Williams J, Bartlett NL, et al. Assessment of the Stanford V regimen and consolidative radiotherapy for bulky and advanced Hodgkin's disease: Eastern Cooperative Oncology Group Pilot Study E1492. *J Clin Oncol* 2000; **18:** 972–80.

3 Diehl V, Franklin J, Hasenclever D, et al. BEACOPP, a new dose-escalated and accelerated regimen, is at least as effective as COPP/ABVD in patients with advanced-stage Hodgkin's lymphoma: interim report from a trial of the Germany Hodgkin's Lymphoma Study Group. *J Clin Oncol* 1998; **16:** 3810–21.

4 Rodriguez J, Rodriguez MA, Fayad L, et al. ASHAP: a regimen for cytoreduction of refractory or recurrent Hodgkin's disease. *Blood* 1999; **93:** 3632–36.

5 Fermé C, Bastion Y, Lepage E, et al. The MINE regimen as intensive salvage chemotherapy for relapsed and refractory Hodgkin's disease. *Ann Oncol* 1995; **6:** 543–49.

6 Pfreundschuh MG, Rueffer U, Lathan B, et al. Dexa-BEAM in patients with Hodgkin's disease refractory to multidrug chemotherapy regimens: a trial of the German Hodgkin's Disease Study Group. *J Clin Oncol* 1994; **12:** 580–86.

7 Tourani J-M, Levy R, Colonna P, et al. High-dose salvage chemotherapy without bone marrow transplantation for adult patients with refractory Hodgkin's disease. *J Clin Oncol* 1992; **10:** 1086–94.

8 Lohri A, Barnett M, Fairey RN, et al. Outcome of treatment of first relapse of Hodgkin's disease after primary chemotherapy: identification of risk factors from the British Columbia Experience 1970 to 1988. *Blood* 1991; **77:** 2292–98.

9 Bonfante V, Santoro A, Viviani S, et al. Outcome of patients with Hodgkin's disease failing after primary MOPP-ABVD. *J Clin Oncol* 1997; **15:** 528–34.

10 Longo DL, Duffey PL, Young RC, et al. Conventional-dose salvage combination chemotherapy in patients relapsing with Hodgkin's disease after combination chemotherapy: the low probability for cure. *J Clin Oncol* 1992; **10:** 210–18.

11 Sweetenham JW, Taghipour G, Milligan D, et al. High-dose therapy and autologous stem cell rescue for patients with Hodgkin's disease in first relapse after chemotherapy: results from the EBMT. *Bone Marrow Transplant* 1997; **20:** 745–52.

12 Crump M, Smith AM, Brandwein J, et al. High-dose etoposide and melphalan, and autologous bone marrow transplantation for patients with advanced Hodgkin's disease: importance of disease status at transplant. *J Clin Oncol* 1993; **11:** 704–11.

13 Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet* 1993; **341:** 1051–54.

14 Pocock SJ. Clinical trials. Chichester: John Wiley and Sons, 1983: 84–87.

15 Pfreundschuh M, Hasenclever D, Loeffler M, et al. Dose escalation of cytotoxic drugs using haematopoietic growth factors: a randomized trial to determine the magnitude of increase provided by GM-CSF. *Ann Oncol* 2001; **12:** 471–77.

16 Dreger P, Kloess M, Petersen B, et al. Autologous progenitor cell transplantation: prior exposure to stem cell-toxic drugs determines yield and engraftment of peripheral blood progenitor cell but not of bone marrow grafts. *Blood* 1995; **86:** 3970–78.

17 Yuen AR, Rosenberg SA, Hoppe RT, Halpern JD, Horning SJ. Comparison between conventional salvage therapy and high-dose therapy with autografting for recurrent or refractory Hodgkin's disease. *Blood* 1997; **89:** 814–22.

18 Reece DE, Connors JM, Spinelli JJ, et al. Intensive therapy with cyclophosphamide, carmustine, etoposide ± cisplatin, and autologous bone marrow transplantation for Hodgkin's disease in first relapse after combination chemotherapy. *Blood* 1994; **83:** 1193–99.

19 Brice P, Bouabdallah R, Moreau P, et al. Prognostic factors for survival after high-dose therapy and autologous stem cell transplantation for patients with relapsing Hodgkin's disease: analysis of 280 patients from the French registry. *Bone Marrow Transplant* 1997; **20:** 21–26.

20 Chopra R, McMillan AK, Linch DC, et al. The place of high-dose BEAM therapy and autologous bone marrow transplantation in poor-risk Hodgkin's disease: a single-center eight-year study of 155 patients. *Blood* 1993; **81:** 1137–45.

21 André M, Henry-Amar M, Pico J-L, et al. Comparison of high-dose therapy and autologous stem cell transplantation with conventional therapy for Hodgkin's disease induction failure: a case-control study. *J Clin Oncol* 1999; **17:** 222–29.

22 Sweetenham JW, Carella AM, Taghipour G, et al. High-dose therapy and autologous stem-cell transplantation for adult patients with Hodgkin's disease who do not enter remission after induction chemotherapy: results in 175 patients reported to the European Group for Blood and Marrow Transplantation. *J Clin Oncol* 1999; **17:** 3101–09.

23 van Leeuwen FE, Swerdlow J, Valagussa P, Tucker MA. Second cancers after treatment of Hodgkin's disease. In: Mauch PM, Armitage JO, Diehl V, Hoppe RT, Weiss LM, eds. Hodgkin's disease. Philadelphia: Lippincott, Williams, and Wilkins, 1999: 607–32.

24 Engert A, Diehl V, Schnell R, et al. A phase-I study of an anti-CD25 ricin A-chain immunotoxin (RFT5-SMPT-dgA) in patients with refractory Hodgkin's lymphoma. *Blood* 1997; **89:** 403–10.

25 Hartmann F, Renner C, Jung W, et al. Treatment of refractory Hodgkin's disease with an anti-CD16/CD30 bispecific antibody. *Blood* 1997; **89:** 2042–47.

26 Heslop HE, Ng CYC, Li C, et al. Long-term restoration of immunity against Epstein-Barr virus infection by adoptive transfer of gene-modified virus-specific T lymphocytes. *Nat Med* 1996; **2:** 551–55.

27 Milpied N, Fielding AK, Pearce RM, et al. Allogeneic bone marrow transplant is not better than autologous transplant for patients with relapsed Hodgkin's disease. *J Clin Oncol* 1996; **14:** 1291–96.

28 Gajewski JL, Phillips GL, Sobocinski KA, et al. Bone marrow transplants from HLA-identical siblings in advanced Hodgkin's disease. *J Clin Oncol* 1996; **14:** 572–78.

29 Slavin S, Nagler A, Naparstek E, et al. Non-myeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with cytoreduction for the treatment of malignant and non-malignant hematologic diseases. *Blood* 1998; **91:** 756–63.

30 Carella AM, Cavaliere M, Lerma E, et al. Autografting followed by nonmyeloablative immunosuppressive chemotherapy and allogeneic peripheral blood hemopoietic stem cell transplantation as treatment of resistant Hodgkin's disease and non-Hodgkin's lymphoma. *J Clin Oncol* 2000; **18:** 3918–24.