

AUTOLOGOUS BONE MARROW TRANSPLANTATION AS COMPARED WITH SALVAGE CHEMOTHERAPY IN RELAPSES OF CHEMOTHERAPY-SENSITIVE NON-HODGKIN'S LYMPHOMA

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Abstract *Background.* High-dose chemotherapy followed by autologous bone marrow transplantation is a therapeutic option for patients with chemotherapy-sensitive non-Hodgkin's lymphoma who have relapses. In this report we describe a prospective randomized study of such treatment.

Methods. A total of 215 patients with relapses of non-Hodgkin's lymphoma were treated between July 1987 and June 1994. All patients received two courses of conventional chemotherapy. The 109 patients who had a response to chemotherapy were randomly assigned to receive four courses of chemotherapy plus radiotherapy (54 patients) or radiotherapy plus intensive chemotherapy and autologous bone marrow transplantation (55 patients).

Results. The overall rate of response to conventional chemotherapy was 58 percent; among patients with relapses after chemotherapy, the response rate was 64 percent, and among those with relapses during chemo-

therapy, the response rate was 21 percent. There were three deaths from toxic effects among the patients in the transplantation group, and none among those in the group receiving chemotherapy without transplantation. The two groups did not differ in terms of prognostic factors. The median follow-up time was 63 months. The response rate was 84 percent after bone marrow transplantation and 44 percent after chemotherapy without transplantation. At five years, the rate of event-free survival was 46 percent in the transplantation group and 12 percent in the group receiving chemotherapy without transplantation ($P=0.001$), and the rate of overall survival was 53 and 32 percent, respectively ($P=0.038$).

Conclusions. As compared with conventional chemotherapy, treatment with high-dose chemotherapy and autologous bone marrow transplantation increases event-free and overall survival in patients with chemotherapy-sensitive non-Hodgkin's lymphoma in relapse. (N Engl J Med 1995;333:1540-5.)

IT is generally agreed that patients with intermediate- or high-grade non-Hodgkin's lymphoma who have a relapse after initial therapy have a poor prognosis.^{1,2} A retrospective study in 1984 from France and England showed a clear relation between the responsiveness of the lymphoma to treatment and the outcome.³ In 1987, the combination of high-dose chemotherapy and autologous bone marrow transplantation in patients with non-Hodgkin's lymphoma in relapse was considered promising but experimental and appropriate for use only at research centers.¹ The value of that treatment remains an open question, because conventional salvage treatment without autologous bone marrow transplantation can induce lengthy remissions; long-term survival after a relapse has been reported with at least five different chemotherapy regimens.⁴⁻⁸

In a preliminary study, our group (the Parma Group, formed in 1986 during a meeting in Parma, Italy) found

that salvage chemotherapy followed by radiotherapy of the involved field, high-dose chemotherapy, and autologous bone marrow transplantation induced prolonged, but unmaintained, remissions in 40 percent of patients who had treatment-sensitive lymphomas in relapse. The death rate from toxic effects among these patients was only 10 percent.⁹ We now report the results of a prospective randomized trial of this treatment.¹⁰

METHODS

Patients

We enrolled a total of 215 patients with non-Hodgkin's lymphoma of intermediate grade (163 patients) or high grade (52 patients) in relapse. The patients were 18 to 60 years old at the time of the first relapse (188 patients) or the second relapse (27 patients). The patients were enrolled between July 1987 and June 1994 at 51 participating centers (see the Appendix).

To be eligible for enrollment, patients had to have received previous treatment with a doxorubicin-containing regimen.¹⁰ All patients had a complete response to an initial induction regimen, with the response maintained for at least four weeks. Relapses during and after therapy were defined by the investigators at the participating centers. Patients with central nervous system or bone marrow involvement at the time of the relapse were excluded. Informed consent was obtained from each patient according to the Parma protocol and the rules of each participating center and country.

All patients were given dexamethasone, cisplatin, and cytarabine (DHAP).⁵ After one course of DHAP, bone marrow was harvested (except in 41 patients with clearly progressive disease) while the patients were under general anesthesia. The bone marrow was frozen,⁹ unless marrow had been stored previously (in the case of 24 patients). Bone marrow-biopsy specimens obtained at the time of harvesting were normal in all patients. None of the patients received hematopoietic growth factors before the bone marrow was harvested. Peripheral-blood stem cells were not collected. A second course of DHAP was given beginning on day 1 after the harvesting. Twenty days later, the

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stage of the disease was reevaluated according to the sites involved when the first course of DHAP therapy was initiated. Patients with complete or partial responses were considered to have relapses of chemotherapy-sensitive lymphoma and were eligible for random assignment to one of the treatment groups.

Randomization was performed as early as possible between day 20 and day 60 after the initiation of the second course of DHAP. Interactive computerized procedures were used to monitor data at the time of enrollment and randomization. Patient assignments were stratified according to center, and the computer assigned each patient to a treatment group on the basis of a permuted-block design. All data were checked for validity and coherence by the coordinating center. Errors and missing values were reported to the investigators for correction or confirmation. The plausibility of the data and consistency among variables were checked. On-site monitoring was not performed systematically, but before the final analysis, an effort was made to obtain missing data.

Treatment

Eligible patients were randomly assigned to receive autologous bone marrow transplantation or conventional treatment. The conditioning regimen in the transplantation group consisted of carmustine, etoposide, cytarabine, cyclophosphamide, and mesna (BEAC), with or without radiotherapy of the involved field, followed by bone marrow transplantation. Radiotherapy was part of the transplantation protocol and was indicated if the sites of bulky disease at the time of relapse were at least 5 cm in diameter or if there were extranodal T3 or T4 lesions (according to the classification of the European Organization for Research and Treatment of Cancer).⁹ The total dose of radiation was 26 Gy, given in fractions of 1.3 Gy each, delivered twice daily with at least four hours between the two treatments. An involved field was defined according to the Ann Arbor staging system¹¹ and the diameter of bulky disease at the time of the relapse (i.e., during the enrollment phase), not at the time of randomization.⁹ BEAC was administered 48 hours after the completion of radiotherapy, on days 21 through 60 after the second course of DHAP.

The regimen consisted of 300 mg of carmustine per square meter of body-surface area (administered intravenously for 30 to 60 minutes) on day 1; a total daily dose of 200 mg of etoposide per square meter (100 mg per square meter given intravenously for 30 to 60 minutes twice daily) on days 2 through 5; a total daily dose of 200 mg of cytarabine per square meter (100 mg per square meter given intravenously for 30 minutes twice daily) on days 2 through 5; a total daily dose of 35 mg of cyclophosphamide per kilogram of body weight (given as a short infusion for 60 minutes) on days 2 through 5; and a total daily dose of 50 mg of mesna per kilogram (optional) on days 2 through 5 (given intravenously in six fractions every 4 hours for 30 minutes). Autologous bone marrow transplantation was performed through a central line 48 hours after the last dose of etoposide, with a minimum of 100 million nucleated cells per kilogram injected. Patients received care in single rooms according to the protocol for supportive care at each participating center.¹⁰

The conventional treatment consisted of four additional courses of DHAP given at intervals of three to four weeks, followed, if no progression occurred, by radiotherapy of the involved field according to the same definition of bulky disease used at the time of enrollment (i.e., ≥ 5 cm). The radiotherapy was administered as complementary treatment. The dose of radiation was 35 Gy delivered in 20 fractions of 1.75 Gy per fraction.

After randomization, each patient was evaluated in the group to which he or she had been assigned, even if the treatment was incomplete. The objective was to compare groups, not treatments. In both groups, additional treatment was allowed if the assigned treatment had failed. Such additional treatment included high-dose chemotherapy and autologous bone marrow transplantation for patients in the conventional-treatment group. No specific conditioning regimen was recommended at this stage.

Statistical Analysis

Survival curves were calculated according to the Kaplan-Meier method¹² and compared by the two-sided log-rank test,¹³ with the use of the Lifetest procedure in the SAS statistical package. Differences

were considered significant if the P value was less than 0.05. Other comparisons were performed with the chi-square and Fisher's exact tests.¹⁴

An event was defined as a relapse, evidence of disease progression, or death, whatever the cause. The date of the first event was used in calculating event-free survival.

A steering committee and policy board (see the Appendix) were set up in 1987 to monitor the interim analysis. The first analysis was performed in June 1990 to detect any abnormal toxic effects in the transplantation group (>15 percent).⁹ A second analysis was performed in June 1992, with differences considered significant if the P value was less than 0.01. The policy board decided to stop the study in June 1994, before further analysis of the data had been performed.

RESULTS

Enrollment and Treatment

A total of 215 patients were enrolled in the study. There were 126 men and 89 women, with a median age of 43 years. A total of 163 patients had intermediate-grade lymphoma, and 52 had high-grade lymphoma. A central review of the pathological findings was not mandatory. Forty-three percent of the patients had elevated serum lactic dehydrogenase values at the time of enrollment.

The rate of response to the initial doxorubicin-containing regimen was 58 percent. Fifty-three patients (25 percent) had complete responses and 72 (34 percent) had partial responses. Among the 187 patients who had relapses after therapy with the doxorubicin-containing regimen, 64 percent had responses to two courses of DHAP. Among the 28 patients who had relapses during therapy with the doxorubicin-containing regimen, the rate of response to DHAP was 21 percent.

Ninety patients were excluded before randomization because they did not have a response to DHAP, and 16 of the 125 patients with responses (8 with complete responses and 8 with partial responses) were not included for reasons defined in the protocol.

The remaining 109 patients were randomly assigned to high-dose chemotherapy, irradiation of the involved field (if indicated), and autologous bone marrow transplantation (55 patients) or conventional treatment (54 patients). Of these 109 patients, 95 were having a first relapse, and 14 were having a second relapse; all 109 had had complete responses after the first-line therapy. The serum concentration of lactate dehydrogenase was elevated in 36 of the 105 randomized patients (34 percent) for whom data were available at the time of enrollment (Table 1). At the time of randomization, the lactate dehydrogenase concentration was still abnormal in 20 patients in the transplantation group and 21 in the conventional-treatment group. Of the 109 patients, 45 had complete responses (41 percent) and 64 had partial responses (59 percent) at the time of randomization.

The time of relapse (during or after therapy), histologic type of lymphoma, and number of second relapses (nine in the conventional-treatment group and five in the transplantation group, $P=0.24$) were similar in the two groups (Table 1). The site of the relapse, proportion of patients with elevated lactate dehydrogenase concentrations at the time of the relapse (36 percent in the

transplantation group and 33 percent in the conventional-treatment group), and size of the tumor at the time of the relapse were also similar in the two groups.

Six of the 55 patients randomly assigned to high-dose chemotherapy and autologous bone marrow transplantation did not undergo transplantation but were analyzed with the other patients in this group.¹⁵ One of the six died early in the course of a relapse, before receiving BEAC. Two had progressive disease before receiving BEAC, were treated with other chemotherapeutic regimens, and died. Another patient who had progressive disease before the administration of BEAC received salvage treatment and then BEAC, had a relapse four months later, received another rescue treatment, and survived. The other two patients received DHAP: one because of a cardiac problem after randomization and before the administration of BEAC, and one because no stem cells were present in the bone marrow before the initiation of BEAC. These two patients underwent autologous bone marrow transplantation outside the pro-

tolocol after relapse (with a second harvest performed in one), and both died.

Overall and Event-free Survival

Thus, 49 patients received high-dose chemotherapy and autologous bone marrow transplantation. Three (6 percent) died from toxic effects: one from septic shock on day 63 after transplantation, one from a fungal infection on day 97, and one from cardiac toxicity on day 83. An additional patient, who was in complete remission, died from pulmonary infection on day 406 after transplantation (this death was classified as due to late toxicity). Twenty-two of the 55 patients in the transplantation group received radiotherapy. Two of these patients had relapses before receiving BEAC. Morbidity after treatment with high-dose chemotherapy and autologous bone marrow transplantation was high, with 1 case of septic shock and 30 episodes of bacterial infection (septicemia in 17), 8 of viral infection, 6 of fungal infection, 5 of renal toxicity, 4 of hepatic toxicity (grade 3 in 2 patients), and 3 of pneumonitis. Twenty-seven patients had mucositis (grade 3 in 7 patients and grade 4 in 2), 16 had diarrhea (grade 3 in 6), and 1 had grade 4 cardiac toxicity.

None of the 54 patients randomly assigned to the conventional-treatment group died from toxic effects of treatment, and 37 patients received at least three courses of DHAP. Only 12 of the 54 patients received radiotherapy of the involved field after four additional courses of DHAP (essentially because 26 patients had relapses during the four courses of DHAP and before receiving radiotherapy). Morbidity was lower in this group than in the transplantation group, with one case of septic shock and six episodes of bacterial infection (septicemia in three), two of viral infection, one of fungal infection, three of pneumonitis, and one of hepatic toxicity. Four patients had mucositis, three had diarrhea (grade 3 in one patient), and two had cardiac toxicity (grade 1 in both). Only renal toxicity (14 cases, 1 of which was grade 3) was more frequent than in the transplantation group.

The median follow-up period was 63 months. The response rate was 84 percent after bone marrow transplantation and 44 percent after chemotherapy without transplantation. The overall survival at five years in the group of 109 randomized patients was 42 percent, as compared with 45 percent in the group of 16 patients excluded from randomization (5 of the 8 survivors had no evidence of disease) and 11 percent in the group of 90 patients without initial responses to chemotherapy ($P < 0.001$). The rate of event-free survival was 46 percent in the transplantation group and 12 percent in the conventional-treatment group ($P = 0.001$) (Fig. 1). At five years, the overall survival was 53 percent in the transplantation group and 32 percent in the conventional-treatment group ($P = 0.038$) (Fig. 2).

Relapses

Twenty-six of the patients who received high-dose chemotherapy and autologous bone marrow transplan-

Table 1. Base-Line Characteristics of the 109 Patients with Non-Hodgkin's Lymphoma Randomly Assigned to Autologous Bone Marrow Transplantation or Conventional Treatment.*

CHARACTERISTIC	TRANSPLANTATION (N = 55)	CONVENTIONAL TREATMENT (N = 54)
	no. of patients	
Histologic type of lymphoma		
High-grade large-cell immunoblastic	10	12
High-grade lymphoblastic	0	2
High-grade, with small noncleaved cells	1	2
Intermediate-grade follicular, with predominantly large cells	3	3
Intermediate-grade diffuse, with small cleaved cells	0	3
Intermediate-grade diffuse, with mixed small and large cells	12	9
Intermediate-grade diffuse, with large cells	22	15
Other diffuse	7	8
Relapse		
During therapy	2	3
Not during therapy	53	51
First	50	45
Second	5	9
Serum lactate dehydrogenase concentration		
Normal value	34	35
1 to 2× normal value	18	14
>2× normal value	1	3
Unknown	2	2
Size of tumor at main location		
Not measurable	1	4
≤5.0 cm	38	28
5.1–10.0 cm	8	9
>10.0 cm	1	4
Unknown	7	9
Main location		
Nodal thoracic	11	4
Nodal abdominal	12	14
Nodal head and neck	13	14
Other nodal	8	5
Extranodal thoracic	1	1
Extranodal abdominal	7	5
Extranodal head and neck	1	3
Other extranodal	2	8

*Patients in the transplantation group underwent radiotherapy; a regimen of carmustine, etoposide, cytarabine, cyclophosphamide, and mesna (optional); and autologous bone marrow transplantation. Patients in the conventional-treatment group received four courses of dexamethasone, cisplatin, and cytarabine, plus radiotherapy.

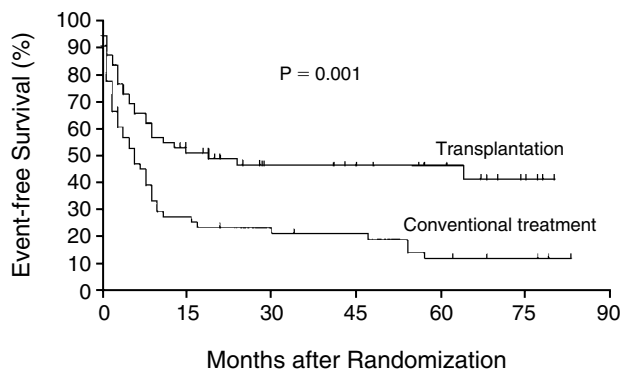


Figure 1. Kaplan–Meier Curves for Event-free Survival of Patients in the Transplantation and Conventional-Treatment Groups.

The data are based on an intention-to-treat analysis. Tick marks represent censored data.

tation had relapses. There was no significant difference in the proportion with relapses between the subgroup of patients who had received radiotherapy of the involved field (22 patients, 8 with relapses) and the subgroup who had not received radiotherapy (33 patients, 18 with relapses; $P=0.19$). Relapses occurred at the primary site of the disease at the time of the first relapse in 4 of the 22 patients who underwent irradiation and in 12 of the 33 who did not ($P=0.15$).

In the conventional-treatment group, 45 patients had relapses, also with no statistical difference between those who received radiotherapy of the involved field (12 patients, 10 with relapses) and those who did not (42 patients, 35 with relapses; $P=0.66$). Relapses occurred at the primary site of disease at the time of the first relapse in 5 of the 12 patients who underwent irradiation and in 26 of the 42 who did not ($P=0.21$).

Transplantation in the Conventional-Treatment Group

Among the 45 patients in the conventional-treatment group who had relapses, 24 did not have at least a partial response to reinduction therapy, and 3 did not undergo autologous bone marrow transplantation, despite a previous response to a rescue protocol. Eighteen of the 45 patients who had relapses with progressive disease subsequently were treated with a high-dose regimen of chemotherapy and bone marrow transplantation, as allowed in the protocol. Sixteen of these 18 patients underwent induction chemotherapy according to a conventional rescue protocol (MIME [mitoguazone, ifosfamide, methotrexate, and etoposide] in 7, and other treatments in 9). The conditioning regimen was BEAC in eight patients, cyclophosphamide and total-body irradiation in five, and other treatments in five (data not shown). Fourteen of the 18 died, and 2 survived with relapses; only 2 were alive and free of disease 333 and 1911 days after autologous bone marrow transplantation.

DISCUSSION

This study demonstrates a significantly higher survival rate after high-dose chemotherapy and autologous

bone marrow transplantation than after conventional chemotherapy in adults with relapses of chemotherapy-sensitive, intermediate- or high-grade non-Hodgkin's lymphoma. Since we selected patients who were optimally suited for chemotherapy, the result in the conventional-treatment group is disappointing. Furthermore, 11 of the 20 patients still alive at the time of the analysis had progressive disease. These results are similar to those reported by Bosly et al. in a nonrandomized, retrospective study.⁸

One patient had a relapse 26 months after undergoing autologous bone marrow transplantation. On review the tumor was found to be a small lymphocytic follicular lymphoma, at the time of both this relapse and the initial relapse, not an intermediate-grade, diffuse, mixed-cell type, as originally diagnosed. The patient died 53 months after the transplantation.¹⁶ In another patient, who had a relapse at 66 months, the disease was diagnosed after a review of the slides (performed by Dr. D.D. Weisenburger, Omaha, Nebr.) as diffuse, large-cell non-Hodgkin's lymphoma at the time of the initial diagnosis and the first and second relapses. This patient survived.

The prognosis is poor for patients with intermediate- or high-grade non-Hodgkin's lymphoma who have a relapse after a complete remission, regardless of whether any further treatment is given.^{6,17-19} The most important prognostic factor is the duration of the remission.¹⁷ Second complete remissions do occur, however, after further treatment with combination chemotherapy at standard doses, and 10 percent of patients survive for long periods.^{17,20-22} Cures with high-dose chemotherapy and autologous bone marrow transplantation were first reported by Appelbaum et al.²³; this approach, however, is restricted to a minority of patients in relapse, since it cannot be used in patients who are elderly (i.e., older than 60 to 65 years).¹⁷

We believe that patients with chemotherapy-sensitive lymphomas in relapse are most likely to have good results with additional chemotherapy.^{2,3} In our study we selected the patients most likely to benefit from either

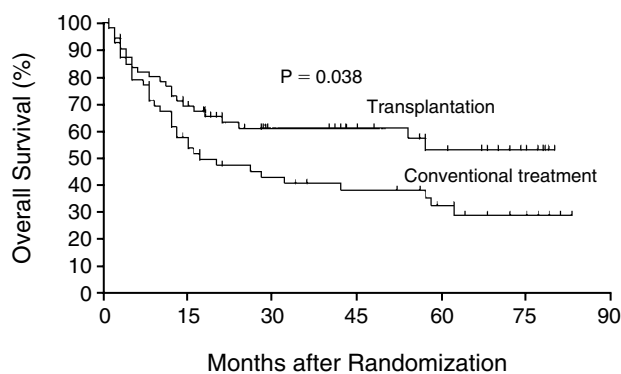


Figure 2. Kaplan–Meier Curves for Overall Survival of Patients in the Transplantation and Conventional-Treatment Groups.

The data are based on an intention-to-treat analysis. Tick marks represent censored data.

type of treatment: those younger than 60 years with previous complete responses, no central nervous system or bone marrow involvement, and previous responses to a conventional rescue protocol. Because of these stringent selection criteria, only 129 patients were enrolled between July 1987 and November 1989. Only 43 patients were enrolled between December 1989 and November 1991, because 29 of the 51 participating centers had stopped enrolling patients in the study. Only 18 centers were still enrolling patients after November 1991, and the policy board stopped the study in June 1994 because of the low rate of accrual. The rates of response and survival did not differ significantly among these three periods of enrollment.

The two groups of randomized patients were similar with regard to prognostic factors. Only 22 of 88 patients who could be evaluated had an intermediate or high tumor burden, and only 36 of 105 had high lactate dehydrogenase levels. The six patients with intermediate-grade, follicular, large-cell lymphoma¹⁶ were equally distributed in the two groups. Only two patients (both in the conventional-therapy group) had lymphoblastic lymphoma.²⁴ We thus succeeded in selecting a group of patients with favorable prognostic indicators in order to compare high-dose chemotherapy and autologous bone marrow transplantation with conventional therapy under the best possible conditions for the conventional approach.^{16-19,22,25,26}

The rates of mortality from toxic effects and morbidity were higher in the transplantation group than in the conventional-treatment group. Future studies should be conducted to determine whether toxicity can be reduced by the use of peripheral-blood stem cells and growth factors.^{17,27,28} Some unanswered questions about the management of relapses of lymphoma concern the roles of total-body irradiation (although retrospective studies indicate no marked effect²⁹), bone marrow purging and allogeneic marrow transplantation,^{28,30-32} and peripheral-blood stem cells in increasing survival and reducing relapses and toxicity.^{22,33}

We conclude that radiotherapy of the involved field and BEAC followed by autologous bone marrow transplantation is the best available treatment for patients with relapses of chemotherapy-sensitive, intermediate- or high-grade non-Hodgkin's lymphoma without bone marrow or central nervous system involvement.

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APPENDIX

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