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COMPARISON OF CHOP CHEMOTHERAPY WITH AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR SLOWLY RESPONDING PATIENTS WITH AGGRESSIVE NON-HODGKIN'S LYMPHOMA

Leo F. Verdonck, M.D., Wim L.J. van Putten, M.Sc., Anton Hagenbeek, M.D.,
Harry C. Schouten, M.D., Pieter Sonneveld, M.D., Gustaaf W. van Imhoff, M.D.,
Hanneke C. Kluin-Nelemans, M.D., John M.M. Raemaekers, M.D., Rien H.J. van Oers, M.D.,
Hans L. Haak, M.D., Rik Schots, M.D., Adriaan W. Dekker, M.D., Gijsbert C. de Gast, M.D.,
and Bob Löwenberg, M.D.

Abstract *Background.* High-dose chemoradiotherapy combined with autologous bone marrow transplantation can cure patients with disseminated, aggressive non-Hodgkin's lymphoma in whom first-line chemotherapy has failed. In contrast, cure is rare with second-line chemotherapy. It has been suggested that patients with slow responses to the initial phase of first-line chemotherapy are at high risk for relapse. Therefore, such patients are potential candidates for early bone marrow transplantation.

Methods. To investigate whether patients with slow responses, defined as only a partial response after three courses of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), would benefit from early transplantation, we conducted a prospective, randomized trial. The early application of high-dose chemoradiotherapy and autologous bone marrow transplantation was compared with the continuation of CHOP therapy for another five courses. Patients with complete responses after three courses of CHOP (fast responses) and patients who responded partially but still had tumor-positive marrow continued with another five courses of CHOP. The study end points were the response rate, overall survival, disease-free survival, and event-free survival.

Results. Of 286 patients who could be evaluated for the rapidity of their response after three courses of CHOP, 38 percent had fast responses, 47 percent had slow responses, and 15 percent had no response. Among 106 patients with slow responses who had lymphoma-negative marrow, 69 patients (65 percent) were randomized. Seventy-four percent of the CHOP group and 68 percent of the transplantation group had complete remissions (P=0.54). At four years the rates of overall, disease-free, and event-free survival were 85, 72, and 53 percent, respectively, in the CHOP group and 56, 60, and 41 percent in the transplantation group (P>0.10). The disease-free survival in both groups did not differ significantly from that of nonrandomized patients with fast responses (54 percent at four years).

Conclusions. The early application of high-dose, marrow-ablative chemoradiotherapy with autologous bone marrow transplantation does not improve the outcome in patients with aggressive non-Hodgkin's lymphoma that responds slowly to first-line CHOP chemotherapy. (N Engl J Med 1995;332:1045-51.)

C OMBINATION chemotherapy can cure about 45 percent of patients with disseminated intermediate-grade or high-grade non-Hodgkin's lymphoma.[1] Several institutions have reported that aggressive regimens of chemotherapy containing six to eight drugs gave better results than the CHOP regimen (which contains cyclophosphamide, doxorubicin, vincristine, and prednisone),[2-7] but in two large, multicenter, randomized, phase 3 trials[8,9] the more aggressive regimens were not found to be superior to CHOP, which is widely used as first-line chemotherapy for non-Hodgkin's lymphoma. However, CHOP fails to cure the disease when remissions are incomplete or unstable. Retreatment of patients who have relapsed with second-line, so-called salvage chemotherapy is generally unsuccessful.[10] High-dose chemoradiotherapy with autologous bone marrow transplantation may, however, cure some of these patients if they have disease that responds to chemotherapy.[10-18]

Early in the course of treatment, or even at diagnosis, it is important to identify patients who are unlikely to have complete remissions. These high-risk patients may benefit from high-dose chemoradiotherapy with bone marrow transplantation while their lymphomas can still respond to first-line chemotherapy. It has been suggested that patients in whom complete remission occurs rapidly with first-line chemotherapy — i.e., within three cycles of conventional chemotherapy —

have a better chance of cure than patients who respond more slowly.[19,20]

In 1987 we began assessing the efficacy of high-dose marrow-ablative therapy combined with autologous bone marrow transplantation in patients with disseminated, aggressive non-Hodgkin's lymphoma who have slow responses to chemotherapy. All patients were treated with CHOP, and their responses were evaluated after three courses. Those with partial responses were considered to have slow responses, and those with complete responses after three courses of CHOP were considered to have fast responses. We report here the results of a multicenter study in which patients with slow responses and lymphoma-negative bone marrow were eligible for random assignment to either another five courses of CHOP (the standard regimen) or marrow-ablative chemoradiotherapy with autologous bone marrow transplantation.

METHODS

Between January 1987 and April 1994, we enrolled 320 patients in the study. Patients from 15 to 60 years of age were eligible if they had measurable, biopsy-confirmed intermediate-grade or high-grade non-Hodgkin's lymphoma (groups D through H, according to the classification system of the Working Formulation),[21] including unclassifiable intermediate-grade and high-grade lymphoma, and stage II, III, or IV disease according to the Ann Arbor classification. The B or T immunotype was determined in either snap-frozen or paraffin-embedded tissue with mouse monoclonal antibodies against B-cell antigens CD20 and MB2 and T-cell antigens CD3 and CD45. Patients were determined to be ineligible if they had previous chemotherapy or radiotherapy; a history of low-grade malignant lymphoma; group I or J high-grade cancer; prior cancer, except non-melanoma skin cancer or cervical carcinoma stage I; a positive serologic test for the human immunodeficiency virus; involvement of the central nervous system by lymphoma; or severe cardiac, pulmonary, neurologic, or metabolic disease. Informed consent was obtained from all patients. The pathology slides for 88 percent of the patients underwent central pathology review. The protocol was approved by the institutional review board of each center.

Staging of the extent of disease, performed before therapy, included a history taking and physical examination; complete blood counts, including a search for abnormal lymphoid cells in the blood by morphologic and immunologic studies using flow cytometry; tests of renal and liver function; determination of the erythrocyte sedimentation rate; measurement of serum albumin and serum electrolytes; protein electrophoresis and immunoelectrophoresis; measurement of serum lactate dehydrogenase (upper limit, 250 U per liter); chest radiography; computed tomography of the abdomen and thorax; consultation with an ear, nose, and throat specialist; and bone marrow biopsy and aspiration from the iliac crest, including immunophenotyping by immunoperoxidase. As clinically indicated, lumbar puncture or liver biopsy was performed.

Complete restaging of each patient's condition was performed after three courses of CHOP chemotherapy and after the completion of therapy. During follow-up, staging procedures were repeated in their entirety at least every six months for the first three years and thereafter as clinically indicated.

Of the 320 patients enrolled, 34 patients were not eligible for the following reasons: they did not meet the criteria for entry into the study (6 patients), they had localized disease (5 patients), they had been treated before registration (2 patients), they had severe concomitant disease (4 patients), or the diagnosis was not confirmed (17 patients). Thus, 286 patients were eligible for analysis.

Treatment Protocol

CHOP was administered every 21 days as follows: 750 mg of cyclophosphamide per square meter of body-surface area intravenously on day 1; 50 mg of doxorubicin per square meter intravenously on day 1; 1.4 mg of vincristine per square meter intravenously on day 1 (maximal dose, 2.0 mg); and 100 mg of prednisone orally on days 1 through

5. Dose reductions were made as previously described if there was hematologic toxicity[22]; however, the first course was given in full. If there was mild neurotoxicity (i.e., paresthesias or decreased tendon reflexes), the dose of vincristine was reduced to 50 percent, and if there was severe neurotoxicity (i.e., marked loss of motor function), the vincristine was omitted. All patients were to receive three courses of CHOP and were then to be evaluated for their response.

To assess the response to CHOP, all tests that had abnormal results on staging before therapy were repeated. Complete remission was defined as the disappearance of all clinical evidence (physical and radiographic) of disease. Lymph nodes less than 1 cm in diameter on radiography were considered uninvolved. Patients with residual abnormalities detected with computed tomography, especially patients with bulky disease (tumor ≥10 cm) at diagnosis, were not considered to be in complete remission unless the abnormality had decreased in size by 90 percent or more or unless biopsy proved it to be uninvolved. Partial remission was defined as a reduction by at least 25 percent of the sum of the largest tumor diameters. Progressive disease was defined as an increase of at least 25 percent in the size of the original tumor mass or as the development of new lesions. Patients who did not meet any of the preceding definitions were classified as having no response.

When they had completed the evaluation after the third cycle of CHOP, patients with partial remissions and no bone marrow infiltration were asked about entering the trial. Those who agreed to do so were randomized. The patients randomly assigned to transplantation underwent bone marrow collection as soon as complete marrow repopulation had occurred. They were given a fourth course of CHOP the day after the collection. They then received high-dose chemotherapy, radiation, and infusion of autologous marrow.

Patients randomly assigned to CHOP began their fourth course on schedule. Those who had complete remissions and those with partial responses but with marrow involvement were treated with five additional courses of CHOP. Patients who had no response or whose disease progressed were not studied further and were given other therapy at the discretion of the investigators.

Bone marrow collection and cryopreservation were performed as soon as the marrow was repopulated after the third course of CHOP.[12] At least 2×10^8 nucleated cells per kilogram of body weight were collected. Reference samples of cells were frozen in small ampules and thawed during the first week after freezing in order for the investigators to check the quality of cryopreservation (with myeloid and erythroid colony growth in vitro). The absence of marrow involvement by the lymphoma was checked again at the time of the marrow collection by histologic and cytologic methods. None of the patients assigned to transplantation had detectable marrow involvement at the time of the marrow collection.

So that there would be time after the collection to evaluate the quality of the marrow graft and prepare for transplantation, the patients randomly assigned to transplantation received a fourth course of CHOP immediately after the bone marrow collection. The conditioning regimen for transplantation was scheduled to be carried out within six weeks after the fourth course of CHOP.

The high-dose chemoradiotherapy administered before the reinfusion of autologous marrow consisted of cyclophosphamide (60 mg per kilogram, infused on each of two consecutive days), followed two days later by total-body irradiation (800 cGy in one fraction). The autologous (unpurged) marrow graft was thawed rapidly and reinfused through a central venous catheter the day after the total-body irradiation.

Statistical Analysis

The study was designed on the assumption that for patients in partial remission after three courses of CHOP, two-year event-free survival would be improved from 35 percent with the continuation of CHOP to 70 percent with bone marrow transplantation, which would mean an improvement for patients with slow responses so that their outcome would be equivalent to that of patients with fast responses.[19] Therefore, a total of 60 patients had to be randomly assigned to the two treatments for the study to have a power of 80 percent to detect such a difference with a one-sided test at a significance level of 0.05. It was expected that 25 percent of the patients would have partial remissions without marrow infiltration after three courses of CHOP. Thus, according to estimates before the study began, about 240 patients had to be enrolled for the induction treatment with CHOP in order to meet the

objective of 60 randomized patients. Eventually, 286 eligible patients were enrolled, 106 of whom (37 percent) had partial remissions without marrow infiltration and 69 of whom (24 percent) were randomized.

No further patients were admitted to the study after December 31, 1993. The data were analyzed in April 1994, with the last follow-up data available for all patients still alive, except two patients (not randomized) who were lost to follow-up after one year. The median duration of follow-up for the 181 patients still alive at the final update was three years (range, two months to seven years). Sixty-one patients had follow-up of more than four years.

Logistic-regression analysis, univariate and multivariate, was used to test and determine the strength of the association between the probability of complete remission and prognostic factors and to determine the difference between the treatment groups. In these analyses, only complete remissions in patients treated according to the protocol were considered — i.e., complete remission after three courses of CHOP, after continuing treatment with CHOP, or after bone marrow transplantation for patients in partial remission after the first three cycles of CHOP. Patients whose complete remissions occurred only later, with second-line treatment, were classified as having no complete remission.

The actuarial method of Kaplan and Meier was used to calculate probabilities of survival. Cox regression analysis was used for statistical tests and the analysis of prognostic factors. The following end points were analyzed: overall survival, with failure defined as death from any cause; disease-free survival, which was restricted to patients entering complete remission while being treated according to the protocol, with failure defined as relapse or death during a first complete remission; and event-free survival, with failure defined as no complete remission during treatment according to the protocol, relapse after a complete remission, or death during a first complete remission. Time was measured from the start of the first treatment with CHOP or, in the comparison of the randomized treatment groups, from the time of randomization. Disease-free survival was measured from the date of complete remission. From the estimate of the relative death rate (R) in the transplantation (ABMT) group as compared with the CHOP group, obtained from the Cox model, the corresponding difference in overall survival (OS) between the two groups ($OS_{ABMT} - OS_{CHOP}$) was calculated by the formula $OS_{ABMT} = OS^R_{CHOP}$. In this formula, the overall survival after CHOP therapy was set at 70 percent. The 95 percent confidence interval for this difference in survival was calculated by substituting for R the 95 percent confidence intervals of the estimated relative death rate.

The following variables were included in the analysis of prognostic factors: age, sex, histologic grade of cancer (i.e., intermediate vs. high), Ann Arbor stage, number of extranodal sites, bone marrow involvement, bulky disease, immunologic phenotype, serum concentration of lactate dehydrogenase, and performance status (assessed according to the classification system of the World Health Organization). For all the statistical tests, a significance level of 0.05 was used. All reported P values are two-sided and unadjusted.

Interim analyses with rules for stopping in the event of extreme differences in outcome favoring the transplantation group were planned and performed twice during the study. The statistical crite-

rion for stopping the accrual of patients was an improvement in overall survival in the transplantation group that was statistically significant at the level of P<0.005. Because of this stringent criterion, no adaptation of the nominal significance levels at the final evaluation was required.

RESULTS

Response after Three Courses of CHOP Chemotherapy

Table 1 shows the characteristics of all 286 eligible patients at diagnosis and the subgroups of patients according to their responses after three courses of CHOP. Among the 286 patients, 110 (38 percent) had com-

Table 1. Characteristics of the 286 Patients According to Their Responses after Three Courses of CHOP Chemotherapy.*

CHARACTERISTIC	COMPLETE REMISSION (N=110)	PARTIAL REMISSION, RANDOMIZED CHOP (n=35)	PARTIAL REMISSION, RANDOMIZED Transplantation (n=34)	PARTIAL REMISSION, NONRANDOMIZED (N=37)	PARTIAL REMISSION, MARROW INVOLVEMENT (N=27)	PROGRESSION OR NO RESPONSE (N=43)	ALL PATIENTS (N=286)
		percentage of patients in group					
Sex							
Male	64	63	56	54	70	74	64
Female	36	37	44	46	30	26	36
Tumor histology†							
Follicular, large cell	5	17	4	8	26	7	9
Diffuse, small cleaved cell	4	3	3	5	19	12	6
Diffuse, mixed	11	14	23	8	33	21	16
Diffuse, large cell	39	26	38	40	11	23	33
Unclassifiable, intermediate grade	4	3	9	10	4	3	5
Immunoblastic	34	20	20	24	7	26	25
Unclassifiable, high grade	3	17	3	5	0	9	6
Stage							
II	53	43	50	35	0	23	40
III	24	26	18	24	0	14	20
IV	23	31	32	41	100	63	40
Extranodal sites (no.)							
0	64	49	50	57	48	30	53
1	23	37	35	16	23	42	28
2–4	13	14	15	27	29	28	19
Bone marrow involvement							
No	93	94	89	91	0	67	80
Yes	7	6	11	9	100	33	20
Immunologic phenotype							
B-cell	64	77	79	62	67	67	68
T-cell	20	3	9	24	11	19	16
Neither	3	0	0	0	0	0	1
Unknown	13	20	12	14	22	14	15
B symptoms							
Absent	60	68	56	51	63	42	57
Present	40	32	44	49	37	58	43
Lactate dehydrogenase (U/liter)							
<250	42	17	20	27	26	23	30
250 to <750	51	59	62	62	67	49	56
≥750	7	24	18	11	7	28	14
Bulky disease (tumor ≥10 cm)							
No	76	54	41	59	63	69	65
Yes	24	46	59	41	37	31	35
Performance status‡							
0	49	43	38	46	56	33	45
1	43	51	53	41	41	39	44
2–4	8	6	9	13	3	28	11
International Index§							
Low	25	3	9	10	0	7	13
Low intermediate	43	53	47	38	26	30	40
High intermediate	28	41	41	41	70	37	39
High	4	3	3	11	4	26	8

*The median age of the patients was 45 years (range, 15 to 60).

†According to the classification system of the Working Formulation.[21]

‡According to the classification system of the World Health Organization.

§As defined by the International Non-Hodgkin's Lymphoma Prognostic Factors Project.[23]

plete remissions after the first three courses of CHOP, 133 (47 percent) had partial remissions, and 43 (15 percent) had either no response or progression of disease (Table 2). Of the 133 patients who had partial responses, 27 still had lymphoma in the bone marrow and were therefore ineligible for randomization. Thus, 106 patients qualified for randomization, and 69 of them (65 percent) were randomized. Thirty-seven patients (35 percent) were not randomized for the following reasons: refusal by the patient (22 patients), psychological reasons (4), medical reasons (5), and administrative errors (6).

Response of the Randomized Patients

Table 1 shows the clinical features of the patients randomly assigned to CHOP or bone marrow transplantation. The two groups were well balanced, especially with regard to the prognostic variables defined by the international index established by the International Non-Hodgkin's Lymphoma Prognostic Factors Project.[23] At randomization, 35 patients were assigned to continue standard treatment with CHOP, and 34 patients were assigned to transplantation. However, eight patients assigned to the transplantation group did not proceed to that treatment; three declined the treatment, and five had progressive disease. Of the patients assigned to CHOP who continued that treatment, seven patients did not complete all eight courses because of progressive disease.

The conditioning regimen for transplantation was started a median of 27 days (range, 17 to 60) after the fourth course of CHOP. In fact, 26 of 28 patients started the conditioning regimen within 39 days after the fourth course of CHOP. The results were analyzed on an intention-to-treat basis. Twenty-six of the 35 patients (74 percent) randomly assigned to CHOP had complete remissions, as compared with 23 of the 34 patients (68 percent) randomly assigned to transplantation (Table 2). This difference was not significant (P=0.54). The exclusion of the 15 patients who did not complete the treatment as planned could have biased the outcome, because 12 of these patients had early progressive disease. Analysis according to actual treat-
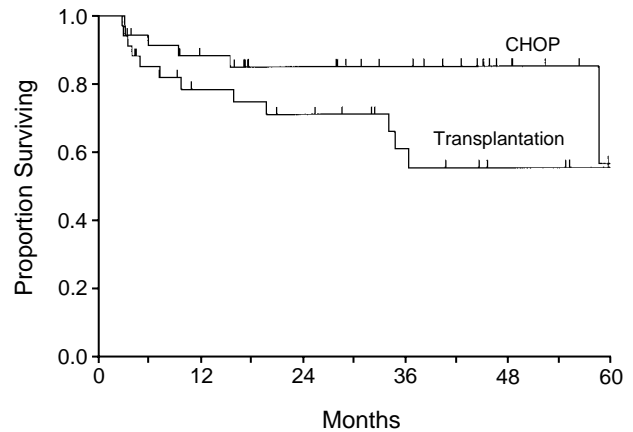

Figure 1. Overall Survival from the Time of Randomization, According to Treatment Group.

Among 35 patients assigned to receive eight courses of CHOP and 34 patients assigned to receive high-dose chemoradiotherapy and autologous bone marrow transplantation, there were 6 and 12 deaths, respectively.

ments did not change the results; among the 28 patients in the CHOP group who completed eight courses of CHOP, 26 reached complete remission, 6 relapsed, and only 1 died, whereas among the 26 patients in the transplantation group who underwent transplantation, 23 reached complete remission, 7 relapsed, and 9 died.

Survival of the Randomized Patients

The mean (±SE) estimated overall survival four years from randomization was 85±6 percent in the CHOP group and 56±10 percent in the transplantation group (Fig. 1). Disease-free survival at four years was 72±10 percent in the CHOP group and 60±12 percent in the transplantation group. Event-free survival at four years was 53±9 percent in the CHOP group and 41±10 percent in the transplantation group (Fig. 2). There were no significant differences between the two treatment methods in overall survival (hazard ratio for transplantation vs. CHOP, 2.2; 95 percent confidence interval, 0.82 to 5.9; P=0.12), disease-free survival (hazard ratio, 1.5; 95 percent confidence interval, 0.49 to 4.3; P=0.50), or event-free survival (hazard ratio, 1.3; 95 percent confidence interval, 0.66 to 2.61; P=0.43). Six patients in the CHOP group and seven patients in the transplantation group relapsed. Six patients assigned to the CHOP group died, all of lymphoma, whereas 12 patients in the transplantation group died, 10 of lymphoma and 2 of treatment-related toxic effects.

Response of the Nonrandomized Patients

The 110 patients in complete remission, the 27 patients with partial responses and marrow involvement, and the 37 nonrandomized patients

Table 2. Treatment Outcome According to the Response after Three Courses of CHOP Chemotherapy.*

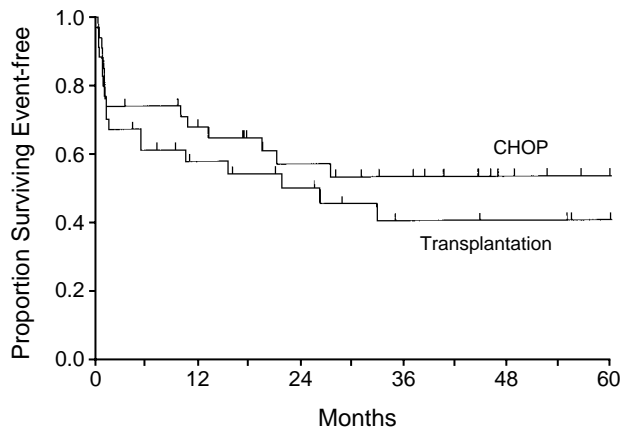| VARIABLE	RESPONSE AND RANDOMIZATION STATUS					
	COMPLETE REMISSION (N=110)	PARTIAL REMISSION, RANDOMIZED		PARTIAL REMISSION, NONRAN-DOMIZED (N=37)	PARTIAL REMISSION, MARROW INVOLVEMENT (N=27)	PROGRESSION OR NO RESPONSE (N=43)
		CHOP (n=35)	Trans-plantation (n=34)			
			no. of patients			
Complete remission after CHOP or transplantation	NA	26	23	23	10	NA
Relapse after complete remission	44	6	7	5	4	NA
Death	35	6	12	14	9	29
Treatment-related toxic effects	4	0	2	2	3	1
Lymphoma	30	6	10	11	4	23
Other	1	0	0	1	2	5

*NA denotes not applicable.

Figure 2. Event-free Survival from the Time of Randomization, According to Treatment Group.

Among 35 patients assigned to receive eight courses of CHOP and 34 patients assigned to receive high-dose chemoradiotherapy and autologous bone marrow transplantation, there were 15 and 18 treatment failures, respectively.

with partial responses but no marrow involvement were all scheduled to continue with another five courses of CHOP (Table 2). Among the 110 patients in complete remission, 44 patients (40 percent) relapsed during CHOP treatment or thereafter. Among the 27 patients with partial responses but with bone marrow involvement, 10 patients (37 percent) had complete remissions. The rate of complete remission in these patients was significantly lower (P=0.006) than that in the patients who had partial remissions but who had no marrow infiltration. Among the 37 nonrandomized patients with partial responses and no bone marrow involvement, 23 (62 percent) had complete remissions during CHOP therapy. For these 37 patients, overall, disease-free, and event-free survival at four years was 55, 70, and 43 percent, respectively.

Survival of the Eligible Patients

Among all 286 study patients, actuarial overall survival at four years was 59 ± 3 percent (Fig. 3), and for the 192 patients with complete responses disease-free survival at four years was estimated to be 58 ± 3 percent. For the nonrandomized group of patients with fast responses (those in complete remission after three courses of CHOP), disease-free survival at four years was 54 ± 5 percent. Table 2 shows the causes of death in the various treatment groups. Figure 4 shows that there was no significant difference in survival between patients in complete remission after three courses of CHOP (those with fast responses) and patients with partial (slow) responses. The outcome in patients with either no response or progressive disease was significantly worse (P<0.001) than in patients who had complete or partial remissions.

Analysis of Prognostic Factors

Multivariate analysis showed that for all eligible patients enrolled in the study, the following prognostic factors were predictive of overall survival: Ann Arbor

stage (II vs. III vs. IV; P<0.001), histologic grade of cancer (intermediate vs. high; P=0.01), serum concentration of lactate dehydrogenase (<750 vs. ≥750 U per liter; P<0.001), and performance status (0 or 1 vs. 2, 3, or 4; P<0.001). Other prognostic factors did not have additional predictive value. Except for the grade of cancer, these prognostic factors agree with those defined by the international index.[23] Adjustment for these factors did not affect the nonsignificant differences between the randomized treatment groups.

DISCUSSION

We assessed the value of early intervention with high-dose, marrow-ablative chemoradiotherapy and autologous bone marrow transplantation in patients with disseminated, aggressive non-Hodgkin's lymphoma who had slow responses to standard CHOP chemotherapy. There were no significant differences in the rates of complete remission, estimated overall survival, disease-free survival, and event-free survival between patients who received bone marrow transplantation and those who continued with the conventional therapy.

The number of patients randomized was only sufficient to show the expected difference in outcome of 35 percent between the two treatment methods. The relative risk of death in the transplantation group as compared with the CHOP group was 2.2 (95 percent confidence interval, 0.8 to 5.9). This value corresponds to a difference in the probability of overall survival of −23 percent (95 percent confidence interval, +5 percent to −58 percent), if a 70 percent probability of long-term overall survival in the CHOP group is assumed. This result implies that a small benefit of transplantation cannot be excluded, but any substantial benefit is extremely unlikely. Considering the cost of bone marrow transplantation and the failure of this very intensive treatment to improve overall survival and disease-free survival, we conclude that the early use of transplantation in patients with slow responses is not useful. It remains to be clarified whether autologous bone marrow transplantation may have a role among patients in the recently defined high-risk subgroup of the international
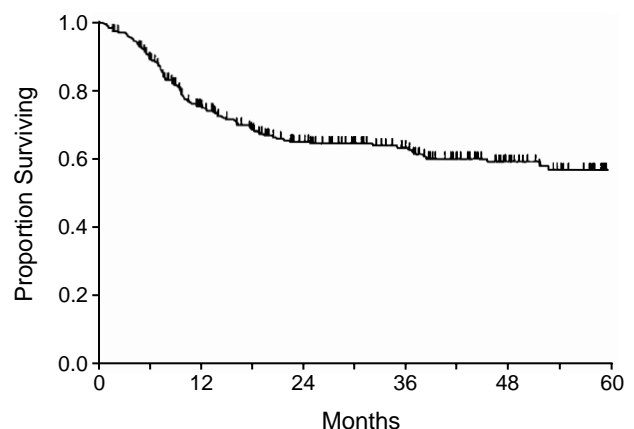

Figure 3. Overall Survival among All Eligible Patients from the Start of the First Course of CHOP.

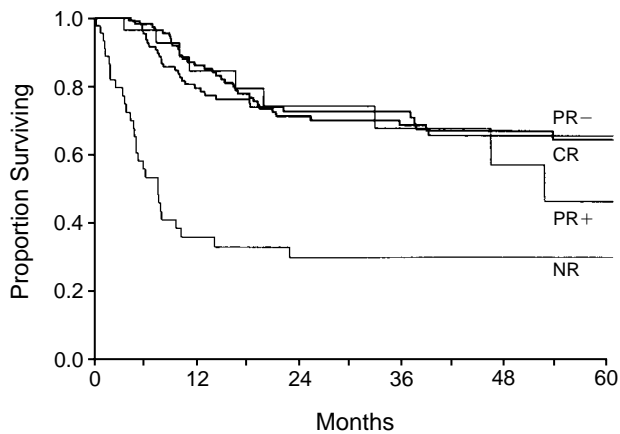Among 286 eligible patients, there were 105 deaths.

Figure 4. Overall Survival from the Time of Evaluation among All Eligible Patients, According to the Response after Three Courses of CHOP.

PR− denotes partial remission without bone marrow involvement, PR+ partial remission with bone marrow involvement, CR complete remission, and NR progressive disease or no response.

index who have very poor survival after conventional first-line chemotherapy or among patients with a response but with proved residual disease after first-line chemotherapy.

When our study began, it was suggested that patients with aggressive non-Hodgkin's lymphoma[19,20] or other hematologic cancers[24,25] who had complete responses rapidly might have a better probability of cure than those with slower responses to chemotherapy. A recent comprehensive review of several phase 2 studies supports this hypothesis.[26] The ability to stratify patients early in the course of disease as being at either high or low risk appears clinically important; high-risk patients may benefit from experimental approaches such as high-dose therapy with transplantation, whereas low-risk patients should not receive unusually hazardous treatments. With its international index, the International Non-Hodgkin's Lymphoma Prognostic Factors Project has defined factors present at diagnosis that distinguish patients in groups with good, intermediate, or poor survival.[23] The value of these prognostic factors was confirmed in our study; application of the international index to all study patients gave probabilities of four-year overall survival comparable to those reported by the international index,[23] ranging from 78 percent in the low-risk group to 24 percent in the high-risk group (data not shown).

Although 106 patients were eligible for random assignment to transplantation or to another five courses of CHOP, only 69 patients (65 percent) were actually randomized. Thus, 37 patients were not randomized, mainly because the patients declined randomization. There were no significant differences in rates of complete remission or overall, disease-free, or event-free survival between patients who were randomly assigned to the two treatment groups, or among the two groups and the 37 nonrandomized patients who also received five more courses of CHOP. In fact, the estimated rates of disease-free and event-free survival at four years were 72 and 53 percent, respectively, for the randomized CHOP group and 60 and 41 percent for the transplantation group, as compared with 70 and 43 percent for the 37 nonrandomized patients. Procedure-related deaths occurred in 6 percent of the transplantation group; mortality was similar (5 percent) in the nonrandomized CHOP groups. Probably by chance, procedure-related deaths did not occur in the randomized CHOP group. Furthermore, 54 percent of the nonrandomized group of patients with fast responses (those in complete remission after three courses of CHOP) who continued with another five courses of CHOP were alive without disease at four years. Thus, those who responded slowly did as well as those who responded rapidly. Apparently, it was the fact that they had complete remissions that was predictive of outcome, rather than the time required to attain them. Although most phase 2 studies of the value of a rapid response reported that the speed with which patients achieved complete remissions was an important prognostic factor,[19,20,26] two studies could not confirm this finding.[26] This discrepancy may be caused by the follow-up periods, which were relatively short in most of these studies.

We are aware of only two other studies in which high-dose therapy and autologous bone marrow transplantation were compared with chemotherapy in patients with aggressive non-Hodgkin's lymphoma. In these studies transplantation was not used early, but was applied after the completion of conventional chemotherapy. A multicenter Italian study[27] compared high-dose chemotherapy and transplantation with salvage chemotherapy in patients who were in partial remission after the completion of first-line chemotherapy. The results suggested a better disease-free survival for the transplantation group. A multicenter French study[28] compared intensive, but not marrow-ablative, chemotherapy and bone marrow transplantation with intensive sequential chemotherapy in patients who were in complete remission after first-line chemotherapy. This study found no difference in disease-free survival between the two treatments. Although both studies differ from this one on several points, their data suggest that high-dose therapy combined with bone marrow transplantation does not improve outcome in patients who are in either very good partial remission (with residual abnormalities of unknown importance) or complete remission after chemotherapy.

We conclude that the early use of marrow-ablative chemoradiotherapy with autologous bone marrow transplantation offers no significant benefit in patients with aggressive non-Hodgkin's lymphoma who have responded slowly to first-line chemotherapy. Furthermore, the rapidity with which complete remission is achieved appears to have no prognostic importance.

REFERENCES

1. Armitage JO. Treatment of non-Hodgkin's lymphoma. N Engl J Med 1993; 328:1023-30.
2. Laurence J, Coleman M, Allen SL, Silver RT, Pasmantier M. Combination chemotherapy of advanced diffuse histiocytic lymphoma with the six-drug COP-BLAM regimen. Ann Intern Med 1982;97:190-5.
3. Skarin AT, Canellos GP, Rosenthal DS, et al. Improved prognosis of diffuse histiocytic and undifferentiated lymphoma by use of high dose methotrexate alternating with standard agents (M-BACOD). J Clin Oncol 1983; 1:91-8.
4. Fisher RI, DeVita VT Jr, Hubbard SM, et al. Diffuse aggressive lymphomas: increased survival after alternating flexible sequences of ProMACE and MOPP chemotherapy. Ann Intern Med 1983;98:304-9.
5. Klimo P, Connors JM. MACOP-B chemotherapy for the treatment of diffuse large-cell lymphoma. Ann Intern Med 1985;102:596-602.
6. Shipp MA, Harrington DP, Klatt MM, et al. Identification of major prognostic subgroups of patients with large-cell lymphoma treated with m-BACOD or M-BACOD. Ann Intern Med 1986;104:757-65.
7. Longo DL, DeVita VT Jr, Duffey PL, et al. Superiority of ProMACE-CytaBOM over ProMACE-MOPP in the treatment of advanced diffuse aggressive lymphoma: results of a prospective randomized trial. J Clin Oncol 1991;9:25-38. [Erratum, J Clin Oncol 1991;9:710.]
8. Gordon LI, Harrington D, Andersen J, et al. Comparison of a second-generation combination chemotherapeutic regimen (m-BACOD) with a standard regimen (CHOP) for advanced diffuse non-Hodgkin's lymphoma. N Engl J Med 1992;327:1342-9.
9. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993;328:1002-6.
10. Salles G, Shipp MA, Coiffier B. Chemotherapy of non-Hodgkin's aggressive lymphomas. Semin Hematol 1994;31:46-69.
11. Phillips GL, Herzig RH, Lazarus HM, et al. Treatment of resistant malignant lymphoma with cyclophosphamide, total body irradiation, and transplantation of cryopreserved autologous marrow. N Engl J Med 1984;310: 1557-61.
12. Verdonck LF, Dekker AW, van Kempen ML, et al. Intensive cytotoxic therapy followed by autologous bone marrow transplantation for non-Hodgkin's lymphoma of high-grade malignancy. Blood 1985;65:984-9.
13. Philip T, Armitage JO, Spitzer G, et al. High-dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults with intermediate-grade or high-grade non-Hodgkin's lymphoma. N Engl J Med 1987;316:1493-8.
14. Takvorian T, Canellos GP, Ritz J, et al. Prolonged disease-free survival after autologous bone marrow transplantation in patients with non-Hodgkin's lymphoma with a poor prognosis. N Engl J Med 1987;316:1499-505.
15. Gribben JG, Goldstone AH, Linch DC, et al. Effectiveness of high-dose combination chemotherapy and autologous bone marrow transplantation for patients with non-Hodgkin's lymphomas who are still responsive to conventional-dose therapy. J Clin Oncol 1989;7:1621-9.
16. Philip T, Chauvin F, Armitage J, et al. Parma international protocol: pilot study of DHAP followed by involved-field radiotherapy and BEAC with autologous bone marrow transplantation. Blood 1991;77:1587-92.
17. Bosly A, Coiffier B, Gisselbrecht C, et al. Bone marrow transplantation prolongs survival after relapse in aggressive-lymphoma patients treated with the LNH-84 regimen. J Clin Oncol 1992;10:1615-23.
18. Verdonck LF, Dekker AW, de Gast GC, van Kempen ML, Lokhorst HM, Nieuwenhuis HK. Salvage therapy with ProMACE-MOPP followed by intensive chemoradiotherapy and autologous bone marrow transplantation for patients with non-Hodgkin's lymphoma who failed to respond to first-line CHOP. J Clin Oncol 1992;10:1949-54.
19. Coiffier B, Bryon P-A, Berger F, et al. Intensive and sequential combination chemotherapy for aggressive malignant lymphomas (protocol LNH-80). J Clin Oncol 1986;4:147-53.
20. Armitage JO, Weisenburger DD, Hutchins M, et al. Chemotherapy for diffuse large-cell lymphoma — rapidly responding patients have more durable remissions. J Clin Oncol 1986;4:160-4.
21. The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. Cancer 1982;49:2112-35.
22. McKelvey EM, Gottlieb JA, Wilson HE, et al. Hydroxyldaunomycin (adriamycin) combination chemotherapy in malignant lymphoma. Cancer 1976; 38:1484-93.
23. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993;329:987-94.
24. Hoelzer D, Thiel E, Löffler H, et al. Intensified therapy in acute lymphoblastic and acute undifferentiated leukemia in adults. Blood 1984;64:38-47.
25. Longo DL, Young RC, Wesley M, et al. Twenty years of MOPP therapy for Hodgkin's disease. J Clin Oncol 1986;4:1295-306.
26. Haw R, Sawka CA, Franssen E, Berinstein HL. Significance of a partial or slow response to front-line chemotherapy in the management of intermediate-grade or high-grade non-Hodgkin's lymphoma: a literature review. J Clin Oncol 1994;12:1074-84.
27. Tura S, Zinzani PL, Mazza P, et al. ABMT vs DHAP in residual disease following third generation regimens for aggressive non-Hodgkin's lymphomas. Blood 1992;80:719. abstract.
28. Haioun C, Lepage E, Gisselbrecht C, et al. Comparison of autologous bone marrow transplantation (ABMT) with sequential chemotherapy for aggressive non-Hodgkin's lymphoma (NHL) in first complete remission: a study on 464 patients (LNH87 protocol). Blood 1993;82:334. abstract.

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