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

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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.)

COMBINATION chemotherapy can cure about 45 percent of patients with disseminated intermediate-grade or high-grade non-Hodgkin's lymphoma. 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), but in two large, multicenter, randomized phase 3 trials 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. High-dose chemoradiotherapy with autologous bone marrow transplantation may, however, cure some of these patients if they have disease that responds to chemotherapy.

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.\textsuperscript{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),\textsuperscript{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-melanotic 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 hepatic 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 days 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;\textsuperscript{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 \( \geq 10 \) cm) at diagnosis, were then 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, irradiation, 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.\textsuperscript{19} At least 2 \( \times 10^8 \) 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 (200 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.\textsuperscript{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...
CHOP VS. BONE MARROW TRANSPLANTATION FOR NON-HODGKIN'S LYMPHOMA

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

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>COMPLETE REMISSION (N = 110)</th>
<th>PARTIAL REMISSION, RANDOMIZED</th>
<th>PARTIAL REMISSION, NON-RANDOMIZED (N = 37)</th>
<th>PROGRESSION, MARROW INVOLVEMENT (N = 27)</th>
<th>PROGRESSION, NO RESPONSE (N = 43)</th>
<th>ALL PATIENTS (N = 286)</th>
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<td>63</td>
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†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.22
¶As defined by the International Non-Hodgkin's Lymphoma Prognostic Factors Project.23

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 criterion 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-
complete 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.25 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 treatments 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
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. 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 −38 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
was confirmed in our study; application of the interna-
distinguish patients in groups with good, intermediate,
high-dose therapy with transplantation, whereas low-
or poor survival. The value of these prognostic factors
Project has defined factors present at diagnosis that
risk patients should not receive unusually hazardous
may benefit from experimental approaches such as
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 Interna-
tional Non-Hodgkin's Lymphoma Prognostic Factors
Project has defined factors present at diagnosis that
distinguish patients in groups with good, intermediate,
or poor survival. The value of these prognostic factors
was confirmed in our study; application of the interna-
tional index to all study patients gave probabilities of
four-year overall survival comparable to those reported
by the international index, 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 as-
ignment 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 com-
plete 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 random-
ized CHOP group and 60 and 41 percent for the trans-
plantation 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 nonran-
domized CHOP groups. Probably by chance, procedure-related deaths did not occur in the randomized
CHOP group. Furthermore, 54 percent of the nonran-
domized 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 rap-
idly. 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 remis-
sions was an important prognostic factor, two studies
could not confirm this finding. This discrep-
ancy 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 trans-
plantation 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 che-
motherapy. A multicenter Italian study27 compared
high-dose chemotherapy and transplantation with sal-
vage chemotherapy in patients who were in partial
remission after the completion of first-line chemothera-
py. The results suggested a better disease-free survival
for the transplantation group. A multicenter French
study29 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 dif-
fer 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 res-
dual abnormalities of unknown importance) or com-
plete remission after chemotherapy.

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

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