

HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS BONE MARROW TRANSPLANTATION COMPARED WITH MACOP-B IN AGGRESSIVE B-CELL LYMPHOMA

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ABSTRACT

Background We compared a regimen of six chemotherapeutic agents administered sequentially at high doses, followed by myeloablative treatment and bone marrow transplantation, with a regimen of methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B) as initial or salvage treatment for adults with diffuse large-cell lymphoma.

Methods Ninety-eight eligible patients with diffuse large-cell lymphoma of the B-cell type were randomly assigned to receive either MACOP-B (50 patients) or high-dose sequential therapy (48 patients). If the assigned treatment failed, the study design allowed patients to cross over to the other treatment group.

Results After a median follow-up of 55 months, the patients given high-dose sequential therapy, as compared with those treated with MACOP-B, had significantly higher rates of complete response (96 percent vs. 70 percent, $P=0.001$), freedom from disease progression (84 percent vs. 49 percent, $P<0.001$), freedom from relapse (88 percent vs. 70 percent, $P=0.055$), and event-free survival (76 percent vs. 49 percent, $P=0.004$). The difference in overall survival at seven years, which also favored the group assigned to high-dose sequential therapy, was marginally significant (81 percent vs. 55 percent, $P=0.09$).

Conclusions High-dose sequential therapy is superior to standard-dose MACOP-B for patients with diffuse large-cell lymphoma of the B-cell type. (N Engl J Med 1997;336:1290-7.)

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HIGH-DOSE chemotherapy for non-Hodgkin's lymphomas is feasible because of improvements in patient care, especially the use of hematopoietic growth factors and stem-cell support.¹⁻⁴ In late 1987, we started a randomized study to compare MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin)⁵ with a regimen of high-dose sequential chemotherapy, followed by myeloablative therapy and hematopoietic stem-cell support, as initial treatment for high-risk, diffuse B-cell lymphomas.

The high-dose regimen we used entailed the administration of several non-cross-resistant drugs,

each at the maximal tolerated dose, mainly as single agents, within the shortest possible interval. The purpose of this high-dose sequential regimen is to prevent the emergence of drug-resistant lymphoma cells.⁶ The applicability and activity of this approach have been tested in pilot studies in patients with refractory or relapsed Hodgkin's disease⁷ or multiple myeloma.⁸

We report here a comparison of MACOP-B with high-dose sequential therapy (Fig. 1) in patients with B-cell non-Hodgkin's lymphomas and a poor prognosis. The aim of the study was to determine the relative efficacy of high-dose sequential therapy as either first-line or salvage treatment.

METHODS

Eligibility

Patients 17 to 60 years of age were eligible if they had measurable, biopsy-confirmed non-Hodgkin's lymphoma of the B-cell immunophenotype, group G (diffuse large-cell lymphoma) or H (diffuse large-cell immunoblastic lymphoma), according to the working formulation for the classification of lymphoma.⁹ Other criteria for eligibility included bulky disease classified as stage I or II (any mass more than 10 cm in diameter), stage III, or stage IV, according to the Ann Arbor system; an Eastern Cooperative Oncology Group performance status of 0 through 4; and normal cardiac, renal, pulmonary, and hepatic function on the basis of routine clinical and laboratory examinations, radionuclide ventriculography, and lung-function tests. Patients were excluded if they had a positive serologic test for hepatitis B or C virus or the human immunodeficiency virus, liver cirrhosis, any follicular component in their biopsy specimens, lymphoma-cell infiltration of the bone marrow (detected morphologically), or a T-cell immunophenotype. The protocol was approved by the institutional review board of each participating center, and written informed consent was obtained from all patients.

After the pretreatment evaluation, the patients were stratified according to the presence or absence of bulky disease (defined as any mass more than 10 cm in diameter) and the number of sites of extranodal disease (none or one vs. more than one).¹⁰ The pa-

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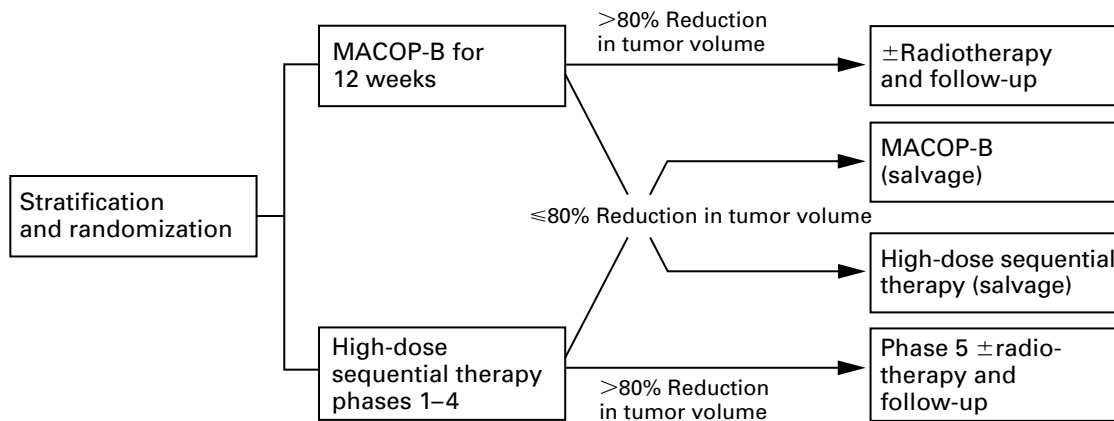


Figure 1. Study Design for the Comparison of High-Dose Sequential Therapy with MACOP-B in the Treatment of B-Cell Lymphoma. In phase 5 of high-dose sequential therapy, high-dose melphalan was administered plus either total-body irradiation (in the first 30 patients) or mitoxantrone (in the last 18 patients), followed by hematopoietic-progenitor-cell autografting.

tients were then randomly assigned to receive either MACOP-B or high-dose sequential therapy as initial treatment. Patients who had a relapse or a progression of disease during treatment or in whom the size of measurable lesions was reduced by 80 percent or less after either 12 weeks of MACOP-B or high-dose etoposide were crossed over to the other treatment group (Fig. 1).

Of the 101 patients who were enrolled, 3 were excluded at the final assessment because they had concomitant liver disease and were thus ineligible. Of the 98 eligible patients, 50 were assigned to receive MACOP-B, and 48 were assigned to receive high-dose sequential therapy. The characteristics of the 98 patients are shown in Table 1. The two groups were similar with regard to the main prognostic variables, with the exception of the performance status. When prognostic indexes were considered,^{11,12} there was a non-significant difference favoring the MACOP-B group.

Treatment Regimens

MACOP-B was administered according to the regimen described in the original report on the treatment.⁵ Except in the case of disease progression, all patients had to complete the 12-week course of MACOP-B and undergo staging afterward. Starting 15 to 30 days after the final MACOP-B cycle, consolidation radiotherapy was delivered to areas where prior lesions had been larger than 5 cm in diameter and to areas of documented or suspected residual disease, defined as any radiologic or gallium-67 scintigraphic evidence of an abnormality remaining in an area of previously detected disease. To be eligible for radiotherapy, patients had to have a reduction of more than 80 percent in the dimensions of measurable lesions after the completion of MACOP-B treatment. Patients with a reduction of 80 percent or less and those with stable or progressive disease were given high-dose sequential therapy as salvage treatment. Radiotherapy was delivered in a total dose of 3060 to 3420 cGy, given in 17 to 19 daily fractions of 180 cGy each, with the use of a 6-MeV linear accelerator.

Table 2 shows the regimen of high-dose sequential therapy. The first phase consisted of one or two courses of doxorubicin (50 mg per square meter of body-surface area administered intravenously on day 1), prednisone (40 mg per square meter orally from day 1 to day 21), and vincristine (1.4 mg per square meter intravenously on days 1, 8, and 15). During this phase, patients with epidural disease or sinus or testicular involvement received four weekly doses of intrathecal methotrexate at a dose of 12.5 mg. The regimen of high-dose cyclophosphamide, high-dose methotrexate with leucovorin rescue, and high-dose etoposide has been reported in detail previously.^{4,13,14} The dose of cyclo-

phosphamide was calculated according to the corrected ideal body weight, as follows:

$$[(\text{actual weight} - \text{ideal weight}) \times 25 \text{ percent}] + \text{ideal weight}.$$

Patients underwent one to four (median, three) leukaphereses during the rapid recovery phase that followed the administration of high-dose cyclophosphamide plus either granulocyte-macrophage colony-stimulating factor or granulocyte colony-stimulating factor, with the aim of collecting at least 8×10^6 CD34+ cells per kilogram of body weight. In addition, 28 patients underwent harvesting of at least 2×10^8 nucleated bone marrow cells.

For the first 30 patients assigned to high-dose sequential therapy, the myeloablative phase consisted of fractionated total-body irradiation (a total dose of 12.5 Gy, given in five fractions on days 1 through 3) and 120 to 140 mg of melphalan per square meter, administered on day 4 by rapid intravenous infusion in three fractions given every two hours. Both autologous cryopreserved bone marrow and peripheral-blood nucleated cells were thawed and rapidly infused 24 hours after the beginning of the administration of melphalan. The toxic effects of total-body irradiation were substantial. Approximately half the patients had severe mucositis (grade 3 or 4), and three patients died of complications due to this treatment (see the Results section). For this reason, the last 18 patients assigned to high-dose sequential therapy received as the final course 60 mg of mitoxantrone per square meter, administered intravenously over a period of one hour in three fractions given every two hours, followed by melphalan (180 mg per square meter) on day 4 and autografting on day 5. After they had recovered from the high-dose melphalan, these 18 patients received consolidation radiotherapy according to the indications and procedures described above, starting 30 to 100 days after transplantation. For the first 30 patients receiving total-body irradiation, a total dose of 2520 cGy was administered in 14 daily fractions of 180 cGy each.

Supportive care during the entire course of high-dose sequential therapy has been described in detail elsewhere.^{7,8} Two important components of supportive care were the administration of growth factor (either granulocyte-macrophage colony-stimulating factor or granulocyte colony-stimulating factor, given subcutaneously or intravenously at a dose of 5 µg per kilogram per day, as shown in Table 2) and prophylactic acyclovir. Acyclovir (250 mg per square meter given intravenously twice per day or 800 mg given orally twice per day) was given after each course of high-dose myelotoxic therapy to prevent a reactivation of herpes simplex virus infection and other less well defined complications of suspected viral origin.

TABLE 1. CHARACTERISTICS OF 98 PATIENTS WITH B-CELL LYMPHOMA ASSIGNED TO RECEIVE TREATMENT WITH MACOP-B OR HIGH-DOSE SEQUENTIAL THERAPY.

CHARACTERISTIC	MACOP-B (N=50)	HIGH-DOSE SEQUENTIAL THERAPY (N=48)
Median age (range) — yr	35 (17–60)	34 (18–59)
	% of patients*	
Female sex	56	58
Performance status (ECOG 2 or 3)†	68	87‡
Histologic group		
G	88	91
H	12	10
Stage		
I	12	2§
II	20	26
III or IV	68	72
Extranodal disease	70	78
Bulky disease	70	76
Systemic symptoms	42	46
High lactate dehydrogenase level	74	78
Coiffier's index¶		
1	12	2
2	16	15
3	72	83
Age-adjusted international index		
Low risk	2	0
Low-intermediate risk	24	6**
High-intermediate risk	36	48
High risk	38	46

*Percentages are for the total number of patients in each category. Percentages may not sum to 100 because of rounding.

†ECOG denotes Eastern Cooperative Oncology Group.

‡P=0.03.

§P=0.10.

¶The index is described in Coiffier et al.¹¹

||The index is described in a report from the International Non-Hodgkin's Lymphoma Prognostic Factors Project.¹²

**P=0.06.

Response to Treatment and Follow-up

All patients underwent repeated evaluations to detect disease during and after therapy. For patients who received consolidation radiotherapy, the final assessment of a response was made after its completion, according to standard criteria.¹⁵ Residual lymph nodes measuring up to 1 cm in diameter were considered to be uninvolved. Larger lymph nodes in the area of prior bulky disease that were scintigraphically normal and failed to enlarge over a period of three months after therapy were also considered to be uninvolved. Follow-up evaluation consisted of physical examination, biochemical analysis, and chest radiography or computed tomographic scanning or both, performed at least every six months during the first two years and annually thereafter.

Statistical Analysis

Our starting assumption was that any complex treatment, including autotransplantation, would be justified only if it offered a large advantage over an optimal standard treatment. Therefore,

the study was designed to permit the detection of a 25 percent improvement in the rate of freedom from disease progression at three years (with failure defined as an incomplete response to treatment or a relapse after a prior complete remission), with a one-sided test, a significance level of 0.05, and a statistical power of 80 percent. The following end points were also analyzed: freedom from relapse, with failure defined as a relapse after a prior complete remission; event-free survival, with failure defined as an incomplete response, a relapse, a second cancer, or death from any cause; and overall survival, with failure defined as death from any cause.

The characteristics of the patients and their responses to treatment were compared by chi-square tests or Fisher's exact test, depending on the size of the sample evaluated. The distribution of outcomes was estimated from the date on which drug therapy was started, with the Kaplan-Meier product-limit method.¹⁶ Differences between treatment groups were tested with the log-rank test,¹⁷ and all reported P values are two-sided. The 95 percent confidence intervals for responses to treatment and outcomes were calculated with standard statistical procedures. The median follow-up at the time of the current analysis (as of April 1996) was 55 months (range, 13 to 103).

RESULTS

Response to Initial Treatment

Among the 48 patients who received high-dose sequential therapy plus radiotherapy as the initial treatment, 46 (96 percent; 95 percent confidence interval, 86 to 99 percent) had complete responses, and 2 (4 percent) had partial responses.¹⁵ Of the 50 patients who received MACOP-B plus radiotherapy, 35 (70 percent; 95 percent confidence interval, 55 to 82 percent) had complete responses by the end of the treatment, 13 had partial responses, and 2 had less-than-partial responses or progression of lymphoma. The difference in the rate of complete responses in the two groups was statistically significant (P=0.001).

Figure 2 shows that at seven years, the rate of freedom from progression of disease was 84 percent (95 percent confidence interval, 71 to 97 percent) for the patients receiving high-dose sequential therapy and 49 percent (95 percent confidence interval, 32 to 65 percent) for those receiving MACOP-B (P<0.001); the event-free survival was 76 percent (95 percent confidence interval, 60 to 89 percent) for the patients receiving high-dose sequential therapy and 49 percent (95 percent confidence interval, 32 to 65 percent) for those receiving conventional treatment with MACOP-B (P=0.004). The higher rates of complete remission and freedom from progression of disease among the patients assigned to high-dose sequential therapy meant that the rate of freedom from relapses was higher among these patients (88 percent; 95 percent confidence interval, 74 to 100 percent) than among those receiving MACOP-B (70 percent; 95 percent confidence interval, 50 to 89 percent; P=0.055). The results of an intention-to-treat analysis of data from all 101 initially randomized patients were similar (data not shown).

TABLE 2. TREATMENT PLAN FOR HIGH-DOSE SEQUENTIAL THERAPY.*

PHASE	DAY OF PHASE																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1																					
Doxorubicin (50 mg/m ² intravenously)	•																				
Prednisone (40 mg/m ² orally)	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Vincristine (1.4 mg/m ² intravenously)	•							•							•						
2																					
Cyclophosphamide (7 g/m ² intravenously)	•																				
G-CSF or GM-CSF (5 μg/kg subcutaneously)†‡		•	•	•	•	•	•	•	•	•	•	•	•	•	(•)	(•)					
Leukapheresis (≥8×10 ⁶ CD34+ cells/kg)‡														•	(•)	(•)					
Bone marrow harvesting (≥2×10 ⁸ cells/kg)																•					
3																					
Vincristine (1.4 mg/m ² intravenously)	•																				
Methotrexate (8 g/m ² intravenously)	•																				
Leucovorin (9 mg/m ² every 6 hr intravenously [12 doses])		•	•	•																	
4																					
Etoposide (2 g/m ² intravenously)	•																				
G-CSF or GM-CSF (5 μg/kg subcutaneously) (with TBI)				•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
5 (with TBI)																					
TBI (2.5 Gy every 12 hr [5 doses])	•	•	•																		
Melphalan (120–140 mg/m ² intravenously)				•																	
Autografting (peripheral-blood progenitor cells ± bone marrow cells intravenously)§					•																
G-CSF or GM-CSF (5 μg/kg intravenously) (without TBI)						•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
5 (without TBI)																					
Mitoxantrone (60 mg/m ² intravenously)	•																				
Melphalan (180 mg/m ² intravenously)				•																	
Autografting (peripheral-blood progenitor cells ± bone marrow cells intravenously)§					•																
G-CSF or GM-CSF (5 μg/kg intravenously)						•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

*Each subsequent phase was started when the neutrophil count was ≥1.5×10⁹ per liter, the platelet count was ≥100×10⁹ per liter, and there was no liver toxicity of a grade higher than 1. Each vertical bar indicates the anticipated end of the cycle. TBI denotes total-body irradiation.

†Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) was administered until the neutrophil count was ≥1.0×10⁹ per liter for three consecutive days or until the last post-cyclophosphamide leukapheresis had been performed.

‡The leukapheresis procedures on days 14 and 15 were performed only if they were required in order to collect the optimal amount of CD34+ cells per kilogram.

§The last 13 patients underwent autografting with peripheral-blood progenitor cells only.

Response to Salvage Treatment

Five patients who initially received high-dose sequential therapy did not have complete responses (two patients) or had relapses (three patients). None of these patients had complete responses after salvage treatment with MACOP-B, and all five died because of progressive disease. Of the 23 patients who did not have responses to initial treatment with MACOP-B or who subsequently relapsed, 6 either refused high-dose salvage therapy or could not receive it because of a poor performance status at the time of crossover, 3 started to receive high-dose salvage therapy but could not receive the full course, and 14 received the full course. Of these 14 patients, 4 remained in complete remission for 2.5 to 6 years.

Overall Survival

With a median follow-up of 55 months, there were 9 deaths among the patients given high-dose

sequential therapy as initial treatment plus MACOP-B as salvage treatment and 18 deaths among the patients treated first with MACOP-B, with high-dose sequential therapy as a salvage option. At seven years, the estimated overall survival was 81 percent (95 percent confidence interval, 68 to 91 percent) for the patients randomly assigned to receive high-dose sequential therapy first, and 55 percent (95 percent confidence interval, 36 to 73 percent) for those assigned to MACOP-B. There was a trend toward a significant difference in overall survival between the two treatment groups in favor of the patients receiving high-dose sequential therapy as the initial treatment (P=0.09).

Treatment Characteristics

The median and average duration of the MACOP-B regimen was 13 weeks (range, 12 to 16). The duration of high-dose sequential therapy varied, because each cycle was delivered as soon as the patient

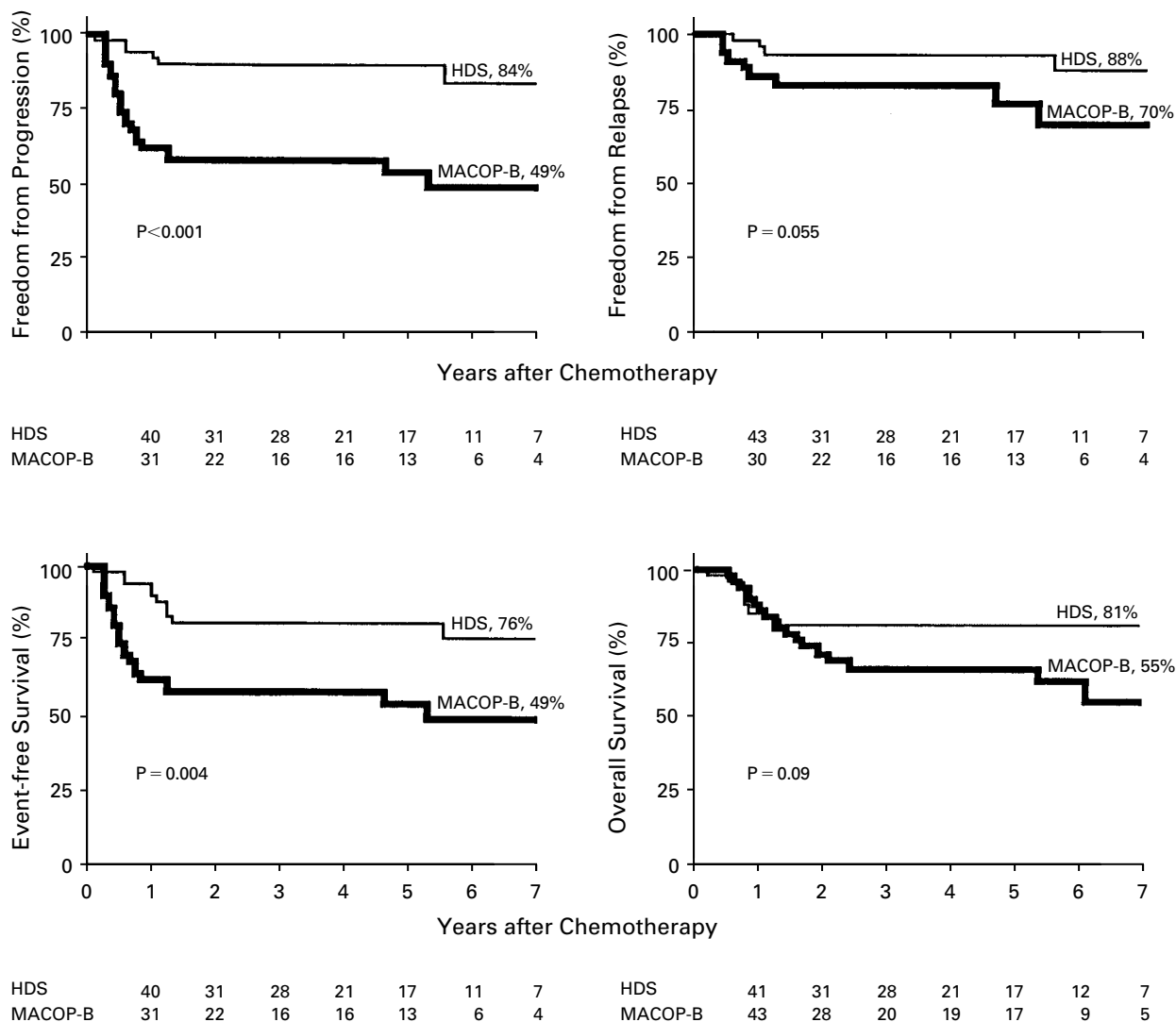


Figure 2. Kaplan-Meier Plots of Freedom from Disease Progression, Freedom from Relapse, Event-free Survival, and Overall Survival for 48 Patients Initially Assigned to High-Dose Sequential Therapy (HDS) and 50 Assigned to MACOP-B.

The initial number of patients in complete remission and at risk for relapse was 46 for HDS and 35 for MACOP-B. The median follow-up was 55 months. The number of patients at risk is shown below each time point. Percentages at right are for each category of survival (free from disease progression, free from relapse, event-free, and overall) at seven years.

had recovered from the hematologic and nonhematologic toxic effects of the previously administered drug. The median time from the administration of cyclophosphamide to the administration of melphalan was 55 days (range, 43 to 87), and the median duration of the overall treatment (from the administration of cyclophosphamide to the final hospital discharge) was 12 weeks (range, 9 to 15). The median hospital stay was 48 days (range, 31 to 65). The last 13 patients assigned to high-dose sequential therapy completed the treatment within a median of 10 weeks (range, 9 to 13), with a median hospital stay of 36 days (range, 31 to 47).

Toxic Effects of Treatment

The hematologic and extramedullary toxic effects of treatment are shown in Tables 3 and 4, respectively. The toxic effects of MACOP-B (Table 4) were similar to those reported.⁵ The patients treated with high-dose sequential therapy had more toxic reactions than those treated with MACOP-B (Table 4), but the incidence of fatal toxic reactions in the group receiving high-dose sequential therapy (8 percent) was similar to that in the MACOP-B group (6 percent). Three second cancers developed: acute myelogenous leukemia (in continuous complete remission 20 months after allogeneic bone marrow

TABLE 3. HEMATOLOGIC TOXIC EFFECTS AND SUPPORTIVE CARE AFTER HIGH-DOSE SEQUENTIAL THERAPY.*

VARIABLE	AFTER MELPHALAN AND TBI		
	AFTER CYCLOPHOSPHAMIDE	AFTER ETOPOSIDE	OR MITOXANTRONE
Absolute neutrophil count — no. of days			
<0.1×10 ⁹ /liter	4 (0–7)	0 (0–4)	3 (0–7)
<0.5×10 ⁹ /liter (toxic grade 4)	6 (4–11)	3 (0–8)	5 (1–9)
<1.0×10 ⁹ /liter (toxic grade ≥3)	7 (4–11)	5 (0–13)	6 (3–13)
<2.0×10 ⁹ /liter (toxic grade ≥1)	7 (5–11)	5 (0–14)	7 (3–14)
Platelet count (no. of days)			
<25×10 ⁹ /liter (toxic grade 4)	0 (0–5)	0 (0–2)	2 (0–8)
<50×10 ⁹ /liter (toxic grade ≥3)	3 (0–9)	0 (0–10)	5 (1–6)
<100×10 ⁹ /liter (toxic grade ≥1)	7 (0–16)	5 (0–15)	9 (2–22)
Mean no. of platelet transfusions	0.5 (0–4)	0 (0–1)	1.8 (0–6)
Mean no. of red-cell transfusions	4 (0–8)	2.7 (0–8)	4 (0–10)
Last platelet transfusion — day			8 (6–17)
Last red-cell transfusion — day			8 (1–20)
Duration of hospital stay after chemotherapy — no. of days	17 (13–24)	12 (3–21)	16 (10–22)

*Unless otherwise specified, median values are shown, with ranges in parentheses. TBI denotes total-body irradiation.

TABLE 4. INCIDENCE OF EXTRAMEDULLARY TOXIC EFFECTS IN THE TWO TREATMENT GROUPS, ACCORDING TO TOXIC GRADE.

TOXIC EFFECT	HIGH-DOSE SEQUENTIAL THERAPY				MACOP-B			
	GRADE 1 OR 2	GRADE 3	GRADE 4	GRADE 5	GRADE 1 OR 2	GRADE 3	GRADE 4	GRADE 5
	percentage of patients							
Thrombosis*		10			2			
Documented infection	6		10	4	5	2		6
Fever of unknown origin	88	19						
Genitourinary abnormality	2	2			2			
Vomiting	81	10						
Diarrhea	33							
Mucositis	54	23	10		46	26		
Liver-enzyme abnormality	52	10				8	4	
Veno-occlusive disease	2			4				
Pulmonary abnormality		2	2					
Cardiac abnormality	8					6		
Hypertension	6							
Conjunctivitis					10			
Dermatitis					5			
Bone necrosis						5	2	
Neurologic abnormality	12	2	2			19	2	
Psychiatric impairment						2		
Hyperglycemia	6				2			

*Thrombosis was induced by catheterization.

transplantation) and bladder cancer in one patient each in the MACOP-B group and clear-cell carcinoma of the kidney in one patient assigned to high-dose sequential therapy.

DISCUSSION

In this comparison of MACOP-B and high-dose sequential therapy for aggressive B-cell lymphoma, the main exclusion criteria were an age over 60 years, morphologic evidence of lymphoma cells in bone marrow, and liver disease or viral hepatitis. The exclusion of patients with viral hepatitis was prompted by the severe toxic effects on the liver in patients with hepatitis B surface antigen who were treated with the high-dose sequential regimen as therapy in a pilot study at our institute. All patients initially assigned to high-dose sequential therapy received one or two cycles of doxorubicin, prednisone, and vincristine, with the aim of achieving rapid cytoreduction and improving performance status. When the next phase of high-dose sequential therapy began, all the patients had a performance status of 0 or 1. All the patients received consolidation radiotherapy in areas of prior lesions greater than 5 cm in diameter or residual lesions.¹⁸ Salvage chemotherapy¹⁹ was an integral part of the study, which was designed to assess the efficacy of high-dose sequential therapy as either initial or salvage treatment. By all measures used, we found that as initial treatment for large-cell lymphoma, high-dose sequential therapy was superior to MACOP-B. Moreover, the superiority of high-dose sequential therapy cannot be explained by an unbalanced distribution of prognostic factors between the two treatment groups or by poorer-than-anticipated results with the MACOP-B regimen.¹²

The original regimen of high-dose sequential therapy, which included total-body irradiation, was associated with substantial morbidity and mortality (three patients died because of toxic effects, and 40 percent of the patients had grade 3 or 4 mucositis), whereas the toxic effects of the regimen without total-body irradiation were within the range observed after induction courses of chemotherapy for acute leukemia. After a median follow-up of more than five years, the only long-lasting toxic effect was infertility.

Our results with high-dose sequential therapy are in only partial agreement with the findings of other recently reported randomized trials.²⁰⁻²⁴ The differences may be due to the inclusion of patients with widely different histologic features, the use of high-dose regimens with less-than-optimal antilymphoma activity,²⁰ and differences in the selection of patients.²⁰ Vitolo et al.²⁴ and Haioun et al.²¹ reported longer disease-free survival in the high-dose groups in their trials only for patients with lymphoma classified as high-intermediate or high risk. In the study by Verdonck et al.,²⁰ more than half the patients had

lymphoma classified as placing them at low or low-intermediate risk, according to the international prognostic index.¹² Another difference between these studies and ours is that our patients did not receive a single course of high-dose chemotherapy, but instead received multiple courses, which were started as early as possible after the diagnosis.²⁵

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