Shortened First-Line High-Dose Chemotherapy for Patients With Poor-Prognosis Aggressive Lymphoma

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Purpose: **Randomized trial LNH93-3 was conducted on patients who had poor-prognosis aggressive lymphoma and were younger than 60 years with two to three factors of the age-adjusted International Prognostic Index to evaluate the benefit of early high-dose therapy (HDT) with autologous stem-cell transplantation (ASCT).**

Patients and Methods: **Patients were randomized between doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP) chemotherapy followed by sequential consolidation and an experimental shortened treatment consisting of three cycles with escalated doses of cyclophosphamide, epirubicin, vindesine, bleomycin, and prednisone and collection of peripheral-blood stem cells. On day 60, HDT was administered with 1,3-*bis*(2-chloroethyl)-1-nitrosourea, etoposide, cytarabine, and melphalan followed by ASCT.**

Results: **Eligible patients (n = 370) with aggressive lymphoma were analyzed. For ACVBP (181 patients) and HDT (189 patients), respective complete remission rates were 64% and 63%. With a median follow-up of 60 months, 5-year overall survival and event-free survival for ACVBP and HDT were 60% ± 8% and 46% ± 8% (*P* = .007) and 52 ± 8% and 39 ± 8% (*P* = .01), respectively. Survival was independently affected by age greater than 40 years (*P* = .0003), T-cell phenotype (*P* = .009), bone marrow involvement (*P* = .003), and HDT treatment group (*P* = .04).**

Conclusion: **Early HDT with ASCT in high-risk patients was inferior to the ACVBP chemotherapy regimen. These results indicate that the received dose-intensity before HDT was too low when compared with ACVBP and HDT and was given too early.**

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TO IMPROVE THE cure rate for aggressive non-Hodgkin's lymphoma (NHL) with adverse prognostic factors, different chemotherapy regimens have been tried over the past 20 years, but none has been proved to be clearly superior to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in randomized studies.[1] However, most of those regimens were designed before the use of hematopoietic growth factor or high-dose chemotherapy (HDT) with autologous stem-cell transplantation (ASCT) and could not explore high-dose intensive treatment. Since the PARMA study on patients with chemosensitive relapses,[2] several studies have examined HDT with ASCT as first-line treatment for aggressive NHL.[3-10] Patients were selected when their responses to CHOP were considered insufficient; data obtained in those pilot studies suggested an advantage for HDT. Later, two randomized trials[11-13] showed prolonged disease-free survival (DFS), whereas one performed in slow-responding patients to CHOP failed to demonstrate any benefit.[14] However, three of those studies had limited numbers of patients,[12-14] and for the largest one, our patient selection criteria for the LNH87-2 trial[11] was not that of a recognized and validated prognostic index,[15] such as the age-adjusted International Prognostic Index (AAIPI). Subsequent analysis of the data using AAIPI demonstrated that HDT consolidation could improve overall survival (OS) and DFS only for patients who had at least two adverse prognostic factors at diagnosis and entered complete remission (CR). One of the major obstacles of this design was that the CR rate was only 61%. In an attempt to improve the response rate and thus survival, a novel first-line regimen that incorporated HDT with early ASCT on day 60 was designed. This regimen was compared with conventional doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP),[16] which has shown benefit in event-

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free survival (EFS) over CHOP and methotrexate, bleomycin, cyclophosphamide, and etoposide regimens for patients with at least two adverse prognostic factors.[17,18] At the first interim analysis in September 1995, the trial was stopped because of the poor experimental arm results.[19] We report the final analysis of this trial with a median follow-up of 60 months.

PATIENTS AND METHODS

Eligibility Criteria

This study was conducted by the Groupe d'Etude des Lymphomes de l'Adulte (GELA) in France and Belgium. Between March 1993 and September 15, 1995, 397 consecutive patients were included in the LNH93-3 protocol. Patients had to be between 15 and 60 years of age, have newly diagnosed aggressive NHL, and present at least two of the following adverse prognostic factors as defined by the AAIPI: elevated lactate dehydrogenase (LDH) level, performance status ≥ 2, and Ann Arbor stage 3/4.[15] Patients who had lymphoblastic or Burkitt's lymphoma with meningeal or bone marrow involvement or had primary cerebral NHL were excluded. Other noninclusion criteria were positive serology for human immunodeficiency virus, concomitant or previous cancer (except in situ cervical carcinoma), congestive heart failure, and liver or kidney failure. The trial was approved by our institution's ethics committee, and all patients gave their written informed consent.

Histologic and Immunophenotypic Analysis

Histologic slides were reviewed by two independent pathologists from the GELA for 70% of the enrolled patients, and lymphomas were classified first according to the updated Kiel classification[20] and then to the World Health Organization classification.[21] Immunophenotyping studies were performed as previously described,[22] and the B- or T-cell phenotype was determined for 90% of the cases. A total of 370 patients were eligible for the study, and 27 were excluded for the following reasons: incorrect histology (n = 15), Burkitt's NHL with bone marrow involvement (n = 1), human immunodeficiency virus seropositivity (n = 1), and missing data (n = 10).

Staging

The extent of the disease was evaluated by physical examination, computerized tomography (CT) scan of the chest and abdomen, CSF examination, bone marrow biopsy, and other investigational procedures depending on the clinical symptoms. Patients were staged according to the Ann Arbor classification. Performance status and toxicity were assessed according to the National Cancer Institute common toxicity criteria grading system; LDH was expressed as the maximum/normal value ratio.

Treatments

Patients were randomized between arm A and arm B. Briefly, arm A consisted of four cycles of ACVBP (doxorubicin 75 mg/m^2 on day 1, cyclophosphamide 1,200 mg/m^2 on day 1, vindesine 2 mg/m^2 and bleomycin 10 mg on days 1 and 5, prednisone 60 mg/m^2 from days 1 to 5, and intrathecal methotrexate 15 mg on day 2) at 2-week intervals followed by outpatient consolidation that lasted 4 months.[15] Supportive granulocyte colony-stimulating factor (G-CSF; 5 μg/kg/d; Filgrastim, Amgen/Roche, Neuilly, France) was given on day 6 after each cycle. Patients then received consolidation at 2-week intervals, with two cycles of methotrexate (3 g/m^2) plus leucovorin rescue, four cycles of etoposide (300 mg/m^2) and ifosfamide (1,500 mg/m^2), and two cycles of cytarabine (100 mg/m^2) subcutaneously for 4 days.

Arm B comprised a shortened intensive induction phase that consisted of one cycle of cyclophosphamide, epirubicin, vincristine, and prednisone (CEOP) (cyclophosphamide 750 mg/m^2 on day 1, epirubicin 70 mg/m^2 on day 1, vincristine 1 mg/m^2 on day 1, and prednisone 40 mg/m^2 on days 1 to 5, and intrathecal methotrexate 15 mg on day 1) and two cycles of epirubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ECVBP) on days 15 and 36 (epirubicin 120 mg/m^2 on day 1, cyclophosphamide 2,000 mg/m^2 on day 1, vindesine 2 mg/m^2 on days 1 and 5, bleomycin 10 mg on days 1 and 5, prednisone 40 mg/m^2 on days 1 to 5, and intrathecal methotrexate 15 mg). G-CSF was given on day 6 after each ECVBP cycle. On day 60, intensified chemotherapy with 1,3-*bis*(2-chloroethyl)-1-nitrosourea, etoposide, cytarabine, and melphalan (BEAM) (1,3-*bis*(2-chloroethyl)-1-nitrosourea 300 mg/m^2 on day -7, etoposide 200 mg/m^2 from day -6 to day -3, cytarabine 200 mg/m^2 from day -6 to day -3, and melphalan 140 mg/m^2 on day -2) was given followed by ASCT.

Stem-Cell Harvesting

Peripheral-blood stem cells (PBSC) were collected and cryopreserved after the first or second ECVBP cycle when bone marrow involvement was present at diagnosis, as previously reported,[23] until analysis confirmed collection of $> 2.5 \times 10^6$ CD34$^+$ cells/kg.

Supportive Care

All patients had an indwelling central venous catheter and were housed in a protected environment for the duration of aplasia. Broad-spectrum antibiotics were given for any clinical or microbiologic infection or for a persistent undocumented fever > 38°C after blood had been drawn for culture.

Assessment of Response and Follow-up

CR was defined as the disappearance of all clinical evidence of disease and normalization of all laboratory values, radiographs, and biopsies from sites that had initially been abnormal. Patients with persistent CT abnormalities but $> 75\%$ regression of the initial tumor were considered to be in unconfirmed CR (CRu) if in CR on all other parameters.[24] Partial response (PR) was defined as a 50% to 75% reduction of tumor volume. A lower response, progressive disease (PD), and treatment-related death were considered treatment failures. Patients whose disease progressed at any time were withdrawn from the study and given another treatment at the discretion of the treating physician. Responses were evaluated by repeating the staging procedure 1 month after completion of each treatment arm. In addition, responses in the main disease sites were assessed after ACVBP and just before HDT to detect PD. Follow-up procedures included physical examination every 3 months for the first 2 years, then every 6 months for 2 years, then annually. Thoracic and abdominal CT scans were performed every 6 months during the first 2 years, then at the discretion of the treating physician.

Statistical Analyses

For this prospective, randomized study, randomization was stratified according to the participating centers for the treatment arm and was generated by the GELA coordinating center after confirmation of the patient's eligibility. Case report forms were sent by participating centers and keyed in twice for verification. Outliers and erroneous values were checked routinely. The main objective of the trial was to

obtain a 10% difference in EFS at 2 years. With a risk $\alpha = 0.05$ and a risk $\beta = 0.1$ based on the assumption of 40% 2-year EFS in the ACVBP versus 50% in the experimental arm, this design required the randomization of 700 eligible patients over 5 years. Secondary end points were response rate after completion of each treatment arm and OS. After 300 patients had been enrolled and followed for at least 6 months, the Data and Safety Monitoring Committee undertook an interim analysis, which was completed in July 1995.[18] Results indicated that EFS was significantly lower in the experimental arm. The committee recommended that the study be stopped on September 15, 1995, by which time 397 patients had been randomized and were followed to assess survival and relapses. The revised risk β of the study with 400 patients is 0.5.

Statistical Methods

Patient characteristics and CR rates were compared using χ^2 and Fisher's exact tests. EFS was measured from the date of randomization to disease progression, relapse, or death from any cause or from the stopping date, which, for this analysis was, July 1, 1999. DFS was measured from the first date of remission to either relapse or death from any cause. OS was measured from the date of randomization to the date of death from any cause. Data were censored at the date of the last follow-up evaluation when the stopping date was not reached. In an intent-to-treat analysis, survival was estimated using the Kaplan-Meier method[25] and compared with the log-rank test.[26] Differences were considered significant when the two-sided *P* value was less than .05. Estimated hazard rate of mortality was calculated.[27] Multivariate analyses were performed using the Cox model for survival data and logistic regression for categorical data,[28] with SAS software (v.8. SAS Institute, Cary, NC). Treatment × risk factor interactions were also included in the model.

RESULTS

Patient Characteristics and Response to Treatment

Among the 370 eligible patients (median age, 46 years; range, 60 to 15 years), 181 were randomized to receive ACVBP and 189 were randomized to receive HDT with ASCT. Their main characteristics were similar (Table 1), differing significantly only for the higher percentage of arm-B patients with extranodal site ≥ 2 ($P = .0004$). Responses could be evaluated in 174 patients in arm A and 187 patients in arm B. CR + CRu rates were 64% and 63% for arms A and B, respectively. During treatment, 19% of patients in arm A and 16% of patients in arm B progressed, and, respectively, 8% and 6% died (NS). HDT with ASCT was given to 139 patients (74%). The main reasons for not receiving intensification were disease progression (n = 24), refusal (n = 3), severe toxicity during induction (n = 9), early death (n = 8), and miscellaneous (n = 6). According to univariate analysis, adverse factors that significantly affected response rates were age > 40 years ($P = .04$), T-cell phenotype ($P = .005$), B symptoms ($P = .02$), extranodal localizations ≥ 2 ($P = .0005$), β2 microglobulin ($P = .0001$), bone marrow involvement ($P = .003$), and AAIPI 3 ($P = .05$).

Table 1. Initial Characteristics of the Patients According to the Treatment Group: ACVBP Versus HDT With ASCT

Characteristic	All Patients (N = 370) (n)	ACVBP (n = 181) (%)	HDT + ASCT (n = 189) (%)	*P*
Median age, years	46	46	46	
Age, n				
≤ 40 years	130	68	62	.3
> 40 years	240	113	127	
Sex, no.				
Male	220	105	116	.5
Female	150	76	73	
Histology				
Diffuse large-B cell	227	62.5	60	.07
Non-anaplastic PTCL	55	10.5	19	
Anaplastic PTCL	29	10.5	5	
Lymphoblastic	12	4	3	
Burkitt's	7	0.5	3	
Diffuse aggressive, unclassifiable	40	12	9.5	
Cell phenotype				
B	257	79	75	.3
T	76	20	24	
B symptoms				
Absent	111	33	27	.2
Present	258	67	73	
Performance status grade				
0-1	197	52	55	.4
> 1	169	47	45	
Ann Arbor stage				
I-II	21	5	6	.5
III-IV	349	95	94	
No. of extranodal sites				
0-1	136	46	28	.0004
≥ 2	234	54	72	
Bone marrow involvement				
Absent	255	74	68	.2
Present	104	26	32	
Tumor bulk				
< 10 cm	193	52	56	.4
≥ 10 cm	165	48	44	
Meningeal involvement	13	3.5	4	.8
Hemoglobin				
≥ 10 g/dL	290	80	78	.8
< 10 g/dL	78	20	22	
Serum LDH level				
< normal	26	9	6	
≥ normal	342	91	94	.17
Serum albumin level				
≥ 35 g/L	193	44	55	
< 35 g/L	157	56	45	.8
β2 microglobulin				
< 3	162	55	54	.7
≥ 3	135	45	46	
No. of AAIPI factors				
1	7	2.8	1	
2	231	61.5	65	.4
3	127	35.5	34	

NOTE. Except for Age and Sex rows, all values in the ACVBP and HDT + ASCT columns are percentages.

Abbreviation: PTCL, peripheral T-cell lymphoma.

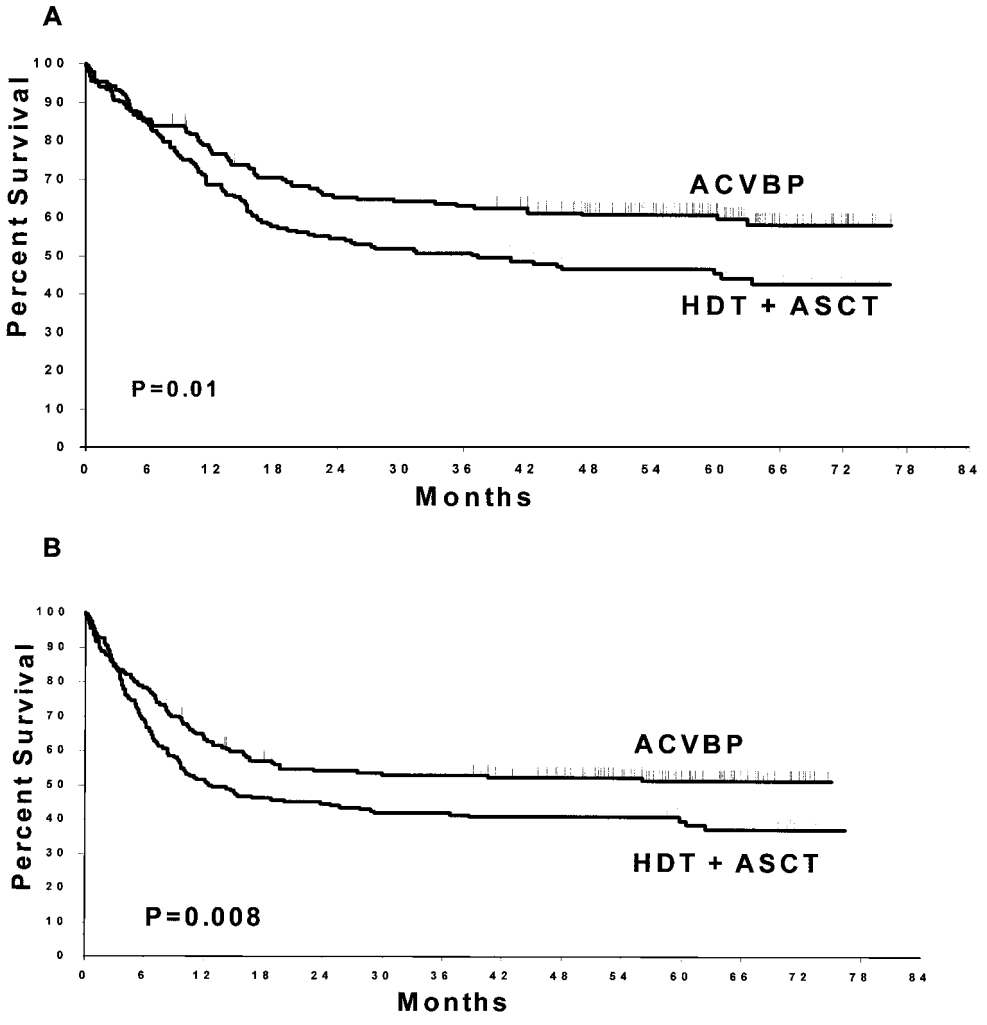

Fig 1. OS (A) and EFS (B) of the 181 patients who were treated with ACVBP and the 189 patients who received early HDT and ASCT.

Dose-Intensity

The median received dose-intensity, calculated for the first 8 weeks of the ACVBP arm, were 35 mg/m^2/wk for doxorubicin and 565 mg/m^2/wk for cyclophosphamide and represents 94% of the planned dose-intensity, respectively, 37.5 mg/m^2/wk and 600 mg/m^2/wk. For arm B, the median received dose-intensities calculated from CEOP to ASCT were 31 mg/m^2/wk for epirubicin and 475 mg/m^2/wk for cyclophosphamide, with a median CEOP-BEAM interval of 72 days (range, 53 to 191 days), meaning a 20% lower-than-planned dose-intensity.

Toxicity

During the first cycle of ACVBP or CEOP, grade 4 hematotoxicity for WBC was observed, respectively, in 82% and 50% of the cases. The respective rates of grade 3 or 4 infections were 26% and 19%, with two infection-related deaths in arm B and one in arm A. For the other cycles, the same percentages of grade 3 to 4 hematotoxicity (80%) and grade 3 to 4 infections (18%) were observed in both arms.

Leukaphereses were performed after the first (57%) or second (38%) ECVBP cycle with a median of two leukaphereses. The median numbers of GM-CFU and CD34+ cells were, respectively, 37.8 $\times$ 10^4/kg (range, 2 to 730 $\times$ 10^4/kg) and 12.4 $\times$ 10^6/kg (range, 1.8 to 111 $\times$ 10^6/kg). After BEAM, all patients recovered neutrophil counts $>$ 0.5 $\times$ 10^9/L after a mean of 12.4 days (range, 7 to 41 days) and a platelets count $>$ 50 $\times$ 109/L after a mean of 15.6 days (range, 9 to 141 days). Severe grade 3/4 infections were observed in 10% of the patients and grade 3/4 mucositis in 14%. The two transplantation-related deaths occurred in

Table 2. Five-Year EFS and OS of Patients Treated in the LNH93-3 Protocol: Chemotherapy ACVBP Versus HDT With ASCT

Parameter	Total No. of Patients	EFS (%)	*P*	OS (%)	*P*
No.	370	45		52	
ACVBP	181	51	.01	60	.007
HDT	189	39		46	
Age					
< 40 years	131	59	.001	66	.0001
≥ 40 years	239	37		44	
LDH					
≥ Normal	341	44		51	
< Normal	26	61	.1	65	.1
Performance status					
0-1	196	43	.9	51	.9
> 1	169	48		53	
Stage					
I-II	21	61	.1	66	.2
II-IV	348	44		51	
Extranodal sites					
0-1	135	51	.04	59	.03
> 1	234	42		48	
Bone marrow involvement					
Negative	254	52		58	
Positive	104	26	.0001	33	.0001
Phenotype					
ACVBP (B cell)	126	53	.09	61	.03
HDT (B cell)	130	43		47	
ACVBP (T cell)	33	30	.4	39	.5
HDT (T cell)	43	20		32	
Bone marrow involvement positive					
ACVBP	45	35	.07	40	.1
HDT	59	20		29	
Extranodal site > 1					
ACVBP	98	51	.05	57	.05
HDT	136	36		42	
LDH > normal					
ACVBP	162	51	.02	59	.009
HDT	179	39		45	
AAIPI > 2					
ACVBP	63	47	.5	52	.9
HDT	64	40		48	

patients in CR. The median duration of hospitalization was 24 days (range, 17 to 44 days).

Survival

After a median follow-up of 5 years, 176 patients had died. For the entire cohort, estimated OS, EFS, and DFS probabilities were 52%, 45%, and 67%, respectively. According to intent-to-treat analysis, arms A and B differed significantly for 5-year OS (60% ± 8% *v* 46% ± 8%; $P = .007$; Fig 1) and 5-year EFS (51% ± 8% *v* 39% ± 8%; $P = .01$) and DFS (76% *v* 58%; $P = .004$). These differences remained when the analysis was restricted to B-cell lymphoma patients who achieved CR (Table 2), with respective DFS for arm A and B of 76% and 61% ($P = .04$). In a multivariate analysis, OS was independently affected by age < 40 years ($P = .0003$), bone marrow involvement ($P = .003$), T-cell phenotype ($P = .009$), and treatment arm ($P = .04$). No risk factor × treatment arm interaction was found. For the 139 patients who received HDT with ASCT, the OS rate was 56% at 5 years, and none of the factors described above as affecting survival was retained in the multivariate analysis.

Relapses

Seventy-three patients relapsed after remission. The estimated hazards rate of mortality during the study period was higher for arm B as a result of relapses (Fig 2). Patients who relapsed and progressed received different salvage chemotherapy regimens: for arms A and B, allogeneic transplan-

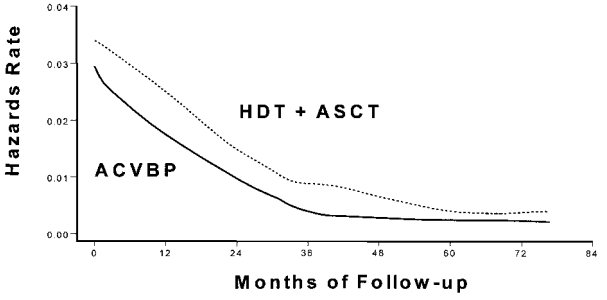

Fig 2. Estimated hazards rates mortality for patients who were treated with ACVBP and those who received early HDT and ASCT.

tations for two and six patients, respectively, and HDT with ASCT for 25 and 17 patients, respectively. The OS rate for this subpopulation was lower for arm B (13% ± 0.04%) than for arm A (21% ± 0.1%; $P = .01$) at 5 years (Fig 3). For relapsing patients only, the respective survival rates were 33% and 13% ($P = .0006$).

DISCUSSION

The AAIPI is now accepted as being able to identify patients who have aggressive lymphoma with different likelihoods of being cured with standard treatment. Fewer than 50% of the patients in the high/intermediate- or high-risk group are cured; consequently, patients younger than 60 years are appropriate candidates for experimental therapy.[3] These features describe the patients with more than one AAIPI factor included in this trial. They differed only from those enrolled onto our previous study that tested HDT after CR[11] by their higher percentages of T-cell lymphomas and with more than two extranodal sites. In the LNH87-2, only 61% (277 of 451) of these higher risk patients achieved CR after induction treatment.[11] The goal of the new shortened regimen was to introduce HDT with BEAM earlier to improve the first CR rate. This result was not achieved, and the response rates were similar in the two arms. This lack of improvement may reflect inadequate dose intensity for the experimental arm during the first 8 weeks. It can be argued that dose equivalence between doxorubicin and epirubicin has not been clearly established, but considering the cumulative dose inducing cardiac toxicity, it might be closer to 1.8 than 1 for epirubicin.[29] Consequently, arm B received less anthracycline and this situation was further aggravated by the 20% reduction of the received median dose intensity as a result of a 12-day delay in performing ASCT, mainly for logistic reasons. Moreover, the lower CEOP dosage in the first cycle did not result in a significant reduction of grade 3 to 4 infections. Intensification of the initial induction phase was first proposed by the Milan group in a different scheme with dose-escalated agents followed, on day 60, by HDT with melphalan mitoxantrone and PBSC.[13] In 98 randomized patients with B large-cell lymphoma without bone marrow involvement, their sequential HDT regimen was superior to conventional chemotherapy in terms of CR rate and 7-year EFS of 76% and 49%, respectively ($P = .004$).

We achieved a 63% CR rate in arm B, and one could expect a similar outcome. Surprising is that more relapses occurred in all situations, B-cell or T-cell lymphoma, with or without bone marrow involvement.

Multivariate analysis identified that age > 40 years, T-cell phenotype, bone marrow involvement, and arm B were independent parameters influencing survival. Several hypotheses were advanced to explain these results. First, there was a potential role of stem-cell contamination in patients with bone marrow involvement. Monitoring of residual disease in aggressive lymphoma is not yet optimal

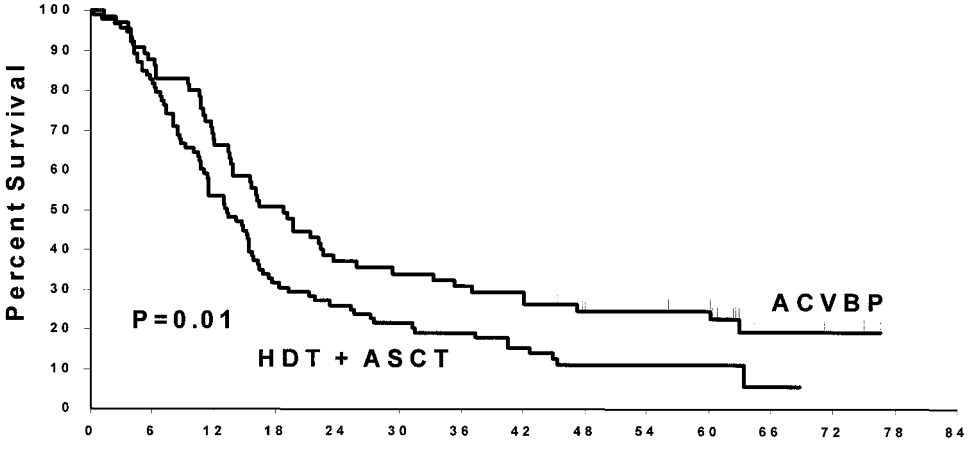

Fig 3. OS of patients who experienced disease progression or relapse and had been receiving ACVBP or early HDT and ASCT.

and was not prospectively scheduled. In this multicenter study, specimens were not available for retrospective analysis. However, a recent quantitative study of PBSC from patients with diffuse large-cell lymphoma showed that one half strongly mobilized a significant number of malignant cells, which could be responsible for relapses.[30] It should be pointed out that the difference between our two arms cannot be explained only by this hypothesis, as a difference was also noted in patients without bone marrow involvement at diagnosis. Moreover, the multivariate analysis performed only on arm B failed to identify any significant independent parameter. Second, relapsing patients in arm B could not be saved easily by introducing HDT with ASCT. In fact, very few (< 15%) patients after relapses from either arm were saved with transplantation as observed in previous studies on high-risk patients and attributed to resistance to salvage chemotherapy.[11,31] Third, the results obtained with ACVBP were better than expected. With a 60% 5-year probability of OS, the results obtained in LNH93 arm A compared favorably with all of our previous reports with this regimen.[32] Perhaps G-CSF played a major role, as the median received ACVBP dose-intensity was 94% with the use of G-CSF in contrast to the 56% for patients who had received, 80% of the dose-intensity planned in the LNH87-2 study before the availability of G-CSF.[33] However, a randomized study of patients who were treated with ACVBP with or without G-CSF failed to demonstrate any EFS advantage[34] between the two arms. Last, the treatment duration seems to play a crucial role as in other hematologic diseases in which consolidation contributes to preventing relapses, and the intermittent use of sequential chemotherapy in the control arm over a longer period of time might result in an effective fractional cell kill in the drug-sensitive patients. In the recent report on the European Organization for Research and Treatment of Cancer randomized study comparing standard chemotherapy with or without HDT, there was no difference between the two arms,[35] but only 60 patients with two AAIPI factors were randomized. The German High-Grade Lymphoma Study Group reported on 312 patients who had elevated LDH and stage 2 to 4 disease and received six cycles of cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone followed by radiation or a shortened protocol with three cycles of cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone followed by ASCT and radiation.[36] After 30 months of follow-up, EFS and OS for patients with high/intermediate- or high-risk factors did not differ. The results obtained in the LNH87-2 study led us to conclude that HDT would benefit only patients who achieved a good response before full standard induction treatment and that it should not be performed too early during the course of treatment. These conclusions resemble to the recognition of the roles of intensive consolidation and treatment duration after remission in other hematologic malignancies, eg, acute leukemia. Nevertheless, improving the CR rate remains the major goal for these high-risk patients. Incorporating new agents, such as anti-CD20,[37] might be the easiest way to improve the results obtained with chemotherapy[1,17] followed or not by consolidation with HDT and are presently under investigation. For avoiding exposing patients unnecessarily to experimental approaches, close monitoring and respect of planned interim analyses of randomized trials are mandatory. However, owing to the need for sufficient follow-up before analyzing data, a sequential test approach might be more appropriate to speed up decision making but requires timely communication between clinical investigators and the experienced statisticians.

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APPENDIX

The appendix listing participating investigators is available online at www.jco.org.

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