

Survival Benefit of High-Dose Therapy in Poor-Risk Aggressive Non-Hodgkin's Lymphoma: Final Analysis of the Prospective LNH87-2 Protocol—A Groupe d'Etude des Lymphomes de l'Adulte Study

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Purpose: To present the final analysis, with a median follow-up of 8 years, of the LNH87-2 randomized study, which compares consolidative sequential chemotherapy (ifosfamide plus etoposide, asparaginase, and cytarabine) with high-dose therapy (HDT) using cyclophosphamide, carmustine, and etoposide (CBV regimen) followed by stem-cell transplantation in patients with aggressive non-Hodgkin's lymphoma in first complete remission after induction, focusing on high/intermediate- and high-risk patients identified by the age-adjusted international prognostic index.

Patients and Methods: Among the 916 eligible patients, 451 presented with two ($n = 318$) or three ($n = 133$) risk factors. After reaching complete remission to induction therapy, 236 of these higher risk patients were assessable for the consolidation phase, with 125 patients in the HDT arm and 111 in the sequential chemotherapy arm.

Results: Among these 451 higher risk patients, 277 (61%) achieved complete remission after induction treatment. In the population of 236 randomized patients, HDT was superior to sequential chemotherapy, with 8-year disease-free survival rates of 55% (95% confidence interval [CI], 46% to 64%) and 39% (95% CI, 30% to 48%), respectively ($P = .02$; relative risk, 1.56). The 8-year survival rate was significantly superior in the HDT arm (64%; 95% CI, 55% to 73%) compared with the sequential chemotherapy arm (49%; 95% CI, 39% to 59%) ($P = .04$; relative risk, 1.51).

Conclusion: On the basis of the final analysis of this prospectively treated series of patients, retrospectively analyzed on the basis of the International Prognostic Index, we hypothesize that HDT benefits patients at higher risk who achieve complete remission after induction treatment.

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HIGH-DOSE THERAPY (HDT) followed by autologous stem-cell transplantation is the treatment of choice for patients with relapsed aggressive non-Hodgkin's lymphoma still responding to salvage chemotherapy.¹⁻³ Whether autologous transplantation has a role as front-line therapy in the higher risk patients is still a matter of debate. Phase II studies suggested a potential benefit in poor-risk patients unlikely to be cured by conventional strategies.⁴⁻⁹ Until now, several randomized phase III studies, including the present one,¹⁰⁻¹² have shown that such an approach is beneficial in terms of freedom from progression in higher risk patients younger than 60 years. These studies seemed to support the use of either consolidative HDT^{10,11} or of up-front high-dose induction therapy.¹² By contrast, other prospective randomized trials designed with an abbreviated standard induction therapy followed by early HDT gave negative results.^{13,14} In 1997, we published the first interim analysis of the LNH87-2 study with a separate analysis of the high/intermediate- and high-risk patients.¹⁰ With a median follow-up of 8 years, we report in this article the results of the final analysis on this higher risk group.

PATIENTS AND METHODS

Patients

From October 1987 to February 1993, 1,043 patients were enrolled onto the LNH87-2 study at 35 participating centers. Inclusion criteria

has been previously described¹⁰; patients that were included were adults under 55 years old with newly diagnosed intermediate- or high-grade non-Hodgkin's lymphoma according to the International Working Formulation and with at least one of the following adverse factors: Eastern Cooperative Oncology Group performance status of 2 to 4, two or more extranodal sites, tumor burden of at least 10 cm in largest dimension, bone marrow or CNS involvement, and Burkitt or lymphoblastic subtypes (the latter two without bone marrow or CNS involvement). Patients were retrospectively staged according to the age-adjusted International Prognostic Index.¹⁵ Histologic review was performed in 87% of patients, and the B or T phenotype was

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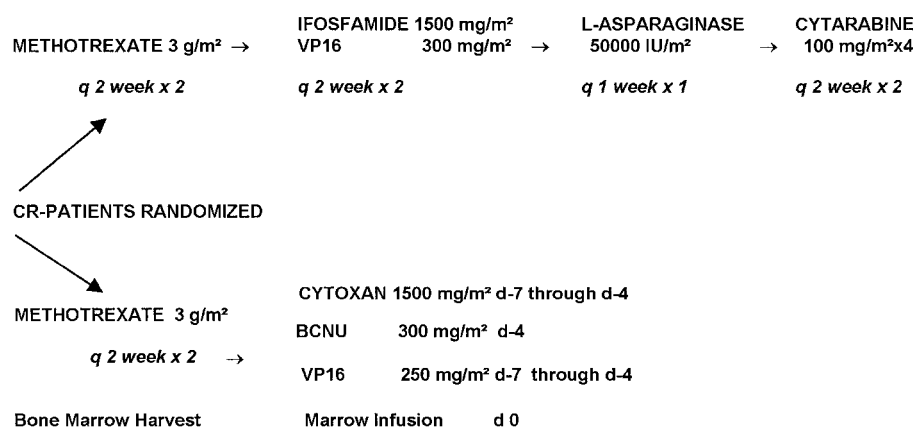


Fig 1. Diagram of the two randomized consolidative procedures.

determined in 84%. Nine hundred sixteen patients were eligible for the first interim analysis, among which 451 were identified as high/intermediate- or high-risk patients.¹⁰

Treatment

After the patients gave informed consent and underwent a standardized staging evaluation, patients were randomized to receive four courses of two of the following anthracycline-containing regimens given every 2 weeks: the LNH84 induction regimen with doxorubicin (75 mg/m²), cyclophosphamide, vinblastine, and bleomycin (ACVB arm) or mitoxantrone (12 mg/m²), cyclophosphamide, vinblastine, and bleomycin (NCVB arm), given intravenously on day 1. The remainder of the two induction regimens were the same: cyclophosphamide 1,200 mg/m² given intravenously on day 1, vindesine 2 mg/m² given intravenously on days 1 and 5, bleomycin 10 mg given intravenously on days 1 and 5, prednisone 60 mg/m² given orally on days 1 through 5, and intrathecal methotrexate 15 mg on day 2. The NCVB arm was stopped in December 1991 because of a significant advantage of the ACVB regimen in terms of complete response rate.

Response to induction was evaluated and patients who achieved a complete remission were subsequently randomized (Fig 1) between a sequential chemotherapeutic consolidation as defined in the LNH84 regimen¹⁶ or a consolidative HDT with the CBV regimen followed by autologous bone marrow transplantation as described. No radiotherapy was planned in either consolidative group.

Assessment of Response

Complete remission was defined as the disappearance of all clinical evidence of disease and normalization of all laboratory values, radiographs, and biopsies that were abnormal before therapy. Additionally, patients with persistent computed tomography abnormalities but regression greater than 75% of the initial tumor were deemed to be in complete remission if in complete remission on all others parameters. Partial response was defined as a 50% to 75% reduction in tumor volume. Lesser response, progressive disease, and treatment-related death were considered as treatment failures.

Statistical Methods

Patient characteristics were analyzed using the χ^2 test. The rates of disease-free survival and survival were estimated by the Kaplan-Meier method and compared by the log-rank test,^{17,18} using the SAS Lifetest

procedure (SAS Institute, Carry, NC). Survival was also analyzed by using a stratified log-rank test, which provides a comparison of the two treatment groups adjusting for the International Prognostic Index (high/intermediate and high risk). Differences were considered significant if the two-sided *P* value was less than .05. All analyses were performed on an intent-to-treat basis. The results are reported as of August 15, 1999.

RESULTS

Patients Characteristics and Response to Induction Therapy

Four hundred fifty-one patients were individualized as high/intermediate-risk patients (two risk factors, *n* = 318) or high-risk patients (three risk factors, *n* = 133) on the basis of the age-adjusted International Prognostic Index. Included in the high/intermediate subgroup of patients presenting with two risk factors are 11 patients with one of the three index parameters unknown (ie, Ann Arbor stage, lactate dehydrogenase level, and performance status). There were 274 men and 177 women, with a median age of 41 years. Table 1 lists the pretreatment characteristics of these 451 higher risk patients. Of note, the vast majority of these patients had diffuse large-cell (including immunoblastic and anaplastic) lymphoma; T-cell phenotype was demonstrated in 17% of the tested cases; 34% of the patients presented with a bone marrow involvement; and 70% had bulky disease. Two hundred seventy-seven patients (61%) reached complete remission after induction treatment, 58 (13%) had partial response, 76 (17%) had no response, and 40 (9%) died during the induction phase mainly from toxicity.

Consolidation Treatment

Among the 277 patients who achieved complete remission after induction treatment, 41 were not randomized to receive the consolidation phase mainly because of refusal.

Table 1. Characteristics of the High/Intermediate- and High-Risk Patients

Characteristic	High/Intermediate- and High-Risk Patients Randomized for Consolidative Procedures (%)		
	High/Intermediate- and High-Risk Patients (n = 451)	Sequential Chemotherapy (n = 111)	Autologous Bone Marrow Transplantation (n = 125)
Histologic groups*			
Follicular, large-cell	3	3	2
Diffuse, small cleaved-cell	2	2	0
Diffuse, mixed	6	4	3
Diffuse, large-cell	54	55	60
Immunoblastic	13	13	11
Lymphoblastic	2	2	2
Small noncleaved	4	5	6
Other			
Anaplastic (Ki-1)	7	11	8
Unclassified	6	4	4
Unclassifiable	3	1	3
Immunologic phenotype			
B-cell	69	71	75
T-cell	17	16	11
Neither	14	13	14
Performance status			
0	16	19	21
1	34	37	37
2-4	50	44	42
Bulky disease, tumor ≥ 10 cm			
No	30	30	26
Yes	70	70	74
Bone marrow involvement			
No	66	66	74
Yes	34	34	26
Extranodal sites (no)			
0-1	65	70	67
≥ 2	35	30	33
Stage			
I-II	7	7	9
III-IV	93	93	91
Lactate dehydrogenase ratio†			
≤ 1	11	8	14
> 1	89	92	86
Beta-2 microglobulin ratio†			
≤ 3	66	81	73
> 3	34	19	27
Age-adjusted International Prognostic Index			
High/intermediate	70	76	81
High	30	24	19

*According to the classification system of the International Working Formulation.

†Denotes the ratio of the lactic dehydrogenase or beta-2 microglobulin concentrations to the upper limit of the normal range. Values for lactic dehydrogenase were available for 445 (99%) of 451 patients, and values for beta-2 microglobulin were available for 273 patients (60%).

Of 236 patients randomized, 111 were in the sequential chemotherapy arm and 125 were in the autologous transplantation arm. The characteristics of these groups are listed in Table 1. Importantly, the two groups were well-balanced,

especially with regard to International Prognostic Index parameters. Of the 125 patients scheduled to receive consolidative HDT followed by autologous bone marrow transplantation, 86 (69%) did so.

Disease-Free Survival

The overall 8-year disease-free survival of the 236 randomized patients was 47% (95% confidence interval [CI], 40% to 54%) compared with 51% (95% CI, 37% to 67%) for the 41 patients in complete remission who were not randomized to receive consolidative treatment.

In this high-risk randomized population, HDT was superior to sequential chemotherapy, with 8-year disease-free survival rates of 55% (95% CI, 46% to 64%) and 39% (95% CI, 29% to 49%), respectively ($P = .02$; relative risk, 1.51) (Fig 2).

Survival

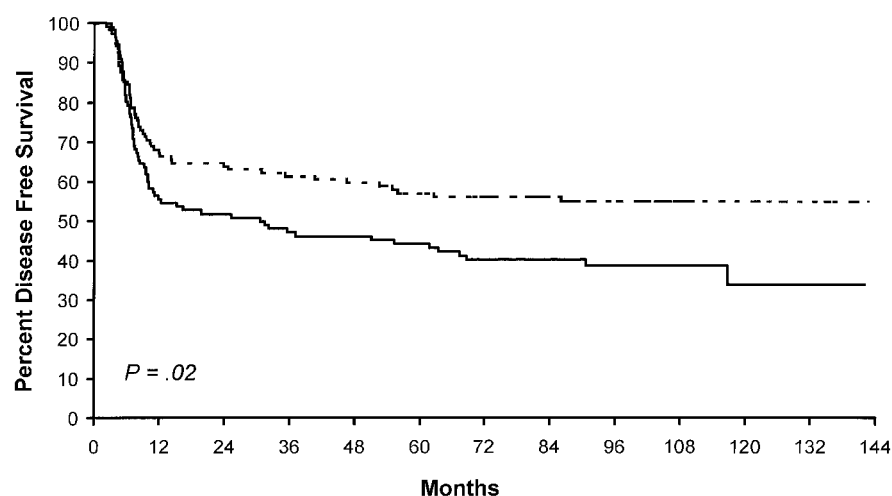
The overall 8-year survival rate of the 451 high/intermediate- and high-risk patients was 42% (95% CI, 37% to 47%). The 8-year survival rate was superior in the HDT arm (64%; 95% CI, 55% to 73%) compared with the sequential chemotherapy arm (49%; 95% CI, 39% to 59%) ($P = .04$; relative risk, 1.56) (Fig 3). In addition, stratified analysis on the International Prognostic Index (high/intermediate- and high-risk groups) confirmed the superiority of HDT over sequential chemotherapy ($P = .03$).

Relapses

Of the 236 patients randomized to either consolidative phase, 109 patients relapsed, including 59 (53%) of 111 patients randomized to the sequential chemotherapy arm and 50 (40%) of 125 patients randomized to the transplantation. The median delay from diagnosis to relapse was 7 months in each arm. Among the 59 patients who relapsed in the sequential chemotherapy group, 21 (35%) received HDT followed by stem-cell transplantation as salvage treatment and 38 did not, mainly because of chemorefractoriness. The 8-year survival rates of the 21 transplanted and 38 nontransplanted patients were 36% and 8%, respectively. Among the 50 patients who relapsed in the autotransplantation group, 12 (24%) were treated with HDT followed by stem-cell transplantation (autologous in 10 patients and allogenic in two patients), and 38 patients did not receive a second transplantation mainly because of chemoresistance. The 8-year survival rates of these patients were only 19% and 11%, respectively.

Toxicities

Among the 236 randomized patients, no toxic death was reported during the consolidation phase. At the time of analysis, 99 patients (42%) have died, lymphoma being the



Patients	101	86	80	78	73	65	54	41	25	15	6
at risk	84	72	61	58	53	49	40	30	17	9	2

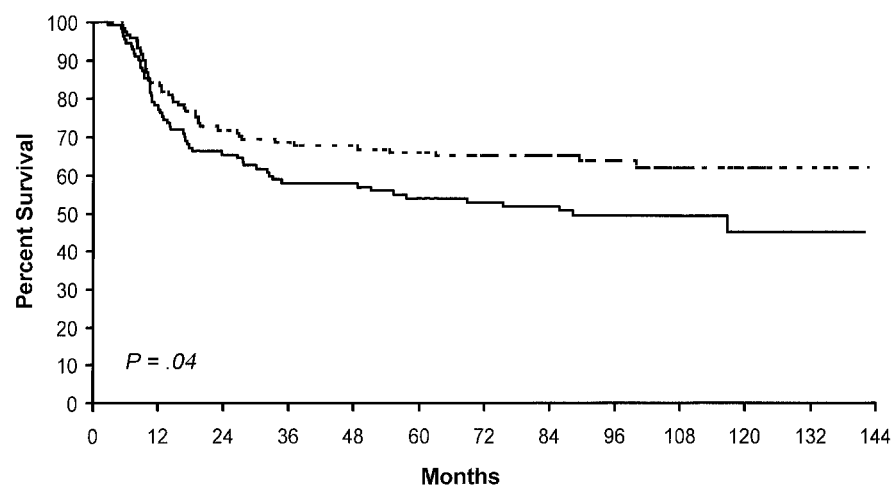
Fig 2. Estimated disease-free survival according to randomized consolidation procedure for the high/intermediate- and high-risk patients. (—) Sequential chemotherapy (patients at risk, $n = 111$; 8-year estimate, 39%); (---) Autologous bone marrow transplantation (patients at risk, $n = 125$; 8-year estimate, 55%) ($P = .02$).

cause of death in the vast majority. Two patients treated by consolidative sequential chemotherapy developed a second malignancy. In one patient, chronic myeloid leukemia was diagnosed 2 years after the end of the treatment, and death ultimately occurred as a result of blastic phase. In the second patient, the diagnosis of uterine carcinoma was made 5 years after the end of the treatment and 2 years after she underwent autotransplantation as salvage treatment for lymphoma relapse. It is noteworthy that no myelodysplastic

syndrome was observed at 8 years of follow-up in the 125 patients assigned to undergo autotransplantation.

DISCUSSION

We now report the results of the final analysis of the LNH87-2 study and show a survival advantage of first-line consolidative HDT in higher risk patients with aggressive non-Hodgkin's lymphoma. With a median follow-up of surviving patients of 8 years, the trial may be considered as



Patients	80	76	72	69	63	56	46	35	20	13	6
at risk	60	54	49	46	43	36	28	19	10	6	0

Fig 3. Estimated survival according to randomized consolidation procedure for the high/intermediate and high-risk patients. (—) Sequential chemotherapy (patients at risk, $n = 111$; 8-year estimate, 49%); (---) Autologous bone marrow transplantation (patients at risk, $n = 125$; 8-year estimate, 64%) ($P = .04$).

mature. In this higher risk randomized population of 236 patients who reached complete remission after induction phase, consolidative HDT was superior to sequential chemotherapy, with 8-year disease free survival rates of 55% and 39%, respectively ($P = .02$). Moreover, survival advantage for the HDT arm was confirmed with 8-year rates of 64% compared with 49% in the sequential chemotherapy arm ($P = .04$). It is noteworthy that in the latter group, only 21 (35%) out of 59 patients who subsequently relapsed received a salvage treatment including autotransplantation because the majority of these higher risk patients could not be proposed for this therapeutic approach as a result of refractoriness to salvage chemotherapy.¹⁹ Importantly, we did not observe any myelodysplastic syndrome among the 125 patients assigned to receive autotransplantation. This finding is consistent with reports that in the setting of autotransplantation such a complication is mainly associated with total-body irradiation conditioning regimens and long interval between diagnosis of lymphoma and transplantation.²⁰⁻²¹

The age-adjusted International Prognostic Index is the model commonly used to identify patients with aggressive lymphoma who have different likelihoods of being cured with standard induction therapy. It is now accepted that less than 50% of the higher risk patients defined on the basis of this index (ie, high/intermediate and high risk) are cured with standard therapy and, consequently, that patients younger than 60 years who fall into these subgroups are appropriate candidates for experimental therapy. Trials completed to date regarding the role of HDT in newly diagnosed, poor-prognosis patients, have been initiated before the International Prognostic Index was available and, therefore, have identified patients using a variety of clinical parameters. Treatment strategies for such patients have consisted of increasing the dose of chemotherapy (with or without irradiation) using stem-cell support to limit hematopoietic toxicity. Several prospective trials have compared, in a randomized fashion, conventional treatments with consolidative HDT after initial response to standard induction regimens, or up-front inductive HDT, or abbreviated induction therapy.

A trial designed by the Italian Non-Hodgkin's Lymphoma Study Group also supports the use of consolidative HDT in high/intermediate- and high-risk patients.¹¹ One hundred twenty-four patients younger than 60 years were randomized with bulky stage II or III/IV disease to receive standard induction therapy alone or the same regimen followed by autologous bone marrow transplantation. After a etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin inductive regimen delivered during 12 weeks, patients who were randomized to receive

standard induction therapy and who achieved complete remission were observed, those in partial or no response underwent the dexamethasone, cisplatin, and cytarabine regimen as salvage treatment. Patients randomized to receive autologous bone marrow transplantation did so independently of their response to induction therapy. With a median follow-up of 42 months, a statistical improvement in terms of disease-free survival was observed in favor of HDT, compared with standard induction therapy, for the age-adjusted International Prognostic Index high/intermediate- and high-risk group of 51 patients (3-year disease-free survival rates, 87% and 48%, respectively; $P = .008$).

Another approach developed by the Milan group for the treatment of higher risk patients was to intensify the initial induction phase.¹² Ninety-eight selected patients with bulky or advanced-stage diffuse large B-cell lymphoma and no bone marrow involvement were randomly assigned to receive either methotrexate-leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin or inductive high-dose sequential therapy followed by bone marrow or peripheral-blood stem-cell support. With a median follow-up of 55 months, sequential HDT was superior to standard induction in terms of complete response rate, freedom from progression, and event-free survival rates (7-year event-free survival 76% and 49%, respectively; $P = .004$). Overall survival did not significantly differ between the two treatment groups because of early treatment-related toxicity and the cross-over design of the study.

Two other studies in which HDT followed an abbreviated induction phase did not demonstrate a benefit of HDT over a conventional treatment. In the LNH93-3 trial,¹³ 370 patients with high/intermediate- and high-risk disease were randomized to receive either full standard induction therapy or a short induction phase including a debulking course and two cycles of standard therapy followed by HDT. With a median follow-up of 30 months, the event-free survival and overall survival rates for patients receiving standard induction (54% and 63%, respectively) were superior to those who received early HDT (41% and 47%, respectively) ($P = .01$ and $P = .003$, respectively). The German High-Grade Lymphoma Study Group¹⁴ randomized 312 patients with an elevated lactate dehydrogenase level and with disease stages II to IV to receive either five courses of cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide (CHOEP) followed by involved-field radiation or three cycles of CHOEP followed by autologous bone marrow transplantation and involved-field irradiation. After 30 months, there was no difference in event-free survival and survival between both arms, even for patients with high/intermediate- or high-risk factors. These two negative studies have in common the use of HDT after an abbreviated

induction phase. Comparing their results with that of our study led us to consider that HDT will benefit patients only if they prior achieved a good response to full standard induction treatment.

At the time of the International Consensus Conference on High-Dose Therapy With Hematopoietic Stem-Cell Transplantation in Aggressive Non-Hodgkin's Lymphoma held in Lyon, France, in 1998,²² it was felt that determining the benefit of HDT in newly diagnosed patients was the first priority. At that time, ongoing randomized studies were identified that explore the potential benefit of HDT, comparing either early versus late

transplantation in responding patients or standard induction therapy followed by HDT with full-course standard induction therapy.

On the basis of our results, delivered with a median follow-up of 8 years, we hypothesize that HDT benefits higher risk patients who have good response to induction treatment and expect that the results of ongoing prospective trials will definitely clarify this issue.

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