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Initial Treatment of Aggressive Lymphoma with High-Dose Chemotherapy and Autologous Stem-Cell Support

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ABSTRACT

BACKGROUND

The efficacy of first-line intensive chemotherapy plus transplantation of autologous hematopoietic stem cells in adults with disseminated aggressive lymphoma is unknown.

METHODS

We compared high-dose therapy plus autologous stem-cell support with the standard regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in a randomized trial. The patients were 15 to 60 years of age, had untreated aggressive lymphoma, and were at low, low intermediate, or high intermediate risk of death (i.e., a maximum of two adverse prognostic factors) according to the age-adjusted International Prognostic Index. The primary outcome was event-free survival at five years.

RESULTS

Of 207 consecutive patients, 197 underwent randomization; 99 were assigned to receive CHOP, and 98 to receive high-dose chemotherapy plus stem-cell transplantation. Overall, 78 percent of the patients completed the assigned treatment; the median follow-up was four years. The estimated event-free survival rate (\pm SD) at five years was significantly higher among patients who received high-dose therapy than among patients who received CHOP (55 ± 5 percent vs. 37 ± 5 percent, $P=0.037$). Among patients with a high intermediate risk of death, according to the age-adjusted International Prognostic Index, the five-year survival rate was significantly higher after high-dose therapy than after CHOP (74 ± 6 percent vs. 44 ± 7 percent, $P=0.001$).

CONCLUSIONS

High-dose chemotherapy with autologous stem-cell support is superior to CHOP in adults with disseminated aggressive lymphoma.

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THE REGIMEN OF CYCLOPHOSPHAMIDE, doxorubicin, vincristine, and prednisone (CHOP) is the standard initial treatment for disseminated aggressive lymphoma in adults.¹ No other multiagent combination has proved superior.² However, phase 2 trials of short-term conventional chemotherapy followed by high-dose chemotherapy and the transplantation of autologous hematopoietic stem cells have yielded excellent results.³⁻⁸ No formal comparison of such regimens with CHOP has been reported to date. In a randomized study of patients with aggressive lymphoma and a poor prognosis, the Milan group found the duration of failure-free survival was longer after high-dose chemotherapy and autologous stem-cell support than after a chemotherapy regimen containing five drugs.⁹ High-dose chemotherapy plus hematopoietic stem-cell transplantation was also superior to conventional chemotherapy in patients with aggressive lymphoma and a high-intermediate or high risk of death according to the age-adjusted International Prognostic Index¹⁰ who were in complete remission after first-line chemotherapy.¹¹ These results indicate that high-dose chemotherapy and autologous stem-cell support could replace standard chemotherapy as an initial treatment. The present trial, the Groupe Ouest-Est des Leucémies et des Autres Maladies du Sang (GOELAMS) 072 study, was designed to compare these two approaches in patients with disseminated aggressive lymphoma with a low, low intermediate, or high intermediate risk according to the age-adjusted International Prognostic Index. At the time of diagnosis, patients were randomly assigned to receive eight courses of CHOP or high-dose chemotherapy plus autologous stem-cell support.

METHODS

PATIENTS

This multicenter trial enrolled patients 15 to 60 years old with previously untreated, histologically proved aggressive lymphoma (intermediate or high-grade lymphoma) classified according to the working-formulation criteria of the National Cancer Institute.¹² Patients with transformed low-grade, lymphoblastic, mantle-cell, or Burkitt's lymphoma were excluded. Diagnostic slides were reviewed centrally by one pathologist. Other inclusion criteria were an Ann Arbor stage of III or IV or a stage of II with bulky abdominal disease (tumor mass more than 7 cm in largest diameter); a low, low interme-

di-ate, or high intermediate risk (i.e., a maximum of two of the possible adverse prognostic factors [regarding tumor stage, serum lactate dehydrogenase concentration, and performance status]) according to the age-adjusted International Prognostic Index (patients with a high risk were excluded); the absence of underlying organ dysfunction precluding the use of anthracycline or high-dose chemotherapy; and the absence of infection with the human immunodeficiency virus.

The trial was approved by the ethics committee of the Centre Hospitalier Universitaire de Nantes, Nantes, France, and all patients gave written informed consent. Randomization was performed according to center, with no further stratification.

Between November 1994 and December 1999, 207 consecutive patients were enrolled at 16 centers participating in GOELAMS. Ten patients were found to be ineligible: two were older than 60 years of age, and eight were in the high-risk category of the age-adjusted International Prognostic Index. Of the remaining 197 patients, 99 were assigned to the CHOP group and 98 to the high-dose chemotherapy group. The characteristics of the two groups were similar (Table 1), except for a younger median age in the high-dose group than in the CHOP group (45 years vs. 50 years, $P=0.02$).

STAGING

In addition to undergoing history taking, physical examination, routine laboratory tests, and bone marrow biopsy, all patients were evaluated for abdominal and thoracic involvement by means of computed tomography, with or without magnetic resonance imaging or ultrasonography. Whenever possible, a biopsy of suspected lymphomatous lesions was performed.

TREATMENTS

The conventional chemotherapy program consisted of eight courses of the standard CHOP regimen administered every 21 days: 750 mg of cyclophosphamide per square meter of body-surface area intravenously on day 1, 50 mg of doxorubicin per square meter intravenously on day 1, 1.4 mg of vincristine per square meter intravenously on day 1, and 100 mg of prednisone per square meter orally on days 1 through 5 (Fig. 1). Hematopoietic growth factor was given at the discretion of each investigator. An intrathecal injection of methotrexate (15 mg) plus methylprednisolone (20 mg) was routinely given on the first day of the first four courses of

CHOP. After four courses of CHOP, there was an intermediate evaluation of response. Patients who had at least a partial response (defined by a reduction of more than 50 percent in the size of the initial lesions) received four more courses of CHOP. After the completion of the chemotherapy, radiation therapy (30 Gy over a two-week period) was given to sites of previous bulky disease (those with a mass exceeding 7 cm). The patients were then followed without further treatment until relapse, death, or the last follow-up visit.

Patients in the high-dose group first received two courses of the following 15 days apart: 1200 mg of cyclophosphamide per square meter intravenously on day 1, 100 mg of epirubicin per square meter intravenously on day 1, 3 mg of vindesine per square meter intravenously on day 1, and 80 mg of prednisone per square meter orally or intravenously on days 1 through 5 (CEEP). Each course was supported with 5 µg of granulocyte-macrophage colony-stimulating factor (Schering-Plough) per kilogram of body weight per day intravenously or subcutaneously starting on day 5 of each course. An intrathecal injection of methotrexate (15 mg) and methylprednisolone (20 mg) was routinely given on the second day of each of the two courses of CEEP. Two to three leukaphereses were performed after the first or second course, or both courses, to obtain at least 2 million CD34+ hematopoietic stem cells per kilogram for cryopreservation.

An intermediate evaluation of the response was scheduled after the first two courses of CEEP. Patients who had at least a partial response received a combination of methotrexate (3 g per square meter intravenously on day 1) and cytarabine (100 mg per square meter per day by continuous infusion for five days) starting on day 37. The regimen of carmustine (300 mg per square meter intravenously on day 1), etoposide (400 mg per square meter intravenously on days 2 to 5), cytarabine (400 mg per square meter by continuous infusion on days 2 to 5), and melphalan (140 mg per square meter intravenously on day 6) was begun on day 66, followed within 36 to 48 hours after the melphalan by the infusion of peripheral-blood stem cells. Granulocyte-macrophage colony-stimulating factor was given until the neutrophil count recovered. As was the case for patients in the CHOP group, irradiation was given to sites of previous bulky disease. The patients were then followed without further treatment until relapse, death, or the last follow-up visit.

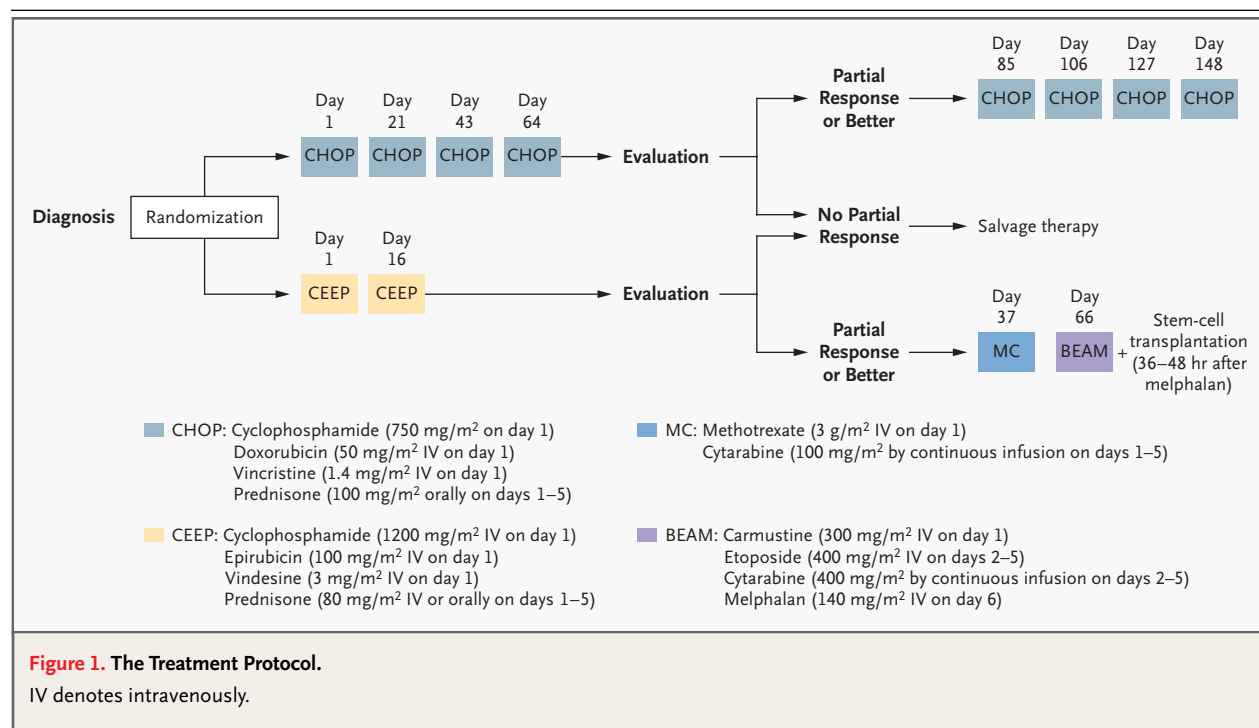
ASSESSMENT OF RESPONSE AND FOLLOW-UP

A complete response was defined by the disappearance of all documented disease. An unconfirmed complete response was defined by a reduction of at least 70 percent in the largest diameter of all measurable lesions in association with a complete response with respect to all other measures. A partial response was defined by a reduction of at least 50 percent in the largest diameter of every measurable lesion, even if bone marrow involvement persisted on the intermediate evaluation. The procedures used to evaluate responses were the same as those used for staging at diagnosis. A biopsy of residual lesion was not mandatory at the time of either the intermediate evaluation or the final evaluation. Gallium or positron-emission tomographic scanning was not routinely performed. Follow-up procedures included a physical examination every three months for the first two years, every six months for the next

Table 1. Base-Line Characteristics of the Patients.*

Characteristic	CHOP (N=99)	High-Dose Therapy (N=98)	P Value
Age			0.02
Median (yr)	50	45	
Range (yr)	20–60	15–60	
≤50 yr (no. of patients)	55	67	
>50 yr (no. of patients)	44	31	0.07
Sex (no. of patients)			0.5
Male	64	59	
Female	35	39	
Histologic findings (no. of patients)			0.3
Diffuse large B-cell lymphoma	74	76	
Anaplastic	5	10	
T-cell lymphoma	4	5	
Diffuse, aggressive, unclassifiable	16	7	
Ann Arbor stage (no. of patients)			0.5
I or II	21	16	
III or IV	78	82	
Performance status (no. of patients)			0.11
0 or 1	80	88	
≥2	19	10	
Elevated serum lactate dehydrogenase (no. of patients)	52	56	0.12
Bone marrow involvement (no. of patients)	24	32	0.2
Age-adjusted prognostic index (no. of patients)			0.5
Low risk	7	5	
Low intermediate risk	43	37	
High intermediate risk	49	56	

* CHOP denotes cyclophosphamide, doxorubicin, vincristine, and prednisone.



two years, and annually thereafter. Thoracic and abdominal computed tomography was performed every six months during the first two years and then at the discretion of the treating physician.

In each group, treatment was considered to have failed if patients did not have at least a partial response at the intermediate evaluation or had disease progression before the end of the treatment program. Such patients were offered salvage therapy, which could vary among the centers.

STATISTICAL ANALYSIS

Statistical analysis was performed with SPSS software (version 10.0).¹³ Overall survival and event-free survival were calculated according to the Kaplan–Meier method.¹⁴ Survival was measured from the time of randomization to death from any cause or the date of last contact. Event-free survival was calculated from the time of randomization; progression, the absence of at least a partial response on the intermediate evaluation, relapse, and death in remission were considered events. The log-rank test was used to compare survival in the two groups.¹⁵ The analysis was performed on an intention-to-treat basis for patients who had data that could be evaluated. Multivariate analysis of survival was performed with the use of the Cox model.¹⁶ Potential interactions between treatment and risk factors were also

assessed in the model. The trial was designed to detect an absolute difference in event-free survival of 20 percent at five years, with an α value of 0.05 and a β value of 0.1. Assuming an event-free survival rate at five years of 35 percent in the CHOP group and 55 percent in the high-dose group, this design required the randomization of 200 patients. Secondary end points were the response rate at the end of treatment, the overall survival rate, and the incidence of adverse effects.

This study was designed by the GOELAMS scientific committee. The data were collected by the principal investigator at each participating center, checked for accuracy by GOELAMS research assistants, and sent to the centralized data base in Nantes. One investigator analyzed and interpreted the data and was the principal writer of this article. The academic investigators had full access to the data. Schering had no role in designing the protocol; collecting, analyzing, or interpreting the data; or writing this article.

RESULTS

FEASIBILITY OF THE TREATMENT

Overall, 78 percent of the patients completed the assigned treatment: 72 percent of those in the CHOP group and 85 percent of those in the high-dose

group. The main reasons for not completing the treatment were the lack of an early response or disease progression (combined incidence, 27 percent in the CHOP group and 13 percent in the high-dose group). There was only one early death related to treatment in the high-dose group and one case of severe treatment-related effects precluding further therapy in each group. Leukaphereses were performed after the first course of CEEP in 21 percent of patients and after the second course in 79 percent; the median number was two (range, one to three). The median number of CD34+ cells harvested was 5.58×10^6 per kilogram.

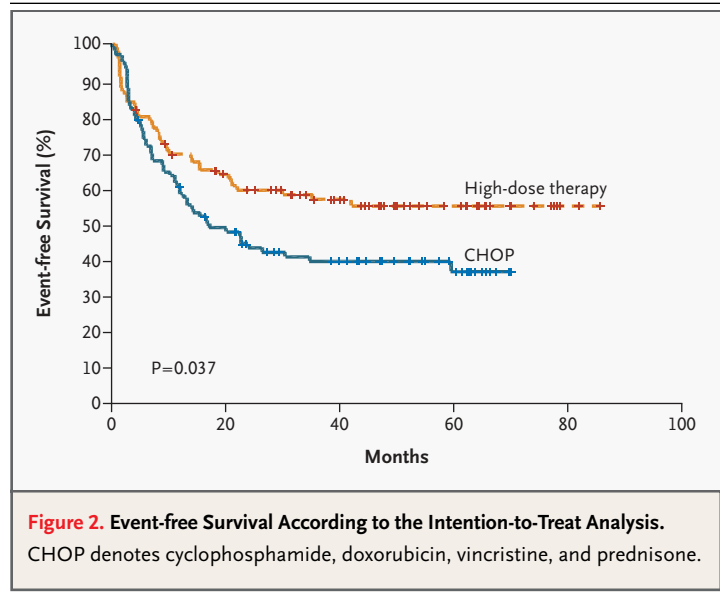
RESPONSE TO TREATMENT

The overall response rates at the intermediate evaluations were 84 percent after four courses of CHOP and 86 percent after two courses of CEEP. The overall response rates at the end of treatment were 62 percent in the CHOP group and 81 percent in the high-dose group; the rates of complete remission plus unconfirmed complete remission were 57 percent and 76 percent, respectively ($P=0.37$). Univariate analysis showed that the only adverse factor that significantly affected the response rate was an elevated lactate dehydrogenase level ($P=0.047$). Age, the B-cell or T-cell phenotype of the tumor, the number of extranodal sites, the presence or absence of bone marrow involvement, performance status, the presence or absence of bulky disease, and risk group according to the age-adjusted International Prognostic Index did not significantly affect the response rate.

SURVIVAL

After a median follow-up of four years for the entire cohort, the estimated rates (\pm SD) of overall survival and event-free survival were 63 ± 4 percent and 46 ± 4 percent, respectively. According to the intention-to-treat analysis, the event-free survival rates at five years differed significantly between the CHOP and high-dose groups (37 ± 5 percent vs. 55 ± 5 percent, $P=0.037$) (Fig. 2 and Table 2). The five-year rate of overall survival did not differ significantly between groups, although there was a trend toward a higher rate in the high-dose group than in the CHOP group (56 ± 5 percent vs. 71 ± 5 percent, $P=0.076$).

Among patients with a high intermediate risk according to the age-adjusted International Prognostic Index, high-dose treatment yielded significantly higher rates of event-free survival (56 ± 7 per-



cent vs. 28 ± 6 percent, $P=0.003$) (Fig. 3) and overall survival (74 ± 6 percent vs. 44 ± 7 percent, $P=0.001$) (Fig. 4) than did CHOP treatment. For patients with a low or low intermediate risk, the rates of overall survival and event-free survival were similar in the two groups (Table 2).

On multivariate analysis, overall survival was independently affected by an elevated lactate dehydrogenase level ($P=0.026$) and, to a lesser extent, by the treatment group ($P=0.066$). The risk according to the age-adjusted International Prognostic Index and age were not significant factors. Event-free survival was independently affected by the type of treatment ($P=0.019$). The lactate dehydrogenase level, age, and risk according to the age-adjusted International Prognostic Index were not retained in the multivariate analysis.

Overall, 65 patients died, 39 in the CHOP group and 26 in the high-dose group. Lymphoma was the main cause of death (in 94 percent of patients).

RELAPSE AND PROGRESSION

Ninety-six patients had progressive disease during the treatment or relapsed (58 of 99 in the CHOP group and 38 of 98 in the high-dose group, $P=0.005$). Among patients who had a complete, unconfirmed complete, or partial response by the time of the intermediate evaluation, the five-year disease-free survival rate was higher in the high-dose group than in the CHOP group (65 ± 6 percent vs. 45 ± 6 percent, $P=0.05$), with no significant difference in the five-year rate of overall survival (75 ± 5

Table 2. Five-Year Event-free and Overall Survival.*

Variable	Total No. of Patients	Event-free Survival %	P Value	Overall Survival %	P Value
Group			0.037		0.076
CHOP	99	37		56	
High-dose therapy	98	55		71	
Age			0.42		0.22
≤50 yr	122	50		68	
>50 yr	75	39		55	
Serum lactate dehydrogenase level			0.03		0.01
Normal	89	52		73	
Elevated	108	41		54	
Ann Arbor stage			0.36		0.4
I or II	37	54		68	
III or IV	160	44		62	
Bone marrow involvement†			0.40		0.69
No	133	49		62	
Yes	56	37		64	
B-cell phenotype			0.1		0.09
CHOP	82	37		56	
High-dose therapy	81	52		71	
T-cell phenotype			0.44		0.9
CHOP	7	21		0	
High-dose therapy	11	45		55	
Bone marrow involvement			0.11		0.06
CHOP	24	22		52	
High-dose therapy	32	52		76	
>1 Extranodal site			0.9		0.3
CHOP	19	37		52	
High-dose therapy	28	41		66	
Elevated serum lactate dehydrogenase			0.02		0.006
CHOP	51	30		40	
High-dose therapy	57	51		68	
Age-adjusted International Prognostic Index			0.9		0.4
Low or low intermediate risk					
CHOP	50	45		68	
High-dose therapy	42	54		66	
High intermediate risk			0.003		0.001
CHOP	49	28		44	
High-dose therapy	56	56		74	

* CHOP denotes cyclophosphamide, doxorubicin, vincristine, and prednisone.

† Data were missing for eight patients.

percent vs. 62 ± 6 percent, $P=0.1$). The patients with progressive or relapsed disease received various salvage chemotherapy regimens with or without allogeneic or autologous stem-cell transplantation. The five-year survival rate among these patients was 26 ± 7 percent in the CHOP group and 36 ± 9 percent in the high-dose group ($P=0.63$).

ADVERSE EVENTS

The median duration of hospitalization after the first course of chemotherapy was 2 days (range, 1 to

26) for CHOP and 4 days (range, 1 to 25) for CEEP. The median duration of hospitalization was 1 day for each of the subsequent courses of CHOP (range, 0 to 31), 3 days for the second course of CEEP (range, 1 to 19), and 7 days for the course with high-dose methotrexate and cytarabine (range, 5 to 23). After chemotherapy with carmustine, etoposide, cytarabine, and melphalan, all patients had neutrophil counts of more than 500 per cubic millimeter after a median of 9 days (range, 1 to 21) and a platelet count of more than 20,000 per cubic millimeter af-

ter a median of 4 days (range, 0 to 44). The median duration of hospitalization after this regimen was 22 days (range, 8 to 53). Fourteen patients had severe infections, and seven had interstitial pneumonitis. There were no grade 4 adverse events, and the most frequent grade 3 adverse events were nausea and vomiting, which occurred in 15 patients, and diarrhea, which occurred in 11 patients. There was one treatment-related death in the CHOP group and three in the high-dose group (one before autografting and two after the autograft).

DISCUSSION

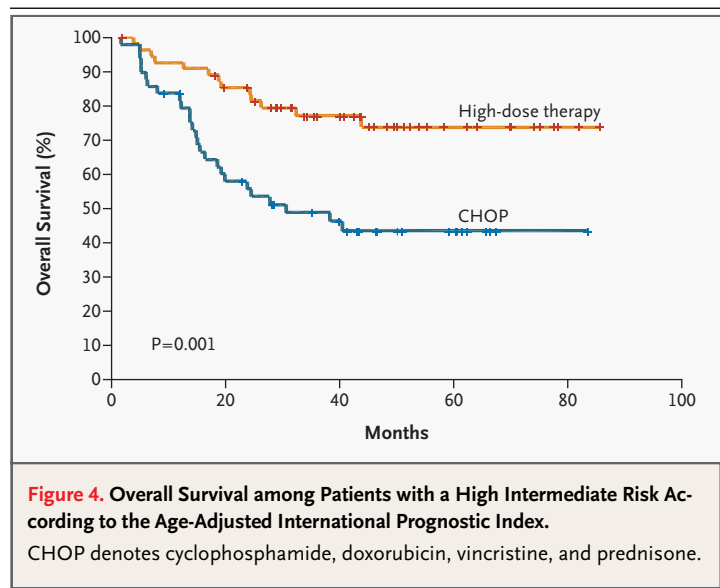
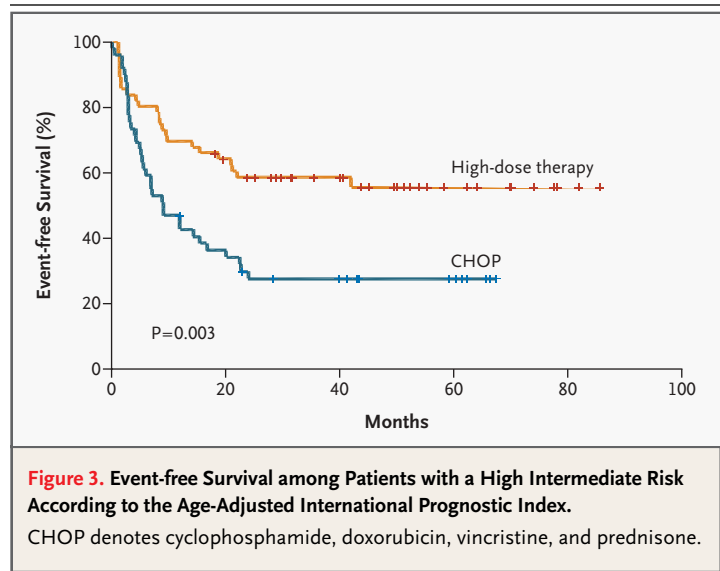
We found that for adults up to the age of 60 years who had newly diagnosed, aggressive non-Hodgkin's lymphoma and no more than two adverse prognostic factors, as defined by the age-adjusted International Prognostic Index, the event-free survival rate at five years was higher after a course of intensive chemotherapy plus hematopoietic stem-cell support than after the CHOP regimen (55 ± 5 percent vs. 37 ± 5 percent, $P=0.037$). There was no significant difference in overall survival at five years between the high-dose and CHOP groups (71 ± 5 percent and 56 ± 5 percent, respectively; $P=0.076$). With a median follow-up of four years among surviving patients, the results of the trial can be considered complete.

Several features of this trial must be taken into account when comparing it with other randomized trials of lymphoma therapy.^{9,17-19} First, we did not include patients classified as at high risk according to the age-adjusted International Prognostic Index, because at the time of its design, the results achieved with standard CHOP in such patients were very poor¹⁰ and phase 2 trials had suggested a benefit of high-dose chemotherapy with stem-cell support.³⁻⁸ For these reasons, we believed that randomly assigning high-risk patients to a treatment known to yield poor results or to one that was expected to end in a good result would be unethical. Subsequently, randomized phase 3 trials have confirmed that high-dose therapy with stem-cell support, as either consolidation therapy^{17,20} or initial treatment,⁹ increases progression-free and overall survival among high-risk patients who are younger than 60 years of age.

Second, since our control group received CHOP, it is difficult to compare our trial with trials that used other agents as the control treatment.^{9,11,17,20} Indeed, it is now debatable whether CHOP should

continue to be used as the control treatment in future trials, in view of the improved results obtained by adding rituximab to CHOP²¹ or by shortening the time between courses of CHOP.²²

Third, our high-dose group first received a brief, intensified course of CHOP-like therapy similar to the induction treatment in the recent Groupe d'Etude des Lymphomes de L'Adulte (GELA) trial,¹⁹ but we added a course of high-dose methotrexate plus cytarabine thereafter. This addition was intended to consolidate the response to CEEP and to



minimize any residual disease at the time of therapy with carmustine, etoposide, cytarabine, and melphalan and stem-cell support. Disease-free survival with this regimen was superior to that among patients who received four additional courses of CHOP (65 percent at five years, as compared with 45 percent; $P=0.05$). Our high-dose treatment and our results are similar to those of the Milan group; both studies showed improved event-free survival after sequential high-dose therapy.⁹

The most likely explanation for the similarity in five-year overall survival rates after CHOP or high-dose therapy (56 percent and 71 percent, respectively; $P=0.076$) is the use of rescue therapy in patients with progressive or relapsed disease in the CHOP group. Among patients who had no response to CHOP, the five-year survival rate was only 26 percent, a value that is similar to the rate of 21 percent among patients with no response to a similar regimen in the GELA trial.¹⁹ Many of these patients in our study had a short interval between diagnosis and progression or relapse (median, 7 months; range, 1 to 59), which is a poor prognostic factor with respect to second-line transplantation.²³

Nearly half the patients in the trial had two adverse prognostic factors, and among these patients, the respective rates of event-free and overall survival were 56 percent and 74 percent in the high-dose group and 28 percent and 44 percent in the CHOP group ($P=0.003$ for event-free survival and $P=0.001$ for overall survival). Similar results were also obtained among patients with at least two adverse factors who were in complete remission after induction therapy with doxorubicin, cyclophosphamide, vincristine, bleomycin, and prednisone followed by high-dose therapy.¹¹

For patients at low or low intermediate risk, there was no significant difference in overall or event-free survival between the two treatment groups; these results are similar to those reported in the European Organization for Research and Treatment of Cancer study.²⁴ This finding suggests there may be no need to expose such patients to the risk of intensive therapy. Indeed, there were three treatment-related deaths in the high-dose group. However, patients in these risk categories who have an elevated lactate dehydrogenase level may have the highest likelihood of a response to high-dose therapy, because a high lactate dehydrogenase level was found to be a predictive factor for survival. Early results from studies employing gene-expression profiles suggest that among patients at low and low intermediate risk, there is a subgroup with activated B-cell-like diffuse large-B-cell lymphomas who have a low likelihood of survival.²⁵⁻²⁷ Once gene-expression profiling becomes widely available, it will be important to evaluate the effect of high-dose treatment in this specific group.

In conclusion, first-line intensive chemotherapy with autologous stem-cell support is superior to CHOP for adults up to the age of 60 years with lymphoma who have a risk of death that is high intermediate, according to the age-adjusted International Prognostic Index. We believe that CHOP can no longer be regarded as the standard treatment for this group of patients.

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APPENDIX

The Groupe Ouest-Est des Leucémies et des Autres Maladies du Sang included the following centers and principal investigators in France: P. Casassus, University Hospital of Bobigny, Bobigny; H. Maisonneuve, Centre Hospitalier Départemental of La Roche Sur Yon, La Roche Sur Yon; C. Le Maignan, Hôpital Européen Georges Pompidou of Paris, Paris; J.-F. Rossi, University Hospital of Montpellier, Montpellier; J.-F. Ramee, Centre Catherine de Sienne, Nantes; A. Le Mevel, Centre René Gauducheau, Nantes; P. Moreau, Centre Hospitalier Départemental of Lorient, Lorient; A.-M. Blaise, University Hospital of Reims, Reims; B. Desablens, University Hospital of Amiens, Amiens; J. Jauvert, University Hospital of St. Etienne, St. Etienne; T. Lamy, University Hospital of Rennes, Rennes; and H. Jarda, Centre Hospitalier Départemental of Vannes, Vannes.

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