

A CONTROLLED STUDY OF RECOMBINANT HUMAN GRANULOCYTE COLONY-STIMULATING FACTOR IN ELDERLY PATIENTS AFTER TREATMENT FOR ACUTE MYELOGENOUS LEUKEMIA

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Abstract Background. Intensive chemotherapy for acute myelogenous leukemia (AML) continues to yield low rates of complete remission and survival among patients over the age of 65 years. Infection-related mortality is particularly high among these patients during the period of neutropenia that follows chemotherapy. We determined the effect of lenograstim (glycosylated recombinant human granulocyte colony-stimulating factor) on mortality at eight weeks (the main end point) and the rate of complete remission among patients with AML who were 65 years old or older.

Methods. After induction chemotherapy with daunorubicin (45 mg per square meter of body-surface area per day for 4 days) and cytarabine (200 mg per square meter per day for 7 days), 173 patients with newly diagnosed AML were randomly assigned on day 8 to receive either lenograstim (5 μ g per kilogram of body weight per day) or placebo, starting on day 9, until there was neutrophil recovery or a treatment failure, or for a maximum of 28 days. Salvage chemotherapy was also followed by lenograstim or placebo. Patients with a complete remission

received two consolidation courses of chemotherapy without lenograstim or placebo.

Results. The mortality rate at eight weeks was similar in the lenograstim and placebo groups (23 and 27 percent, respectively; $P = 0.60$), as was the incidence of severe infections. The median duration of neutropenia (absolute neutrophil count, ≤ 1000 per cubic millimeter) was shorter in the lenograstim group (21 days, as compared with 27 days in the placebo group; $P < 0.001$). Eight percent of the patients in both groups had regrowth of AML cells. The rate of complete remission was significantly higher in the lenograstim group (70 percent, as compared with 47 percent in the placebo group; $P = 0.002$). Overall survival, however, was similar in the two groups ($P = 0.76$).

Conclusions. The administration of lenograstim after chemotherapy for AML did not decrease the mortality rate at eight weeks among patients over the age of 65 years. The patients who received lenograstim had a significantly higher rate of complete remission than those who received placebo. Nevertheless, the overall survival in the two groups did not differ significantly. (N Engl J Med 1995;332:1678-83.)

MORE than 40 percent of patients with acute myelogenous leukemia (AML) are over 65 years old at the time of the diagnosis.^{1,2} A high rate of treatment-related mortality keeps the rate of complete remission below 50 percent and the median survival between 9 and 12 months in these older patients.³⁻⁶

Among patients over 65, the mortality rate during the aplastic phase that follows intensive chemotherapy is 30 to 40 percent.⁴⁻⁸ Infections cause approximately two thirds of treatment-associated deaths.⁹⁻¹¹ Moreover, AML in older patients often has features associated with a poor response to chemotherapy, such as involvement of immature progenitor cells,¹² a prior myelodysplastic syndrome,^{13,14} and particular chromosomal abnormalities.¹⁵⁻¹⁷

We report the results of a multicenter, double-blind, placebo-controlled, randomized clinical trial in which lenograstim (glycosylated recombinant human granulocyte colony-stimulating factor [G-CSF]) or placebo was administered after the completion of intensive induction chemotherapy in elderly patients with newly diagnosed AML. The main objective of the study was to determine the ability of lenograstim to reduce mortality at eight weeks by shortening the duration of marrow

aplasia. We found no difference in mortality at eight weeks between the two treatment groups. There was a significantly higher rate of complete remission in the lenograstim group; however, overall survival in the two groups was essentially the same. There was no evidence of in vivo regrowth of AML cells due to lenograstim, despite evidence that this drug promotes in vitro growth of AML cells.¹⁸

METHODS

Patients

Patients 65 years old or older with newly diagnosed, untreated AML were eligible for enrollment in the study. Patients were excluded if they had a Karnofsky performance status lower than 40 percent; an abnormal left ventricular ejection fraction; central nervous system involvement; AML subtype M3, according to the French-American-British (FAB) classification¹⁹; AML due to prior treatment with chemotherapy or radiation; or a history of myelodysplastic syndrome, documented by examination of a bone marrow specimen, for more than three months. Hypocellular AML was defined as AML with more than 30 percent blast cells in a hypoplastic bone marrow specimen. Cytogenetic features were classified as favorable — $t(8;21)$ or $inv(16)$ — intermediate (normal diploid), or unfavorable (other abnormal karyotypes), according to previously published criteria.²⁰

The induction course of chemotherapy consisted of daunorubicin (45 mg per square meter of body-surface area per day for four days) and a continuous infusion of cytarabine (200 mg per square meter per day for seven days). All enrolled patients gave written informed consent before undergoing induction chemotherapy. The study was approved by the ethics committee at each participating center.

Treatment

On day 8 after the initiation of induction chemotherapy, patients were randomly assigned to receive lenograstim at a daily dose of 5 μ g per kilogram of body weight or placebo administered as a 30-minute intravenous infusion, starting on day 9. The study medication was

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continued until there was evidence of neutrophil recovery (absolute neutrophil count >1000 per cubic millimeter for three consecutive days) or for a maximum of 28 days. Medication was discontinued in patients with resistant disease or regrowth of leukemic cells. Bone marrow was assessed at the time of neutrophil recovery or on day 35 in the case of persistent neutropenia, or earlier if the number of circulating leukemic blasts reached 2000 per cubic millimeter after a period of documented leukopenia.

The presence of resistant disease was not determined before day 21. Patients with resistant disease who were eligible for salvage therapy received cytarabine (500 mg per square meter every 12 hours) on days 1 through 3 and mitoxantrone (12 mg per square meter per day) on days 3 and 4. A second course of the assigned study medication (lenograstim or placebo) was given after the salvage treatment, starting on day 5. Patients with a complete remission, including those who had a response to the salvage therapy, received two courses of consolidation therapy, six weeks apart, and no maintenance therapy. The first course of consolidation therapy consisted of cyclophosphamide (600 mg per square meter) administered intravenously on day 1, vincristine (1.5 mg per square meter, with a maximal dose of 2 mg) administered intravenously on day 1, cytarabine (100 mg per square meter per day) administered subcutaneously on days 1 through 5, and prednisolone (60 mg per square meter per day) administered orally on days 1 through 5. The second consolidation regimen consisted of mitoxantrone (10 mg per square meter per day) for two days and cytarabine (100 mg per square meter every 12 hours) for five days. The study medication was not administered after the consolidation courses.

Criteria for Residual Marrow Leukemia, Leukemic-Cell Regrowth, Response, and Infectious Events

Residual marrow leukemia on day 8 was considered documented when the proportion of abnormal marrow cells was greater than 3 percent.²¹ Leukemic-cell regrowth was defined as more than 2000 leukemic blasts per cubic millimeter after an absolute leukocyte count that was less than 500 per cubic millimeter, or 50 percent more leukemic blasts in the bone marrow sample obtained on day 14 than in the sample obtained on day 8, in samples of equal or greater cellularity. Complete remission, partial remission, and treatment failure were defined according to the criteria of the National Cancer Institute.²² Treatment failure was defined as resistant disease (partial remission or no remission) or death (early death or death during treatment-induced bone marrow hypoplasia). Infectious events were classified by the treating physicians as mild, moderate, severe, or life-threatening. Data on severe and life-threatening infections were compared in the two treatment groups.

Statistical Analysis

The main objective of this study was to reduce the number of deaths within the seven-week period after randomization (eight-week mortality). Assuming an eight-week mortality of 30 percent in the placebo group, we calculated the sample size required to detect a 50 percent reduction in that rate. The secondary objectives were to increase the rate of complete remission and assess the safety of treatment with lenograstim. To allow the study to be stopped early in the event that an early conclusion was reached, we compared the eight-week mortality rate among every 30 patients enrolled, using the triangular test on an intention-to-treat basis (with a type I error of 0.05 and a type II error of 0.10).²³ An independent data-monitoring committee determined whether the study should be continued or stopped after each such analysis.

Comparisons between the two treatment groups were performed with Fisher's exact test for binary variables and the Kruskal-Wallis test for continuous variables. Data on treatment failure were estimated by the Kaplan-Meier method,²⁴ and comparisons were made with the log-rank test.²⁵ Since age, the initial degree of hyperleukocytosis, the presence or absence of marrow blasts after the completion of induction chemotherapy, and cytogenetic status are known to be prognostic factors for complete remission or the duration of complete remission,^{16,17,21,26} comparisons were adjusted for these four prognostic factors with a logistic-regression analysis (for the rate of complete remission)²⁷ and the Cox model (for overall survival and event-free survival)²⁸ and tested by the likelihood-ratio test. Event-free survival and overall survival were calculated from the date of random assign-

ment. Event-free survival was calculated as survival without resistant disease, relapse, or death. The duration of complete remission was calculated from the date of the first complete remission until the date of the first relapse. To determine whether treatment effects were homogeneous among various subgroups of patients defined according to the four prognostic variables noted above, interactions among treatment covariates were tested as described by Gail and Simon.²⁹ Relative risks in the lenograstim group, as compared with the placebo group, were estimated for each end point, with 95 percent confidence intervals. P values were derived from two-sided tests. A P value of 0.05 or less was considered to indicate statistical significance. SAS software (SAS Institute, Cary, N.C.) was used for statistical analyses.

Study Termination

The study was terminated in December 1992 by the data-monitoring committee, because the results of the fifth sequential analysis (with a total of 150 patients) showed no benefit of lenograstim in terms of mortality at eight weeks. At this time, 23 additional patients had entered the study. The results reported here, which are for all 173 patients who had undergone randomization, are based on follow-up data as of January 1, 1995.

RESULTS

Selection of Patients

Between October 1990 and December 1992, 233 eligible patients from 27 centers were registered. Thirty-six patients were judged by physicians to be unsuitable to receive the planned chemotherapy because they had "poor status" (median age, 79 years; range, 65 to 92); two additional patients discontinued the study for personal reasons. The other 195 patients (median age, 70 years; range, 64 to 83) received induction chemotherapy. Ten patients died during induction chemotherapy (three from infection-related events, five from hemorrhage, and two from the acute respiratory distress syndrome). Twelve patients were not randomized because they declined, their condition was too unstable, the induction chemotherapy they received differed from the planned treatment, or the study medication was unavailable. Thus, 173 patients were randomly assigned on day 8 to receive lenograstim or placebo.

Characteristics of the Patients

Eighty-eight patients received lenograstim, and 85 received placebo. The two groups were similar in terms of age, sex, FAB subtype, and initial mean white-cell count (Table 1). Only 3 of the 17 severe infectious events occurring before the time of randomization were responsible for early death (2 in the placebo group and 1 in the lenograstim group). Cytogenetic features were evenly balanced between the two treatment groups (Table 1). Bone marrow aspirates were obtained on day 8 from 171 of the 173 patients. Residual blasts were present in aspirates from 48 percent of the patients in the lenograstim group and in aspirates from 55 percent of the patients in the placebo group.

Mortality at Eight Weeks

The mortality rate at eight weeks was 23 percent in the lenograstim group (20 of 88 patients) and 27 percent in the placebo group (23 of 85 patients). This difference was not statistically significant ($P=0.60$ by Fisher's exact test; relative risk, 0.84; 95 percent confidence interval, 0.50 to 1.40 percent). Table 2 shows the

causes of death and the AML status at the time of death. The median time from randomization to death was 14 days in the lenograstim group and 19 days in the placebo group ($P=0.93$ by the log-rank test).

Duration of Aplasia and Incidence of Infections

In the 88 patients who had a complete remission after one course of induction chemotherapy, the median time from the start of chemotherapy to the measurement of a neutrophil count higher than 1000 per cubic millimeter was 21 days (range, 16 to 28) among the 54 patients in the lenograstim group and 27 days (range, 20 to 34) among the 34 patients in the placebo group ($P<0.001$ by the Kruskal–Wallis test). However, the incidence and type of severe and life-threatening infectious events during the first seven weeks after randomization were similar in the two groups (Table 3).

Response to Induction Therapy

The rate of complete remission was 70 percent in the lenograstim group and 47 percent in the placebo group

Table 1. Characteristics of 173 Patients with AML Assigned to Treatment with Lenograstim or Placebo.

CHARACTERISTIC	LENOGRASTIM GROUP (N = 88)	PLACEBO GROUP (N = 85)
Age (yr)*		
Median	71	71
Range	64–83	64–83
Male sex (%)	54	56
Infection at diagnosis (no. of patients)		
None	55	58
Fever of unknown origin	20	13
Documented infection	13	14
Severe infection at randomization (no. of patients)		
Pneumonia	3	4
Septicemia	1	2
Systemic fungal infection	0	1
Fever of unknown origin	2	4
FAB subtype (no. of patients)		
M0	5	2
M1	21	30
M2	30	24
M4	9	16
M5	11	7
M6	2	1
M7	4	2
Mixed lineage	5	1
Hypocellular	1	2
White-cell count at diagnosis (no. of patients)		
<10,000/mm ³	51	43
10,000–100,000/mm ³	26	36
>100,000/mm ³	11	6
Mean peripheral-blood blast count/mm ³ †	36,000	33,000
Mean marrow blast infiltration (%)	63	57
Cytogenetic analysis (no. of patients)		
Performed	60 (68%)	48 (56%)
Favorable	2	1
Intermediate	28	22
Unfavorable	30	25
+8	4	1
11q23 abnormalities	1	2
Isolated -5, 5q-, -7, 7q-	2	0
-5, 5q-, -7, 7q- and other rearrangements	4	4
Other single or double rearrangements	13	11
Complex rearrangements	5	6
Insufficient metaphases	1	1

*Two patients who were 64 years old (one in each treatment group) were randomized and considered in the statistical analysis according to the intention-to-treat principle.

†Blast counts were available for 81 patients in the lenograstim group and 75 patients in the placebo group.

Table 2. Primary Cause of Death and AML Status at the Time of Death among Patients Who Died within the First Eight Weeks.*

DEATHS	LENOGRASTIM GROUP (N = 88)	PLACEBO GROUP (N = 85)	RELATIVE RISK (95% CI)	P VALUE
	<i>no. of patients (%)</i>			
No. (%)	20 (23)	23 (27)	0.84 (0.50–1.40)	0.60
Immediate cause (no. of patients)				
Infection-related	15	17		
Hemorrhage	3	2		
Chemotherapy toxicity	1	2		
Myocardial infarction	1	0		
Suicide	0	1		
Unknown	0	1		
AML status at the time of death				
Complete remission	2	1		
Resistant disease	7	5		
Not assessable				
Residual marrow blasts	4	6		
No residual marrow blasts	5	7		
Unknown marrow status	2	4		

*CI denotes confidence interval. The P value was determined by Fisher's exact test.

($P=0.002$ by Fisher's exact test; relative risk, 1.50; 95 percent confidence interval, 1.15 to 2.00 percent) (Table 4). Fifty-four patients (61 percent) in the lenograstim group had a complete remission after one course of induction therapy, as compared with 34 patients (40 percent) in the placebo group ($P=0.006$ by Fisher's exact test). Among the patients eligible for salvage therapy, 15 of 22 in the lenograstim group and 23 of 34 in the placebo group actually received this treatment. After salvage chemotherapy, eight patients in the lenograstim group and six in the placebo group had a complete remission. This difference was not statistically significant ($P=0.17$ by Fisher's exact test). The mean time to a complete remission after randomization was 24 days in the lenograstim group and 33 days in the placebo group ($P=0.0015$ by the Kruskal–Wallis test).

After the logistic-regression model had been used to adjust for age, presence or absence of marrow blasts on day 8, and initial white-cell count, the P value for the treatment comparison was 0.004, whereas it was 0.08 after adjustment for the same variables plus cytogenetic status in the subgroup of 108 patients who underwent cytogenetic testing.

The subgroup analysis according to prognostic factors showed that in the lenograstim group, the increase in the rate of complete remission was greater among the patients with residual marrow blasts on day 8 or unfavorable cytogenetic abnormalities than among the patients without those features (Table 5). However, these differences were not statistically significant according to the Gail–Simon interaction test ($P=0.20$ and $P=0.60$, respectively).

Event-free Survival and Duration of Complete Remission

One patient was lost to follow-up in each treatment group. Eighty-three events occurred in the lenograstim group and 81 in the placebo group. Despite the higher rate of complete remission in the lenograstim group, event-free survival was not significantly increased in

this group ($P=0.39$ by the log-rank test; relative risk, 0.87; 95 percent confidence interval, 0.65 to 1.19) (Fig. 1). Event-free survival remained unchanged after adjustment for age, presence or absence of marrow blasts on day 8, and initial white-cell count ($P=0.54$ by the likelihood-ratio test), as well as after adjustment for the same variables plus cytogenetic status in the subgroup of 108 patients who underwent cytogenetic testing ($P=0.81$ by the likelihood-ratio test). The duration of complete remission was similar in the two treatment groups ($P=0.40$ by the log-rank test; relative risk of relapse in the lenograstim group, 1.20; 95 percent confidence interval, 0.77 to 1.90).

Overall Survival

Of the 173 patients, 148 died (75 in the lenograstim group and 73 in the placebo group). Overall survival was similar in the two groups ($P=0.76$ by the log-rank

Table 3. Incidence of Severe Infections.*

INFECTIOUS EVENT	LENOGRASTIM GROUP (N = 88)	PLACEBO GROUP (N = 85)
No.	42	41
Type		
Pneumonia	11	14
Septicemia	14	13
Septic shock	2	3
Systemic fungal infection	4	0
Cellulitis	0	2
Herpes	1	0
Fever of unknown origin	10	9

*Severe and life-threatening infectious events during the interval between randomization and the end of the eighth week after the initiation of induction therapy.

test; relative risk in the lenograstim group, 0.95; 95 percent confidence interval, 0.69 to 1.31) (Fig. 2). At 12 months, the estimated survival was 45 percent in the lenograstim group (95 percent confidence interval, 35 to 56 percent) and 40 percent in the placebo group (95 percent confidence interval, 30 to 50 percent). Adjustment for age, presence or absence of marrow blasts on day 8, and initial white-cell count did not modify these results ($P=0.82$ by the likelihood-ratio test), nor were they altered by adjustment for the same variables plus cytogenetic status ($P=0.99$ by the likelihood-ratio test).

Safety and Side Effects

In each group seven patients (8 percent) had leukemic-cell regrowth in marrow on day 14, leading to their withdrawal from the study. All seven patients in the placebo group had residual marrow blasts on day 8, but four of the seven patients in the lenograstim group did not. Spontaneous regression of marrow blast-cell proliferation was not observed after the withdrawal of lenograstim. No marked side effects were observed in either treatment group.

DISCUSSION

Since the late 1980s, recombinant human colony-stimulating factors have been administered to patients

Table 4. Outcome of Induction Therapy.*

OUTCOME	LENOGRASTIM GROUP (N = 88)	PLACEBO GROUP (N = 85)	RELATIVE RISK (95% CI)*	P VALUE
<i>no. of patients (%)</i>				
Complete remission	62 (70)	40 (47)	1.50 (1.15–2.00)	0.002
After induction therapy	54	34	1.53 (1.13–2.09)	0.006
After induction and salvage therapy	8	6	—	—
No response	26 (30)	45 (53)		
Resistant disease	13	28	0.45 (0.25–0.81)	0.007
Death	13	17	0.74 (0.38–1.43)	0.42

*CI denotes confidence interval. P values were determined by Fisher's exact test.

with AML to reduce the duration of neutropenia and the incidence of fatal infection, to increase the efficacy of cytotoxic agents by inducing the cycling of leukemic cells, or both.³⁰⁻⁴⁰ However, no substantial decrease in treatment-related mortality has been reported in randomized studies of either G-CSF^{30,35} or granulocyte-macrophage colony-stimulating factor (GM-CSF).^{33,34,40}

This randomized trial of lenograstim in patients with AML over the age of 65 years failed to demonstrate a decrease in mortality at eight weeks, despite a significant shortening of the neutropenic phase. However, lenograstim significantly increased the rate of complete remission by reducing the incidence of resistant leukemia. This result suggests that G-CSF contributes to the antileukemic effect of the chemotherapy. Even so, the overall survival in the lenograstim and placebo groups was virtually identical (Fig. 2). A trend toward an increase in the rate of complete remission has been reported among Japanese patients who were given G-CSF after chemotherapy for relapses or refractory acute leukemia³⁰ and older patients with AML given yeast-

Table 5. Rate of Complete Remission According to Prognostic Factors for Complete Remission.

PROGNOSTIC FACTOR	LENOGRASTIM GROUP (N = 88)	PLACEBO GROUP (N = 85)	P VALUE*	P VALUE†
<i>no. with CR/all patients (%)‡</i>				
Age (yr)				
≤70	32/43 (74)	21/42 (50)	0.03	0.002
>70	30/45 (67)	19/43 (44)	0.05	
White-cell count				
<50,000/mm ³	53/73 (73)	33/66 (50)	0.009	0.002
≥50,000/mm ³	9/15 (60)	7/19 (37)	0.30	
Residual marrow blasts on day 8§				
Yes	28/42 (67)	16/46 (35)	0.005	0.002
No	34/45 (76)	24/38 (63)	0.24	
Cytogenetic data¶				
Missing	22/28 (79)	17/37 (46)	0.01	0.002
Favorable	1/2 (50)	0/1	1.00	
Intermediate	19/28 (68)	12/22 (55)	0.39	
Unfavorable	20/30 (67)	11/25 (44)	0.11	

*By Fisher's exact test.

†The P value for the rate of complete remission after adjustment for each covariate, by the Mantel-Haenszel test.

‡CR denotes complete remission.

§Determined in 171 of the 173 randomized patients (87 in the lenograstim group and 84 in the placebo group).

¶Determined in 108 of the 173 randomized patients (60 in the lenograstim group and 48 in the placebo group).

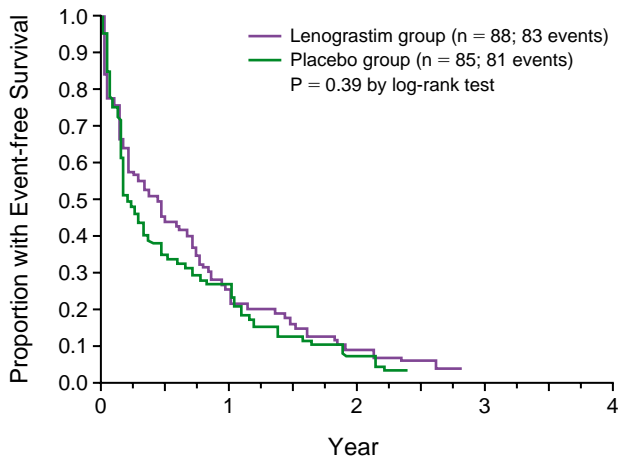


Figure 1. Kaplan-Meier Estimate of Event-free Survival among 173 Patients with AML, According to Treatment Group.

derived GM-CSF after chemotherapy.³³ Our study also suggests that patients with unfavorable or intermediate cytogenetic abnormalities have approximately the same rate of complete remission when treated with lenograstim. A similar result was reported in a nonrandomized study using G-CSF in patients with AML and myelodysplastic syndromes.³⁶

The criteria for complete remission that we used included not only recovery of normal granulocytes but also normal erythropoiesis and thrombopoiesis. By using these criteria, we avoided an underestimation of the percentage of residual marrow leukemic blasts at the time of myeloid recovery and, hence, the misclassification of resistant disease as complete remission.

The higher complete-remission rate associated with the administration of lenograstim was not translated into a significant improvement in survival. The Japanese study also failed to demonstrate prolonged overall survival among patients treated with G-CSF.³⁰ In its study of multiple courses of combined treatment with chemotherapy and GM-CSF, however, the Eastern Cooperative Oncology Group reported a significant in-

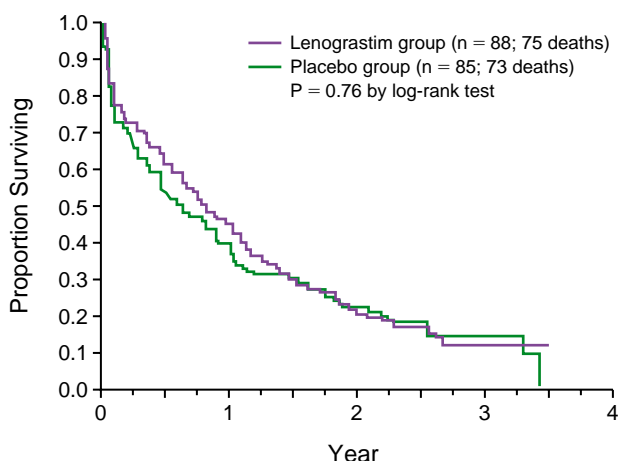


Figure 2. Kaplan-Meier Estimate of Overall Survival among 173 Patients with AML, According to Treatment Group.

crease in median survival among patients with AML, although they were younger than those enrolled in our study.³³

In conclusion, lenograstim appears to be a safe treatment, but it does not reduce mortality at eight weeks when given after intensive chemotherapy in older patients with AML. Although the drug significantly increased the rate of complete remission, it had no effect on overall survival.

APPENDIX

The following institutions and investigators participated in the AML Cooperative Study Group:

Hôpital Saint-Louis, Paris: L. Degos, H. Dombret, J.P. Marolleau, and S. Castaigne; Hôpital Pont-Chaillou, Rennes, France: P.Y. Lep-risé, T. Lamy de la Chapelle, and P. Vanroomen; Hôpital Henri Becquerel, Rouen, France: H. Tilly, A. Stamatoullas, D. Boulet, and M. Varin; Hôpital Sud, Rennes, France: B. Grosbois, R. Leblay, and R. Le Sidener; Hôpital Val-de-Grace, Paris: G. Auzanneau and G. Nedellec; Hôpital Pitié-Salpêtrière, Paris: L. Sutton; Hôpital Lyon Sud, Lyons, France: B. Coiffier, Y. Bastion, and D. Espinouse; Hôpital Sud, Amiens, France: B. Desablens; Hôpital Antoine Bé-clère, Clamart, France: G. Tertian and R. d'Oiron; Hôpital Claude Huriez, Lille, France: P. Fenaux and L. Detournignies; Hôpital Schnaffer, Lens, France: B. Dupriez and D. Resch; Hôpital Dupuytren, Limoges, France: D. Bordessoule, L. Remenieras, I. Cattri-Thomas, and M. Cransac; Hôpital Haut Lévêque, Bordeaux, France: J. Reiffers and P. Cony-Makhoul; Institut Paoli Calmettes, Marseilles, France: J. Gastaut and R. Bouabdallah; Clinique Notre Dame, Char-leroi, Belgium: J.L. Canon; Hôpital Mont Godinne, Vvoir, Belgium: A. Bosly; Cliniques Universitaires Saint-Luc, Brussels, Belgium: A. Ferrant; Hôpital de Jolimont, La Louvière, Belgium: A. Delannoy; Hôpital Saint-Joseph, Gilly, Belgium: P. Mineur; Università La Sapi-enza, Rome: F. Mandelli, A. Spadea, and M. Petti; Kantonspital, Aarau, Switzerland: M. Wernli; Inselspital, Berne, Switzerland: M.F. Fey, P. Straub, A. Tobler, and K. Bruner; Kantonspital, Basel, Switzerland: A. Grathwohl, M. Bargetzi, M. Pless, R. Haberrthür, and J. Charvat; Royal Victoria Hospital, Sunderland, United Kingdom: P. Carey, S. Proctor, A. Taylor, N. Lennard, and G. Jackson; Christie Hospital, Manchester, United Kingdom: J.H. Scarffe, J. Gledhill, E. Richard, L. Jayson, and G. Morgenstern; Saint George's Hospital, London: E.C. Gordon-Smith, D. Bevan, and A. Laurie; University Hospital Wales, Cardiff, United Kingdom: J.A. Whittaker, D. Fegan, D. Holmes, and R. Evelyn.

Trial monitoring: A. Yver, D. Richard, S. Flanagan, E. Quiles, and L. Gautier. Statistical analysis: C. Chastang, S. Chevret, F. Dabouz-Harrouche, and Y. Boudraa. Data management: V. Pellan.

REFERENCES

1. Brincker H. Estimate of overall treatment results in acute nonlymphocytic leukemia based on age-specific rates of incidence and of complete remission. *Cancer Treat Rep* 1985;69:5-11.
2. Groupe Français de Morphologie Hematologique. French registry of acute leukemia and myelodysplastic syndromes: age distribution and hemogram analysis of the 4496 cases recorded during 1982-1983 and classified according to FAB criteria. *Cancer* 1987;60:1385-94.
3. Rees JKH, Gray RG, Swirsky D, Hayhoe FGJ. Principal results of the Medical Research Council's 8th acute myeloid leukaemia trial. *Lancet* 1986;2:1236-41.
4. Preisler H, Davis RB, Kirshner J, et al. Comparison of three remission induction regimens and two postinduction strategies for the treatment of acute nonlymphocytic leukemia: a Cancer and Leukemia Group B study. *Blood* 1987;69:1441-9.
5. Zittoun R, Jehn U, Fièrè D, et al. Alternating v repeated postremission treatment in adult acute myelogenous leukemia: a randomized phase III study (AML6) of the EORTC Leukemia Cooperative Group. *Blood* 1989;73:896-906.
6. Dillman RO, Davis RB, Green MR, et al. A comparative study of two different doses of cytarabine for acute myeloid leukemia: a phase III trial of Cancer and Leukemia Group B. *Blood* 1991;78:2520-6.
7. Rees JKH, Gray R. Comparison of 1+5 DAT and 3+10 DAT followed by COAP or MAZE consolidation therapy in the treatment of acute myeloid leukemia: MRC ninth AML trial. *Semin Oncol* 1987;14:Suppl 1:32-6.

8. Tilly H, Castaigne S, Bordessoule D, et al. Low-dose cytarabine versus intensive chemotherapy in the treatment of acute nonlymphocytic leukemia in the elderly. *J Clin Oncol* 1990;8:272-9.
9. Estey EH, Keating MJ, McCredie KB, Bodey GP, Freireich EJ. Causes of initial remission induction failure in acute myelogenous leukemia. *Blood* 1982;60:309-15.
10. Kahn SB, Begg CB, Mazza JJ, Bennett JM, Bonner H, Glick JH. Full dose versus attenuated dose daunorubicin, cytosine arabinoside, and 6-thioguanine in the treatment of acute nonlymphocytic leukemia in the elderly. *J Clin Oncol* 1984;2:865-70.
11. Tucker J, Thomas AE, Gregory WM, et al. Acute myeloid leukemia in elderly adults. *Hematol Oncol* 1990;8:13-21.
12. Fialkow PJ, Singer JW, Raskind WH, et al. Clonal development, stem-cell differentiation, and clinical remissions in acute nonlymphocytic leukemia. *N Engl J Med* 1987;317:468-73.
13. Johnson PRE, Liu Yin JA. The influence of clinical or morphological myelodysplasia on the outcome of therapy in elderly patients with acute myeloid leukaemia. *Haematologica* 1991;76:Suppl 4:130. abstract.
14. Liu Yin JA, Johnson PRE, Davies JM, et al. Mitozantrone and cytosine arabinoside as first-line therapy in elderly patients with acute myeloid leukaemia. *Br J Haematol* 1991;79:415-20.
15. Rowley JD, Alimena G, Garson OM. A collaborative study of the relationship of the morphological type of acute nonlymphocytic leukemia with patient age and karyotype. *Blood* 1982;59:1013-22.
16. Fenaux P, Preudhomme C, Lai JL, Morel P, Beuscart R, Bauters F. Cytogenetics and their prognostic value in de novo acute myeloid leukaemia: a report on 283 cases. *Br J Haematol* 1989;73:61-7.
17. Schiffer CA, Lee EJ, Tomiyasu T, Wiernik PH, Testa JR. Prognostic impact of cytogenetic abnormalities in patients with de novo acute nonlymphocytic leukemia. *Blood* 1989;73:263-70.
18. Löwenberg B, Touw IP. Hematopoietic growth factors and their receptors in acute leukemia. *Blood* 1993;81:281-92.
19. Bennett JM, Catovsky D, Daniel MT, et al. Proposed revised criteria for the classification of acute myeloid leukemia: a report of the French-American-British Cooperative Group. *Ann Intern Med* 1985;103:620-5.
20. Bloomfield CD, Lawrence D, Arthur DC, Berg DT, Schiffer CA, Mayer RJ. Curative impact of intensification with high-dose cytarabine (HiDAC) in acute myeloid leukemia (AML) varies by cytogenetic group. *Blood* 1994;84: Suppl 1:111a. abstract.
21. Preisler HD, Raza A, Early A, et al. Intensive remission consolidation therapy in the treatment of acute nonlymphocytic leukemia. *J Clin Oncol* 1987; 5:722-30.
22. Cheson BD, Cassileth PA, Head DR, et al. Report of the National Cancer Institute-sponsored workshop on definitions of diagnosis and response in acute myeloid leukemia. *J Clin Oncol* 1990;8:813-9.
23. Whitehead J. The design and analysis of sequential clinical trials. 2nd ed. New York: Ellis Horwood, 1992.
24. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
25. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J R Stat Soc [A]* 1972;135:185-206.
26. Castaigne S, Chevret S, Lepage E, et al. Prognostic factors of acute non lymphoblastic leukemia in children and adults: results from two multicentric trials (705 patients). *Nouv Rev Fr Hematol* 1990;32:297-300.
27. Armitage P, Berry G. Statistical methods in medical research. 2nd ed. Oxford, England: Blackwell Scientific, 1987.
28. Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
29. Gail M, Simon R. Testing for qualitative interactions between treatment effects and patient subsets. *Biometrics* 1985;41:361-72.
30. Ohno R, Tomonaga M, Kobayashi T, et al. Effect of granulocyte colony-stimulating factor after intensive induction therapy in relapsed or refractory acute leukemia. *N Engl J Med* 1990;323:871-7.
31. Estey EH, Dixon D, Kantarjian HM, et al. Treatment of poor-prognosis, newly diagnosed acute myeloid leukemia with ara-C and recombinant human granulocyte-macrophage colony-stimulating factor. *Blood* 1990;75:1766-9.
32. Büchner T, Hiddemann W, Koenigsmann M, et al. Recombinant human granulocyte-macrophage colony-stimulating factor after chemotherapy in patients with acute myeloid leukemia at higher age or after relapse. *Blood* 1991;78:1190-7.
33. Rowe JM, Andersen J, Mazza JJ, et al. Phase III randomized placebo-controlled study of granulocyte-macrophage colony stimulating factor (GM-CSF) in adult patients (55-70 years) with acute myelogenous leukemia (AML): a study of the Eastern Cooperative Oncology Group (ECOG). *Blood* 1993;82:Suppl 1:329a. abstract.
34. Stone R, George S, Berg D, Paciucci P, Schiffer C. GM-CSF 'v' placebo during remission induction for patients ≥ 60 years old with de novo acute myeloid leukemia: CALGB study #8923. *Proc Am Soc Clin Oncol* 1994;13: 304. abstract.
35. Ohno R, Naoe T, Kanamaru A, et al. A double-blind controlled study of granulocyte colony-stimulating factor started two days before induction chemotherapy in refractory acute myeloid leukemia. *Blood* 1994;83:2086-92.
36. Estey E, Thall P, Andreeff M, et al. Use of granulocyte colony-stimulating factor before, during, and after fludarabine plus cytarabine induction therapy of newly diagnosed acute myelogenous leukemia or myelodysplastic syndromes: comparison with fludarabine plus cytarabine without granulocyte colony-stimulating factor. *J Clin Oncol* 1994;12:671-8.
37. Bettelheim P, Valent P, Andreeff M, et al. Recombinant human granulocyte-macrophage colony-stimulating factor in combination with standard induction chemotherapy in de novo acute myeloid leukemia. *Blood* 1991;77:700-11.
38. Estey E, Thall PF, Kantarjian H, et al. Treatment of newly diagnosed acute myelogenous leukemia with granulocyte-macrophage colony-stimulating factor (GM-CSF) before and during continuous-infusion high-dose ara-C + daunorubicin: comparison to patients treated without GM-CSF. *Blood* 1992;79:2246-55.
39. Archimbaud E, Fenaux P, Reiffers J, et al. Granulocyte-macrophage colony-stimulating factor in association to timed-sequential chemotherapy with mitoxantrone, etoposide, and cytarabine for refractory acute myelogenous leukemia. *Leukemia* 1993;7:372-7.
40. Büchner T, Hiddemann W, Rottmann R, et al. Multiple course chemotherapy with or without GM-CSF priming and longterm administration for newly diagnosed AML. *Prog Proc Am Soc Clin Oncol* 1993;12:301. abstract.

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