

## GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR AFTER INITIAL CHEMOTHERAPY FOR ELDERLY PATIENTS WITH PRIMARY ACUTE MYELOGENOUS LEUKEMIA

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**Abstract Background.** Elderly patients with primary acute myelogenous leukemia (AML) are less likely to enter remission than younger adults, in part because of a higher mortality rate related to severe myelosuppression. Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been shown to shorten the duration of neutropenia and decrease infectious complications when administered after chemotherapy to patients with lymphomas and solid tumors.

**Methods.** We randomly assigned 388 patients 60 years of age or older who had newly diagnosed primary AML to receive placebo or GM-CSF (5 µg per kilogram of body weight per day intravenously) in a double-blind manner, beginning the day after the completion of three days of daunorubicin and seven days of cytarabine. If leukemic cells persisted in the marrow three weeks after the initiation of chemotherapy, further daunorubicin (two days) and cytarabine (five days) were administered. GM-CSF or placebo was given daily until the neutrophil count was at least 1000 per cubic millimeter, there was evidence of the regrowth of leukemia, or severe toxic effects attributable to the study infusion occurred. Patients who had a complete remission were then randomly assigned to receive one of two intensification regimens.

COMPLETE remission can be achieved with chemotherapy in approximately 70 percent of adults less than 60 years of age with newly diagnosed primary acute myelogenous leukemia (AML).<sup>1-3</sup> However, only about 45 percent of older patients who receive similar therapy have a complete response.<sup>1,4-7</sup> These poor results indicate that older patients have a form of AML that resists chemotherapy. Chromosomal abnormalities that suggest dysfunctional pluripotent hematopoietic stem cells, such as monosomy 7 or the loss of the long arm of chromosome 5, and that occur in myelodysplasia<sup>8</sup> and AML induced by alkylating agents,<sup>9</sup> are more common in elderly patients with AML than in younger patients.<sup>10</sup> Another reason for the inferior outcome in older patients is that poor tolerance of myelo-

**Results.** Of 388 patients (median age, 69 years), 193 were randomly assigned to receive GM-CSF and 195 to receive placebo. The rate of complete remission was 51 percent (95 percent confidence interval, 44 to 59 percent) among those assigned to GM-CSF and 54 percent (95 percent confidence interval, 47 to 61 percent) among those assigned to placebo (P=0.61). The reasons for failure (early death, death during marrow hypoplasia, and persistent leukemia), the incidence of severe or lethal infection, and the incidence of the regrowth of leukemia (2 percent overall) were similar in the two groups. The median duration of neutropenia was slightly shorter (P=0.02) in the patients who received GM-CSF (15 days) than in those who received placebo (17 days), but the clinical importance of this result was minimal because the growth factor failed to lower the treatment-related mortality rate or improve the rate of complete remission.

**Conclusions.** GM-CSF, in the dose and schedule we used, does not stimulate the regrowth of leukemia, but it also does not decrease the severe myelosuppressive consequences of initial chemotherapy or improve the response rate in patients 60 years of age or older with primary AML. It should not be recommended for use in such patients. (N Engl J Med 1995;332:1671-7.)

suppressive chemotherapy increases the risk of treatment-associated death.<sup>1,4-7</sup> A reduced or qualitatively defective pool of hematopoietic stem cells could prolong myelosuppression after chemotherapy and thus add to the risk of infectious complications.

Improvements in supportive care may decrease treatment-associated mortality among elderly adults with AML, thereby increasing the likelihood of complete remission. Hematopoietic growth factors, used successfully to ameliorate the myelosuppressive complications of chemotherapy in patients with solid or lymphoproliferative tumors,<sup>11-13</sup> might also shorten the duration of neutropenia and reduce deaths from infection among patients with AML. However, unlike solid or lymphoproliferative tumors, leukemia cells possess receptors for hematopoietic growth factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF), which stimulate the cells to proliferate.<sup>14-17</sup> The possibility that the administration of GM-CSF could thus worsen leukemia has elicited caution regarding its use in AML.

The Food and Drug Administration has approved the use of granulocyte colony-stimulating factor (G-CSF, or filgrastim) in patients undergoing myelosuppressive chemotherapy and GM-CSF in those receiving a bone marrow transplant, but neither agent is recommended

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\*The institutions of the Cancer and Leukemia Group B that participated in this study are listed in the Appendix.

for patients with myeloid cancers. However, GM-CSF can be given safely after chemotherapy to patients with AML. Although the patients in this study had a high risk of relapse, the rate of complete remission was actually improved, as compared with that in historical controls.<sup>18</sup> These preliminary results and a strong desire to decrease treatment-related mortality have led some physicians to administer G-CSF or GM-CSF routinely to patients after chemotherapy for AML. But these hematopoietic growth factors add to the expense of treatment and may cause side effects, both of which need to be weighed against the possibility of reducing the costs of supportive care or improving the response. To evaluate this question, the Cancer and Leukemia Group B (CALGB) conducted a randomized, double-blind trial to determine whether the administration of *Escherichia coli*-derived GM-CSF (Schering) could reduce the myelosuppressive complications of induction chemotherapy in older patients (age,  $\geq 60$  years) with primary AML without stimulating the regrowth of leukemia.

## METHODS

### Eligibility

Eligibility was limited to patients 60 years of age or older with the diagnosis of primary AML, as defined morphologically by the French-American-British (FAB) system of classification.<sup>19</sup> To support the diagnosis, the leukemia cells had to have at least one of the following characteristics: Auer rods, cytochemical staining with peroxidase or Sudan black B, staining with chloroacetate esterase or nonspecific esterase, or in the case of acute megakaryocytic leukemia (FAB M-7), platelet peroxidase demonstrable by electron microscopy or platelet antigens demonstrable by the use of appropriate monoclonal antibodies. A bone marrow aspirate had to show that at least 30 percent of nonerythroid elements had been replaced by myeloblasts. Patients were not enrolled in the study if they had a history of myelodysplasia or other hematologic cancer, had previously received nonsteroidal cytotoxic chemotherapy (except hydroxyurea administered for the current case of AML) or radiation therapy, had preexistent liver disease or a history of alcohol abuse (or both), had had a myocardial infarction within the previous year, or had had an uncontrolled infection. Appropriate measures were initiated to control any systemic infection, hydration and allopurinol were administered, and written, informed consent was obtained.

The enrollment period was open from February 1990 to November 1993. Beginning in March 1991, patients with M0 AML (cytochemically negative blasts in which the presence of myeloid, but not lymphoid, antigens could be demonstrated through immunophenotypic analysis)<sup>20</sup> were eligible for the study. After October 1992, patients with acute promyelocytic leukemia were no longer eligible for this study because of the initiation of another study focusing on such patients.

### Quality Control, Quality Assurance, and Monitoring

All data forms were reviewed by the CALGB Statistical Center, and relevant data were entered into the official CALGB data base by the data-entry staff. The study chair or his assistant also reviewed the eligibility of each patient as well as all data forms to verify the institutional assessments of toxicity and response.

Members of the CALGB Data Audit Committee visit all the participating institutions at least once every three years to verify compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, response, and follow-up.<sup>21</sup> The medical records of 79 of the 388 patients treated in this study (20 percent), a cohort in which all the participating institutions were represented, were randomly selected and reviewed in this manner. A data-monitoring committee confidentially reviewed the data on re-

sponse and toxicity in each of the study groups and sent their findings and recommendations to the CALGB group chairman, who was not a member of the committee. As part of this process, the statistical center carried out formal interim analyses of complete-remission rates as described in the Statistical Analysis section.

### Treatment Design

Induction chemotherapy consisted of daunorubicin (45 mg per square meter of body-surface area per day on days 1, 2, and 3) and cytarabine (200 mg per square meter per day by continuous intravenous infusion on days 1 through 7). The study infusion consisted of GM-CSF (5  $\mu\text{g}$  per kilogram of body weight given intravenously daily at a minimal concentration of 15  $\mu\text{g}$  per milliliter in sterile water over a period of six hours, beginning at 8 a.m. on the day after the cytarabine infusion was completed) or placebo (inactive powder containing mannitol and human serum albumin). This was a double-blind study in which the treating physicians, the study chair, and the patients were unaware of the treatment assignments. The study infusion was continued daily until life-threatening toxicity thought to be due to the study drug occurred, the neutrophil count exceeded 1000 per cubic millimeter, or the peripheral myeloblast count exceeded 1000 per cubic millimeter. Bone marrow aspiration and biopsy were performed 22 days after the start of chemotherapy. If this examination revealed more than 5 percent leukemia cells and if the marrow cellularity as determined by the biopsy exceeded 15 percent, a second course of five days of cytarabine and two days of daunorubicin was begun. If bone marrow hypoplasia with less than 5 percent blast cells was achieved, further chemotherapy was deferred and the bone marrow examination was repeated weekly. Failure to achieve a complete remission after a second course of induction chemotherapy constituted treatment failure and resulted in removal of the patient from the study. Once the study drug was stopped, it was not restarted even if a second course of chemotherapy was required. However, if the patient was still receiving the study infusion when the second course of induction chemotherapy was given, the growth factor or placebo was continued until one of the three specified events occurred.

Patients with a documented remission on the basis of bone marrow findings underwent a lumbar puncture. If leukemia cells were identified in the cerebrospinal fluid, the patient was removed from the study and counted as having had resistant disease. Another bone marrow examination was performed two weeks after the initial remission was documented.

### Enrollment and Randomization Procedures

Patients were enrolled and simultaneously randomly assigned to one of the two treatment groups by means of a telephone call to the CALGB Statistical Center. Direct registrations were allowed only from CALGB main-member institutions; registrations from affiliates of the main members were made through the appropriate main member.

The randomization design was a stratified, permuted-block design, with stratification according to the institution registering the patient and a preassigned block size of eight.<sup>22</sup> The computer program controlling the randomization was a general program used for randomized studies of the CALGB.

### Outcome Measures

The definition of complete remission was based on accepted criteria<sup>23</sup> requiring that the bone marrow have normal cellularity with normal erythropoiesis, granulopoiesis, and megakaryocytopenia and contain no more than 5 percent blasts. In addition, the peripheral blood had to contain at least 1500 granulocytes per cubic millimeter and 100,000 platelets per cubic millimeter for at least four weeks in the absence of intervening chemotherapy. Therapeutic failures were categorized as being due to documented resistant leukemia, death during the period of treatment-induced bone marrow hypoplasia, or death less than seven days after the initiation of the first course of induction therapy (early death).<sup>24</sup>

Relapse was defined as a finding of more than 5 percent leukemia cells in previously normal bone marrow or evidence of extramedullary leukemia.

Disease-free survival was measured from the date of complete re-

mission to the date of relapse (bone marrow or extramedullary), the date of death from any cause, or the date the patient was last known to be in remission. Data on patients who were still in remission were censored in the statistical analyses. Overall survival was measured from the time of enrollment in the study to the time of death from any cause.

The duration of neutropenia was calculated as the number of days that the absolute neutrophil count was less than 500 per cubic millimeter, beginning the day after the seven-day induction-chemotherapy regimen was completed (i.e., the day that the study drug was initiated). Data on patients who died, had resistant leukemia, or were removed from the study for other reasons were censored at the time of that event. The duration of hospitalization was calculated as the time from the first day of induction chemotherapy to the date of discharge from the hospital.

### Statistical Analysis

The primary analyses in this study followed the intention-to-treat principle,<sup>25</sup> which requires all patients who are properly randomized to be included in the analysis regardless of eligibility status or the treatment actually received. Since all enrolled patients were randomized, no patients were excluded from the primary analyses.

Fisher's exact two-sided test was used to compare the proportion of patients with complete responses in the two groups.<sup>26</sup> Comparisons of the response rates among patients with specific characteristics were also carried out by exact tests of two-by-k tables<sup>27</sup> and, for characteristics with ordered categories (such as age and leukocyte count), by testing for a linear trend.<sup>28</sup> A logistic-regression model was used to assess the joint effect of the prestudy variables on response. Over the course of the study, interim analyses of this end point were performed for monitoring purposes, as described in the protocol, with the use of O'Brien-Fleming rules for early termination of the induction randomization.<sup>29</sup> The distributions of outcomes (survival, disease-free survival, the time to recovery of the absolute neutrophil count to  $\geq 500$  per cubic millimeter, and the time to discharge from the hospital) were estimated with the Kaplan-Meier method,<sup>30</sup> and differences between induction groups were tested with the log-rank statistic.<sup>31</sup> The 95 percent confidence intervals for response rates and the differences in response rates were calculated with standard statistical procedures.<sup>32</sup> Confidence intervals for the median duration of neutropenia, hospitalization, survival, and remission were calculated by the Brookmeyer-Crowley method.<sup>33</sup> All statistical analyses were carried out with either the SAS software system or standard locally developed software used in CALGB studies.

The study was designed to provide an 80 percent power to detect an improvement in the remission rate from 50 percent to 65 percent (two-sided test) with a significance level of 0.05. To accommodate the O'Brien-Fleming procedure for monitoring, a slight increase in the usual size for such a comparison was required. Thus, a total of 192 patients per treatment group (total, 384 patients) was the target. This accrual goal was expected to require approximately 3.5 years to meet.

## RESULTS

A total of 388 patients were enrolled at 25 main-member institutions of the CALGB. The total enrollment and the total accrual time were very close to those planned in the study design. At the time of study entry (before induction chemotherapy), 193 patients were randomly assigned to receive GM-CSF and 195 to receive placebo. Table 1 gives the characteristics of all enrolled patients. The median age of the patients was 69 years. There were no significant differences in characteristics (age, sex, performance status, FAB classification, and blood counts) between groups.

There were major protocol violations in the cases of seven patients: one received G-CSF instead of the study drug; in four the study drug was restarted after a second course of induction therapy even though it had

Table 1. Characteristics of the Patients at Study Entry.\*

CHARACTERISTIC	GM-CSF (N = 193)	PLACEBO (N = 195)	TOTAL (N = 388)
Median age — yr	70.3	68.5	69.0
Age group — no. (%)			
60–69 yr	95 (49)	121 (62)	216 (56)
70–79 yr	86 (45)	70 (36)	156 (40)
$\geq 80$ yr	12 (6)	4 (2)	16 (4)
Sex — no. (%)			
Male	117 (61)	100 (51)	217 (56)
Female	76 (39)	95 (49)	171 (44)
Performance status — no. (%)†			
0	36 (19)	47 (24)	83 (22)
1–2	138 (72)	137 (71)	275 (72)
3–4	17 (9)	8 (4)	25 (7)
FAB classification — no. (%)			
M0	8 (4)	10 (5)	18 (5)
M1	56 (29)	53 (27)	109 (28)
M2	54 (28)	63 (32)	117 (30)
M3	7 (4)	8 (4)	15 (4)
M4	44 (23)	41 (21)	85 (22)
M5	18 (9)	12 (6)	30 (8)
M6	5 (3)	3 (2)	8 (2)
M7	1 (1)	5 (3)	6 (2)
Hematologic values — no. (%)			
Hemoglobin‡			
5.0–9.0 g/dl	73 (39)	71 (38)	144 (38)
9.1–10.0 g/dl	52 (28)	57 (30)	109 (29)
$\geq 10.1$ g/dl	63 (34)	60 (32)	123 (33)
Platelet count§			
$4–50 \times 10^3/\text{mm}^3$	68 (35)	71 (37)	139 (36)
$51–99 \times 10^3/\text{mm}^3$	59 (31)	56 (29)	115 (30)
$\geq 100 \times 10^3/\text{mm}^3$	65 (34)	63 (33)	128 (34)
White-cell count†			
$0.2–3.0 \times 10^3/\text{mm}^3$	59 (31)	65 (34)	124 (32)
$3.1–30.0 \times 10^3/\text{mm}^3$	68 (35)	74 (39)	142 (37)
$\geq 30.1 \times 10^3/\text{mm}^3$	65 (34)	52 (27)	117 (31)

\*Because of rounding, not all categories total 100 percent.

†Data were available on 383 patients.

‡Data were available on 376 patients.

§Data were available on 382 patients.

been appropriately stopped because of neutrophil recovery; one withdrew consent before receiving the study infusion; and one never received the study drug because of a supply problem. Twenty-seven patients died or were withdrawn because of toxic effects before they received any GM-CSF or placebo (14 randomly assigned to GM-CSF and 13 to placebo). Two patients were considered to be ineligible: one was less than 60 years old at diagnosis, and the other had central nervous system leukemia at diagnosis. The analysis of the responses includes all enrolled patients according to intention-to-treat principles. A secondary analysis that excluded ineligible patients and those who could not be evaluated was performed to determine whether this exclusion changed the results.

Data on the duration of neutropenia and the length of hospitalization were available for 376 patients. The duration of neutropenia (Fig. 1) was shorter in patients receiving GM-CSF than in those receiving placebo (median, 15 days [95 percent confidence interval, 15 to 16] vs. 17 days [95 percent confidence interval, 16 to 19];  $P=0.02$ ). The length of hospitalization (Fig. 2) was not significantly different in the two groups (median, 28 days [95 percent confidence interval, 26 to 31] vs. 30 days [95 percent confidence interval, 28 to 33];  $P=0.11$ ). However, this degree of apparent benefit in

patients randomly assigned to GM-CSF was associated with neither a higher likelihood of complete remission nor a decrease in the rates of life-threatening or fatal toxic reactions (Table 2). The likelihood of infection (either documented or presumed septicemia) and non-hematologic toxic effects did not differ between the two groups.

The overall rate of complete remission was 53 percent (95 percent confidence interval, 48 to 58 percent), with 89 percent of these responses achieved after one course of induction chemotherapy. The rate of complete remission in the 172 patients who were 70 years of age or older was 51 percent (95 percent confidence interval, 43 to 59 percent), virtually identical to the rate of 54 percent (95 percent confidence interval, 47 to 61 percent) in the 216 patients between 59 and 69 years old. Though patients with a histologic diagnosis of M6 (acute erythroblastic leukemia), M7 (acute megakaryoblastic leukemia), or M0 had a complete-remission rate of 31 percent, there was probably no significant difference in the proportion of those who responded among the FAB classes ( $P=0.20$  by Fisher's exact two-sided test). There was no significant association between response and age ( $P=0.12$ ), sex ( $P=0.18$ ), hemoglobin concentration ( $P=0.31$ ), platelet count ( $P=0.28$ ), or leukocyte count ( $P=0.30$ ). However, there was an association between performance status and the response rate ( $P=0.001$ ): of 83 patients with a fully normal activity level, 50 (60 percent; 95 percent confidence interval, 49 to 71 percent) had a response, in contrast to only 5 (20 percent; 95 percent confidence interval, 7 to 41 percent) of 25 patients who were debilitated before therapy. The 275 patients with mild or moderate functional impairment had a re-

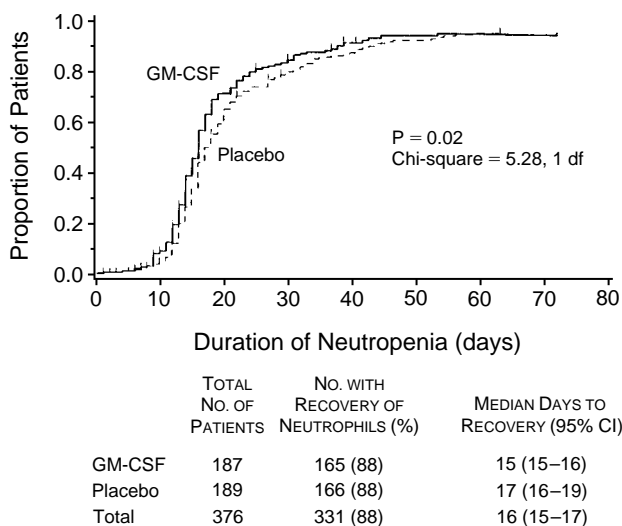


Figure 1. Duration of Neutropenia in All Patients According to Whether They Received GM-CSF or Placebo after Induction Therapy.

Neutropenia was defined as a neutrophil count of less than 500 per cubic millimeter. Tick marks indicate censored observations. CI denotes confidence interval.

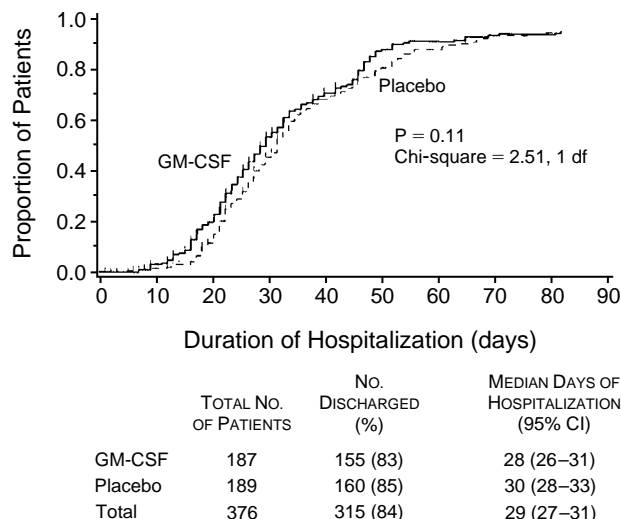


Figure 2. Duration of Hospitalization for All Patients According to Whether They Received GM-CSF or Placebo after Induction Therapy.

Tick marks indicate censored observations. CI denotes confidence interval.

sponse rate of 53 percent (95 percent confidence interval, 47 to 59 percent).

A logistic-regression analysis to assess the joint effect of the prestudy variables on response in 374 patients for whom data were complete identified performance status ( $P=0.001$ ) as the most significant predictor of a complete response. After adjustment for performance status, age also had prognostic significance ( $P=0.04$ ). After adjustment for both these characteristics, no other variable attained statistical significance: sex ( $P=0.08$ ), FAB class ( $P=0.09$ ), hemoglobin level ( $P=0.66$ ), platelet count ( $P=0.10$ ), or white-cell count ( $P=0.45$ ).

The rate of complete remission was not affected by whether patients received GM-CSF or placebo infusion (Table 3). Among 193 patients randomly assigned to GM-CSF, the rate of complete remission was 51 percent (95 percent confidence interval, 44 to 59 percent). For the 195 patients randomly assigned to placebo, the rate was 54 percent (95 percent confidence interval, 47 to 61 percent;  $P=0.61$  by Fisher's exact test). Thus, the difference in the response rates was approximately 3 percent (in favor of placebo), with a 95 percent confidence interval ranging from approximately 13 percent in favor of placebo to approximately 7 percent in favor of GM-CSF. These results effectively rule out any favorable effect of GM-CSF of the magnitude considered in the study design. An analysis that excluded the seven patients with protocol violations and the two ineligible patients yielded similar results (rates of complete remission, 52 percent [95 percent confidence interval, 44 to 59 percent] for GM-CSF and 54 percent [95 percent confidence interval, 47 to 62 percent] for placebo;  $P=0.61$ ).

The reasons for the failure to achieve a complete re-

Table 2. Toxicity of Induction Therapy According to Treatment Assignment.

DEGREE OF TOXICITY OR TOXIC EFFECT	GM-CSF	PLACEBO	TOTAL	P VALUE
Grade 4 or 5 toxicity*				
Infection	32/179 (18)	33/182 (18)	65/361 (18)	1.00
Bilirubinemia	25/178 (14)	29/183 (16)	54/361 (15)	0.66
Cardiac†	17/177 (10)	26/182 (14)	43/359 (12)	0.20
Dyspnea	35/179 (20)	33/182 (18)	68/361 (19)	0.79
Hypotension	20/179 (11)	12/184 (7)	32/363 (9)	0.14
Malaise	24/176 (14)	29/183 (16)	53/359 (15)	0.66
Pulmonary‡	30/175 (17)	40/179 (22)	70/354 (20)	0.23
Documented bacteremia	47/179 (26)	53/184 (29)	100/363 (28)	0.64
Any documented infection	112/179 (63)	118/184 (64)	230/363 (63)	0.83

\*Only toxic effects with an incidence of more than 10 percent in either group are included. The incidence of grade 4 or 5 fever or gastrointestinal, hepatic, renal, central nervous system, or metabolic effects was similar in the two groups.

†Includes nonspecific cardiac events and dysrhythmias.

‡Includes pulmonary edema, pneumonia, and adult respiratory distress syndrome.

mission (i.e., resistant disease or death during marrow hypoplasia) were similar in both treatment groups ( $P=0.79$ ) (Table 3). As would be expected from the policy of randomizing patients eight days before they received the study infusion, the percentages of early deaths (death before the conclusion of the induction therapy) were similar in both treatment groups. Of the 86 patients who were considered to have had resistant disease, 37 (20 who received GM-CSF and 17 who received placebo) were never given a second course of induction therapy, either because their physicians believed they were too ill to tolerate further therapy or because they had cytopenia without excess marrow myeloblasts.

The reasons for discontinuing the study drug were also similar in the GM-CSF and placebo groups ( $P=0.11$  by Fisher's exact test of the three-by-two table) (Table 4). In approximately one third of the patients in each group, the study drug was discontinued because the treating physician thought that the patient had severe GM-CSF-associated toxicity. The side effects that prompted a physician to discontinue the drug were similar in both cohorts (Table 4), except that rash was more common in those receiving GM-CSF. The rates of the regrowth of leukemia (more than 1000 myeloblasts per cubic millimeter in peripheral blood) were not significantly different in the two treatment groups. Of the six patients given GM-CSF who met the criteria for the regrowth of leukemia, only one had a decrease in the peripheral myeloblast count after GM-CSF was stopped (16 days after the start of induction therapy). Induction therapy was readministered, and the patient had a complete remission. Two patients died of complications during myelosuppression, and three others received a second course of induction therapy shortly after the discontinuation of the GM-CSF but did not enter remission.

Because the study drug was stopped prematurely in one third of the patients, we analyzed the outcome in only the patients whose study drug was discontinued because of the recovery of neutrophils (113 patients giv-

en GM-CSF and 99 given placebo). Even in this subgroup, the GM-CSF group and the placebo group were similar in terms of the rates of complete remission (74 percent [95 percent confidence interval, 65 to 82 percent] vs. 79 percent [95 percent confidence interval, 71 to 86 percent]) and the durations of neutropenia (15 days [95 percent confidence interval, 1 to 39] vs. 16 days [95 percent confidence interval, 2 to 57]) and hospitalization (27 days [95 percent confidence interval, 7 to 80] vs. 29 days [95 percent confidence interval, 16 to 81]).

The median overall survival was estimated to be 9.4 months (95 percent confidence interval, 7.6 to 11.2) and was equivalent in the two study groups (Fig. 3). The median duration of remission for all patients with a response was estimated to be 8.2 months (95 percent confidence interval, 7.7 to 10.6) for patients who received GM-CSF and 10.4 months (95 percent confidence interval, 8.8 to 12.2) for patients who received placebo after their induction treatment.

## DISCUSSION

This study demonstrates that *E. coli*-derived GM-CSF has a minimal effect on recovery from the myelosuppressive effects of induction chemotherapy and does not improve the rate of complete remission in elderly patients with primary AML. The failure to receive a complete course of planned therapy, although not uncommon, did not account for the lack of improvement in outcome. This study reaffirms the need for randomized controlled trials before the favorable results of an uncontrolled trial of a new therapy are accepted. The overall rate of complete remission in our trial (53 percent) was similar to that in a cohort of comparable age in a recent CALGB trial (47 percent) that used a similar induction regimen,<sup>1</sup> albeit with a lower dose of dau-

Table 3. Results of Induction Therapy According to Treatment.\*

RESULT	GM-CSF	PLACEBO	TOTAL
Complete remission	99 (51) (44–59)	106 (54) (47–61)	205 (53) (48–58)
One course of induction	86	93	179
Two courses of induction	13	13	26
No response	94	89	183
Resistant disease†	42 (22)	44 (23)	86 (22)
Death during	38 (20)	32 (16)	70 (18)
marrow hypoplasia	14 (7)	13 (7)	27 (7)
Early death			
Total	193	195	388

\*CI denotes confidence interval.

†Of 86 patients with resistant disease, 37 (20 given GM-CSF and 17 given placebo) never received a second course of induction therapy.

norubicin (30 mg per square meter). Although not a focus of this study, the higher dose of daunorubicin chosen for this trial did not increase treatment-related deaths, as compared with the incidence of this complication in the earlier CALGB trial.

The lack of clinically important benefit from GM-CSF was disappointing. The number of days of neutropenia (<500 neutrophils per cubic millimeter) was slightly reduced in the patients treated with GM-CSF, but there was neither a reduction in the incidence of life-threatening infection nor an improvement in the rate of complete remission. In contrast to patients with solid tumors or those undergoing autologous bone marrow transplantation who are hematologically normal before chemotherapy, patients with leukemia generally present in a myelosuppressed state. Because of the disease itself, and the intensely myelosuppressive nature of induction chemotherapy for AML, most episodes of fever and neutropenia occur soon after the initiation of chemotherapy, and many episodes develop before the growth factor therapy begins. It is therefore not surprising that GM-CSF had no effect on the incidence of severe infection in this study. Although shortening the duration of neutropenia could theoretically decrease the need for the prolonged use of potentially toxic antimicrobial therapy, patients in both cohorts were equally likely to recover and receive postremission therapy.

Several groups have evaluated GM-CSF as a means of modulating the myelosuppressive effects of induction chemotherapy in adults with AML. In the uncontrolled trial by Büchner and colleagues,<sup>18</sup> GM-CSF (at a dose of 250  $\mu$ g per square meter per day) beginning four days after the completion of induction therapy was associated with an improvement in the rate of complete remission as compared with the rate in historical controls (50 percent vs. 32 percent). However, other studies, which were small<sup>34</sup> or whose results have thus far been published only in abstract form,<sup>35-38</sup> have not indicated a clear benefit from GM-CSF as an adjunct to chemotherapy for AML.

It is reassuring that large numbers of patients did not have regrowth of leukemia and that the incidence of treatment failure due to persistent leukemia was similar in both groups. Despite theoretical concerns that myeloid growth factors might stimulate the proliferation of leukemia cells, the clinical evidence of this com-

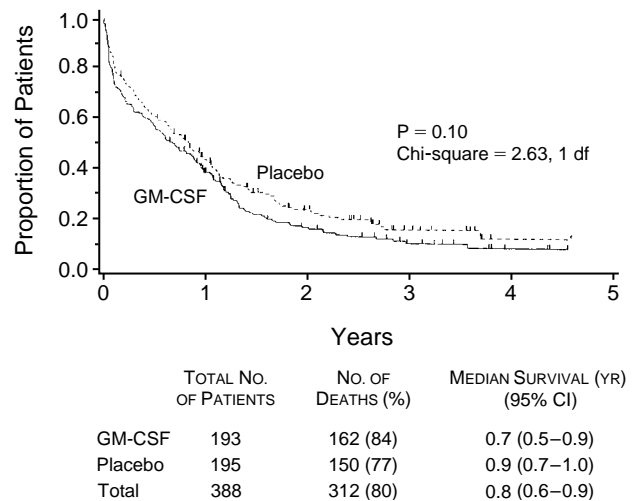


Figure 3. Probability of Survival for All Patients According to Whether They Received GM-CSF or Placebo after Induction Therapy.

Tick marks indicate patients alive at the time of analysis. CI denotes confidence interval.

plication is minimal. No trial in which patients with AML have received growth factors after the completion of chemotherapy has shown such an adverse effect.<sup>39</sup>

A noteworthy finding in this trial was the relatively low rate of administration of a second course of induction therapy among those who eventually entered remission. Eleven percent of the patients with complete responses received two courses of induction therapy, as compared with 31 percent of all patients with primary AML who received nearly identical doses of daunorubicin and cytarabine in a CALGB study conducted from 1985 to 1990 (215 of 693 patients).<sup>1</sup> In contrast to most prior studies of AML, which allowed a second course of chemotherapy two weeks after the initiation of therapy, our trial did not permit retreatment until three weeks after the initiation of therapy, because we thought that it might be difficult to distinguish between persistent leukemia and early myeloid regeneration stimulated by GM-CSF. It is therefore possible that some patients who receive a second course of induction therapy after two weeks might have a complete remission with observation alone.

Our results emphasize that AML in elderly patients remains very difficult to treat successfully. The nine-month median survival in this trial was disappointing. A major effort is required to improve the results in this age group. The use of growth factors as chemosensitizing agents,<sup>40</sup> the development of drugs with novel mechanisms of action,<sup>41</sup> and modulation of the product of the multidrug-resistance gene<sup>42</sup> are a few of the possibilities.

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Table 4. Reasons for the Discontinuation of Treatment.\*

REASON	GM-CSF	PLACEBO	TOTAL
	no. of patients (% of total) (95% CI)		
Severe side effects attributed by physician to GM-CSF	60 (34) (26-40)	56 (31) (24-38)	116 (32)
Pulmonary compromise	10	9	
Cardiac arrest	3	3	
Sepsis	9	12	
Rash	10	1	
Other	28	31	
Resolution of neutropenia	113 (63) (56-70)	125 (69) (61-75)	238 (66)
Regrowth of AML	6 (3) (1-7)	1 (1) (0.01-3)	7 (2)
Total	179	182	361

\*CI denotes confidence interval.

## APPENDIX

The following institutions of the Cancer and Leukemia Group B participated in this study: Bowman Gray School of Medicine, the Central Massachusetts Oncology Group, Dana-Farber Cancer Institute, Dartmouth Medical School, Duke University Medical Center, Long Island Jewish Medical Center, McGill Department of Oncology, Massachusetts General Hospital, Mount Sinai Hospital (New York), New York Hospital-Cornell Medical Center, North Shore University Hospital, Rhode Island Hospital, Roswell Park Cancer Institute, SUNY Health Science Center (Syracuse), University of Alabama (Birmingham), University of California (San Diego), University of Chicago Medical Center, University of Iowa Hospitals, University of Maryland Cancer Center (Baltimore), University of Minnesota, University of Missouri-Ellis Fischel Cancer Center, University of North Carolina (Chapel Hill), University of Tennessee (Memphis), Walter Reed Army Medical Center, and Washington University Medical Center (St. Louis).

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