A Randomized Placebo-Controlled Phase III Study of Granulocyte-Macrophage Colony-Stimulating Factor in Adult Patients (≥55 to 70 Years of Age) With Acute Myelogenous Leukemia: A Study of the Eastern Cooperative Oncology Group (E1490)

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The treatment of adult patients greater than 55 to 70 years of age with acute myelogenous leukemia (AML) is associated with a treatment-related mortality of approximately 25%. This prospective, double-blind randomized study was designed to see if the use of granulocyte-macrophage colony stimulating factor (GM-CSF; yeast-derived) could shorten the period of neutropenia and to determine any effect this would have on therapy-related morbidity and mortality. A total of 124 patients entered this study. Induction consisted of standard daunorubicin and cytarabine. A day-10 bone marrow was examined; if this was aplastic without leukemia, patients received blinded placebo or GM-CSF from day 11 until neutrophil recovery. Patients who entered complete remission received the identical study medication (blinded GM-CSF or placebo) in consolidation that they had received during induction. The overall complete remission rate was 52%; 60% for the GM-CSF arm and 44% for the placebo arm (P = .08). Median times to neutrophil recovery were significantly shortened on the GM-CSF arm. The overall treatment-related toxicity from start of GM-CSF/placebo was reduced on the GM-CSF arm (P = .049). Similarly, the infectious toxicity was significantly reduced on the GM-CSF arm (P = .015). The median survival for all patients was 10.6 months in the GM-CSF group and 4.8 months in the placebo arm (P = .048). It appears that GM-CSF is safe and efficacious for adult patients greater than 55 to 70 years of age with AML; its major impact is in reducing the duration of neutropenia and therapy-related mortality and morbidity. This may result in a better response rate.

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EARLY DEATH DURING induction therapy for acute myelogenous leukemia (AML) still remains an important clinical problem. The mortality rate increases with age. For patients greater than 55 to 60 years of age, the treatment-related early death rate is on the order of 20% to 40%.1-4

Because of the potential for cytokine stimulation of acute leukemia,5,7 there was initially great hesitation in conducting clinical trials with colony-stimulating factors in acute leukemia. It is not surprising, therefore, that, when clinical trials finally did get underway, these studies were conducted in older patients, in whom the risk of death from marrow aplasia was high enough to outweigh the potential risk of stimulating leukemia cells. The first such trial was reported in 1988.8 Since then several clinical trials using colony-stimulating factors in AML have been conducted.9-11 In these studies, the colony-stimulating factors were administered 1 to 5 days after completion of induction therapy without necessarily demonstrating prior marrow hypoplasia. Despite the theoretical concerns, these clinical studies suggest that cytokines administered after the completion of chemotherapy do not adversely affect the response to induction therapy.

In September 1990, a double-blind study was activated by the Eastern Cooperative Oncology Group (ECOG) to evaluate the safety and hematologic effect of yeast-derived granulocyte-macrophage colony-stimulating factor (GM-CSF) in adult patients (≥55 to 70 years of age) with de novo AML.

PATIENTS AND METHODS

Patients. Eligibility criteria for entry in this study included the following: (1) adult patients greater than 55 but not exceeding 70 years of age; (2) adequate hepatic, renal, and cardiac function (bilirubin ≤2.0 mg/dl; creatinine <2.0 mg/dl; and normal cardiac left ventricular ejection fraction); (3) no previous cytotoxic or radiation therapy; (4) morphologic proof of AML (French-American-British [FAB] type MO-M7)13-15; (5) no known antecedent myelodysplasia; and (6) all patients had cytogenetic and immunophenotypic analysis performed on prestudy specimens.

Study design. After written informed consent was obtained, each patient was registered and randomized to the GM-CSF or placebo arm before the initiation of induction chemotherapy. This step allowed all eligible and evaluable patients to be included in an intent-to-treat analysis.

Induction therapy consisted of daunorubicin at 60 mg/m²/day intravenously on days 1 through 3 and cytosine arabinoside at 25 mg/m² intravenously by push on day 1, followed by 100 mg/m²/d by continuous infusion on days 1 through 7. The bone marrow was examined on day 10; if the aspirate was aplastic without leukemia, it appears that GM-CSF is safe and efficacious for adult patients greater than 55 to 70 years of age with AML; its major impact is in reducing the duration of neutropenia and therapy-related mortality and morbidity. This may result in a better response rate.

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patients received GM-CSF or placebo on day 11 (Fig 1). If the day-10 bone marrow showed residual leukemia, an identical course of induction chemotherapy was administered and a bone marrow was performed 3 days after completion of the second cycle. If this specimen was free of leukemia, patients received GM-CSF or placebo as above. If there was still residual leukemia after the second cycle, patients went off study.

Yeast-derived recombinant GM-CSF (Sargramostim; Leukine; Immunex Corp, Seattle, WA) or an equal volume of placebo was used for this trial. The study drug (GM-CSF or placebo) was administered intravenously at 250 μg/m² over 4 hours and was administered daily until the absolute neutrophil count was ≥1,500/μL for 3 consecutive days or for a maximum of 42 days. The study drug was to be discontinued immediately if leukemia regrowth occurred. Patients who entered complete remission received a single course of consolidation therapy with cytosine arabinoside at 1.5 g/m² administered intravenously over 1 hour every 12 hours for 11 doses. On day 11 of consolidation therapy, patients received the identical blinded study medication (GM-CSF or placebo) that they had received during induction therapy.

All patients with neutropenia received empiric broad spectrum antibiotics for fevers greater than 38°C after appropriate cultures had been obtained. Selection of antibiotics was based on the pattern of sensitivity of organisms at each institution, but usually included an aminoglycoside and a cephalosporin or semisynthetic penicillin. Patients with documented fungal infections or with persistent unexplained fevers that were unresponsive to broad-spectrum antibiotics were treated with aminoglycoside and a cephalosporin or semisynthetic penicillin. Patients with documented fungal infections or with persistent unexplained fevers that were unresponsive to broad-spectrum antibiotics received intravenous amphotericin B at a dose of 0.6 mg/kg/d or greater.

Definition of outcome. Toxicity was graded by the National Cancer Institute (NCI) Common Toxicity Criteria. Recovery of neutrophils, platelets, and red blood cells was defined from day 11 of the last cycle of chemotherapy until recovery. This is a uniform start-time for evaluation of recovery and ensures that, for those patients who had a delay in administration of study drug, the duration of aplasia was not underestimated.

Complete remission was defined as the finding of a normocellular bone marrow containing less than 5% blasts (M1) and peripheral blood counts showing at least 1,500/μL neutrophils and 100,000/μL platelets.

Statistical methods. The sample size for this study was calculated to provide greater than 80% power to detect a 7- to 9-day reduction in the median duration of neutropenia. Univariate differences between dichotomous variables were evaluated with Fisher's exact test. Differences in the distribution of hematologic recovery times were compared between groups both with a standard stratified logrank test and with a test based on cumulative incidence that perhaps more appropriately adjusts for the probable informative nature of this censoring. Differences in toxicity grades were compared between treatments using a Wilcoxon test for ordered outcomes. Differences in the distribution of disease-free survival (time from achievement of a complete remission to relapse or last follow-up) and overall survival were compared between groups with a logrank test. Additionally, the significance of the association of GM-CSF with major endpoints is given when adjusted for patient characteristics known to be associated with outcome in acute leukemia trials (age, white blood cell count, and blast cell count) using logistic or proportional hazard regression. Survival curves were estimated by the method of Kaplan and Meier.

RESULTS

Overall demographics. Between September 1990 and November 1992, 124 patients entered the study. Sixty-two patients were randomized to receive GM-CSF and 62 patients were randomized to receive placebo. Of these patients, 117 were eligible and evaluable: 60 on the GM-CSF arm and 57 on the placebo arm. Reasons for exclusion were prior chemotherapy (1 patient), no follow-up (2 patients), and wrong pathology (4 patients). The median age of all 117 patients was 64 years. The number of patients between 56 and 65 was similar on both arms, but there were more patients older than 65 years of age on the GM-CSF arm (Table 1). Eighty-one percent of the patients had an ECOG performance score of 0 or 1 and the two groups were similar. Overall, the presenting hematologic features were similar in

Table 1. Patient Characteristics and Remission

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>GM-CSF</th>
<th>Placebo</th>
<th>CR</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65</td>
<td>40 (48)</td>
<td>44 (52)</td>
<td>48 (57)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>20 (61)</td>
<td>13 (39)</td>
<td>13 (39)</td>
</tr>
<tr>
<td>WBC/μL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5,000</td>
<td>33 (57)</td>
<td>25 (43)</td>
<td>58 (55)</td>
</tr>
<tr>
<td>&gt;5,000</td>
<td>27 (46)</td>
<td>32 (54)</td>
<td>29 (49)</td>
</tr>
<tr>
<td>Platelets/μL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50,000</td>
<td>22 (51)</td>
<td>21 (49)</td>
<td>18 (42)</td>
</tr>
<tr>
<td>&gt;50,000</td>
<td>38 (51)</td>
<td>36 (49)</td>
<td>43 (58)</td>
</tr>
<tr>
<td>Blasts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50%</td>
<td>42 (51)</td>
<td>41 (49)</td>
<td>45 (54)</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>18 (53)</td>
<td>16 (47)</td>
<td>16 (47)</td>
</tr>
<tr>
<td>FAB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1, M2</td>
<td>34 (49)</td>
<td>35 (51)</td>
<td>38 (55)</td>
</tr>
<tr>
<td>M3</td>
<td>2 (33)</td>
<td>4 (67)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Other</td>
<td>24 (57)</td>
<td>18 (43)</td>
<td>21 (50)</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>13 (54)</td>
<td>11 (46)</td>
<td>15 (62)</td>
</tr>
<tr>
<td>1, 2</td>
<td>47 (51)</td>
<td>48 (48)</td>
<td>46 (49)</td>
</tr>
</tbody>
</table>

Values are the number of patients with percentages in parentheses. The total number of patients was 124, 117 of whom were eligible and evaluable.
both groups (Table 1); the median white blood cell count and platelet count was 5,300/µL and 59,000/µL, respectively. The proportion of patients requiring a second cycle of induction therapy (31%) was similar in both arms. Of the 117 eligible and evaluable patients, 18 never received the study drug either due to early death or lack of response; of these patients, 8 patients had been randomized to receive GM-CSF and 10 had been randomized to receive placebo. Thus, of the 60 patients randomized to receive GM-CSF, 52 did receive it as did 47 of 57 patients randomized to receive placebo.

Clinical response. Table 2 summarizes the response to induction therapy. Thirteen patients are technically unevaluable for response: 8 due to early death, 2 due to lack of pathology verification (clinical complete remission was reported without bone marrow documentation), 2 due to lack of documentation of response, and 1 received study drug without an aplastic bone marrow having been achieved. All of these patients are included as nonresponders in the analysis.

Sixty-one patients achieved a complete remission (52%); 60% on the GM-CSF arm and 44% on placebo (P = .08). The median follow-up for complete responding patients was 13.1 months. Among patients 56 to 65 years of age, the overall complete remission rate was 57%; 68% on GM-CSF and 48% on placebo (P = .08). For patients 66 to 70 years of age, the overall complete remission rate was 39%; 45% on GM-CSF and 31% on placebo. The sample sizes of these relatively small groups are too small for meaningful statistical comparisons.

Hematologic response. This was the primary endpoint of the study and the overall recovery is summarized in Table 3. Thirty-one percent of patients required two cycles of therapy. As expected, the median hematologic recovery was prolonged by 3 days in patients receiving two cycles. Therefore, in all assessments of recovery of hematologic parameters, the data were stratified to account for patients receiving one or two cycles of induction therapy. The median time for neutrophil recovery to 500/µL and 1,000/µL was significantly reduced on the GM-CSF arm (13 v 17 days, P = .001 [P = .013 when adjusted for covariates in Table 1] and 14 v 21 days, P = .001 [P = .001 when adjusted], respectively; Fig 2). There was no significant difference in platelet recovery to a self-sustaining level of 20,000/µL and the median time to red blood cell transfusion independence was also essentially identical on both arms. The improved neutrophil recovery with GM-CSF to 500/µL or 1,000/µL remains significant even as one analyzes each group (1 or 2 cycles) separately (data not shown).

Survival. Figure 3 shows an intent-to-treat analysis of overall survival for all 117 randomized patients regardless of whether they received the study drug or not. The median survival for the 60 patients on the GM-CSF arm was 10.6 months and for the 57 patients on the placebo arm was 4.8 months (P = .048; P = .021 when adjusted). The disease-free survival of all 62 patients who went into complete remission (calculated from the time of achievement of a complete remission) is shown in Fig 4. The median disease-free survival for patients randomized to GM-CSF was 8.5 months and 9.6 months for those randomized to receive placebo (P = .95; P = .47 when adjusted). These results reflect an intent-to-treat analysis. The results are qualitatively and quantitatively similar when the analysis is subset to include only patients who received study drug, or only patients who received study drug and have analyzable hematologic data.

Consolidation therapy. Of the 61 patients who achieved complete remission, 49 received consolidation therapy (28 on GM-CSF and 21 on placebo). Patients received the study drug on day 11. As can be seen in Table 4, in this small sample size there was no significant difference in the neutrophil recovery between the GM-CSF and the placebo group. Similarly, there was no difference in the platelet or red blood cell recovery times (data not shown).

Toxicity. The overall therapy-related mortality in induction for all 117 patients was 18%. The overall therapy-related toxicity from start of GM-CSF/placebo was reduced on the GM-CSF arm (P = .049) such that, in general, for all maximal nonhematologic toxicity there were significantly more

<table>
<thead>
<tr>
<th>Table 2. Complete Remission Rate</th>
<th>Overall</th>
<th>GM-CSF</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 117)</td>
<td>52% (61/117)</td>
<td>60% (36/60)</td>
<td>44% (25/57)</td>
</tr>
<tr>
<td>Patients 56 to 65 years of age (n = 84)</td>
<td>57% (48/84)</td>
<td>68% (27/40)</td>
<td>48% (21/44)</td>
</tr>
<tr>
<td>Patients 66 to 70 years of age (n = 33)</td>
<td>39% (13/33)</td>
<td>45% (9/20)</td>
<td>31% (4/13)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Median Time in Days From Start of GM-CSF/Placebo (Day 11 From First or Second Cycle of Induction) to Recovery</th>
<th>GM-CSF</th>
<th>Placebo</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC &gt;500/µL</td>
<td>13 (11, 16)</td>
<td>17 (12, 20)</td>
<td>.001</td>
</tr>
<tr>
<td>ANC &gt;1,000/µL</td>
<td>14 (12, 18)</td>
<td>21 (13, 43)</td>
<td>.001</td>
</tr>
<tr>
<td>Pit &gt;20,000/µLt</td>
<td>11 (7, 18)</td>
<td>12 (9, 90)</td>
<td>.11</td>
</tr>
<tr>
<td>RBCt</td>
<td>13 (9, 36)</td>
<td>14 (9, 78)</td>
<td>.39</td>
</tr>
</tbody>
</table>

Numbers in parentheses refer to 25% and 75% percentiles.
* Competing risk test stratified by number of cycles.
† Recovery of platelets (>20,000/µL) and red blood cells to transfusion independence.
Fig 3. Overall survival of all eligible and evaluable patients entered on this study. The median survival for 60 patients randomized to receive GM-CSF was 10.6 months and was 4.8 months for the 57 patients randomized to receive placebo ($P = .048$). The number of patients at risk at various time points are indicated.

higher-grade toxicities in the placebo arm and more lower-grade toxicities in the GM-CSF arm. Table 5 compares the induction toxicities after GM-CSF/placebo administration. The therapy-related mortality was reduced on the GM-CSF arm ($P = .18$) and grade 4/5 infections were significantly reduced with GM-CSF ($P = .002$). Pneumonia was reported in 14 patients on GM-CSF and in 13 on placebo. However, pneumonia associated with death occurred in only 2 of 14 on GM-CSF compared with 7 of 13 on placebo ($P = .046$).

There was an overall increase among the placebo group in grade 3/4 hepatic and neurologic toxicity during induction (data not shown); however, this could not be shown to be independent of the primary infectious toxicities. Grade 1/2 skin toxicity (but not grade 3/4) was more frequent in the GM-CSF group ($P = .002$). There was no difference between the groups for any other toxicities, including weight gain (8% on GM-CSF and 21% on placebo), cardiac events, or pulmonary events, and no patient withdrew from study drug because of toxicity or leukemia regrowth.

There was only 1 death (2%; from pulmonary hemorrhage) and 5 grade 4 infections (2 on GM-CSF and 3 on placebo) among the 49 patients who received consolidation therapy. Thus, there was no difference, during consolidation, in the toxicity caused by infection between the two randomized treatment groups.

**Length of hospitalization.** Data for duration of hospitalization were available for 98 of 99 patients who received study drug during induction and for 48 of 49 patients who received consolidation therapy. The length of hospitalization of patients who died in hospital, having never been discharged, was estimated using maximum hospital duration. Using this convention, and recognizing that the increased early deaths in the placebo arm may underestimate duration of hospital stay for remission induction in this group, the

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**Fig 4.** Disease-free survival, from time of achievement of complete remission, for all patients who achieved complete remission. There is no evidence for an acceleration of relapse in patients who received GM-CSF. The number of patients at risk at various time points are indicated.
median duration of hospitalization for patients receiving induction therapy was similar in both treatment groups (36 days on GM-CSF and 38 days on placebo; \( P = 29 \)). The overall length of hospitalization among the responders was delayed in some patients by the study requirement of continuing the study drug until the absolute neutrophil count had reached 1,500/μL for 3 consecutive days.

**DISCUSSION**

The use of colony-stimulating factors in acute leukemia has been controversial. The overriding concern has been the potential for stimulation of acute leukemia.\(^5\) However, published clinical studies have suggested that the administration of GM-CSF or G-CSF after completion of chemotherapy for de novo or relapsed AML is not associated with significant regrowth of leukemia or with shorter remissions.\(^9,12,19\)

Whether these cytokines ameliorate the myelosuppressive effects of induction chemotherapy was also uncertain; some reports have indicated a significantly more rapid neutrophil recovery with GM-CSF or G-CSF\(^9,11\) whereas other reports have not confirmed this.\(^10,19\) Moreover, only one study has shown a significant effect on infection rate,\(^11\) and none has shown an effect on survival.

This report describes a double-blind randomized study of GM-CSF versus placebo after both induction and consolidation therapy in adult patients (>55 to 70 years of age) with de novo AML. Such a randomization is critical in eliminating bias due to prognostic variables in different patient populations and, perhaps, different supportive care practices, when historical controls are used.

This study shows a statistically significant improvement in neutrophil recovery for patients receiving GM-CSF. Reports on hematologic reconstitution with growth factors often censor patients who died before hematologic recovery at the date of death.\(^9\) In censoring patients for hematologic recovery who died without recovery, one is in effect using a competing risk analysis in which early death and hematologic recovery are treated as independent events. However, one of the driving hypotheses of this study was that GM-CSF might accelerate hematologic recovery and reduce early treatment-related mortality. Thus, the assumption of independence is untenable, and death without recovery is informative, ie, if a patient died early because of slow recovery of blood counts, then that death provides information about the efficacy of that treatment arm. The results have therefore been reported using statistical techniques and software\(^18\) that adjust for the nonindependence between the competing risk of death and the outcomes of interest (hematologic recovery), although it should be noted that the inferences are unchanged (GM-CSF significantly shortens neutropenia) if a standard logrank analysis is performed with deaths censored.

| Table 4. Median Time in Days From Start of GM-CSF/Placebo, in Consolidation, to Recovery |
|---------------------------------|------------------|-----------------|-----------|
| ANC >500/μL                     | GM-CSF           | Placebo         | \( P \)    |
| 13.5 (10.5, 15.5)               | 14 (12, 17)      | .21             |
| ANC >1,000/μL                   | 14.5 (11, 17)    | 15 (12, 23)     | .17        |

Numbers in parentheses refer to 25% and 75% percentiles.

The overall morbidity from infection and mortality were also significantly reduced among patients receiving GM-CSF. ECOG’s previous study for de novo AML (E3483)\(^30\) showed an overall mortality during induction of 20% for patients greater than 55 to 65 years of age. This study (E1490) had an overall mortality of 18% for an even older patient population (>50 to 70 years of age) with only 3 treatment-related deaths in 52 patients after the institution of GM-CSF compared with 7 treatment-related deaths in 47 patients after the institution of placebo.

The complete remission rate was not statistically different among the two groups, but the trend to an increased complete remission rate among the GM-CSF patients (Table 2) may reflect the effect of reduced mortality in this group. It is worth noting that, for patients 56 to 65 years of age who received GM-CSF, the complete remission rate was 68%; this finding is similar to results in ECOG’s previous studies of patients less than 55 years of age.

Considering all randomized patients and using an intent-to-treat analysis, the median survival was approximately doubled for patients receiving GM-CSF (Fig 3), ie, 10.6 months versus 4.8 months for patients receiving placebo. The difference is attributable mostly to the increased early mortality in the placebo group.

The potential for an increased relapse rate in patients receiving GM-CSF was an additional concern. This issue has only been addressed in one study,\(^2\) which showed long-term comparable disease-free survival in GM-CSF–treated patients versus historical controls. Figure 4 illustrates that, in this double-blind study, there was no difference in the disease-free survival among all patients in complete remission between the two groups.

There has only been one other completed prospective double-blind study of GM-CSF in patients ≥60 years with AML. A preliminary report\(^19\) of this CALGB study described no differences in hematologic recovery, infection rate, or overall survival. The design of that study was different in that all patients received GM-CSF or placebo on day 8, immediately after completion of induction therapy, irrespective of whether marrow aplasia had been achieved. Furthermore, approximately 30% of patients stopped receiving the study drug in either arm because of perceived toxicity. However, there was no withdrawal because of toxicity in this ECOG study. Perhaps it is not possible to compare studies using different GM-CSF products; *Escherichia coli*–derived GM-CSF was used in the CALGB study, compared with yeast-derived GM-CSF in this ECOG study.

In summary, this double-blind study demonstrates that
GM-CSF is safe and efficacious in adult patients (>55 to 70 years of age) with de novo AML undergoing induction therapy. Its main value appears to be in reducing the duration of neutropenia and therapy-related mortality and morbidity.

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REFERENCES
A randomized placebo-controlled phase III study of granulocyte-macrophage colony-stimulating factor in adult patients (> 55 to 70 years of age) with acute myelogenous leukemia: a study of the Eastern Cooperative Oncology Group (E1490)

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