Randomized Placebo-Controlled Trial of Granulocyte-Macrophage Colony-Stimulating Factor in Patients With Chemotherapy-Related Febrile Neutropenia


Purpose: To determine whether granulocyte-macrophage colony-stimulating factor (GM-CSF) used in addition to standard inpatient antibiotic therapy shortens the period of hospitalization due to chemotherapy-induced neutropenic fever.

Patients and Methods: One hundred thirty-four patients with a hematologic (n = 47) or solid tumor (n = 87) who had severe neutropenia (< 0.5 × 10^9/L) and fever (> 38.5°C once or > 38°C twice over a 12-hour observation period) were randomly assigned to receive GM-CSF 5 μg/kg/d (n = 65) or placebo (n = 69) in conjunction with broad-spectrum antibiotics for a minimum of 4 days and a maximum of 14 days. GM-CSF/placebo antibiotics were stopped if the neutrophil count was greater than 1.0 × 10^9/L and temperature less than 37.5°C during 2 consecutive days, or for a leukocyte count ≥ 10 × 10^9/L, both followed by a 24-hour observation period (hospitalization period).

Results: Compared with placebo, GM-CSF enhanced neutrophil recovery. Median neutrophil counts at day 4 were 2.5 × 10^9/L (range, 0 to 25) in the GM-CSF arm and 1.3 × 10^9/L (range, 0 to 9) in the placebo arm (P < .001). No significant difference was observed with regard to median number of days with less than 1.0 × 10^9/L neutrophils (4 vs 4) or days of fever (3 vs 3). The median number of days patients were hospitalized while on study was comparable in the GM-CSF and placebo groups at 6 (range, 3 to 14) versus 7 (range, 4 to 14), respectively, according to an intention-to-treat analysis (P = .27). Quality-of-life scores in 90 patients demonstrated significant differences in favor of the placebo group. Hospital costs were significantly higher for GM-CSF-treated patients if GM-CSF was included in the price (median costs, $4,140 [US] for GM-CSF vs $590 for placebo; P < .05).

Conclusion: These results indicate that GM-CSF does not affect the number of days for resolution of fever or the hospitalization period for this patient group, although a significant effect of GM-CSF was observed on neutrophil recovery.


Chemotherapy-related neutropenia and fever is a complication that occurs frequently during treatment of cancer patients. In particular, the severity and duration of neutropenia determine the risk of infection and the outcome of the patient.1,2 Recently, different hematopoietic growth factors (HGFs) have been produced, which allows the opportunity to modulate the period of granulocytopenia.

Two options are available for applying HGFs after standard chemotherapy.3 First, HGF can be given as an adjunct to chemotherapy until recovery of peripheral-blood counts is noted. In a number of studies, this policy has resulted in a 50% reduction of infectious complications,4,5 while in other studies, no significant effect has been shown with regard to the incidence of bacteremia, days of fever, or hospitalization duration.6,7 A second possibility would be to apply HGF only in the case of infection.8-11 This approach would reduce the number of patients exposed to growth factor and could potentially restrict the costs of treatment. A limited number of studies have tested this approach. Riikonen et al9 demonstrated in a randomized study of 58 children that the application of granulocyte-macrophage colony-stimulating factor (GM-CSF) during fever and neutropenia resulted in a faster recovery of the granulocytic lineage and a shortened period of hospitalization. A recent double-blind study with granulocyte colony-stimulating factor (G-CSF) in febrile neutropenia demonstrated that the greatest benefit was obtained in patients with a documented infection who had a neutrophil count less than 0.1 × 10^9/L at the start of G-CSF administration.10

We describe a prospective multicenter clinical trial designed to compare the effects of GM-CSF versus placebo in 153 adult patients with chemotherapy-related febrile neutropenia. The study focused on whether GM-CSF affects the duration of hospitalization in conjunction with quality-of-life and cost-effectiveness analyses.
PATIENTS AND METHODS

Study Population

This study was performed at the Departments of Hematology and/or Oncology of six university hospitals and the Rotterdam Cancer Institute from September 1991 to September 1994. Eligible patients with chemotherapy-related neutropenia (< 0.5 x 10^9/L) and fever (temperature of > 38°C over a 12-hour observation period or > 38.5°C once) were entered.

Patients with severe heart, lung, and liver impairment of World Health Organization (WHO) grade 3 to 4 were excluded, as were patients with acute myeloid leukemia, myelodysplasia, or autologous or allogeneic bone marrow transplantation and those patients already receiving antibiotics for the suspected infection.

The study protocol was approved by the medical ethical committees of the different hospitals and all patients gave informed consent.

Design and Treatment

This was a double-blind randomized phase III study. Patients were stratified for solid or hematologic tumors and for hospital attended. Enrolled patients were admitted to the hospital and a full medical history was taken and physical examination performed. Baseline investigations included full blood cell counts with differential WBC counts, and sinus and chest radiographs. Cultures of blood (in duplicate), urine, and other suspicious sites were collected. In addition, serum was collected and frozen (−80°C) on days 0 and 1 for cytokine analysis. GM-CSF (5 µg/kg/d) or placebo was administered once daily subcutaneously for a minimum of 4 days and a maximum of 14 days. GM-CSF or placebo was started simultaneously with intravenous empiric antibiotics according to standardized local hospital policy. Both antibiotics and GM-CSF/placebo were discontinued if both the temperature normalized (< 37.5°C) and the granulocyte count was ≥ 1.0 x 10^9/L for 2 consecutive days. However, in the case of a leukocyte count ≤ 1.0 x 10^9/L, application of GM-CSF/placebo was stopped while the antibiotic treatment was continued until the temperature was normalized for 2 consecutive days. The patient was then observed for 24 hours, and if no sign of infection was noted, the patient was discharged from the hospital and monitored twice weekly for a period of 2 weeks or until the next chemotherapy course.

Lymphoblastoid Escherichia coli GM-CSF (Leucomax; Sandoz Pharma, Basel, Switzerland/Scherering-Plough, Kenilworth, NJ) in vials of 400 µg protein per vial was reconstituted in 1 mL of water. A vial identical in appearance to the active drug but containing lyophilized placebo was also provided by Sandoz and used in a similar fashion.

Study End Points

The primary end point was hospitalization time with GM-CSF or placebo, which comprises the period of resolution of neutropenia (> 1.0 x 10^9/L) and fever defined as a temperature less than 37.5°C for 2 consecutive days followed by a 24-hour observation period. For this reason, blood and differential counts were performed daily and temperature was recorded three times daily. Secondary end points were days on antibiotics and incidence of change in antibiotic treatment. Inpatients were allowed to enter the study. Some patients remained in the hospital after study completion for reasons other than continued morbidity related to fever and neutropenia. In these cases, the hospitalization duration was the study duration.

Quality-of-Life Analysis

The quality of life of patients was scored by means of written questionnaires that were filled in by the patients 1 day after GM-CSF or placebo treatment was stopped. Based on methodologic criteria concerning cost-effectiveness studies in cancer trials, the patient questionnaire consisted of a generic health status measurement instrument, a cancer-specific instrument, and a valuation instrument. The Nottingham Health Profile incorporates the dimensions of mobility, emotional reactions, energy, social isolation, pain, and sleep. For the general population, the average score for all dimensions is less than 10. The EuroQol consisted of a descriptive part and a valuation part (a rating scale). The descriptive part allows the calculation of utilities. The utility scores are based on the validation for each health state of patients and of a representative panel of the population. The average EuroQol score for the general population is greater than 90. The Rotterdam Symptom Checklist has the potential to add illness or treatment-related items. In this study, questions were added on possible side effects associated with GM-CSF, namely, constipation, painful joints, palpitation rash/eczema, and sweating/perspiring.

Furthermore, data forms were used to obtain daily information on patients' quality of life during the period of fever and neutropenia. These forms were filled in daily by nurses. The descriptive part of the EuroQol was used, which allowed calculation of utilities.

Cost Analysis

Cost analysis was based on a detailed review of all activities concerning the treatment of patients with fever and leukopenia. These activities included days in hospital, consultations, laboratory services, diagnostics including imaging procedures, antibiotics, and GM-CSF. The data were derived from all registry forms and from daily data forms. The latter included information on type of hospital ward and consultations.

For each of these cost data, unit prices were determined that reflected the real use of resources. The year of study was 1992 ($1 US = 1.8 Dutch guilders). Patients stayed on wards for regular oncologic care, regular hematologic care, protected environment, and intensive care. The costs of hospital days were split into direct and indirect costs. Direct costs concerned manpower (doctors, nurses, etc) and materials (medical devices, supportive patient care, etc). Indirect costs were related to overhead. The cost of hospitalization amounted to approximately $290 (US) per day for regular oncologic care, $350 per day for regular hematologic care, $536 for staying in a protected environment, and $1,223 for intensive care.

The output of hospital laboratories in the Netherlands is measured in terms of a point system. A unit price is associated per point. The unit prices differ across types of laboratories. The unit prices per point varied from $0.62 (biochemistry and hematology laboratories) to $2.81 (virology tests). A routine test (including hemoglobin, leukocytes, and platelets) amounted to 5.75 points and cost $3.58. For diagnostics, the Dutch tariff system has been used as an approximation of unit costs. The drug prices used were wholesale prices. A 300-µg vial GM-CSF cost $138 and a 400-µg vial, $184.

Measurement of Serum Cytokine Levels

GM-CSF, G-CSF, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) serum levels were quantified using a human GM-CSF,
GM-CSF, IL-6, or TNF-α enzyme-linked immunosorbent assay (ELISA) kit (R&D, Cambridge, United Kingdom) as recommended by the manufacturer.

**Statistical Analysis**

The generalized Wilcoxon test was chosen to test the difference in duration of hospitalization between the two treatment groups. The estimated sample size was based on the H0 hypothesis that the median duration of hospitalization is 11 days in both treatment groups versus the H1 hypothesis that assumes a clinically relevant difference between the two treatment groups of 2 days. Using a significance level of .05, a sample size of 70 patients per group showed a power calculation of at least 75%.

For comparison of clinical characteristics, a χ², two-tailed Fisher's exact test, Wilcoxon-Mann-Whitney test, or Student’s t-test as appropriate was used. It was a feature of the study to allow patients to enter more than once. This was the case in 11 patients (GM-CSF v four placebo). All patients who fulfilled the entry criteria and received at least one dose of study medication were included in the intention-to-treat analysis. In the case of premature discontinuation, death, or major protocol violation for the main end point analysis, the patient was right-censored at day 14. Censoring in this way is a worst case scenario in which these patients are regarded as a failure to respond to therapy during the whole study period. Cumulative rates for the days on study, days of neutropenia, and days of fever were estimated by Kaplan-Meier methods. Groups were compared by the generalized Wilcoxon test. Data are reported as median survival and absolute ranges. An additional per-protocol analysis was performed using the same approach, with the exception that in the case of a noninformative drop-out, the patient was censored at the time of discontinuation.

The risk reduction for assigned study medication with the theoretic discharge from hospital as the dependent variable was adjusted for influential baseline covariates, chosen by stepwise selection, by using a Cox proportional regression model. The covariates selected were more than 11 days after last chemotherapy, solid tumor, and fever of unknown origin (FUO).

Only variables whose coefficients had P values less than .05 were included. Adjusted risk reductions are presented.

A two-sided probability level of χ² .05 was considered to indicate statistical significance. All analysis were performed using Statistical Analysis System version 6.08 (SAS Institute, Cary, NC). Quality-of-life items are presented as mean scores. For comparison between items, Mann-Whitney and χ² tests were used. The cost of both groups was compared with the Mann-Whitney test.18

**RESULTS**

One hundred fifty-three patients were entered onto the study (Table 1). Of these, 74 patients received GM-CSF and 79 placebo. Nine patients in the GM-CSF group and 10 in the placebo group were excluded from analysis due to ineligible entry criteria, eg, temperature less than 38°C or granulocyte count greater than 0.5 × 10⁹/ L. Subsequently, 134 patients were analyzed according to intention-to-treat analysis. Eleven patients (five GM-CSF and six placebo) were withdrawn before study completion and were excluded from the per-protocol analysis. Reasons for excluding these patients were as follows:

![Table 1. Patient Inclusion](image)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>GM-CSF</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomized</td>
<td>153</td>
<td>74</td>
<td>79</td>
</tr>
<tr>
<td>Ineligibility of entry criteria</td>
<td>19</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Patients available for intention-to-treat</td>
<td>134</td>
<td>65</td>
<td>69</td>
</tr>
<tr>
<td>analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawals before end of follow-up</td>
<td>11</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Incorrect treatment on study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>medication or concomitant medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possibility of side effects</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Withdrawal consent</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Patients available for per-protocol analysis</td>
<td>123</td>
<td>60</td>
<td>63</td>
</tr>
</tbody>
</table>

incorrect treatment with study medication or concomitant medication (n = 5), adverse event (n = 1), suspected side effects of treatment (n = 3), and refusal of further treatment (n = 2).

The baseline characteristics of the 134 patients are listed in Table 2. The two treatment groups were well matched with regard to age, sex, tumor type, and neutrophil count. Preceding chemotherapy in the GM-CSF
group consisted of a cisplatin-containing (21%), anthracycline-containing (66%), or high-dose cytarabine-containing (10%) regimen. In the placebo group, comparable treatment schedules were applied: 27% cisplatin-containing, 57% anthracycline-containing, and 2% high-dose cytarabine-containing regimen.

With regard to microbiologically or clinically documented infections, no significant difference was observed for bacteremia and culture-positive infections. In addition, no significant difference was observed with regard to the incidence of FUO. Positive blood cultures consisted of 44% gram-positive bacteria and 56% gram-negative bacteria in the GM-CSF group. In the placebo group, 50% of the cultures contained gram-positive and 50% gram-negative bacteria.

**Neutropenia and Fever**

GM-CSF enhanced neutrophil recovery as depicted in Fig 1. A significant difference in absolute neutrophil counts was observed on days 4 and 5 ($P < .001$). A difference was also observed for the numbers of monocytes and eosinophils on the last day of GM-CSF/placebo treatment in 100 assessable patients. In the GM-CSF group, the median number of monocytes was $0.8 \times 10^9/\text{L}$ (range, 0 to 0.4) and of eosinophils $0.5 \times 10^9/\text{L}$ (range, 0 to 1.2). In the placebo group, these values were $1.2 \times 10^9/\text{L}$ (range, 0.1 to 4.9; $P < .03$) and $0.3 \times 10^9/\text{L}$ (range, 0.0 to 0.5, $P = .45$), respectively. However, despite the enhancing effect of GM-CSF on neutrophil recovery, no differences were observed in the median days of neutrophils less than $0.5 \times 10^9/\text{L}$ and $1.0 \times 10^9/\text{L}$ (Table 3).
Table 3. Days of Neutropenia and Fever and Days on Study
(hospitalization) per Treatment Group (N = 134)

<table>
<thead>
<tr>
<th>Variable</th>
<th>GM-CSF</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC &lt; 0.5 × 10⁹/L (days)</td>
<td>3 ± 1-14</td>
<td>4 ± 1-14</td>
</tr>
<tr>
<td>ANC &lt; 1.0 × 10⁹/L (days)</td>
<td>4 ± 1-14</td>
<td>4 ± 1-14</td>
</tr>
<tr>
<td>ANC at day 4 × 10⁹/L</td>
<td>2.9 ± 0-25</td>
<td>1.3 ± 0-9</td>
</tr>
<tr>
<td>Fever (days)</td>
<td>3 ± 1-14</td>
<td>3 ± 1-14</td>
</tr>
<tr>
<td>Days of hospitalization</td>
<td>6 ± 3-14</td>
<td>7 ± 4-14</td>
</tr>
</tbody>
</table>

Abbreviations: ANC, absolute neutrophile count; NS, not significant.

No difference was observed in time to resolution of fever. The median temperature curve was higher in the GM-CSF group compared with the placebo group during the first 6 days of treatment, with a significant difference on day 2 (P < .05, Fig 1).

The estimated median survival for the primary end point of the study (Fig 2), eg, normalization of temperature and a granulocyte count greater than 1.0 × 10⁹/L during 48 hours or a leukocyte count = 10 × 10⁹/L both followed by a 24-hour observation period, was reached after a median of 6 days (range, 3 to 14) in the GM-CSF group and 7 days (range, 4 to 14) in the placebo group (P = .27) according to the intention-to-treat analysis. Comparable results were obtained with the per-protocol analysis: GM-CSF—6 days (range, 3 to 14); placebo—6 days (range, 4 to 14) (P = .33). Finally, the proportion of patients in the GM-CSF and placebo arms was similar with regard to hospitalization period of more than 10 days: 9% in the GM-CSF group and 10% in the placebo group.

Antibiotics and GM-CSF

All patients were treated with intravenous antibiotics. In the GM-CSF group, 15% received imipenem, 23% cefuroxime in combination with an aminoglycoside, 13% augmentin in combination with an aminoglycoside, and 20% cefazidime. In the placebo group, the percentages were, respectively, 11%, 14%, 23%, and 18%. Antibiotic treatment was changed in 29% of the GM-CSF group and 24% of the placebo group. Six patients (9%) treated with GM-CSF and three patients (4%) who received placebo were given intravenous antifungal therapy. The median duration of GM-CSF and placebo application for the total group of patients was 5 days in both the GM-CSF arm (range, 1 to 14) and placebo arm (range, 1 to 13). However, antibiotic treatment was not stopped at the same day of GM-CSF/placebo discontinuation in all cases. In the GM-CSF arm, 16 patients had a prolonged administration of antibiotic treatment between 3 and 5 days, and three patients between 5 and 10 days. In the placebo arm, prolonged antibiotic administration was given in eight patients between 3 to 5 days and two patients between 7 to 9 days.

Subgroup and Adjusted and Multivariate Analysis

First, it was evaluated whether a difference in response was noted in patients with baseline neutrophil counts less than 0.1 × 10⁹/L versus 0.1 to 0.5 × 10⁹/L. No difference was observed between both groups for time to reach a neutrophil count greater than 1.0 × 10⁹/L in combination with time for resolution of fever. Second, Table 4 lists the results of a Cox proportional hazards regression analysis for the primary end point in which the difference between the two treatment regimens was estimated after adjustment for the independent associated covariates: more than 11 days since last chemotherapy, solid tumor, and FUO. GM-CSF application did not influence the primary end point significantly, but a trend was observed. When all prognostic factors were taken into account simultaneously in the Cox regression model, the risk reduction of the primary end point due to GM-CSF treatment was 29% (P = .12). The unadjusted risk reduction of GM-CSF treatment was 23% (P = .20).

Table 4. Analysis of Risk of Hospitalization in a Cox Regression Model

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Risk Reduction (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted, GM-CSF treatment</td>
<td>23</td>
<td>.20</td>
</tr>
<tr>
<td>Multivariate (Cox regression model)</td>
<td>41</td>
<td>.016</td>
</tr>
<tr>
<td>Days since last chemotherapy (&lt;11 days)</td>
<td>55</td>
<td>.001</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>42</td>
<td>.016</td>
</tr>
<tr>
<td>FUO</td>
<td>29</td>
<td>.12</td>
</tr>
<tr>
<td>Adjusted, GM-CSF treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig 2. Estimated median survival for the primary end point of the study. Wilcoxon, P = .27; log-rank, P = .18.
Supportive Care

The median number of RBC transfusions was identical in the GM-CSF group versus the placebo group at two (range, zero to eight) \( (P = .50) \). The number of platelet transfusions given was a median of zero (range, zero to five) in the GM-CSF group and zero (range, zero to four) in the placebo group \( (P = .72) \).

Results of Quality-of-Life Analysis

The results of the quality-of-life analysis are based on 113 daily data forms and 90 quality-of-life questionnaires. The discrepancy between the numbers of questionnaires and data forms is due to a later start of the cost-effectiveness study. The data forms that are not included are center-related, so it is unlikely that as a consequence of this a bias would have been introduced. The results of the patient questionnaires are listed in Table 5. The scores of the Karnofsky performance index were greater among the placebo group, ie, a mean value of 63 in the GM-CSF group versus 73 in the placebo group \( (P < .05) \). Patients in the placebo group reported less complaints than patients who received GM-CSF treatment. Mobility, emotional, and energy problems were less pronounced in the placebo than GM-CSF group \( (P < .05) \). No significant differences were noticed in the EuroQol scores using patient values. The population value was in favor of the placebo group, namely, 54 in the GM-CSF arm and 66 in the placebo arm \( (P < .05) \).

The most important complaints and symptoms reported on the Rotterdam Symptom Checklist were tiredness, lack of appetite, lack of energy, dry mouth, sweating/perspiring, and sore mouth and/or pain when swallowing. Patients in the placebo group experienced less problems concerning appetite and energy than patients in the GM-CSF group \( (P < .01) \). Regarding tiredness, dry mouth, and sweating, no difference was observed.

The results of the population scores (data forms) derived from the descriptive part of the EuroQol are presented in Fig 3. Patients who received placebo treatment felt better during the hospitalization period than patients in the GM-CSF group. From day 8, the observations are biased, as many patients had already been discharged from the hospital.

Results of Cost Analysis

The median number of days in the hospital in the GM-CSF group was 6. Hospital care was classified as follows: 87% regular oncologic or hematologic care, 11% protected environment care, and 2% intensive care. Patients treated with placebo had a median hospital stay of 7 days. This group was divided into 86% regular oncologic or hematologic care, 13% care in a protected environment, and 1% intensive care.

The median cost of hospitalization in the GM-CSF group was $2,130 (range, $860 to $6,420) and in the placebo group $2,450 (range, $1,140 to $7,130). The median cost of antibiotics amounted to $630 (range, $130 to $3,790) in the GM-CSF group and to $580 (range, $144 to $2,930) in the placebo group. The cost of GM-CSF was $1,100 (range, $280 to $3,860). Additional costs included laboratory services, medical procedures, consultations, and blood transfusions. The median costs were equal in both arms and amounted to $470 in the GM-CSF group (range, $120 to $2,830) and in the placebo group (range, $170 to $2,680). The median of all costs was $4,140 (range, $1,710 to $14,650) in the GM-CSF group and $3,590 (range, $1,680 to $10,990) in the placebo group \( (P < .05) \).

Adverse Events

Events observed during the treatment period are listed in Table 6. A great variety in events was observed. Myalgia and/or rash and/or bone pain and/or edema were noted in 20% of GM-CSF–treated patients and 6% of placebo-treated patients (not significant). No difference was observed in the mortality rate between both groups. In the
GM-CSF IN FEBRILE NEUTROPENIA

![Graph showing EuroQol population scores in GM-CSF and placebo groups.](image)

GM-CSF arm, one patient died of acute respiratory distress syndrome. In the placebo arm, two patients died of pulmonary embolism.

Cytokine Analyses

Serum cytokine levels were measured at presentation and 24 hours after initiation of therapy in 60 patients (28 GM-CSF–treated and 32 placebo-treated, Table 7): eight patients with bacteremia, 25 with a clinically documented infection, and 27 with FUO. At presentation, high levels of IL-6 and G-CSF were observed, especially in patients with bacteremia. During the first 24 hours of treatment, no change in the cytokine profile was observed due to the administration of GM-CSF, although significantly higher levels of GM-CSF were measured in the GM-CSF–treated group (Table 7).

DISCUSSION

The present study demonstrates that GM-CSF accelerates neutrophil recovery in patients who receive antibiotics for febrile neutropenia after chemotherapy. Enhancement of neutrophil recovery by GM-CSF was irrespective of whether patients presented with baseline granulocyte counts less than 0.1 × 10⁹/L or between 0.1 and 0.5 × 10⁹/L. However, the enhancing effect of GM-CSF on neutrophil recovery did not occur immediately, but was only observed 4 to 5 days after the start of treatment.

Despite the faster neutrophil recovery in the GM-CSF group, no difference was observed in the resolution of fever between the GM-CSF and placebo groups. Previous studies demonstrated a distinct correlation between resolution of fever and neutrophil recovery. However, these studies were conducted almost entirely in patients with a long-lasting neutropenia. The observations apply particularly to patients with acute leukemia who are treated with intensive chemotherapy. The present study and other studies in cancer patients show that this correlation is less prominent for patients treated with less intensive chemotherapy regimens. In these patients, the febrile period is usually short and depends on the response to antibiotics. In the placebo group, the median duration for resolution of fever (< 37.5°C) was 3 days, while a granulocyte count greater than 1 × 10⁹/L was reached after a median of 4 days. It is possible in the GM-CSF group that GM-CSF administration negatively affected the days for resolution of fever. Phase I to II studies have demonstrated that GM-CSF might induce fever. However, this was observed especially in patients treated with a higher dose of GM-CSF. A recent study of G-CSF in febrile neutropenia also demonstrated that G-CSF hastens neutrophil recovery, but does not affect duration of fever. Since the periods of fever and severe granulocytopenia were not reduced by GM-CSF treatment, no difference was observed in the duration of hospitalization. This lack of difference in hospitalization duration between both arms indicated that GM-CSF treatment was not cost-effective for the total group of patients with chemotherapy-related febrile neutropenia. Treatment costs were significantly higher than those in the placebo group, mainly due to the costs of GM-CSF. In part, this is caused by the fact that GM-CSF is only available in vials of 300 µg and 400 µg. In this study, GM-CSF was administered at a dose of 5.0 µg/kg/d, which means that a 65-kg patient received 325 µg of GM-CSF. Correcting for this loss of GM-CSF or applying a 300-µg vial only would reduce the costs of GM-CSF by approximately 10%.

Adverse events were frequently noted in this study and can be ascribed to the underlying disorder and treatment. Quality-of-life analyses demonstrated significant differences in favor of the placebo group. However, no increased mortality was observed in the GM-CSF–treated group. Different cytokines were measured to analyze whether GM-CSF ap-

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>GM-CSF (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>35</td>
<td>23</td>
</tr>
<tr>
<td>Cardiac dysfunction</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Biochemical abnormalities</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Bone pain</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Edema</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 6. Adverse Events Reported During Treatment With Antibiotics Plus GM-CSF or Placebo
Table 7. Cytokine Profiles on Days 0 and 1 of Treatment

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>GM-CSF</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 1</td>
</tr>
<tr>
<td>GM-CSF (pg/mL)</td>
<td>28 ± 20</td>
<td>709 ± 126*</td>
</tr>
<tr>
<td>G-CSF (pg/mL)</td>
<td>3,459 ± 583</td>
<td>2,858 ± 604</td>
</tr>
<tr>
<td>TNF-α (ng/mL)</td>
<td>1.0 ± 0.43</td>
<td>0.18 ± 0.77</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>304 ± 67</td>
<td>238 ± 57</td>
</tr>
</tbody>
</table>

NOTES. Values are the mean ± SE.
*Significant difference observed on day 1 of treatment (P < .0001).

plication might change IL-6, G-CSF, and TNF-α serum levels during treatment. Elevated levels were measured, but GM-CSF did not modulate these cytokine profiles significantly. Recent studies in mice with noncompromised bone marrow have demonstrated that GM-CSF priming is associated with an enhanced production of cytokines after challenge with endotoxin and results in increased mortality.23 However, the present study showed no major changes in the cytokine profile during administration of GM-CSF.

Four studies have been conducted in patients with febrile neutropenia.8,11 In three studies,8,11 a significant advantage was observed for GM-CSF or G-CSF treatment. In the present study, only a trend toward an advantage for GM-CSF application was seen. The difference might be ascribed to differences in patients categories and treatment protocols. This is supported by the multivariate analysis in which tumor type was an independent prognostic factor for the success rate of treatment. Furthermore, a remarkable difference is observed in the duration of antibiotic application between studies, which seems to be a relevant factor for the hospitalization period. In the study reported by Riikonen et al,9 antibiotic treatment was continued for a minimum of 5 days, while in the study reported by Maher et al,10 antibiotic treatment was continued 4 days after normalization of temperature. In the present study, antibiotic treatment was intended to stop after 2 consecutive days with resolution of fever and granulocytopenia. The differences in antibiotic policy have a great impact on the hospitalization period. The median hospitalization days for the GM-CSF and G-CSF arm of the studies by Riikonen et al and Maher, were 9 and 8, respectively. In the present study, the median hospitalization duration while on study was 6 days in the GM-CSF arm and 7 days in the placebo arm.

The results of this study do not exclude that a subgroup of patients, eg, those with a hospitalization period longer than 10 days and neutropenia, might benefit from the application of GM-CSF. In both previous studies,9,10 of febrile neutropenia, a significant advantage of hematopoietic growth factor application was observed that resulted in a significant reduction in hospitalization duration. However, in the present study, the follow-up period was only 14 days and prolonged hospitalization was only observed in 10% of patients, which makes further analyses inadequate. Finally, the dose of GM-CSF used in this study seems to be adequate. A distinct effect was observed on the neutrophil recovery. Moreover, the results obtained for duration of severe neutropenia were comparable with the G-CSF study, in which a dose of 12 μg/kg/d was used.10

In conclusion, the study presented here demonstrates that the application of GM-CSF in febrile neutropenia did not result in a significant shortening of the hospitalization period, despite a faster recovery of neutrophils for the whole group of patients.

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APPENDIX
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