

## HUMAN GRANULOCYTE COLONY-STIMULATING FACTOR AFTER INDUCTION CHEMOTHERAPY IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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## ABSTRACT

**Background** Recombinant human granulocyte colony-stimulating factor (G-CSF, or filgrastim) hastens the recovery from neutropenia after intensive chemotherapy, but its role in the management of childhood leukemia is unclear.

**Methods** We randomly assigned 164 patients with acute lymphoblastic leukemia (age range, 2 months to 17 years) to receive placebo or G-CSF (10  $\mu$ g per kilogram of body weight per day subcutaneously), beginning one day after the completion of remission-induction therapy and continuing until the neutrophil count was greater than or equal to 1000 per cubic millimeter for two days. The clinical and laboratory effects of this therapy were documented for 21 days. The area under the plasma G-CSF concentration-time curve was measured on days 1 and 7 in both groups.

**Results** Responses to the growth factor could be assessed in 148 patients (73 in the G-CSF group and 75 in the placebo group). G-CSF treatment did not significantly lower the rate of hospitalization for febrile neutropenia (58 percent in the G-CSF group vs. 68 percent in the placebo group; relative risk, 0.85; 95 percent confidence interval, 0.59 to 1.16), increase the likelihood of event-free survival at three years (83 percent in both groups), or decrease the number of severe infections (five in the G-CSF group vs. six in the placebo group). Patients treated with G-CSF had shorter median hospital stays (6 days vs. 10 days,  $P=0.011$ ) and fewer documented infections (12 vs. 27,  $P=0.009$ ). The median total costs of supportive care were similar in the G-CSF and placebo groups (\$8,768 and \$8,616, respectively). Among patients who did not have febrile neutropenia during the first week of G-CSF or placebo injections, higher systemic exposure to the growth factor on day 7 was significantly related to a lower probability of subsequent hospitalization ( $P=0.049$ ).

**Conclusions** G-CSF treatment had some clinical benefit in children who received induction chemotherapy for acute lymphoblastic leukemia, but it did not reduce the rate of hospitalization for febrile neutropenia, prolong survival, or reduce the cost of supportive care. (N Engl J Med 1997;336:1781-7.)

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CURRENT forms of therapy can cure more than 70 percent of children with acute lymphoblastic leukemia. This progress is due largely to intensified regimens of induction and consolidation chemotherapy and improvements in supportive care.<sup>1</sup> However, infectious complications during prolonged neutropenia remain a major cause of morbidity and delay in the delivery of treatment. Granulocyte colony-stimulating factor (G-CSF) has been used to ameliorate drug-induced myelosuppression, as a way of addressing this problem.<sup>2</sup>

G-CSF accelerates the recovery of myeloid cells in adults with cancer who receive intensive chemotherapy<sup>3-14</sup> or myeloablative treatment followed by hematopoietic-stem-cell transplantation.<sup>15-18</sup> Nonetheless, the effect of G-CSF treatment on febrile neutropenia, documented infections, and hospitalization in adults is still unclear, despite numerous randomized, placebo-controlled studies.<sup>3,9,12,13,15</sup> The value of G-CSF in children is even less clear.<sup>19-26</sup>

In 1991, we began a randomized, double-blind, placebo-controlled trial to determine whether G-CSF has a role in the treatment of children with acute lymphoblastic leukemia in first remission. Because the optimal dosage of the growth factor was unknown and our preliminary data suggested that children would tolerate and might benefit from higher doses of colony-stimulating factors than those commonly used in adults,<sup>27,28</sup> we chose a relatively high dose (10  $\mu$ g per kilogram of body weight per day subcutaneously) to avoid undertreatment. The primary aim of the study was to assess the effects of G-CSF therapy on the incidence of febrile neutropenia and consequent hospitalization among children with acute lymphoblastic leukemia who had completed a full course of intensive remission-induction therapy.

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## METHODS

### Patients

Between December 1991 and August 1994, 167 consecutive patients with newly diagnosed acute lymphoblastic leukemia (age range, 2 months to 17 years) were registered in Total Therapy Study XIII A at St. Jude Children's Research Hospital, in Memphis, Tennessee. A total of 164 patients were eligible for random assignment to treatment with recombinant methionyl G-CSF (filgrastim, Amgen, Thousand Oaks, Calif.) or placebo. Three patients were ineligible, one because of an incorrect diagnosis and two because of inadequate renal function. The study was approved by the hospital's institutional review board, with written informed consent obtained from the patients' parents or legal guardians.

### Treatment Protocol

The 164 patients were stratified according to age, leukocyte count, and DNA index (the ratio of the DNA content in leukemic  $G_0/G_1$  cells to that in normal diploid  $G_0/G_1$  cells), and then randomly assigned to receive either high- or lower-dose methotrexate as initial therapy.<sup>29</sup> Beginning 96 hours after the start of methotrexate treatment, all patients received remission-induction therapy, consisting of prednisone (40 mg per square meter of body-surface area daily for four weeks), vincristine (1.5 mg per square meter weekly for four weeks), asparaginase (10,000 units per square meter three times weekly for three weeks), daunorubicin (25 mg per square meter on days 1 and 8), and etoposide and cytarabine (300 mg of each per square meter on days 22, 25, and 29). One day after remission-induction therapy was completed (day 30), the patients were stratified according to the methotrexate dose and the risk of a relapse (determined on the basis of the leukemic-cell DNA index, age, leukocyte count, and presence or absence of the Philadelphia chromosome) and randomly assigned to receive either placebo (84 patients) or G-CSF (80 patients). G-CSF was administered subcutaneously at a dose of 10  $\mu$ g per kilogram per day for 15 days or until the postnadir neutrophil count was 1000 per cubic millimeter or higher for 2 days; normal saline, administered in an equivalent volume in identical syringes, was used as placebo. Complete blood counts were performed at least once every other day. Subsequent consolidation and continuation treatments are described elsewhere.<sup>30</sup>

### Management of Fever and Neutropenia

Published guidelines for the management of febrile neutropenia<sup>31,32</sup> were followed throughout the study. Briefly, fever was defined as an oral temperature of 38.3°C or higher on any occasion or a temperature of 38° to 38.2°C on two or more occasions within 12 hours, and neutropenia was defined as an absolute neutrophil count of less than 500 per cubic millimeter. The severity of infections was classified according to the Common Toxicity Criteria of the National Cancer Institute.

Treatment with oral trimethoprim-sulfamethoxazole to prevent *Pneumocystis carinii* infection was begun on day 15 of the remission-induction protocol.<sup>33,34</sup> With the onset of fever and neutropenia, four blood samples were collected for bacterial and fungal cultures,<sup>35</sup> and a combination of amikacin, vancomycin, and ticarcillin was administered empirically. Cultures of the urine, throat, anterior nares, and rectum and of accessible lesions, as well as chest radiographs, were included in the initial evaluation. If patients became afebrile within the first four days after the start of antibiotic treatment, the antibiotics were continued for a total of seven days, or until the neutrophil count equaled or exceeded 500 per cubic millimeter. Patients who remained febrile were switched to ceftazidime, with the addition of amikacin and ticarcillin, in cases of colonization by *Pseudomonas aeruginosa*, or vancomycin, in cases of methicillin-resistant *Staphylococcus aureus*. If fever persisted for seven days, amphotericin B was administered empirically for a period that depended on the presence or absence of disseminated fungal infection.

### Pharmacokinetics

Blood samples were collected before and 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hours after the G-CSF or placebo injections on days 1 and 7, kept at 4°C, and centrifuged within 3 hours. The serum (frozen at -20°C) was subsequently analyzed for colony-stimulating activity with a cell-proliferation assay, as previously described.<sup>36</sup> Day 1 and day 7 specimens were analyzed during the same run to eliminate bias due to changes in assay conditions. A one-compartment pharmacokinetic model, with zero-order absorption of the drug and first-order elimination constants, was fit to the G-CSF concentration-time data for each patient with the use of a Bayesian algorithm and ADAPT II software,<sup>37</sup> as previously described.<sup>36</sup> The area under the plasma G-CSF concentration-time curve was calculated according to a standard equation.<sup>36</sup>

### Cost Analysis

We calculated the median total cost (per patient) of intravenous antibiotics, transfusions, and hospitalization for both groups, adding the median cost of the growth factor for the G-CSF group. The analysis was based on daily costs (for a child with a weight of 40 kg and 1.3 m<sup>2</sup> of body-surface area) of \$205 for G-CSF, \$118.50 for antibiotics, and \$10.11 for amphotericin B; \$1,574.73 per day for a hospital room (the average cost at children's hospitals in the United States<sup>38</sup>); \$150 for one transfusion of leukocyte-reduced, packed red cells; and \$550 for a transfusion of leukocyte-reduced, pheresed platelets.

### Statistical Analysis

We selected a group sequential design with 80 percent power to detect a reduction in the rate of hospitalization from 40 to 20 percent, at a significance level of 0.05, with two interim analyses and one final analysis, on the basis of experience with 399 similarly treated patients in two previous trials at our institution. The period of observation for adverse events associated with myelosuppression was 21 days, starting from the first day on which G-CSF or placebo was administered.

Differences in the distribution of base-line characteristics between the two groups were assessed with Fisher's exact test, and differences in the frequency of complications were determined with an exact stratified Mantel-Haenszel test. A Wilcoxon rank-sum test was used to compare the duration of hospitalization for febrile neutropenia, the time from the start of G-CSF therapy or placebo to the initiation of consolidation treatment, and the costs of supportive care. Differences in the neutrophil count and the area under the curve for G-CSF on day 1 and day 7 were analyzed by either the Wilcoxon rank-sum test (for comparisons between the two groups) or the Wilcoxon signed-rank test (for comparisons within a group). A logistic-regression model was used to correlate the area under the curve with the probability of hospitalization for febrile neutropenia. Changes in neutrophil and platelet counts were modeled and compared by the method of Jennrich and Schluchter.<sup>39</sup> Probabilities of event-free survival based on data on all 164 randomized patients were estimated by the Kaplan-Meier method and compared with use of a stratified Mantel-Haenszel test. Cumulative risks of secondary acute myeloid leukemia were compared by Gray's test.<sup>40</sup> Only two-sided P values are reported.

## RESULTS

Of the 164 randomized patients, 7 in the G-CSF group and 9 in the placebo group were hospitalized for parenteral antibiotic treatment at the time growth factor therapy was scheduled to begin, leaving 148 patients who could be evaluated. The two groups had similar clinical characteristics at the time of the diagnosis of leukemia and the start of treatment with G-CSF or placebo (Table 1). A longitudinal model

demonstrated a more rapid recovery from neutropenia in the G-CSF group than in the placebo group ( $P=0.007$ ). The periods during which the absolute neutrophil counts were less than 500 per cubic millimeter and less than 1000 per cubic millimeter were 5.3 and 6.1 days, respectively, in the G-CSF group, as compared with 12.7 and more than 14 days in the placebo group (Table 2). There was no indication that treatment with G-CSF affected platelet recovery.

**Hospitalization for Fever and Neutropenia**

All children in whom fever and neutropenia developed were hospitalized. The rate of hospitalization for febrile neutropenia (Table 2) did not differ significantly between the G-CSF and placebo groups (58 and 68 percent, respectively;  $P=0.23$ ; relative risk for the G-CSF group, 0.85; 95 percent confidence interval, 0.59 to 1.16) or between subgroups defined on the basis of age, risk of relapse, leukocyte count at presentation, neutrophil count at randomization, or prior hospitalization (data not shown). Although fever persisted for a median of 2 days in both groups, the median hospital stay was significantly shorter for the patients receiving G-CSF (6 vs. 10 days,  $P=0.011$ ). Only 11 percent of the G-CSF group spent more than nine days in the hospital, as compared with 37 percent of the placebo group (Fig. 1). The G-CSF group had fewer documented infections overall (12 vs. 27,  $P=0.009$ ) (Table 2), but the difference in the number of severe infections (grade 3 or 4) was not significant (5 vs. 6) (Table 3). The use of parenteral antibiotic therapy and transfusions was similar in the two groups. None of the patients had fatal complications.

**Outcome of Antileukemic Therapy**

Ninety-eight percent of the patients treated with G-CSF and 99 percent of those given placebo had complete remissions. The time to the start of consolidation therapy was significantly shorter in the G-CSF group ( $P<0.001$ ) (Fig. 2), but the probability of event-free survival at three years was the same in the two groups (83 percent; 95 percent confidence interval, 71 to 95 percent in the G-CSF group and 72 to 94 percent in the placebo group). The cumulative incidence of acute myeloid leukemia at three years did not differ significantly between the two groups (5.1 percent [95 percent confidence interval, 0.1 to 10] in the G-CSF group and 3.9 percent [95 percent confidence interval, 0 to 8.4] in the placebo group;  $P=0.36$ ).

**Relation between Systemic Exposure to G-CSF and Clinical Response**

There was considerable variability in systemic exposure to G-CSF among both the patients receiving G-CSF and those receiving placebo. Although the

**TABLE 1. CLINICAL CHARACTERISTICS OF 148 PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA ASSIGNED TO RECEIVE G-CSF OR PLACEBO.\***

CHARACTERISTIC	G-CSF GROUP (N=73)	PLACEBO GROUP (N=75)
<b>At diagnosis</b>		
Age		
Median (yr)	5.8	5.7
Range (yr)	0.2–17.9	1.0–16.9
1–10 yr (no. of patients)	52	52
Male sex (no. of patients)	40	42
White race (no. of patients)	61	66
Leukocyte count		
Median ( $\times 10^{-3}/\text{mm}^3$ )	17	11.6
Range ( $\times 10^{-3}/\text{mm}^3$ )	0.8–1512	0.7–581
<25,000/ $\text{mm}^3$ (no. of patients)	43	49
Neutrophil count		
Median ( $\times 10^{-3}/\text{mm}^3$ )	0.777	0.864
Range ( $\times 10^{-3}/\text{mm}^3$ )	0–18.18	0–74
<100/ $\text{mm}^3$ (no. of patients)	13	10
<500/ $\text{mm}^3$ (no. of patients)	30	29
Platelet count ( $\times 10^{-3}/\text{mm}^3$ )		
Median	60	59
Range	9–511	4–703
Immunophenotype (no. of patients)†		
T lineage	11	11
B lineage	59	62
<b>At start of G-CSF or placebo regimen</b>		
Leukocyte count ( $\times 10^{-3}/\text{mm}^3$ )		
Median	2.3	2.0
Range	0.7–11.9	0.5–6.9
Neutrophil count		
Median ( $\times 10^{-3}/\text{mm}^3$ )	0.528	0.442
Range ( $\times 10^{-3}/\text{mm}^3$ )	0–5.016	0–5.589
Mean ( $\pm$ SE)	0.818 $\pm$ 0.106	0.809 $\pm$ 0.124
<100/ $\text{mm}^3$ (no. of patients)	15	14
<500/ $\text{mm}^3$ (no. of patients)	35	40
Platelet count ( $\times 10^{-3}/\text{mm}^3$ )		
Median	110	124
Range	7–424	27–401
Previous hospitalization for fever (no. of patients)	50	43

\* $P>0.05$  for all comparisons.

†Data were unavailable for five patients.

mean ( $\pm$ SE) area under the curve did not change significantly from day 1 to day 7 in the G-CSF group ( $362\pm 54.6$  ng per milliliter·hour on day 1 and  $366\pm 58.0$  on day 7), it did increase significantly in the placebo group (from  $6.8\pm 2.7$  to  $23\pm 8.2$  ng per milliliter·hour,  $P<0.001$ ), reflecting an endogenous response to the decreased neutrophil counts in the patients receiving placebo (from  $809\pm 124$  per cubic millimeter on day 1 to  $60\pm 16$  on day 7).<sup>42-45</sup> Systemic exposure to G-CSF on day 1 was not significantly related to the probability of hospitalization from day 1 to day 7 (data not shown); however, higher values on day 7 were related to a lower probability of subsequent hospitalization (from day 8 to day 21) for the 61 patients who had not been hospitalized between day 1 and day 7 ( $P=0.049$ ) (Fig. 3). The odds of hospitalization increased 1.63 times

**TABLE 2. HEMATOLOGIC TOXIC EFFECTS, HOSPITALIZATION FOR FEBRILE NEUTROPENIA, AND SUPPORTIVE CARE IN THE G-CSF AND PLACEBO GROUPS.**

VARIABLE	G-CSF GROUP (N = 73)	PLACEBO GROUP (N = 75)
<b>Hematologic toxic effects</b>		
Neutrophil count		
Nadir — $\times 10^{-3}/\text{mm}^3$		
Median	0	0
Range	0–3.6	0–0.93
<1000/ $\text{mm}^3$ — no. of days	6.1	>14*
<500/ $\text{mm}^3$ — no. of days	5.3	12.7*
Platelet count		
Nadir — $\times 10^{-3}/\text{mm}^3$		
Median	14	18
Range	2–330	3–120
<75,000/ $\text{mm}^3$ — no. of days	8.9	8.3
<b>Hospitalization for febrile neutropenia</b>		
No. of patients (%)	42 (58)	51 (68)
No. of days		
Median	6	10†
Range	1–37	1–30
No. of days with fever		
Median	2	2
Range	0–36	0–27
No. of documented infections	12	27‡
No. of grade 3 or 4 infections	5	6
<b>Supportive care</b>		
Intravenous antibiotics		
No. of patients	42	51
No. of days		
Median	6	9
Range	2–36	2–30
Amphotericin B		
No. of patients	6	12
No. of days		
Median	7	6
Range	4–8	1–28
Platelet transfusions		
No. of patients	40	34
No. of transfusions		
Median	1	1
Range	1–26	1–7
Packed red-cell transfusions		
No. of patients	68	71
No. of transfusions		
Median	2	2
Range	1–7	1–6

\*P=0.007 in a longitudinal model.

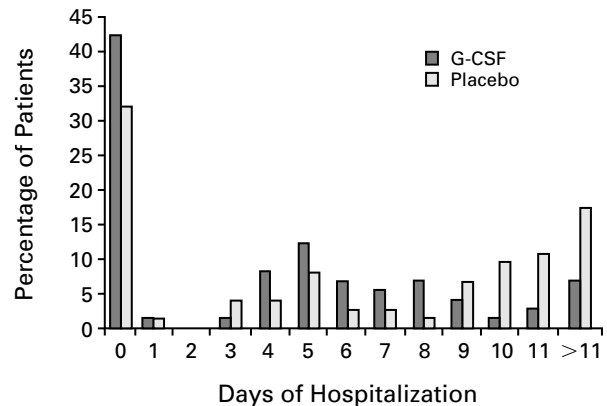
†P=0.011.

‡P=0.009.

(95 percent confidence interval, 1.0 to 2.67) for each decrease of 100 ng per milliliter · hour in the area under the curve.

**Cost Analysis**

All patients treated with G-CSF or placebo were included in the cost analysis. The median estimated cost of all supportive care was \$8,768 (range, \$1,435 to \$79,674) per patient in the G-CSF group and \$8,616 (range, \$0 to \$55,830) in the control group (P=0.83). The median cost of G-CSF per patient



**Figure 1.** Distribution of Total Days of Hospitalization in 148 Patients with Acute Lymphoblastic Leukemia Assigned to Receive G-CSF or Placebo.

was \$1,845 (range, \$1,435 to \$2,665). Therefore, any savings that might have resulted from the use of G-CSF were offset by its cost. A separate analysis based on a hypothetical, lower dose of G-CSF (5  $\mu\text{g}$  per kilogram per day) also showed no significant reduction in the costs of supportive care in the G-CSF group (P=0.67).

**DISCUSSION**

We found that G-CSF therapy, as compared with placebo, accelerated the recovery from neutropenia after myelosuppressive remission-induction therapy in children and adolescents with acute lymphoblastic leukemia but did not result in a decreased rate of hospitalization for febrile neutropenia, a higher probability of event-free survival, or a lower cost of supportive care. An expert panel judged the last three of these outcomes to have the greatest clinical importance.<sup>46</sup> The beneficial effects of reducing the period of neutropenia included decreases in the incidence of documented infections, duration of hospitalization, and likelihood of a delay in starting consolidation chemotherapy on schedule.

Our results are similar to those reported for adults with solid tumors<sup>3,5,12</sup> but are generally more favorable than the findings in adults with acute lymphoblastic leukemia.<sup>4,8,11,14</sup> Only two small randomized trials of G-CSF in children with acute lymphoblastic leukemia have been reported, and neither included a placebo group.<sup>19,23</sup> In one study, the growth factor had no benefit in 32 children,<sup>19</sup> and in the other, an open-label evaluation of G-CSF in 34 patients with high-risk leukemia treated with nine cycles of myelosuppressive chemotherapy, the G-CSF group had significantly shorter and fewer episodes of febrile neutropenia, required less parenteral antibiotic therapy, and had fewer documented infections.<sup>23</sup> Neither trial included a cost–benefit analysis.

TABLE 3. DOCUMENTED INFECTIONS.\*

TYPE OR SITE OF INFECTION	G-CSF	PLACEBO
	GROUP	GROUP
	(N=73)	(N=75)
	no. of patients	
Severe infection (grade 3 or 4)		
Pneumonia	3	2
Bacteremia†	1	3
Disseminated fungal infection‡	0	1
Typhlitis	1	0
Mild to moderate infection (grade 1 or 2)		
Cellulitis	0	5
Urinary tract infection	1	1
Infection at exit site or within tunnel track of central venous catheter	0	4
Otitis media	1	3
Herpes simplex	3	3
<i>Clostridium difficile</i> enterocolitis	0	3
Sinusitis	1	1
Lymphadenitis	0	1
Conjunctivitis	1	0

\*Infections were documented according to the following criteria: pneumonia, pulmonary infiltrates on radiography plus compatible clinical signs and symptoms; bacteremia, blood-culture isolate of any bacterium; disseminated fungal infection, isolation of a fungal organism from an otherwise sterile specimen of tissue or fluid (e.g., blood or cerebrospinal fluid) plus a clinically compatible illness or histologic demonstration of yeast, pseudohyphae, or hyphae in biopsy specimens, with isolation of a corresponding fungal species in culture from the same tissue; typhlitis and sinusitis, typical radiographic findings with compatible symptoms; cellulitis and catheter-site infections, as described by Hughes et al.<sup>41</sup>; urinary tract infection, bacterial count (for a single organism) of at least 100,000 per milliliter of urine plus compatible symptoms; herpes simplex infection, typical lesions and a viral isolate by cell culture; and *Clostridium difficile* infection, diarrhea with toxin in fecal sample. Otitis media was documented on the basis of an otoscopic evaluation by the patient's physician. Gastroenteritis, upper respiratory tract infections, mucositis, and oral thrush were not included because of variable diagnostic criteria.

†The infecting organism was *Streptococcus sanguis*, *Staph. epidermidis*, *Klebsiella pneumoniae*, or *Acinetobacter calcoaceticus*.

‡The infecting organism was *Histoplasma capsulatum*.

We believe that treatment with G-CSF did not result in a significant decrease in episodes of febrile neutropenia because it failed to prevent extreme neutropenia in most patients (median nadir, 0 neutrophils per cubic millimeter in both groups). It is likely that the chemotherapy suppressed hematopoietic stem cells too severely to allow an effective early response to stimulation with growth factor. Even though the rate of documented infection was lower in the G-CSF group, the incidence of severe infections (e.g., pneumonia or septicemia) was not. This finding may reflect the relatively low overall incidence of life-threatening infections in this study (<10 percent), a result that may be due to the low incidence of mucositis with our induction regimen or to prophylactic treatment with trimethoprim-sulfamethoxazole.<sup>33</sup>

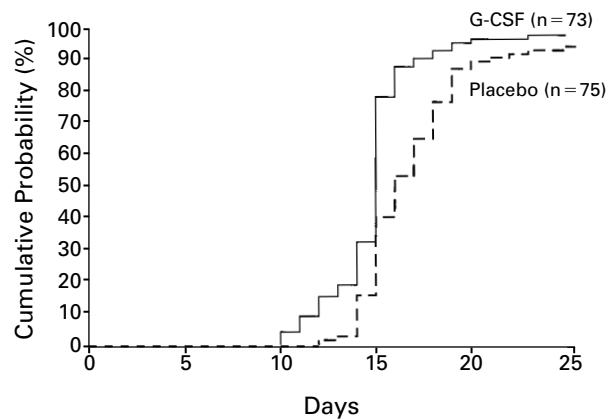
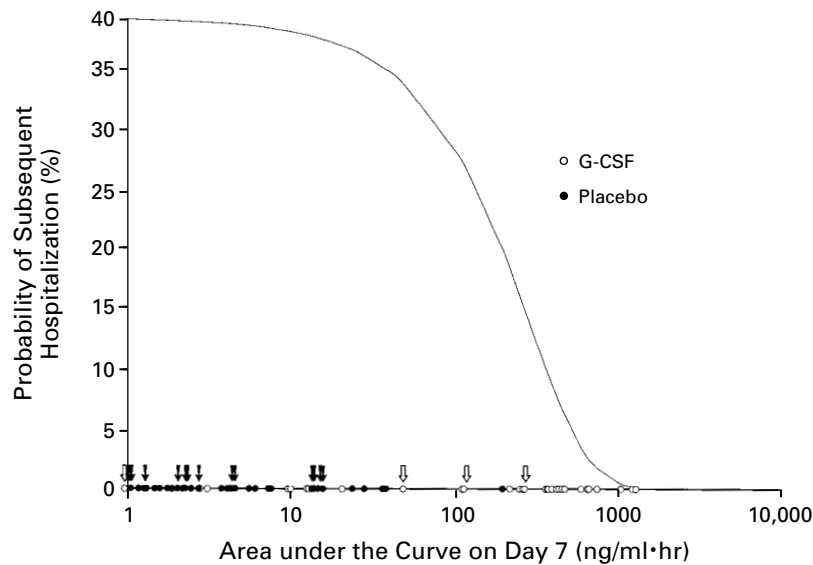


Figure 2. Cumulative Probability of Starting Consolidation Therapy at Specific Times after the Start of the G-CSF or Placebo Regimen.

The time to the start of consolidation therapy was significantly shorter in the G-CSF group (P<0.001).

The few studies that have determined the effect of G-CSF treatment on long-term survival did not show an improvement in the outcome with such treatment.<sup>4,9,13,14,16</sup> Likewise, in our study, the probability of event-free survival at three years did not differ significantly between the G-CSF and placebo groups. This result was not surprising, since the median time to the start of consolidation chemotherapy was reduced by only two days in the G-CSF group, a difference hardly sufficient to influence long-term responses. Nonetheless, the ability to adhere to the planned treatment schedule could prove advantageous in the treatment of malignant diseases that require timely delivery of multiple courses of intensive chemotherapy (e.g., advanced-stage Burkitt's lymphoma and B-cell acute lymphoblastic leukemia).

One concern is that G-CSF treatment in patients with leukemia may increase the proliferation of leukemic cells that express G-CSF receptors.<sup>47,48</sup> However, we found similar rates of complete remission and long-term event-free survival in the G-CSF and placebo groups. The development of acute myeloid leukemia in patients with aplastic anemia or congenital neutropenia treated with G-CSF raises another issue.<sup>49-51</sup> In fact, the diagnosis of epipodophyllotoxin-related acute myeloid leukemia in four of our patients early in the study prompted us to evaluate possible risk factors. Of the variables analyzed, only the administration of asparaginase immediately before etoposide was significantly related to an increased incidence of myeloid leukemia.<sup>52,53</sup> This finding, together with the similar cumulative risks of this complication in the G-CSF and placebo groups, indicates that treatment with the cytokine did not contribute to leukemogenesis.



**Figure 3.** Relation of Systemic Exposure to G-CSF on Day 7 of Treatment to the Probability of Subsequent Hospitalization for Febrile Neutropenia (from Day 8 to Day 21).

Arrows indicate hospitalized patients. The trend toward fewer hospitalizations with increasing values for the area under the plasma G-CSF concentration–time curve was significant ( $P=0.049$ ).

Although a dose-dependent increase in the neutrophil count in response to G-CSF treatment has been observed with doses ranging from 1 to 60  $\mu\text{g}$  per kilogram,<sup>54-56</sup> the optimal dosage remains uncertain, especially in children. We previously observed considerable variation between patients in systemic exposure to G-CSF at three dose levels,<sup>36</sup> suggesting that systemic exposure may be more predictive of the clinical response than dosage itself. We found a significant association between a higher level of systemic exposure to G-CSF on day 7 of treatment (but not on day 1) and a lower probability of subsequent hospitalization in the subgroup of patients with no prior hospitalization. This suggests that the exposure to G-CSF immediately after chemotherapy is not critical in accelerating the recovery of the neutrophil count. Indeed, another study showed no adverse effect on the time to neutrophil engraftment when G-CSF treatment was started on day 6 instead of day 1 after autologous bone marrow transplantation.<sup>57</sup>

The long hospital stays during intensive remission-induction therapy in children with acute lymphoblastic leukemia have substantial physical, psychological, and financial costs. We found that treatment with G-CSF shortened the duration of hospitalization but did not lower the rate of hospitalization for febrile neutropenia, the primary end point of the study. Nor were the savings associated with the use of G-CSF sufficient to offset its cost. Whether the benefits of G-CSF therapy justify its use in individual cases is ultimately a matter of clinical judgment.

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