

GRANULOCYTE COLONY-STIMULATING FACTOR IN SEVERE CHEMOTHERAPY-INDUCED AFEBRILE NEUTROPENIA

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ABSTRACT

Background Randomized trials of colony-stimulating factors in febrile patients with neutropenia after chemotherapy have not consistently shown clinical benefit. Nevertheless, the use of colony-stimulating factors to treat patients with chemotherapy-induced neutropenia is widespread.

Methods We performed a randomized, double-blind, placebo-controlled trial of granulocyte colony-stimulating factor (G-CSF) in afebrile outpatients with severe chemotherapy-induced neutropenia. We measured the number of days of neutropenia, rate of hospitalization, number of days in the hospital, number of days the patient received parenteral antibiotics, and number of culture-positive infections.

Results We randomly assigned 138 patients to receive G-CSF (n = 71) or placebo (n = 67). The median time to an absolute neutrophil count higher than 500 per cubic millimeter was significantly shorter for patients who received G-CSF (two days, vs. four days for the patients given placebo). However, there was no effect on the rate of hospitalization, number of days in the hospital, duration of treatment with parenteral antibiotics, or number of culture-positive infections.

Conclusions Routine therapeutic application of G-CSF in afebrile patients with severe neutropenia can reduce the duration of neutropenia, but this does not appear to provide practical clinical benefit. (N Engl J Med 1997;336:1776-80.)

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NEUTROPENIA and resultant infection are potentially life-threatening side effects of cancer chemotherapy. The use of dose-intensive chemotherapeutic regimens has made the management of myelosuppression increasingly important. Recombinant hematopoietic colony-stimulating factors, which stimulate the production of granulocytes, may be a way of reducing the infectious complications of myelotoxic cancer treatment.¹⁻³

The efficacy of colony-stimulating factors has been studied in several settings. Initially, attention was focused on preventing infection by starting treatment with the agents immediately after chemotherapy and continuing through the anticipated period of neutropenia.⁴⁻⁶ These agents were then used therapeutically in patients with established neutropenia after chemotherapy, although their efficacy in this context had not been established. When given as adjuncts to antibiotics for febrile neutropenia,⁷⁻¹¹ granulocyte

colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), or both were found to shorten the duration of severe neutropenia, but they had no effect on mortality due to infections or other clinical end points, such as duration of hospital stay and number of days of antibiotic therapy.⁷⁻¹¹ For this reason, the guidelines of the American Society of Clinical Oncology do not recommend the routine use of colony-stimulating factors in patients with febrile neutropenia.^{12,13} However, a recently published survey revealed that most physicians surveyed prescribe colony-stimulating factors for patients with febrile neutropenia.¹⁴

The therapeutic use of a colony-stimulating factor in afebrile patients with severe chemotherapy-induced neutropenia has not been studied in a large, placebo-controlled trial. Theoretically, the administration of colony-stimulating factors before the onset of fever could prevent serious infectious consequences in patients with severe neutropenia. A third of recently surveyed physicians use colony-stimulating factors in afebrile patients with neutropenia.¹⁴ To test this idea, we performed a randomized, double-blind, placebo-controlled trial of G-CSF in afebrile patients with severe neutropenia after chemotherapy. We investigated the effect of G-CSF on the duration of severe neutropenia, rate of hospitalization for febrile neutropenia, length of hospital stay, and number of days of antibiotic therapy.

METHODS

Study Characteristics

We conducted a double-blind, placebo-controlled trial from November 1992 to December 1995 in patients with severe neutropenia after chemotherapy. Neither the treating physicians nor their patients knew the identity of the administered agent, which was prepared by pharmacists in this trial. Our primary aim was to determine if G-CSF, instituted at the time of onset of chemother-

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apy-induced neutropenia, could reduce the duration of grade 4 neutropenia, defined as an absolute neutrophil count of 500 or less per cubic millimeter. The secondary aims of this study included assessing the effect of G-CSF on the duration of grade 3 neutropenia (absolute neutrophil count, 501 to 1000 per cubic millimeter), rate of hospitalization for febrile neutropenia, number of days in the hospital, number of days of parenteral antibiotic therapy, and number of culture-positive infections.

Patients who were eligible for the trial were at least 18 years of age, had solid tumors or lymphomas (non-Hodgkin's or Hodgkin's), had received standard combination chemotherapy regimens, and had an absolute neutrophil count of 500 or less per cubic millimeter. Patients were identified at the time of routine blood-count checks in the outpatient clinic. To avoid inclusion of patients with protracted neutropenia, eligible patients had to have a white-cell count of at least 1000 per cubic millimeter during the 3-to-10-day period before their enrollment. Patients were excluded if they had acute or chronic leukemia or myelodysplastic syndromes, or had received autologous or allogeneic stem cells. Patients were also excluded if they had taken prophylactic oral antibiotics or received colony-stimulating factors within the previous 10 days. No chemotherapy could be given during the period of the study. We excluded pregnant or lactating women and patients who were already hospitalized for other reasons. All patients gave written informed consent before randomization. The study protocol was approved by the institutional review boards of all participating institutions.

To ensure balance between the two treatment groups, we used a stratified randomization scheme. The three stratification factors were time since the last dose of chemotherapy (<10 days or ≥ 10 days), extent of cancer treatment before the most recent regimen (none, some, or extensive), and use or lack of use of carboplatin or nitrosoureas in the most recent chemotherapeutic regimen. "Some" prior therapy was defined as radiation to 30 percent or less of marrow-bearing sites or one previous chemotherapy regimen, or both. "Extensive" prior therapy was radiation to more than 30 percent of marrow-bearing sites, more than one previous chemotherapy regimen, or both.

Treatment and Test Schedule

The study medication (G-CSF [Neupogen, Amgen, Thousand Oaks, Calif.] at 5 μg per kilogram of body weight or placebo) was administered subcutaneously in a double-blind fashion daily until the absolute neutrophil count reached 2000 per cubic millimeter and parenteral antibiotics were discontinued, or for a maximum of 14 days after study entry. Patients in whom fever developed were continued on their study medication and hospitalized. Chest films and appropriate cultures were obtained, and broad-spectrum antibiotic therapy was begun according to guidelines for the use of antibiotics in patients with febrile neutropenia published by the Infectious Diseases Society of America.¹⁵ Protocol registration required a history, physical examination, temperature reading, assessment of level of activity, complete blood count with differential count, and pregnancy test (for women of childbearing potential). Temperatures were recorded daily for all patients. A complete blood count and differential count were performed daily in hospitalized patients, and every other day in outpatients.

After completion of the protocol treatment, the treating physician and the patient could learn the identity of the study medication by contacting the randomization center. Subsequent treatment decisions for each patient could incorporate the information gained from participation in this study.

Statistical Analysis

All eligible patients who participated in the study were included in the assessment of study end points. A two-sample test of proportions was used to assess whether the proportions of patients hospitalized for infectious complications differed significantly between the treatment groups. Given that the proportion of patients hospitalized for infectious complications in the placebo

group was 0.13, a two-sided test of proportions with an alpha level of 0.05 (with the arc-sine transformation) would have at least 88 percent power to detect a difference of 0.12 or more. The time-to-event distributions were estimated by the Kaplan-Meier product-limit method.

When length of hospitalization and days of parenteral antibiotic use were assessed, data on patients who died were censored on the date of death. When times to absolute neutrophil counts higher than 500 per cubic millimeter and higher than 1000 per cubic millimeter were assessed, data on patients who did not achieve the end point were censored on the day on which the first of the following occurred: the patient refused to continue (five patients), the patient died (two), the patient was mistakenly advised to discontinue the study medication (one), the attending physician discontinued treatment because of other medical problems (one), and the patient was unable to obtain the study drug (one).

The log-rank test was used to assess whether length of hospitalization and days of parenteral antibiotic use differed between the treatment groups and whether time to recovery of the absolute neutrophil count differed with respect to any of the following: treatment group, extent of prior therapy, use of carboplatin or nitrosoureas in most recent regimen, time since last dose of chemotherapy (<10 vs. ≥ 10 days), sex, age, or performance score. A two-sided P value of ≤ 0.05 was considered to indicate statistical significance. We used Cox proportional-hazards modeling to assess whether the type of treatment had a significant effect on the time to recovery of the absolute neutrophil count, after accounting for the stratification factors.¹⁶

RESULTS

Patient Characteristics

A total of 143 outpatients with afebrile neutropenia were enrolled in the study. Three were found to be ineligible: one had not had a complete blood count 3 to 10 days before entering the study, and two were in the hospital for other reasons before randomization. Two additional patients withdrew because of concern about insurance. We randomly assigned 71 of the remaining 138 patients to receive G-CSF and 67 to receive placebo. The two groups were well balanced with respect to age, type of cancer, performance score, extent of prior therapy, recent exposure to carboplatin or nitrosoureas, and time since last dose of chemotherapy (Table 1).

Duration of Neutropenia

The median time to recovery of an absolute neutrophil count higher than 500 per cubic millimeter was two days in the G-CSF group and four days in the placebo group (Fig. 1). The median time to recovery of an absolute neutrophil count higher than 1000 per cubic millimeter was three days in the G-CSF group and five days in the placebo group. Both these differences were significant ($P < 0.001$).

Features Associated with Recovery of Absolute Neutrophil Counts

There was no evidence that the times to recovery of absolute neutrophil counts higher than 500 or higher than 1000 per cubic millimeter differed with respect to sex, age, extent of cancer treatment before the most recent regimen, or performance score. The times to recovery of absolute neutrophil counts

TABLE 1. CHARACTERISTICS OF THE 138 STUDY PATIENTS.

CHARACTERISTIC	G-CSF (N = 71)	PLACEBO (N = 67)
Age — yr		
Median	63	62
Age	21–86	26–80
Cancer — no. of patients (%)		
Solid tumor	56 (79)	51 (76)
Non-Hodgkin's lymphoma	11 (15)	14 (21)
Hodgkin's disease	4 (6)	2 (3)
Performance score — no. of patients (%)		
0 (Fully functional)	25 (35)	27 (40)
1	33 (46)	25 (37)
2	11 (15)	13 (19)
3 (Bedridden)	2 (3)	2 (3)
Cancer treatment before most recent regimen — no. of patients (%)*		
None	50 (70)	48 (72)
Some	15 (21)	13 (19)
Extensive	6 (8)	6 (9)
Most recent treatment contained carboplatin or nitrosoureas — no. of patients (%)		
Yes	4 (6)	2 (3)
No	67 (94)	65 (97)
Days since last dose of chemotherapy — no. of patients (%)		
<10	29 (41)	23 (34)
≥10	42 (59)	44 (66)
Days from first documented neutropenia to study entry — no. of patients (%)		
0–1	70 (99)	65 (97)
2–3	1 (1)	2 (3)

*“Some” prior therapy was defined as radiation over 30 percent or less of marrow-bearing sites or one previous chemotherapy regimen, or both. “Extensive” prior therapy was radiation over more than 30 percent of marrow-bearing sites, more than one previous chemotherapy regimen, or both.

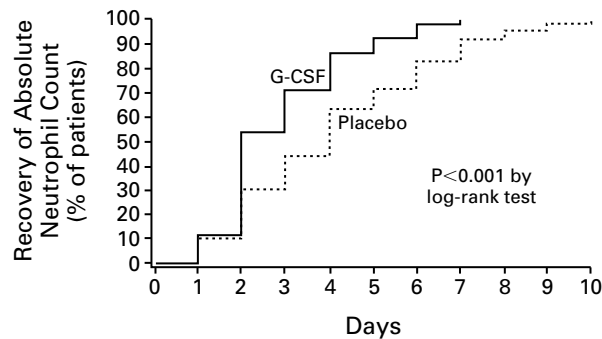


Figure 1. Time to Recovery of the Absolute Neutrophil Count to >500 per Cubic Millimeter among Afebrile Patients in the G-CSF and Placebo Groups.

higher than 500 and higher than 1000 per cubic millimeter were significantly shorter among patients who received their last dose of chemotherapy 10 days or more before entry into the study ($P = 0.002$ and $P < 0.001$, respectively). The results of Cox proportional-hazards modeling indicated that, as compared with placebo, treatment with G-CSF was significantly associated with the time to recovery of neutrophil counts, after adjustment for the time between the patient's last dose of chemotherapy and entry into the study, extent of prior therapy, and whether carboplatin or nitrosoureas were included in the current regimen.

Need for Hospitalization

The clinical end point of greatest interest was the rate of hospitalization for febrile neutropenia. Among the 71 initially afebrile patients who received G-CSF, 9 (13 percent) required hospitalization (Table 2 and Fig. 2). Of these 9, 7 had febrile neutropenia; 1 had weakness, dyspnea, hypotension, and sepsis (without fever) and subsequently died; and 1 had dehydration. Among the 67 afebrile patients given placebo, 11 (16 percent) required hospitalization. Eight of these 11 patients had febrile neutropenia (1 of whom died of sepsis), and 3 were not febrile: 1 had nausea and vomiting; another had an infected venous port (without fever); and a third was admitted with weakness, confusion, and a sodium concentration of 110 mmol per liter. Thus, 8 of the G-CSF group (11 percent) and 9 of the placebo group (13 percent) were hospitalized with infectious complications.

There was no significant difference between the G-CSF and placebo groups in the proportion of patients hospitalized for infectious complications ($P = 0.70$) or in the proportion hospitalized for any reason ($P = 0.50$). The 95 percent confidence interval for the difference between treatment groups in the percentage of patients hospitalized for infectious complications was 0 to 13.2 percent; for hospitalization for any reason it was 0 to 15.5 percent.

Clinical Outcomes of Hospitalized Patients

Among patients who required hospitalization, the median number of days in the hospital was 6 (range, 2 to 21) in the G-CSF group and 5 (range, 4 to 23) in the placebo group (Table 2). The median number of days of antibiotic therapy in both the G-CSF and the placebo groups was five. Five patients in each group had positive cultures. With so few hospitalizations, the study had insufficient power to address whether the clinical course of hospitalized patients differed between treatment groups.

DISCUSSION

In this study of afebrile outpatients with severe neutropenia after chemotherapy, we found that

TABLE 2. CLINICAL END POINTS IN THE 138 STUDY PATIENTS.

END POINT	G-CSF (N = 71)	PLACEBO (N = 67)
No. hospitalized		
For infectious complications	8	9
For other reasons	1	2
Percent hospitalized*		
For infectious complications	11 (5-21)	13 (6-24)
For any reason	13 (6-23)	16 (8-27)
Days hospitalized†		
Median	6	5
Range	2‡-21	4‡-23
Days receiving parenteral antibiotics†		
Median	5	5
Range	1‡-8	0-12
No. of patients with positive cultures‡	5	5

*Values in parentheses are 95 percent confidence intervals.

†All hospitalizations are included.

‡Data were censored because of death.

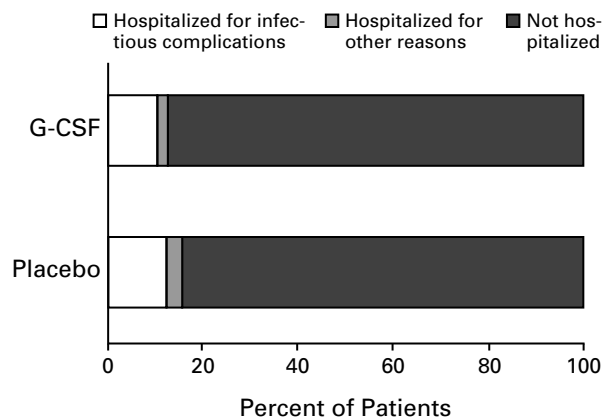


Figure 2. Need for Hospitalization in the G-CSF and Placebo Groups.

G-CSF significantly shortened the duration of grade 3 and grade 4 neutropenia but did not affect the clinical outcome. Specifically, the rates of hospitalization among patients who received G-CSF or placebo did not differ significantly, and among patients who were later hospitalized, G-CSF did not alter the duration of the hospital stay, the number of days of antibiotic therapy, or the likelihood of having a positive culture.

For cancer therapy, colony-stimulating factors were originally licensed for prophylactic use in patients who had just completed chemotherapy. The rationale was to reduce the likelihood of febrile neutropenia in patients receiving dose-intensive therapy. Soon, however, these hematopoietic growth factors were employed with therapeutic intent in patients who already had chemotherapy-induced neutropenia. A recent study of the use of colony-stimulating

factors found that 73 percent of physicians surveyed prescribed them for febrile patients with neutropenia and 34 percent used them for afebrile patients with neutropenia.¹⁴

Eight randomized, controlled trials have studied GM-CSF,^{8,10,11,17,18} G-CSF,^{7,19} or both⁹ in febrile patients with chemotherapy-induced neutropenia. Six of these studies were placebo-controlled.^{7-9,11,17,19} The largest was an Australian multicenter trial in which 218 patients were randomly assigned to receive G-CSF (12 µg per kilogram per day, by continuous subcutaneous infusion) or placebo, along with intravenous antibiotics.⁷ These febrile patients with neutropenia had received chemotherapy for solid tumors, acute lymphocytic leukemia, or lymphoma. No stratification was performed. The duration of neutropenia was reduced by one day in the patients treated with G-CSF, but the duration of fever, duration of antibiotic therapy, and median period of hospitalization were not affected, despite continuous infusion of G-CSF at a dose more than twice that routinely used in practice. These negative results were generally corroborated by the other randomized trials.^{11,17-19}

The American Society of Clinical Oncology convened an expert panel that published guidelines for the use of colony-stimulating factors after a thorough review of the available data,¹² and these guidelines have recently been updated.¹³ The panel concluded that these randomized studies did not support the routine use of colony-stimulating factors as adjuncts to antibiotics in febrile patients with neutropenia.

The guidelines also state that the data concerning the therapeutic use of colony-stimulating factors in afebrile patients with severe neutropenia are inadequate.^{12,13} Nonetheless, the agents are widely used in this setting. There is a theoretical basis for initiating treatment with a colony-stimulating factor on detection of severe neutropenia but before the development of fever. It is possible that the number of microorganisms is relatively low early in the course of neutropenia, and since G-CSF enhances both the number and the function of neutrophils, intervention before the onset of fever could be more effective than initiating treatment after fever appears. Thus, if found to be successful, the selective administration of colony-stimulating factors to afebrile patients with neutropenia would limit an expensive therapy to those most likely to benefit. Gerhartz et al.²⁰ attempted to evaluate GM-CSF in afebrile patients. However, not all patients in their study had severe neutropenia, some were already hospitalized, and various types and doses of GM-CSF were used. The expert panel of the American Society of Clinical Oncology could not draw conclusions from this study about the merit of GM-CSF in this setting.¹²

The therapeutic use of colony-stimulating factors for afebrile neutropenia adds considerable cost to

cancer care. Grade 4 neutropenia occurs in 25 to 75 percent of patients treated for lung cancer, breast cancer, and lymphoma with standard chemotherapy regimens.^{12,21} By comparison, hospitalization for febrile neutropenia occurs in only 10 to 15 percent of these patients, as seen in our study and others.^{12,21} Standard outpatient charges per cycle for chemotherapy such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); cyclophosphamide, doxorubicin, and fluorouracil (CAF); or etoposide or cisplatin are about \$600 to \$700. The charge for a seven-day course of treatment with G-CSF for a 70-kg, afebrile patient with grade 4 neutropenia is approximately \$1,900 to \$2,000. Thus, colony-stimulating factor therapy in this setting multiplies charges two to three times.

Lyman et al.²² have modeled the cost effectiveness of colony-stimulating factors in patients receiving chemotherapy. They consider prophylactic colony-stimulating factor treatment to be cost effective when the risk of febrile neutropenia and hospitalization is 40 percent or more and the colony-stimulating factor reduces the likelihood of hospitalization for febrile neutropenia by 35 percent. Therapeutic use of a colony-stimulating factor in our study and others has not demonstrated this degree of effectiveness.

It is important not to judge the efficacy of a colony-stimulating factor solely on the basis of a favorable change in neutrophil counts. The neutrophil count is a surrogate or intermediate end point that cannot substitute for clinically relevant outcomes.²³ The routine therapeutic use of G-CSF in afebrile patients with severe neutropenia can significantly reduce the duration of neutropenia but has little practical clinical benefit.

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APPENDIX

This study was conducted as a trial of the North Central Cancer Treatment Group. Additional participating institutions and investigators included the following: Carle Cancer Center Community Clinical Oncology Program (CCOP), Urbana, Ill. (A.K. Hatfield); Missouri Valley CCOP, Omaha-Lincoln, Nebr. (J.A. Mailliard); Grand Forks Clinic, Grand Forks, N.D. (J.A. Laurie); Mayo Clinic Scottsdale CCOP, Scottsdale, Ariz. (R.F. Marschke, Jr.); Duluth CCOP, Duluth, Minn. (R.J. Kirschling); Illinois Oncology Research Association CCOP, Peoria (J.W. Kugler); Quain and Ramstad Clinic, Bismarck, N.D. (D.M. Pfeifle); Geisinger Clinical Oncology Program, Danville, Pa. (S. Nair); CentraCare Clinic, St. Cloud, Minn. (H.E. Windschitl); and Toledo CCOP, Toledo, Ohio (P.L. Schaefer).

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