REDUCTION BY GRANULOCYTE COLONY-STIMULATING FACTOR OF FEVER AND NEUTROPENIA INDUCED BY CHEMOTHERAPY IN PATIENTS WITH SMALL-CELL LUNG CANCER

JEFFREY CRAWFORD, M.D., HOWARD OZER, M.D., PH.D., RONALD STOLLER, M.D., DAVID JOHNSON, M.D., GARY LYMAN, M.D., IMAD TABBARA, M.D., MARK KRIS, M.D., JOHN GROUS, M.D., VINCENT PICOZZI, M.D., GREGORY RAUSCH, M.D., ROY SMITH, M.D., WILLIAM GRADISHAR, M.D., ANNE YAHANDA, M.D., MARTHA VINCENT, PH.D., MORGAN STEWART, PH.D., AND JOHN GLASPY, M.D.

Abstract *Background.* Neutropenia and infection are major dose-limiting side effects of chemotherapy. Previous studies have suggested that recombinant methionyl granulocyte colony-stimulating factor (G-CSF) can reduce chemotherapy-related neutropenia in patients with cancer. We conducted a randomized clinical trial to test this hypothesis and the clinical implications.

Methods. Patients with small-cell lung cancer were enrolled in a multicenter, randomized, double-blind, placebo-controlled trial of recombinant methionyl G-CSF to study the incidence of infection as manifested by fever with neutropenia (absolute neutrophil count, $<1.0\times10^9$ per liter, with a temperature $\geq$38.2°C) resulting from up to six cycles of chemotherapy with cyclophosphamide, doxorubicin, and etoposide. The patients were randomly assigned to receive either placebo or G-CSF, with treatment beginning on day 4 and continuing through day 17 of a 21-day cycle.

Results. The safety of the study treatment could be evaluated in 207 of the 211 patients assigned to either drug, and its efficacy in 199. At least one episode of fever with neutropenia occurred in 77 percent of the placebo group, as compared with 40 percent of the G-CSF group ($P<0.001$). Over all cycles of chemotherapy, the median duration of grade IV neutropenia (absolute neutrophil count, $<0.5\times10^9$ per liter) was six days with placebo as compared with one day with G-CSF. During cycles of blinded treatment, the number of days of treatment with intravenous antibiotics, the number of days of hospitalization, and the incidence of confirmed infections were reduced by approximately 50 percent when G-CSF was given, as compared with placebo. Mild-to-moderate medullary bone pain occurred in 20 percent of the patients receiving G-CSF.

Conclusions. The use of G-CSF as an adjunct to chemotherapy in patients with small-cell cancer of the lung was well tolerated and led to reductions in the incidence of fever with neutropenia and culture-confirmed infections; in the incidence, duration, and severity of grade IV neutropenia; and in the total number of days of treatment with intravenous antibiotics and days of hospitalization. (N Engl J Med 1991; 325:164-70.)

THE combination of fever and neutropenia is a life-threatening complication of chemotherapy in patients with cancer. Before modern management, mortality rates approached 80 percent, particularly in association with gram-negative bacteremia.[1,2] Current standard therapy for patients presenting with fever in association with neutropenia includes hospitalization and the immediate institution of treatment with empirically selected broad-spectrum intravenous antibiotic drugs until the neutropenia and any associated infection have resolved. Despite this approach, mortality remains approximately 10 percent among patients with documented infection.[3]

Fever with neutropenia is a primary end point in trials of antimicrobial agents in patients receiving chemotherapy for cancer.[4,5] The most important prognostic factor in patients with this complication is the recovery of the neutrophil count. Bodey et al.[6] showed a direct correlation between the duration of granulocytopenia and the risk of infection; in patients whose granulocyte counts remained below 1.0×10^9 per liter for one week, the chance that infection would develop was more than 50 percent; as the duration of granulocytopenia increased, the risk approached 100 percent. In addition, these investigators showed that patients with such low counts had a mortality rate above 50 percent if their counts continued to fall, but patients with incremental increases in their counts had a more favorable prognosis.

Hematopoietic growth factors are glycoproteins that stimulate the proliferation of bone marrow progenitor cells and their maturation into fully differentiated circulating blood cells.[7] Two of these factors — granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor — enhance both the production of mature myeloid elements and the function of these effector cells.[8] These factors hold great promise for improving host defenses that may be impaired owing to disease or treatment.[7-9] Human G-CSF is a hematopoietic growth factor that promotes the proliferation and differentiation of neutrophils, both in vitro[10] and in vivo.[11] The presumed target cells of this regulator molecule include a late precursor committed to the neutrophil lineage and the mature neutrophil. G-CSF also enhances the functional properties of mature cells by increasing phagocytic activity, antimicrobial killing, and antibody-dependent cell-mediated cytotoxicity.[12]

G-CSF (in the form of recombinant methionyl G-CSF, Amgen, Thousand Oaks, Calif.) has been demonstrated to increase the neutrophil count in pa-

From Duke University Medical Center and Durham Veterans Affairs Medical Center, Durham, N.C. (J.C.); the University of North Carolina, Chapel Hill (H.O.); the University of Pittsburgh, Pittsburgh (R. Stoller); Vanderbilt University, Nashville (D.J.); H. Lee Moffitt Cancer Center, Tampa, Fla. (G.L.); the University of Virginia, Charlottesville (I.T.); Memorial Sloan-Kettering Cancer Center, New York (M.K.); Saint Elizabeth's Hospital, Boston (J. Grous); Virginia Mason Clinic, Seattle (V.P.); Johns Hopkins University, Baltimore (G.R.); Medical College of Wisconsin, Milwaukee (R. Smith); the University of Chicago, Chicago (W.G.); Stanford University, Stanford, Calif. (A.Y.); Amgen, Inc., Thousand Oaks, Calif. (M.V., M.S.); and the University of California, Los Angeles (J. Glaspy). Address reprint requests to Dr. Crawford at P.O. Box 3198, Duke University Medical Center, Durham, NC 27710.

tients with advanced neoplasms[13] and to reduce the magnitude of chemotherapy-induced neutropenia.[14-16] In a phase I–II trial of recombinant methionyl G-CSF in patients with small-cell lung cancer treated with a regimen of ifosfamide, doxorubicin, and etoposide,[14] G-CSF was administered after chemotherapy during alternating treatment cycles. The degree of neutropenia was found to be substantially reduced after chemotherapy cycles in which G-CSF was given prophylactically, as compared with cycles in which it was not given. With these results, the present phase III, double-blind, randomized, placebo-controlled trial of recombinant methionyl G-CSF as an adjunct to chemotherapy was initiated in patients with small-cell lung cancer.

The primary objective of the present trial was to assess the effect of G-CSF on the incidence of infection as manifested by fever with neutropenia after the administration of cyclophosphamide, doxorubicin, and etoposide. Secondary objectives included an assessment of the efficacy of G-CSF as compared with placebo in reducing chemotherapy-induced hematopoietic toxicity, as documented by a reduction in the duration and severity of neutropenia. In addition, the clinical effect of G-CSF therapy on the infectious complications of neutropenia was examined, including its effect on the incidence and duration of antibiotic use and hospitalization. Finally, a thorough analysis of any toxic reactions associated with G-CSF was conducted.

Methods

This multicenter trial involved 14 investigators and centers. The study was designed, coordinated, and analyzed in conjunction with Amgen, the supplier of the G-CSF. It was initiated in May 1988 and was closed to enrollment in November 1989. This report presents the final analysis of findings in 211 patients studied after randomization.

The study drug is a human protein produced in *Escherichia coli* by recombinant-DNA technology.[10] The 175-amino-acid protein is nonglycosylated and has a molecular weight of 18,800. The product is a clear, colorless, sterile solution with a concentration of 300 μg of protein per milliliter. Placebo was supplied in matching vials for double blinding. Cyclophosphamide, doxorubicin, and etoposide, which are approved oncologic agents, were obtained from commercial sources.

Eligibility

Patients were eligible for enrollment if they had newly diagnosed, histologically or cytologically documented small-cell lung cancer, whether extensive or limited, and a performance status of 0 to 2 as defined by the Eastern Cooperative Oncology Group (ECOG) (i.e., they ranged from being fully active to being ambulatory and capable of self-care). In addition, patients had to meet standard criteria for renal, hepatic, and hematologic status, to have received no previous radiation therapy, and to have no other serious medical illnesses that would preclude participation. Informed consent was obtained from all patients according to the guidelines of the Food and Drug Administration and the individual institutional review boards.

Treatment Procedure

Patients were randomized within each center and stratified according to ECOG performance status and the presence or absence of bone marrow involvement. The patients were randomly assigned to chemotherapy followed by study drug (either placebo or G-CSF) in a double-blind fashion. Each 21-day cycle of chemotherapy consisted of the following agents, administered intravenously: 1000 mg of cyclophosphamide per square meter of body-surface area on day 1, 50 mg of doxorubicin per square meter on day 1, and 120 mg of etoposide per square meter on days 1 to 3. On day 4, approximately 24 hours after chemotherapy ended, treatment with placebo or G-CSF was initiated in a fixed dosage of 230 μg per square meter per day, self-administered subcutaneously once daily. The study drug was continued through day 17 unless the postnadir neutrophil count exceeded 10.0×10^9 per liter after day 12, in which case the study drug was discontinued for the remainder of the cycle. The cycle of treatment was planned to be repeated every 21 days for up to six cycles.

The primary end point of the trial was fever with neutropenia, indicated by a temperature ≥38.2°C associated with an absolute neutrophil count below 1.0×10^9 per liter. To monitor for this end point, patients were instructed to keep daily diaries of their drug administration and oral temperature and to undergo complete blood counts three times per week. As long as fever with neutropenia did not occur, double-blinded treatment was continued throughout the study. No reduction of the dose was allowed for nadir blood counts in the absence of this complication, although the next cycle could be delayed if adequate platelet and neutrophil recovery had not occurred. In all cycles of chemotherapy with double-blind administration of study drug, doses were given in full unless grade IV nonhematologic toxicity supervened. If patients had fever with neutropenia during a given cycle of treatment, they were hospitalized, with the institution of daily complete blood counts and treatment with standard parenteral antibiotic agents according to protocol guidelines until fever, neutropenia, and all signs of infection resolved. In subsequent cycles, these patients were withdrawn from the double-blind study and allowed to receive open-label G-CSF for the duration of their treatment.

During all cycles of therapy, patients were monitored for other adverse events, the use of concomitant medications, and other clinical events. Serum samples were collected at base line and at one or more points after treatment began, to detect the production of antibodies to G-CSF by radioimmunoassay. Restaging of the patients' condition was performed after the third cycle and after the completion of all six cycles of therapy. After completion of treatment, the patients' response status was determined and they were followed for relapse and survival.

Statistical Analysis

The calculated size of the sample was based on an expected difference of 20 percent in the incidence of fever with neutropenia (the primary outcome) throughout six cycles of chemotherapy (an incidence of 25 percent in the placebo group vs. 5 percent in the G-CSF group).

The 199 patients in whom efficacy could be evaluated underwent a total of 998 cycles of treatment. The analysis of the incidence of initial episodes of fever with neutropenia (as well as the secondary outcome, the time to the initial event) was limited to 194 of the 199 patients because of protocol violation or inadequate data in 5 patients. The results presented here focus on the cycles during which study medication was administered in blinded fashion. Because of the higher event rate (and consequent unblinding) in the placebo group, this group had a total of 248 such cycles, as compared with 352 cycles in the G-CSF group.

All statistical tests were conducted with adjustment for the effects of study center and disease status at entry. The rates of initial episodes of fever with neutropenia, as well as all dichotomous variables related to the secondary outcomes, were compared by the Mantel–Haenszel chi-square test. In addition, strata-adjusted relative risks were estimated with use of the G-CSF group as the referent.[17] The time to the initial episode was estimated according to stratified Kaplan–Meier time-to-event analysis, with comparison of the distributions of the two treatment groups by the generalized Wilcoxon and Tarone–Ware test statistics.[18] Continuous secondary-outcome variables were analyzed with the nonparametric Cochran–Mantel–Haenszel adjusted Wilcoxon rank-sum test.[17]

Although the primary end point of the study — infection as manifested by fever with neutropenia — was based on the association of a temperature ≥38.2°C with an absolute neutrophil count below 1.0×10^9 per liter, the majority of events were associated with a count below 0.5×10^9 per liter. Therefore, the evaluation of both episodes of fever with neutropenia and indicators of neutropenia focused on grade IV neutropenia ($<0.5\times10^9$ per liter).

Results

A total of 211 patients were randomly assigned to receive placebo (n = 110) or G-CSF (n = 101). Four patients (one assigned to placebo and three assigned to G-CSF) were not included in the evaluation of treatment for safety or efficacy because they were withdrawn from the study before they received treatment. Eight other patients (five assigned to placebo and three assigned to G-CSF) could not be evaluated for efficacy because they were ineligible (five patients), received an incorrect dose of a chemotherapeutic agent (two), or received concurrent radiation (one). Therefore, a total of 199 patients underwent at least one cycle in which efficacy could be evaluated — 104 patients assigned to placebo and 95 assigned to G-CSF. The characteristics of these 199 patients are shown in Table 1. The treatment groups were balanced in their performance status, bone marrow involvement, disease stage, and demographic characteristics.

Analysis of primary efficacy focused on the results of double-blinded treatment that was to be given in full doses in the absence of grade IV nonhematologic toxicity.

Fever with Neutropenia

The event rate for fever with neutropenia during cycle 1 was reduced by 50 percent in the G-CSF group as compared with the placebo group (Table 2) (28 percent vs. 57 percent, respectively; risk ratio = 2.01; 95 percent confidence limits, 1.4 and 2.9). Fifty-five percent of patients given placebo in cycle 1 both had fever with neutropenia and were hospitalized during that cycle, as compared with 26 percent of patients given G-CSF. Figure 1 shows Kaplan–Meier curves for the time to first episode of fever with neutropenia in the placebo and G-CSF groups. The difference in the cumulative event rate between the placebo group (77 percent) and the G-CSF group (40 percent) across all cycles was statistically significant (risk ratio = 1.9; 95 percent confidence limits, 1.5 and 2.5). The median duration of an episode for all cycles was five days in the placebo group and four days in the G-CSF group.

A total of 135 patients successfully completed all six cycles of chemotherapy. Seventy-six patients had fever with neutropenia that led to unblinding of drug administration. Of the 59 patients who continued to receive study drug in blinded fashion during all six cycles, 18 were receiving placebo (17 percent of those in whom efficacy could be evaluated), as compared with 41 (43 percent) receiving G-CSF.

Table 1. Characteristics of the 199 Patients in the Study Groups Who Could Be Evaluated.

Characteristic	Placebo (N = 104)	G-CSF (N = 95)
ECOG performance status (% of group)		
0	25	17
1 or 2	75	83
Bone marrow involvement (% of group)		
Yes	18	16
No	82	84
Status of lung cancer (% of group)		
Extensive	72	72
Limited	28	28
Sex (% of group)		
Male	63	65
Female	37	35
Age (yr)		
Median	63	62
Range	31–80	31–78
Weight (kg)		
Median	70	74
Range	36–122	35–113
Race (% of group)		
White	90	88
Nonwhite	10	12

Table 2. Indicators of Neutropenia during Cycle 1 (Double-Blinded Administration).

Indicator	Placebo*	G-CSF*	Adjusted P Value†
Incidence of neutropenia with fever — %	57 (102)	28 (92)	<0.001
Incidence of absolute neutrophil count $<0.5\times10^9$/liter — %	98 (102)	84 (93)	0.001
Median neutrophil nadir — 10^{-9}/liter	0.036 (98)	0.068 (86)	0.004
Median duration — days			
Neutrophil count $<0.5\times10^9$/liter	6.0 (94)	3.0 (86)	<0.001
Fever with neutropenia‡	5.0 (57)	4.0 (25)	NS

*Values in parentheses are numbers of patients.

†Adjusted for disease status and center by the Cochran–Mantel–Haenszel adjusted chi-square or the Wilcoxon rank-sum test. NS denotes not significant.

‡Among patients who had fever with neutropenia.

Clinical End Points

Figure 2 shows the data for the major secondary clinical end points of the study. The overall use of antibiotics and days of hospitalization are expressed as the mean duration of treatment with intravenous antibiotics in days per cycle and the mean duration of the hospital stay in days per cycle for all cycles with blinding. Means are presented rather than medians since less than 50 percent of the patients were hospitalized or given antibiotics within a cycle, and the resulting median values were 0. In conjunction with an overall reduction in the event rate for fever with neutropenia, approximately 48 percent in the G-CSF group, there was a reduction in the mean number of days of antibiotic use by 47 percent and a reduction in the mean number of days of hospitalization by 45 percent in this group, as compared with the placebo group, during cycles with blinding. The placebo group had a relative risk of requiring intravenous antibiotics of 1.9 (95 percent confidence limits, 1.44 and 2.51) and a relative risk of hospital-

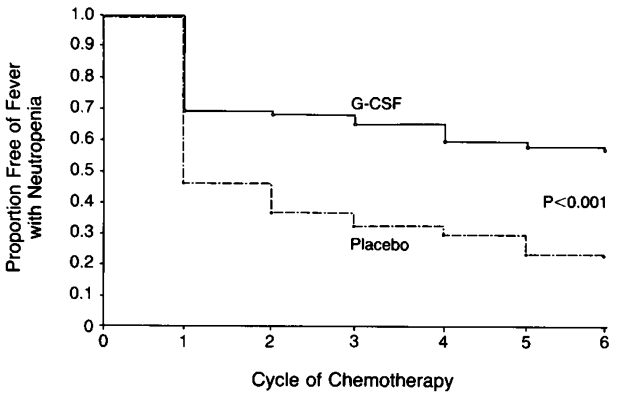

Figure 1. Kaplan–Meier Curve for the Proportion of Patients Remaining Free of Fever with Neutropenia, According to Treatment Cycle.

A total of 194 patients could be evaluated for the presence of an absolute neutrophil count below 0.5×10^9 per liter and a temperature ≥38.2°C.

ization of 1.55 (95 percent confidence limits, 1.26 and 1.91), as compared with the G-CSF group. The durations of individual episodes of antibiotic use and hospital stay, however, were similar in both treatment groups.

The rate of culture-confirmed infections was examined across all cycles. A reduction of 51 percent was observed per cycle — i.e., the rate was 13.3 percent in the placebo group and 6.5 percent in the G-CSF group. This rate of reduction was consistent with the rate of culture-confirmed infections in patients with fever and neutropenia in other studies[4,5] and internally consistent with the overall reductions in the incidence of fever with neutropenia, days of hospitalization, and days of antibiotic use in the present study. The overall percentage of cycles with both a culture-confirmed infection and fever with neutropenia was 11.7 percent in the placebo group and 4.8 percent in the G-CSF group.

Neutrophil Profiles

Cycle 1

Figure 3 presents the median absolute neutrophil count during cycle 1 in the placebo and G-CSF groups, on both a linear and a $\log_{10}$ scale. Patients given placebo had a prolonged period of neutropenia. By contrast, the patients given G-CSF had a prompt increase in the neutrophil count on day 5, one day after the initiation of G-CSF treatment, followed by an earlier nadir, a substantially shorter duration of neutropenia, and a more rapid recovery than the patients given placebo. The logarithmic analysis emphasizes the differences in the degree and duration of grade IV neutropenia (neutrophil count, $<0.5\times10^9$ per liter).

These indicators of neutropenia are compared according to treatment group in Table 2. There were significant differences between the groups in the overall incidence of grade IV neutropenia (98 percent in the placebo group vs. 84 percent in the G-CSF group, P = 0.001), the median absolute neutrophil nadirs (0.036×10^9 vs. 0.068×10^9 per liter, P = 0.004), and the median duration of grade IV neutropenia (six vs. three days, P<0.001).

Cycles 1 through 6

Figure 4 shows the absolute neutrophil nadir and duration of neutropenia during each cycle of chemotherapy in all patients continuing to receive double-blind treatment throughout the study. There were statistically significant differences between the treatment groups in the nadir during all six cycles. As shown in the lower panel of the figure, after cycle 1 the median duration of grade IV neutropenia in the placebo group consistently lasted six to seven days. By contrast, the median duration of neutropenia in the G-CSF group lasted one day or less; there were statistically significant differences between the two treatment groups in all six cycles of therapy. For all treatment cycles combined, the median duration of grade IV neutropenia was six days per cycle in the placebo group, as compared with one day per cycle in the G-CSF group.

The treatment of patients who had fever with neutropenia was unblinded, and in subsequent cycles they received open-label G-CSF. Figure 5 shows the neutrophil profiles in the patients assigned to placebo in cycle 1 and in cycle 2. The neutrophil profile of those continuing to receive placebo during cycle 2 was very similar to the profile during cycle 1, with a median duration of grade IV neutropenia of six days. By contrast, the patients who were assigned to placebo but who received open-label G-CSF during cycle 2 had a shorter duration of grade IV neutropenia (median of 2.5 days) despite receiving the same dose of chemotherapeutic agents that had resulted in fever with neutropenia during cycle 1. This reduction in the duration of neutropenia in these patients during cycle 2 was

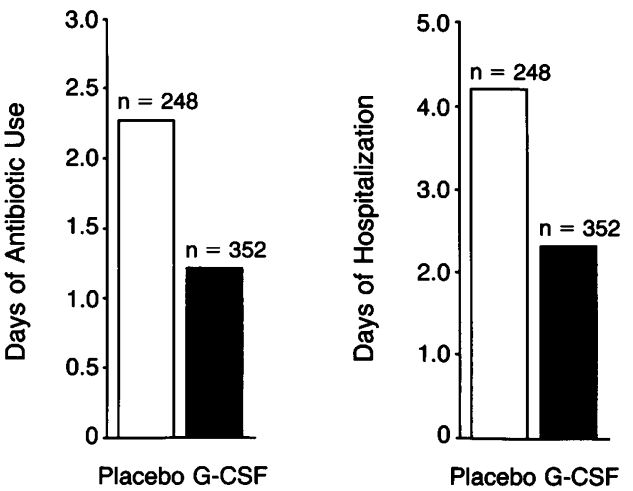

Figure 2. Secondary Clinical End Points in the Study Groups.

The mean duration of use of intravenous antibiotic drugs is expressed as the number of days per cycle during all patient cycles in which the study drug was given in blinded fashion, as is the mean duration of hospital stay.

associated with a reduction in the rate of fever with neutropenia, from 100 percent during cycle 1 to 23 percent during cycle 2.

Other Hematologic Indicators

Although there were significant differences between the placebo and G-CSF groups in their neutrophil profiles, there were no similar trends in their hemoglobin or platelet counts or in their counts of other subtypes of leukocytes. The median hemoglobin levels were 8.1 mmol per liter and 8.6 mmol per liter at base line in the placebo and G-CSF groups, respectively, and 6.2 and 6.0 mmol per liter during cycle 6. Transfusions of red cells were frequent in both treatment groups during later cycles of the study. The median platelet counts at the start of each cycle dropped successively in both groups throughout the study, but were still above 200×10^9 per liter by cycle 6. For all cycles with blinding, the incidence of grade IV thrombocytopenia was 12.5 percent in the placebo group and 13.4 percent in the G-CSF group. No serious hemorrhagic complications related to thrombocytopenia were observed in either group.

Drug Safety

The use of a placebo control in the study design allowed adverse events due to G-CSF treatment to be examined in relation to the toxicity of chemotherapy or the symptoms of underlying disease. The only consistent clinical symptom attributed to G-CSF was mild-to-moderate skeletal pain in approximately 20 percent of all patients given the drug. This generally

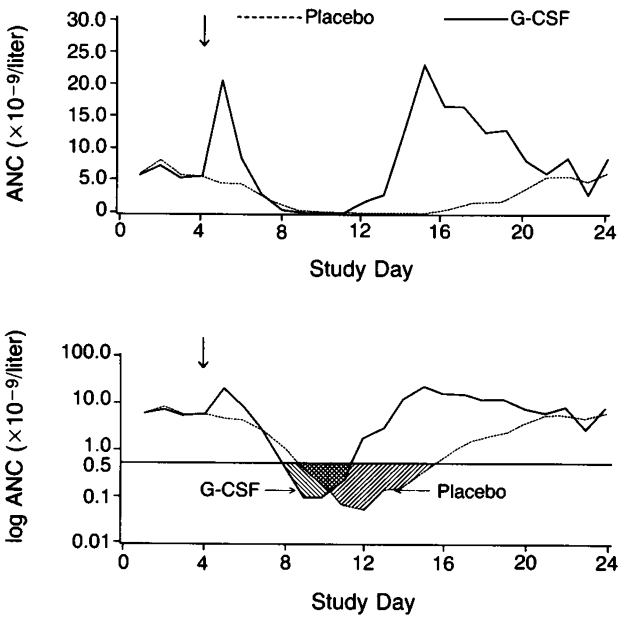

Figure 3. Median Absolute Neutrophil Count (ANC) in the Study Groups during Cycle 1.

The counts are shown on a linear scale (top) and log scale (bottom). The arrow denotes the start of placebo or G-CSF administration. The hatching highlights the degree and duration of neutropenia (counts $<0.5\times10^9$ per liter).

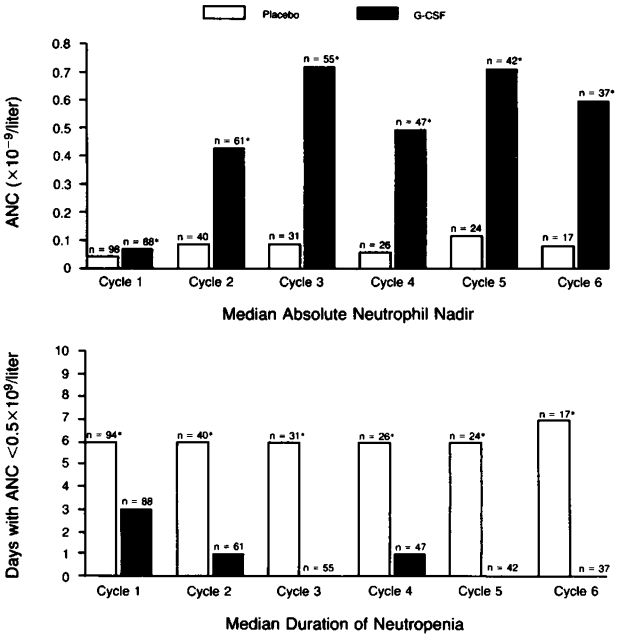

Figure 4. Neutrophil Nadir and Duration of Neutropenia during All Six Cycles of Chemotherapy in Patients Continuing to Receive the Study Drug in Blinded Fashion.

The number of patients who could be evaluated during each cycle is shown. There were significant differences between the study groups during every cycle of treatment (asterisk denotes $P<0.005$ by the adjusted Wilcoxon rank-sum statistic); ANC denotes absolute neutrophil count.

occurred over a period of one to two days before the recovery of myeloid function at sites containing bone marrow, including the sternum, spine, pelvis, and long bones, and was ameliorated with oral analgesic agents. Six percent of patients in both treatment groups reported a mild generalized rash or itching. Three patients experienced an adverse event thought to be related to G-CSF administration that led to their request to withdraw from the study; these events were abdominal pain, diffuse "aches and pains," and a flare-up of preexisting eczema.

Other clinical toxic reactions similar to those seen with other cytokines, such as fever, hypotension, fluid retention, serositis, arthralgia, myalgia, local skin reaction, and malaise, were not associated with G-CSF. No patient among 109 tested was positive for serum antibodies to the protein of G-CSF. Biochemical abnormalities that could be attributed to G-CSF were transient and reversible and included elevations of the levels of lactate dehydrogenase, alkaline phosphatase, leukocyte alkaline phosphatase, and uric acid, which appeared to correlate with changes in the neutrophil turnover.

Response and Survival

Disease response and survival were not major end points for evaluating efficacy in this study. However, because of the hypothetical potential of growth factors to promote tumor growth in vitro, clinical response (in 186 patients) and the time to disease progression (in

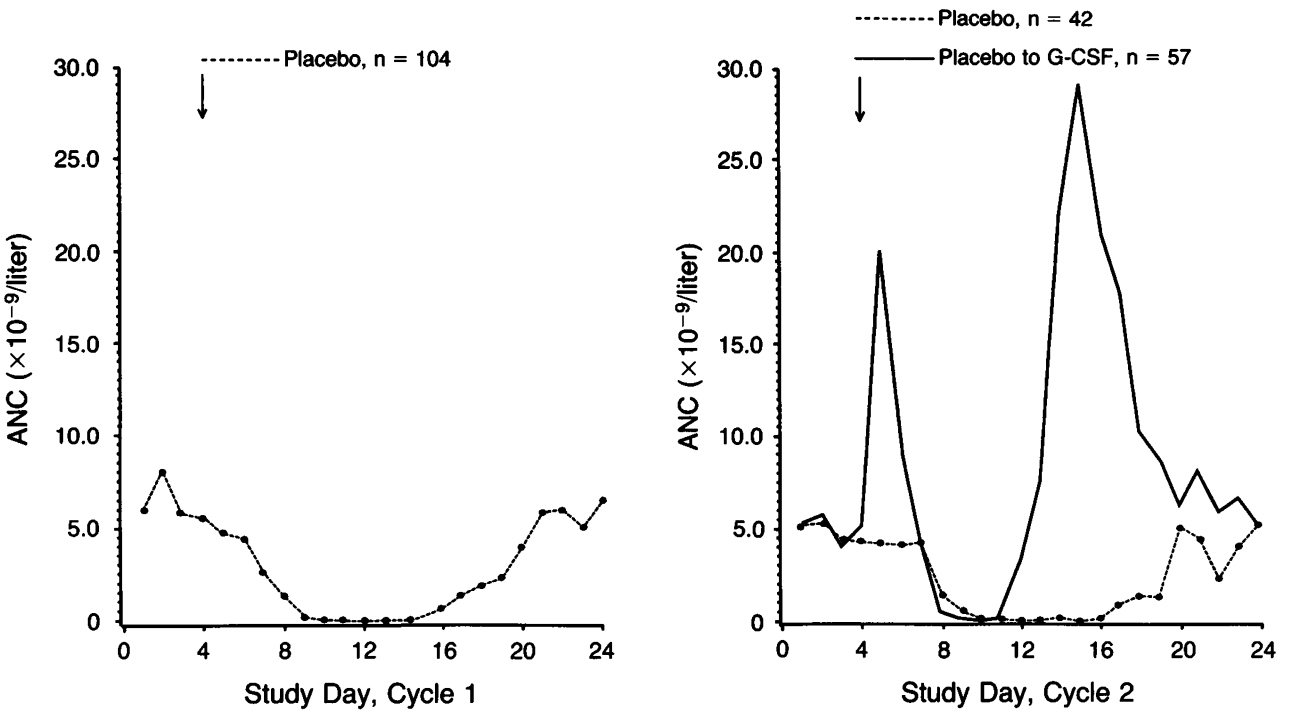

Figure 5. Median Absolute Neutrophil Count (ANC) in Patients Assigned at Randomization to Placebo during Cycles 1 and 2. The arrow denotes the start of study-drug administration on day 4. During cycle 2, patients were crossed over from treatment with placebo to open-label G-CSF.

199) were assessed. The treatment groups were analyzed according to assignment through randomization, although the majority of patients assigned to placebo subsequently received at least one cycle of G-CSF. The rate of complete responses was 19 percent among patients assigned to placebo and 30 percent among those assigned to G-CSF, with overall response rates of 80 percent and 72 percent, respectively. The median time to tumor progression in the placebo and G-CSF groups was 7.9 months and 8.4 months, respectively; the median survival period was 12.2 months and 11.4 months, respectively. None of the differences were statistically significant. Seventeen patients died during the study, including two who died before receiving placebo or G-CSF: nine had been assigned to placebo and eight to G-CSF. Thus, the overall mortality rate was 8.1 percent. The primary causes of death were cardiopulmonary events (four patients in the placebo group and five in the G-CSF group), infection (three in each treatment group), and aneurysm (one in the placebo group); the cause was unknown in one patient in the placebo group.

Discussion

The results of this trial clearly demonstrate that recombinant methionyl G-CSF administered as an adjunct to chemotherapy in patients with small-cell lung cancer resulted in significant reductions in the incidence of fever with neutropenia; the incidence, duration, and severity of grade IV neutropenia; and the overall number of days of intravenous antibiotic use and hospitalization. Both histograms in Figure 4 show the consistency of the neutrophil response to G-CSF, which was maintained throughout all six cycles of therapy. Treatment with G-CSF was associated with minimal toxicity, mostly mild-to-moderate medullary bone pain. Side effects seen with other cytokines (fever [without neutropenia], malaise, arthralgia, myalgia, pericarditis, fluid retention, hypotension, and dyspnea) were not associated with G-CSF.

Before this study, several phase II trials had suggested that colony-stimulating factors were capable of decreasing the degree of chemotherapy-induced neutropenia in small-cell lung cancer,[14] bladder cancer,[16] and other neoplasms[15] and in transplantation.[19] An open-label phase III trial of G-CSF has also shown a reduction in the number of days of neutropenia after one cycle of chemotherapy for relapsed or refractory leukemia.[20] The present prospective, randomized, double-blind, placebo-controlled phase III trial documents the magnitude of clinical benefit associated with the reduction in chemotherapy-induced neutropenia over multiple cycles of intensive treatment.

The high rate of episodes of fever with neutropenia observed in this trial may reflect in part the unusually vigilant monitoring for chemotherapy-induced fever and neutropenia. However, the high rate during cycle 1 may also be due to the substantial comorbidity of neoplastic disease in the study population. The frequency of culture-confirmed infections supports the clinical importance of these episodes of neutropenia. Furthermore, as shown by Talcott et al.,[21] patients

with uncontrolled cancer or other concurrent disease are at a higher risk for serious complications of such an episode than are other outpatients.

This study also showed that patients in the placebo group in whom fever with neutropenia developed after chemotherapy could receive full doses of chemotherapy along with adjunctive G-CSF in the subsequent cycle, with a reduction in the rate of episodes of fever with neutropenia from 100 percent in cycle 1 to 23 percent in cycle 2. This reduction was associated with a substantial decrease in the duration of neutropenia. Patients who continued to receive placebo continued to have prolonged grade IV neutropenia throughout the six cycles, with this complication lasting a median of six days (Fig. 5).

Previous trials of prophylactic antibiotic drugs as adjuncts to chemotherapy have shown only a moderate benefit in reducing infections in patients with small-cell lung cancer.[22,23] Therefore, their use has not been adopted as the standard of care, and they were not used in this trial. However, in view of the ability of G-CSF to shorten the duration of neutropenia, and the potential complementary role of prophylactic antibiotics during this period of risk of infection, studies evaluating this combination in dose-intensive treatment would be of interest.

Although there have been reports of cell-surface receptors for colony-stimulating factors on cell lines derived from small-cell lung tumors, there was no evidence in this study of a deleterious effect of G-CSF on tumor response or overall survival. The usefulness of G-CSF and other colony-stimulating factors in improving response rates and survival is an area of active investigation in the treatment of small-cell lung cancer, breast cancer, lymphomas, leukemia, and other chemosensitive neoplasms.

The incidence of fever with neutropenia correlated with the overall mean durations of antibiotic use and hospitalizations, all of which were reduced by approximately 50 percent in the G-CSF group. Likewise, the rate of culture-confirmed infections was reduced by 50 percent. Therefore, in addition to the substantial clinical impact of G-CSF as an adjunct to chemotherapy, there may be a substantial economic impact. We conclude that recombinant methionyl G-CSF significantly reduced the degree and duration of chemotherapy-associated neutropenia. This resulted in a substantial reduction in infection and associated morbidity.

We are indebted to Dianne Tomita, M.P.H., and William Rich, M.S., for the statistical analysis; to Sherri Brown, M.D., and Richard Stead, M.D., for their expertise in oncology and hematology; to the clinical research associates, data managers, and research coordinators for monitoring and data collection; and to Debra Stott for assistance in the preparation of the manuscript.

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