Comparative Safety of Filgrastim versus Sargramostim in Patients Receiving Myelosuppressive Chemotherapy

Gary Milkovich, B.S., Ronald J. Moleski, Pharm.D., John F. Reitan, Pharm.D., David M. Dunning, M.D., Gene A. Gibson, Pharm.D., Thomas A. Paivanas, M.H.S.A., Susan Wyant, Pharm.D., and R. Jake Jacobs, M.P.A.

Study Objective. To compare rates of adverse events with filgrastim versus sargramostim when given prophylactically to patients receiving myelosuppressive chemotherapy.

Design. Retrospective review with center crossover.

Setting. Ten United States outpatient chemotherapy centers.

Patients. Four hundred ninety patients treated for lung, breast, lymphatic system, or ovarian tumors.

Intervention. Prophylactic use of filgrastim or sargramostim, with dosages at investigator discretion.

Measurements and Main Results. The frequency and severity of adverse events and the frequency of switching to the alternative CSF were assessed. There was no difference in infectious fever. Fever unexplained by infection was more common with sargramostim (7% vs 1%, p<0.001), as were fatigue, diarrhea, injection site reactions, other dermatologic disorders, and edema (all p<0.05). Skeletal pain was more frequent with filgrastim (p=0.06). Patients treated with sargramostim switched to the alternative agent more often (p<0.001).

Conclusion. Adverse events were less frequent with filgrastim than with sargramostim, suggesting that quality of life and treatment costs also may differ.

Colony-stimulating factors (CSFs) are recommended in certain situations to reduce the likelihood of febrile neutropenia induced by myelosuppressive chemotherapy.[1] Recombinant forms of granulocyte (G)-CSF and granulocyte-macrophage (GM)-CSF are synthesized using a variety of host expression systems. In the United States, G-CSF is commercially available as filgrastim, derived from bacterial cells, and GM-CSF is available as sargramostim, derived from yeast cells.

Only two studies directly compared the safety of these two agents.[2, 3] Reviews of safety based on placebo-controlled trials[1, 4, 5] are problematic, as the trials often include populations with different underlying diseases and concomitant drug therapy. Bone pain is the most commonly reported adverse event with filgrastim,[6, 7] but exacerbation of preexisting inflammatory conditions,[8–10] rash,[11] allergic reactions,[12] Sweet syndrome,[13] and injection site reactions[14] have been reported. With sargramostim, the most common adverse event is fever.[2, 4, 15] Nausea, fatigue, headache, bone pain, chills, myalgia, and injection site reactions also have been reported.[16–20]

Sargramostim is almost certainly less toxic than GM-CSF expressed in bacterial cells (molgramostim). Compared with molgramostim, fluid retention, dyspepsia, fever, and myalgia and arthralgia are all less frequent with sargramostim.[21] The initial dose of molgramostim may cause significant hypoxia and hypotension, particularly in patients receiving

high dosages or intravenous administration.[22]

The perception that sargramostim is less safe than filgrastim may be due to confusion regarding data describing GM-CSF synthesized using bacterial or mammalian cells. This was the principal rationale for the only randomized comparison of CSF tolerability, in which 137 patients receiving myelosuppressive chemotherapy were assigned to filgrastim 7 µg/kg or sargramostim 193 µg/m^2, with regimens at investigators' discretion.[2] The agents were compared on the frequency of 11 adverse events, graded by Eastern Cooperative Oncology Group (ECOG) or similar criteria. The frequency of fever, mainly 98.7–100.4°F, was 2-fold greater with sargramostim (p=0.01). Statistically insignificant trends were seen, indicating more frequent bone pain, chills, and nausea with sargramostim, and more frequent headache with filgrastim. The comparative safety of these agents also was assessed in a drug use evaluation, which included 60 patients undergoing bone marrow transplantation, dose-intensive chemotherapy, and standard chemotherapy.[3] No differences were noted in frequencies of fever, nausea and vomiting, musculoskeletal pain, diarrhea, myalgia, or local reactions.

Our study was undertaken to provide additional data on the comparative safety of filgrastim and sargramostim in patients receiving myelosuppressive chemotherapy. We sought to avoid what we considered important limitations of earlier comparative studies; namely, inadequate statistical power, data obtained from a single or small number of centers, and pooling of patients receiving CSFs prophylactically and therapeutically.

From the School of Pharmacy, Medical College of Virginia, Richmond, Virginia, and Northern Virginia Cancer Center, Alexandria, Virginia (Mr. Milkovich); RJM Associates, Guilford, Connecticut (Dr. Moleski); The Reitan Company, Inc., Crown Point, Indiana (Dr. Reitan); Northern Virginia Oncology Group, Fairfax, Virginia (Dr. Dunning); the Department of Pharmacy, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania (Dr. Gibson); the School of Public Health and Health Services, George Washington University Medical Center, Washington, D.C. (Mr. Paivanas); The Dominion Group, McLean, Virginia (Dr. Wyant); and Capitol Outcomes Research, Inc., Alexandria, Virginia ((Mr. Jacobs).

Address reprint requests to Ronald J. Moleski, Pharm.D., RJM Associates, 195 Maupas Road North, Guilford, CT 06437.

Methods

This was a multicenter, retrospective examination in which patients receiving CSFs for primary or secondary prophylaxis were identified, and their clinical experiences assessed through medical record review. To minimize selection bias common to retrospective studies, we employed a center crossover design in which participating sites substituted sargramostim for filgrastim or vice versa as CSF of choice. We anticipated that patients treated before and after the policy decision would not differ systematically with respect to risk factors for adverse events. By contrast, a traditional retrospective study would be biased by self-selection if one agent were reserved for patients at greater risk of adverse events.

Centers

Ten U.S. outpatient chemotherapy centers participated. All provided chemotherapy to 20 or more patients/month and made a decision before participation to substitute one CSF for the other as agent of choice for patients receiving myelosuppressive chemotherapy. Nine substituted sargramostim for filgrastim, and one substituted filgrastim for sargramostim. Each center was assigned a crossover date representing the first day of the first month during which 90% of new patients received the subsequent agent. Filgrastim and sargramostim eras were defined for each center. For centers substituting sargramostim for filgrastim, the sargramostim era began with the crossover date and continued through 12 months or agreement to participate in the study, whichever was earlier; the filgrastim era began and ended exactly 12 months earlier. The process was reversed for the site substituting filgrastim for sargramostim. The mean duration of filgrastim and sargramostim eras was 8 months (range 4–12 mo).

Patients

Records of all patients having received one or more doses of CSF during the filgrastim and sargramostim eras were examined. Patients were included if they were aged 18 years or older and received chemotherapy for a lung, breast, lymphatic system, or ovarian tumor. Those with a history of any autoimmune disease or disease of the blood or blood-forming organs were excluded, as were recent (< 90 days) recipients of bone marrow transplants or experimental drugs.

Table 1. Baseline Characteristics

Variable	Filgrastim	Sargramostim	p Value
No. of patients (by initial CSF)	239	251	
Mean (SD) age, yrs[a]	62 (14)	61 (14)	0.43[b]
No. (%) women[c]	176 (74)	176 (71)	0.56[d]
Mean (SD) body surface area,[e] m^2	1.8 (0.2)	1.8 (0.3)	0.38[b]
Mean (SD) months since cancer diagnosis[f]	26 (48)	19 (36)	0.62[b]
No. (%) of patients covered by Medicare[g]	115 (51)	122 (47)	0.49[d]
No. (%) of patients covered by managed care[g]	6 (3)	10 (4)	0.33[d]
No. (%) of patients by tumor type			0.07[d]
Breast	97 (41)	88 (35)	
Lung	52 (22)	84 (33)	
Lymphoma	56 (23)	48 (19)	
Ovarian	34 (14)	31 (12)	
No. (%) of patients by study center			0.41[d]
A	10 (4)	20 (8)	
B	31 (13)	39 (16)	
C	22 (9)	26 (10)	
D	19 (8)	16 (6)	
E	10 (4)	12 (5)	
F	8 (3)	7 (3)	
G	9 (4)	18 (7)	
H	5 (2)	6 (2)	
I	70 (29)	61 (24)	
J	55 (23)	46 (18)	

[a]Missing data for one sargramostim recipient.
[b]Wilcoxon rank sum test.
[c]Missing data for four sargramostim recipients.
[d]χ^2 test.
[e]Missing data for 15 filgrastim and 20 sargramostim recipients.
[f]Missing data for 13 filgrastim and 21 sargramostim recipients.
[g]Missing data for 12 filgrastim and 19 sargramostim recipients.

Chemotherapy and CSF Cycles

Data describing chemotherapy regimens, CSF dosing, blood counts, and adverse events were recorded for all cycles, to a maximum of six/patient. Daily CSF doses were established at investigators' discretion. Mean doses were 369 µg (5.5 µg/kg) for filgrastim and 474 µg (6.9 µg/kg) for sargramostim. Eligible cycles were those beginning within 7 days of the most recent chemotherapy dose, if the patient was afebrile (< 100.0°F) and did not otherwise meet criteria for therapeutic administration of CSFs.[1] If inclusion and exclusion criteria no longer were met during follow-up, all subsequent cycles were excluded.

Recording the Response

Case report forms were completed by four clinical monitors, and their accuracy was confirmed by center investigators. Data were recorded covering inclusion and exclusion criteria, demographic and clinical characteristics, CSF dosages and cycle duration, and adverse events including symptom description, onset and resolution dates, and assessments of severity and relationship to CSF. Adverse events were monitored beginning with the first CSF dose through 24 hours after the last dose. Most patients received one CSF dose/day on consecutive days, as evidenced by the similarity between mean (SD) doses/cycle [7.5 (3.1)] and cycle duration [8.0 days (3.3 days)]. During occasional gaps of 1 or more days between doses, adverse event monitoring was suspended. Clinical monitors recorded information explicitly stated in medical records, including verbatim description of adverse events.

Two reviewers blinded to CSF reviewed adverse event reports and classified them into predetermined categories: fever, fatigue, chills, headache, skeletal pain, nausea and vomiting, constipation, diarrhea, other digestive disorder, injection site reaction, other dermatologic disorder, chest discomfort, edema, hematologic reaction, central nervous system disorder, or other. Disagreement between reviewers on adverse event classification was rare (9/555 cases) and resolved through consultation with the prescribing physician or nursing staff. Febrile episodes were defined as a single reading of 100.4°F or greater obtained by any health professional and were subclassified as being of

Table 2. Chemotherapy Regimens[a]

Variable	Filgrastim	Sargramostim	p Value
No. of patients (by initial CSF)	239	251	
No. (%) receiving each agent			
Bleomycin	9 (4)	5 (2)	0.24[b]
Carboplatin	51 (21)	73 (29)	0.05[b]
Cisplatin	24 (10)	22 (9)	0.63[b]
Cyclophosphamide	104 (44)	90 (36)	0.08[b]
Cytarabine	6 (3)	6 (2)	0.93[b]
Dacarbazine	3 (1)	4 (2)	1.0[c]
Docetaxel	21 (9)	20 (8)	0.74[b]
Doxorubicin	93 (39)	81 (32)	0.13[b]
Etoposide	42 (18)	35 (14)	0.27[b]
Fludarabine	9 (4)	5 (2)	0.24[b]
Fluorouracil (5-FU)	39 (16)	42 (17)	0.90[b]
Gemcitabine	2 (1)	15 (6)	<0.01[b]
Ifosfamide	8 (3)	10 (4)	0.71[b]
Melphalan	1 (< 1)	0 (0)	0.49[c]
Methotrexate	19 (8)	23 (9)	0.63[b]
Mitoxantrone	11 (5)	12 (5)	0.93[b]
Nitrogen mustard	0 (0)	1 (< 1)	1.0[c]
Paclitaxel	52 (22)	73 (29)	0.06[b]
Procarbazine	1 (< 1)	1 (< 1)	1.0[c]
Rituximab	0 (0)	2 (1)	0.50[c]
Topotecan	20 (8)	14 (6)	0.22[b]
Vinblastine	6 (3)	7 (3)	0.85[b]
Vincristine	39 (16)	35 (14)	0.46[b]
Vinorelbine	7 (3)	11 (4)	0.39[b]

[a]Includes agents administered during any of up to six chemotherapy cycles.
[b]χ^2 test.
[c]Fisher's exact test.

presumed infectious cause or unexplained by infection, based on the presence or absence of documented pathogen(s) or other clinical signs of infection (e.g., dark, cloudy urine; positive chest radiograph).

Adverse events other than fever were rated for severity. They were considered at least moderate if drug therapy or other intervention was required, and severe if intervention included a narcotic, invasive procedure, or hospitalization. Otherwise, they were categorized based on expressions in medical records and considered mild unless evidence was recorded to the contrary. Relationship to CSF was categorized based on World Health Organization definitions[23] as probably, possibly, or probably not related. The last category included conditions present before CSF was begun or attributed in medical records to an underlying disease or concomitant drug. Otherwise, events were considered possibly related unless medical records indicated a stronger association.

Statistical Methods

The study was powered to detect a 3% versus 9% difference in frequency of fever unexplained by infection, with anticipated fever risk derived from an earlier comparative study[2] adjusted to reflect an expected three cycles/patient. We intended to conduct analyses on a per-patient basis and determined 245 patients in each arm would provide 80% power, assuming an α of 0.05 and a two-tailed test. Patients first prescribed sargramostim frequently switched to filgrastim, requiring modification of the analysis because duration of follow-up differed between CSFs. We therefore assessed adverse event frequency on a per-cycle basis, assigning cycles after a switch to the alternative CSF. Based on the actual numbers of 958 filgrastim and 644 sargramostim cycles, the sample provided abundant statistical power to detect meaningful differences. For adverse events occurring in one arm at rates of 3%, 4%, and 5%/cycle, the sample provides 82%, 91%, and 96% power to detect 2-fold greater rates in the other arm.

Categoric data were compared by χ^2, unless a low frequency of adverse events required Fisher's exact test. For interval data, the normality of distributions was determined by Kolmogorov D test. Student's *t* test was used when data were

Table 3. Numbers of CSF Cycles and Doses

Variable	Filgrastim	Sargramostim	p Value[a]
No. of patients (by initial CSF)	239	251	
Use of either CSF			
Mean (SD) cycles	3.5 (1.9)	3.4 (1.9)	0.76
Mean (SD) doses	24.1 (15.9)	25.1 (17.1)	0.65
Use of first prescribed CSF			
Mean (SD) cycles	3.4 (1.9)	2.6 (1.6)	<0.001
Mean (SD) doses	23.9 (16.0)	19.5 (15.3)	<0.001
Use of alternative CSF			
Mean (SD) cycles	< 0.1 (0.2)	0.8 (1.5)	<0.001
Mean (SD) doses	0.1 (1.5)	5.5 (10.8)	<0.001

[a]Wilcoxon rank sum test.

Table 4. Frequency of Fever

Variable	Filgrastim	Sargramostim	p Value[a]
No. of cycles	958	644	
No. (%) of cycles with report of			
Fever ≥ 100.4°F	39 (4)	57 (9)	<0.001
Fever of presumed infectious origin	25 (3)	15 (2)	0.72
Fever unexplained by infection	14 (1)	42 (7)	<0.001

[a]χ^2 test.

normally distributed, and Wilcoxon rank sum test when the distribution was not normal. All tests were two-tailed, and a p value below 0.05 was considered statistically significant.

Results

There were no significant differences in baseline characteristics between patients initially receiving filgrastim versus sargramostim (Table 1). Patients were typical of those seen in office-based oncology practices. The sargramostim arm had proportionally more patients with lung cancer, and the filgrastim arm had more with breast cancer and lymphoma. No differences in disease stage were detected between arms (data not shown).

Patients received 24 chemotherapeutic agents (Table 2), with cyclophosphamide, doxorubicin, paclitaxel, carboplatin, and etoposide most common in both groups. Those in the sargramostim arm were most likely to receive carboplatin (29% vs 21%, p=0.05) and gemcitabine (6% vs 1%, p<0.01). Given the large number of comparisons, these differences approximate what would be expected by chance. We found no differences between arms with respect to combinations of chemotherapeutic agents or chemotherapy dosages (data not shown).

We found no differences in numbers of chemotherapy-CSF cycles (p=0.76) or CSF doses (p=0.65) between patients initially prescribed filgrastim versus sargramostim (Table 3). The proportions of filgrastim recipients proceeding to second, third, fourth, fifth, and sixth CSF cycles were 80%, 58%, 44%, 29%, and 18%, versus 77%, 58%, 41%, 28%, and 21% for sargramostim (all NS). Patients first prescribed sargramostim were more likely to be switched to filgrastim than vice versa. Consequently, they received fewer cycles (2.6 vs 3.4, p<0.001) and doses (19.5 vs 23.9, p<0.001) of their initial CSF.

Table 4 shows the frequency of fever during filgrastim and sargramostim cycles. Febrile episodes occurred more than twice as frequently with sargramostim (9% vs 4%, p<0.001), with the entire difference represented by fever unexplained by infection (7% vs 1%, p<0.001). Among the 56 febrile episodes, no differences were seen between CSFs in fever duration or maximum recorded temperature. Fever unexplained by infection was most common during the first sargramostim cycle (10% vs 1% with filgrastim, p<0.001), although a lesser relationship persisted during subsequent cycles (4% vs 2%, p<0.01).

The most frequently reported adverse event was skeletal pain (Table 5), which tended to occur more frequently with filgrastim (11% vs

Table 5. Frequency of Adverse Events other than Fever

Variable	Any Adverse Event		Adverse Event Possibly or Probably Related to Cytokine		Adverse Event of Moderate or Greater Severity	
	Filg	Sarg	Filg	Sarg	Filg	Sarg
% of cycles with report of						
Fatigue	2	4[a]	1	4[b]	< 1	3[b]
Chills	< 1	1	< 1	1	< 1	< 1
Headache	< 1	1	< 1	1	< 1	1
Skeletal pain	11	8	11	8	7	6
Nausea, vomiting	3	3	2	2	2	2
Constipation	1	1	1	1	< 1	1
Diarrhea	2	3[a]	1	3	1	2
Other digestive disorder	< 1	1	< 1	1	< 1	1
Injection site reaction	< 1	6[b]	< 1	6[b]	0	5[b]
Other skin disorder	< 1	3[b]	< 1	2[b]	< 1	1[b]
Chest discomfort	< 1	1	< 1	1	< 1	1
Edema	< 1	2[b]	< 1	2[b]	< 1	2[b]
Hematologic reaction	0	1	0	< 1	0	< 1
CNS disorder	2	1	1	1	1	< 1
Other adverse event	1	1	< 1	1	< 1	1

Filg = filgrastim; Sarg = sargramostim; CNS = central nervous system.
[a]$p<0.05$, χ^2 or Fisher's exact test.
[b]$p<0.01$, χ^2 or Fisher's exact test.

Table 6. Switching between CSFs

Variable	Filgrastim	Sargramostim	p Value
No. of patients (by initial CSF)	239	251	
No. (%) of patients switching CSF for any reason	2 (1)	74 (29)	<0.001[a]
No. (%) of patients switching CSF due to			
Adverse event	0 (0)	45 (18)	<0.001[a]
Poor ANC response	0 (0)	11 (4)	<0.001[a]
Formulary restriction	0 (0)	2 (1)	0.50[b]
Undetermined reason	2 (1)	17 (7)	<0.001[a]
Frequency of switching by cycle[c]			
Cycle 1	0/239 (0)	11/251 (4)	<0.001[a]
Cycle 2	1/192 (1)	33/193 (17)	<0.001[a]
Cycle 3	1/138 (1)	16/146 (11)	<0.001[a]
Cycle 4	0/104 (0)	8/103 (8)	<0.01[b]
Cycle 5	0/ 69 (0)	4/ 71 (6)	0.12[b]
Cycle 6	0/ 43 (0)	2/ 53 (4)	0.50[b]

ANC = absolute neutrophil count.
[a]χ^2 test.
[b]Fisher's exact test.
[c]Patients switched during cycle/patients beginning cycle (%).

8%, p=0.06). Several adverse events occurred significantly more frequently with sargramostim—fatigue (4% vs 2%, p<0.05), diarrhea (3% vs 2%, p<0.05), injection site reaction (6% vs < 1%, p<0.01), other dermatologic disorders (3% vs < 1%, p<0.01), and edema (2% vs < 1%, p<0.01). Limiting the analysis to adverse events judged probably or possibly related to CSFs lowered total event rates, but the frequency of fatigue (p<0.01), injection site reactions (p<0.01), other dermatologic disorders (p<0.01), and edema (p<0.01)

remained higher with sargramostim. Results were similar when the analysis was limited to adverse events rated moderate or severe. The lone injection site reaction attributed to filgrastim was rated mild. With sargramostim, 4 of 41 injection site reactions were severe and 29 were moderate.

Switching from filgrastim to sargramostim was uncommon, whereas more than one-fourth of sargramostim recipients switched to filgrastim (p<0.001; Table 6). Adverse events were the most frequent reason for switching, with

injection site reactions (10), fever (8), skeletal pain (6), and other dermatologic disorders (5) being most common. Although the reason for CSF switching was considered undetermined unless medical record notations were specific, adverse events were probably most often responsible in these cases as well. In the undetermined category, both switches of filgrastim to sargramostim and 8 of 17 switches of sargramostim to filgrastim followed cycles with adverse events. The determination that switching was due to poor absolute neutrophil count (ANC) response was based on medical record notations (e.g., "ANC still falling after X days sargramostim"). In 9 of 11 cases the ANC was below baseline after 5–14 days of sargramostim. We investigated whether suboptimal dosages were responsible for poor ANC response but found mean daily doses were similar for these (6.7 µg/kg) and other (6.9 µg/kg) sargramostim cycles. Switching was most frequent during the second and third cycles. Only 11 (4%) sargramostim recipients switched during the first cycle, and the rate of switching declined consistently between cycles 2 and 6.

Discussion

In the 6 years since the American Society of Clinical Oncology called for more investigation of the comparative toxicity of filgrastim and sargramostim,[1] few data have been published on the subject. Adverse events were assessed in a retrospective cohort study considering 680 days of CSF administration[3] and a randomized trial that included 820 days of CSFs.[2] Neither study detected differences between CSFs, with the exception of more grade 1 fever (98.7–100.4°F) with sargramostim.[2] We assessed adverse events during 12,060 days of CSF treatment and found important differences that generally favored filgrastim over sargramostim.

The dissimilarity between our results and those of other studies may be due to several factors, including our exclusion of patients receiving CSFs therapeutically, passive surveillance for adverse event reporting, method of categorizing adverse events, and greater statistical power. It is unlikely to be due to differences in composition of patient samples. Although our study was limited to patients with lung, breast, lymphatic system, or ovarian tumors, these diagnoses represented 65–80% of patients in earlier studies.[2, 3] Our sample was somewhat older, but this was unlikely to have had an effect, as we detected no relationship between age and frequency of adverse events.

Our decision to limit the study to prophylactic CSF may have affected results, but the extent and direction of such an effect are unclear. In other studies, 18–28% of patients received CSFs therapeutically,[2, 3] and results were not stratified by therapeutic versus prophylactic administration. It is unclear how earlier studies examined fever frequency for patients already febrile at the first CSF dose.

Our study used passive adverse event surveillance, similar to the other retrospective study.[3] By contrast, the prospective CSF safety trial[2] included rigorous monitoring. Patients completed evaluation forms and home diaries, and were telephoned every 1–2 days to review adverse events. Although passive surveillance probably provides more false negative results, this is unlikely to have impaired our ability to assess comparative safety. Active surveillance seems to increase the number of mild adverse events rather than moderate or severe events. In our study, for example, only 26% of reports of nausea and vomiting were rated mild, versus 67% in the prospective trial. Corresponding data for reports of skeletal pain and chills were 31% and 43% in our study versus 57% and 75% in the prospective trial. Unfortunately, medical records did not provide sufficient information to allow us to categorize adverse events by ECOG or similar criteria, as was done in the prospective trial.[2] Although we cannot determine whether our methods caused more or fewer adverse events to be identified, we see no reason why either method would cause more events to be detected with one cytokine versus the other.

This study most likely detected differences not found in prior research due to its greater statistical power. We studied 490 patients through 1602 chemotherapy-CSF cycles, whereas other studies included 60 and 137 patients, all followed through a single cycle.[2, 3] Given the frequency of grade 2 fever with filgrastim in the prospective trial, the study had only 9% power to detect a 2-fold increase with sargramostim.

Our most important results relate to switching between CSFs, and frequencies of injection site reactions and fever unexplained by infection. Whereas switching from sargramostim to filgrastim was common, this partially may reflect study design; 9 of 10 centers substituted sargramostim for filgrastim, thereby being experienced with both agents when patients in the sargramostim arm were treated. They may

have been inexperienced with sargramostim during the filgrastim era, making a switch to sargramostim in the face of efficacy or safety concerns unusual. Unlike earlier studies that reported no differences in local reactions, we identified just 1 (< 1%) injection site reaction during 958 filgrastim cycles, but 41 (6%) during 644 sargramostim cycles. Most were rated moderate or severe, and in 10 patients (24%) led to a switch to filgrastim. Like the prospective trial, fever unexplained by infection was more common with sargramostim in this series of patients. With a threshold of 100.4°F, we found a difference of 7% versus 1%. In the prospective trial, the difference in fever 100.5°F or greater was 4% versus 2%.

Despite lack of documented pathogens, the febrile episodes we detected were costly. Those occurring with filgrastim resulted in 15 days of inpatient care and 115 doses of antiinfective drugs/1000 chemotherapy-CSF cycles. Episodes occurring with sargramostim resulted in 93 days of inpatient care and 634 doses of antiinfective drugs/1000 cycles. Blood chemistries, microbiology tests, and radiologic examinations were commonly performed.

Assessments of CSF prophylaxis should consider the agents' ability to extend survival, improve quality of life, and reduce use of other health care services. In certain populations, CSFs have lowered antibiotic requirements[6, 24, 25] and hospitalization for febrile neutropenia.[6, 24–26] These end points are reasonable markers for both cost savings and quality of life. Based on the experience of this series, filgrastim may offer benefits of less fever, fatigue, diarrhea, local reactions, other dermatologic disorders, and edema. Whether such differences significantly affect survival, quality of life, and costs in the presence of considerable background toxicity from chemotherapy has not been determined and warrants further study.

Acknowledgments

References

1. **American Society for Clinical Oncology**. Recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. J Clin Oncol 1994;12:2471–508.
2. **Beveridge RA, Miller JA, Kales AN, et al**. Randomized trial comparing the tolerability of sargramostim (yeast-derived RhuGM-CSF) and filgrastim (bacteria-derived RhuG-CSF) in cancer patients receiving myelosuppressive chemotherapy. Support Care Cancer 1997;5:289–98.
3. **Rotella DL**. A medication use evaluation of adverse events associated with colony-stimulating factors. Hosp Pharm 1999;34:286–91.
4. **Root RK, Dale DC**. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor: comparisons and potential for use in treatment of infections in nonneutropenic patients. J Infect Dis 1999;179(suppl 2):S342–52.
5. **Kellihan MJ**. Drug formulary review process for sargramostim and filgrastim: focus on analysis of adverse drug reactions. Clin Ther 1993;15:927–37.
6. **Crawford J, Ozer H, Stoller R, et al**. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med 1991;325:164–70.
7. **Pettengell R, Gurney H, Radford JA, et al**. Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: a randomized controlled trial. Blood 1992;80:1430–6.
8. **Ross HJ, Moy LA, Kaplan R, Figlin RA**. Bullous pyoderma gangrenosum after granulocyte colony-stimulating factor treatment. Cancer 1991;36:441–3.
9. **Negrin RS, Haeuber DH, Nagler A, et al**. Treatment of myelodysplastic syndromes with recombinant human granulocyte colony-stimulating factor: a phase I/II trial. Ann Intern Med 1989;110:976–84.
10. **Glaspy JA, Baldwin GC, Robertson PA, et al**. Therapy for neutropenia in hairy cell leukemia with recombinant human granulocyte colony-stimulating factor. Ann Intern Med 1988;109:789–95.
11. **Dale DC, Bonilla MA, Davis MW, et al**. A randomized controlled phase III trial of recombinant human granulocyte colony-stimulating factor (filgrastim) for treatment of severe chronic neutropenia. Blood 1993;81:2496–502.
12. **Hudis C, Lebwohl D, Crown J, et al**. Feasibility of adjuvant dose-intensive cyclophosphamide with G-CSF after doxorubicin in women with high-risk stage II/III resectable breast cancer [abstr]. Proc Am Soc Clin Oncol 1992;11:55.
13. **Park JW, Mehrotra B, Barnett BO, Baron AD, Vernook AP**. The Sweet syndrome during therapy with granulocyte colony-stimulating factor. Ann Intern Med 1988;116:996–8.
14. **Mueller BU, Jacobsen F, Butler KM, Husson RN, Lewis LL, Pizzo PA**. Combination treatment with azidothymidine and granulocyte colony-stimulating factor in children with human immunodeficiency virus infection. J Pediatr 1992;121:797–802.
15. **Peters WP, Shogan J, Shpall EJ, Jones RB, Kim CS**. Recombinant human granulocyte-macrophage colony-stimulating factor produces fever [letter]. Lancet 1998;1(8591):950.
16. **Neidhart JA, Mangalik A, Stidley CA, et al**. Dosing regimen of granulocyte-macrophage colony-stimulating factor to support dose-intensive chemotherapy. J Clin Oncol 1992;10:1460–9.
17. **Vadhan-Raj S, Keating M, LeMaistre A, et al**. Effects of recombinant human granulocyte-macrophage colony-stimulating factor in patients with myelodysplastic syndromes. N Engl J Med 1987;317:1445–52.
18. **Ganser A, Volkers B, Gerher J, et al**. Recombinant human granulocyte-macrophage colony-stimulating factor in patients with myelodysplastic syndromes: a phase I/II trial. Blood 1989;73:31–7.
19. **Nemunaitis J, Singer J, Buckner C, et al**. Use of recombinant human granulocyte-macrophage colony-stimulating factor in graft failure after bone marrow transplantation. Blood 1990;76:245–53.
20. **Jones SE, Schottstaedt MW, Duncan LA, et al**. Randomized double-blind prospective trial to evaluate the effects of sargramostim versus placebo in a moderate-dose fluorouracil, doxorubicin, and cyclophosphamide adjuvant chemotherapy program for stage II and III breast cancer. J Clin Oncol 1996;14:2976–83.
21. **Dorr RT**. Clinical properties of yeast-derived versus *Escherichia*

coli-derived granulocyte-macrophage colony-stimulating factor. Clin Ther 1993;15:19–29.

22. **Lieschke GJ, Cebon J, Morstyn G**. Characterization of the clinical effects after the first dose of bacterially synthesized recombinant human granulocyte-macrophage colony-stimulating factor. Blood 1989;74:2634–43.

23. **World Health Organization**. International drug monitoring. The role of the hospital. WHO Tech Rep Ser 1969;425:5–24.

24. **Trillet-Lenoir V, Green J, Manegold C, et al**. Recombinant granulocyte colony-stimulating factor reduces the infectious complications of cytotoxic chemotherapy. Eur J Cancer 1993;29A:319–24.

25. **Gerhartz HH, Engelhard M, Meusers P, et al**. Randomized, double-blind, placebo-controlled phase III study of recombinant human granulocyte-macrophage colony-stimulating factor as adjunct to induction treatment of high-grade malignant non-Hodgkin's lymphomas. Blood 1993;82: 2329–39.

26. **Kaplan LD, Kahn JO, Crowe F, et al**. Clinical and virological effects of recombinant human granulocyte-macrophage colony-stimulating factor in patients receiving chemotherapy for human immunodeficiency virus-associated non-Hodgkin's lymphoma: results of a randomized trial. J Clin Oncol 1991;9:929–40.