Original Article

Comparison of Hospitalization Risk and Associated Costs Among Patients Receiving Sargramostim, Filgrastim, and Pegfilgrastim for Chemotherapy-Induced Neutropenia

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BACKGROUND: Sargramostim is a granulocyte-macrophage–colony-stimulating factor (GM-CSF). Unlike filgrastim and pegfilgrastim, which are granulocyte–colony-stimulating factors (G-CSFs), sargramostim activates a broader range of myeloid lineage-derived cells. Therefore, GM-CSF might reduce infection risk more than the G-CSFs. This study compared real-world infection-related hospitalization rates and costs in patients using G/GM-CSF for chemotherapy-induced neutropenia. **METHODS:** This retrospective matched-cohort study analyzed nationally representative health insurance claims in the United States from 2000 through 2007. The sample population included patients who received chemotherapy and G/GM-CSF. G/GM-CSF treatment episodes began with the first administration of G/GM-CSF and ended when a subsequent administration was >28 days after a prior administration. Sargramostim patients were matched 1:1 with filgrastim and pegfilgrastim patients based on gender and birth year. Outcomes included infection-related hospitalization rates and the associated costs. Hospitalization rates were analyzed using univariate and multivariate Poisson methods; covariates included myelosuppressive agents received, tumor type, anemia, and comorbidities. **RESULTS:** A total of 990 sargramostim-filgrastim and 982 sargramostim-pegfilgrastim matched pairs were analyzed. Cohorts were similar with regard to age, gender, and comorbid conditions. Several differences were observed with regard to tumor type, anemia, and chemotherapy, but no systematic trends were apparent. Sargramostim patients experienced a 56% lower risk of infection-related hospitalizations compared with filgrastim and pegfilgrastim patients. Infection-related hospitalization costs were 84% and 62% lower for sargramostim patients compared with patients treated with filgrastim and pegfilgrastim, respectively. **CONCLUSIONS:** Among patients with or at risk for chemotherapy-induced neutropenia, these data indicated that use of sargramostim was associated with a reduced risk of infection-related hospitalization and lower associated costs compared with filgrastim or pegfilgrastim. **Cancer 2009;115:4839–48. © 2009 American Cancer Society.**

KEY WORDS: neutropenia, colony-stimulating factors, infection, treatment costs.

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Chemotherapy-induced neutropenia is a principal side effect of myelosuppressive chemotherapeutic agents.[1] Chemotherapy-induced neutropenia increases the risk of serious infections and can compromise the effectiveness of chemotherapy by resulting in dose reductions or treatment delays, negatively affecting chemotherapy dose intensity. Although patients with a low risk of complications can be treated in an outpatient setting, the standard treatment of care for high-risk patients (ie, those with fever and neutropenia) is immediate hospitalization and empiric administration of broad-spectrum antibiotics.[2,3] In the United States, the incidence rate of neutropenia hospitalization (including diagnoses for neutropenia, infection, or fever) is estimated to be 34.2 cases per 1000 chemotherapy-treated patients, or approximately 60,000 cases per year.[4] The incidence rate varies according to the intensity of the chemotherapy regimen and the underlying type of cancer. For example, the neutropenia hospitalization rates are lower for breast cancer patients receiving chemotherapy than for leukemia or lymphoma patients.[4] The cost and mortality rates associated with neutropenia hospitalizations are substantial; estimates of the mean cost range from approximately $19,000 to $27,000 per hospitalization (adjusted for inflation to 2007 dollars); estimates of inpatient mortality rates range from approximately 7% to 10%.[4,5]

Myeloid growth factors have become an important part of supportive care to treat or prevent neutropenia in cancer patients undergoing intensive chemotherapy. The American Society of Clinical Oncology 2006 guidelines recommend primary prophylactic use of colony-stimulating factor when the risk of febrile neutropenia is $\geq$20% and suggest therapeutic use in patients with fever and neutropenia who are at high risk for infection-associated complications.[6] In the United States, commercially available myeloid growth factors include filgrastim and pegfilgrastim, which are granulocyte–colony-stimulating factors (G-CSFs), and sargramostim, which is a granulocyte-macrophage–colony-stimulating factor (GM-CSF). GM-CSF differs from G-CSF in that, in addition to stimulating the production of neutrophils, it also stimulates other myeloid cells including monocyte/macrophages and dendritic cells, potentially conferring broader immune-stimulatory properties. Thus, GM-CSF may offer additional protection against infections compared with the G-CSFs. In fact, GM-CSF is often used as an adjuvant in cancer vaccine studies owing to its ability to stimulate antigen-presenting cells and induce an enhanced immune response.[7-9]

Although many placebo-controlled studies have demonstrated that both G-CSF and GM-CSF are effective at reducing febrile neutropenia and infection complications in cancer patients receiving chemotherapy,[10-13] to our knowledge there are few studies published to date comparing the efficacy, safety, and infection rates of G-CSF versus GM-CSF in this setting. Two retrospective studies reported that adverse events and/or febrile neutropenia occurred more frequently with sargramostim than filgrastim.[14,15] However, 2 randomized trials and a prospective medication-use evaluation study found that sargramostim and filgrastim have similar efficacy, safety, and tolerability.[16-18] To the best of our knowledge, no head-to-head studies comparing the clinical outcomes of sargramostim versus pegfilgrastim in a chemotherapy-induced neutropenia setting have been published to date. Similarly, there is limited published information on the comparative costs associated with the use of G-CSF versus GM-CSF for chemotherapy-induced neutropenia.

We used a large health claims database to examine the hypothesis that GM-CSF and G-CSFs are associated with different rates of infection-related hospitalization and the associated costs for patient care. In this retrospective study, based on real-world clinical practice data, we found that GM-CSF administered in association with myelosuppressive chemotherapy resulted in lower rates of infection-related hospitalization and reduced costs compared with G-CSFs. These results provide a rationale for incorporating sargramostim as part of the supportive care for patients receiving chemotherapy with a significant risk of inducing febrile neutropenia.

MATERIALS AND METHODS

Data Source

Health insurance claims data from the Ingenix/IHCIS Impact National Managed Care Database (Impact) between January 2000 and December 2007 were used to conduct the analysis. This large, nationally representative database was designed to support benchmarking projects, healthcare outcomes research, and other research initiatives. To create the Impact database, Ingenix compiles claims data submitted by healthcare providers and

pharmacies to approximately 45 health plans for reimbursement. Ingenix places significant emphasis on the quality of the data and uses a series of data evaluation and reconciliation steps to ensure the completeness, validity, and consistency of the data. Ingenix also standardizes the information across contributing health plans, which is critical for creating valid benchmarks.

The Impact database includes complete medical and pharmacy claims for more than 80 million managed care lives, covering all census regions of the United States. Data elements used in the present analysis included health plan enrollment records, patient demographics, inpatient and outpatient medical services, and outpatient prescription drug dispensing records. Finally, data included in the Impact database are de-identified and are in compliance with the Health Insurance Portability and Accountability Act of 1996 to preserve patient anonymity and confidentiality.

Study Design

We conducted a retrospective matched-cohort analysis of patients treated with sargramostim, filgrastim, and pegfilgrastim for chemotherapy-induced neutropenia. Included in the study were patients who had ≥2 claims of sargramostim or filgrastim or ≥1 claim of pegfilgrastim (the date of the first G/GM-CSF administration is referred to as the index date); ≥1 cancer claim within 120 days before the index date; and ≥1 chemotherapy claim within 60 days before the index date. The 120-day period before the index date was defined as the baseline period. Patients were further required to have no claims of G/GM-CSF during the baseline period to study the incident use of G/GM-CSF and to focus the analysis on G/GM-CSF treatment episodes that were most likely to be associated with the first chemotherapy cycle, because the incident risk of febrile neutropenia is highest during that period.[2] Healthcare Common Procedure Coding System (HCPCS) codes were used to identify sargramostim (J2820), filgrastim (J1440 or J1441), and pegfilgrastim (J2505); International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes were used to identify cancer diagnoses (ICD-9-CM 140-208); and Current Procedural Terminology (CPT), HCPCS, ICD-9-CM procedural codes, and Revenue codes were used to identify chemotherapy claims.

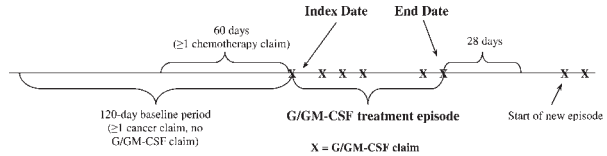

FIGURE 1. The study design scheme is shown. G/GM-CSF indicates granulocyte/granulocyte-macrophage–colony-stimulating factor.

The treatment episode began with the first G/GM-CSF service date and ended on the last claim date for sargramostim and filgrastim episodes; pegfilgrastim episodes ended on the last claim date plus a mean therapeutic duration of 19 days due to its long-acting nature. The 19-day therapeutic duration reflected the average number of days between 2 pegfilgrastim claims for those patients with multiple pegfilgrastim claims in a treatment episode. If a patient had claims that switched between G/GM-CSF types, the switch was considered as marking a separate treatment episode. A G/GM-CSF claim >28 days after a prior claim was considered to be a new treatment episode. This analysis only considered the first treatment episode (Fig. 1).

Finally, patients had to be age ≥18 years as of the index date and continuously enrolled in a health plan throughout the 120-day period preceding the index date to the episode end date. Sargramostim patients were matched 1:1 with filgrastim and pegfilgrastim patients based on gender and year of birth.

Outcome Measures

The main outcomes of the study included infection-related hospitalization rates and the associated costs per patient per month. A patient was identified as having an infection-related hospitalization if, during the treatment episode, the patient had a hospitalization with an ICD-9-CM diagnosis code for infectious and parasitic diseases (ICD-9-CM 001.x-139.x). Febrile neutropenia-related hospitalization, identified by the combined presence of neutropenia (ICD-9-CM 288.0) and fever (ICD-9-CM 780.6), was an additional outcome considered in the analysis. However, febrile neutropenia-related hospitalization was considered a secondary outcome due to the concern that neutropenia and fever are likely undercoded in reimbursement claims.[4] Infection-related and febrile neutropenia-related hospitalization rates were calculated as the

total number of infection-related hospitalizations (or febrile neutropenia-related hospitalizations) within a G/GM-CSF cohort divided by that cohort's patient-years of observation.

The costs associated with an infection-related hospitalization included both inpatient facility costs and inpatient medical costs. Inpatient facility costs are the costs of inpatient admissions to acute care and rehabilitation institutions and were included if the hospital admission date occurred during the patient's G/GM-CSF treatment episode. Inpatient medical costs are the costs associated with the medical claims that occurred from the hospital admission date to the discharge date. Ingenix reports payer-perspective cost data that have been adjusted for inflation, based in part on the US Consumer Price Index, to reflect 2007 US dollars and that have been standardized across health plans, data sources, and geographic areas to allow for comparisons across patients.

Statistical Analysis

Univariate statistics were generated to compare the sargramostim-filgrastim and the sargramostim-pegfilgrastim matched cohorts, respectively. The selected baseline patient characteristics for comparison included age, gender, Charlson comorbidity index, comorbid conditions, tumor types, history of anemia, and absolute neutrophil counts (ANC). The Charlson comorbidity index is a score of 17 comorbid diseases that are weighted for disease severity.[19] A patient with a higher index value has a higher risk of morbidity and mortality. Additional characteristics included neutropenia diagnosis at index date and treatment patterns for chemotherapy and G/GM-CSF administrations.

To quantify the frequency of infection-related (or febrile neutropenia-related) hospitalizations, the incidence rate was calculated as the number of relevant hospitalizations divided by the patient-years of observation in each cohort. This person-time approach was used to account for different lengths of observation periods among study subjects in a nonexperimental naturalistic setting.

The infection-related and febrile neutropenia-related hospitalization rates were then compared between sargramostim and filgrastim and between sargramostim and pegfilgrastim using univariate and multivariate incidence rate ratios. The univariate (crude or unadjusted) incidence rate ratio was calculated as the incidence rate in the sargramostim group divided by that in the matched filgrastim (or pegfilgrastim) group. Ninety-five percent confidence intervals (95% CI) of incidence rate ratios were computed based on the Poisson probability distribution. If a 95% CI includes the null value of 1, it indicates that there is no statistically significant difference in the infection- (or febrile neutropenia-) related hospitalization rates between sargramostim and G-CSFs at a 2-sided α error level of .05.

Multivariate Poisson regression analysis was further performed to isolate the incremental effect of GM-CSF over G-CSF on infection- (or febrile neutropenia-) related hospitalization rates by adjusting for differences between the groups. The covariates included the Charlson comorbidity index; the number of distinct chemotherapy agents received; use of myelosuppressive agents (during the period 7 days before the index date to the end date); neutropenia at the index date; metastases; localized malignancy (breast cancer, lung cancer, and non-Hodgkin lymphoma [NHL]); and indicator variables for the presence of various comorbid conditions, including heart disease, renal disease, liver disease, and history of anemia. The Poisson regression model offsets differences in observation periods across patients. Results are presented as adjusted incidence rate ratios, and their 95% CIs were calculated using robust standard errors for a matched design.

The costs associated with the primary endpoint, infection-related hospitalizations, were based on the standardized cost amounts paid by the insurers in the billing claims and were analyzed using univariate methods. A 2-part, multivariate regression model was also used to analyze costs but was found to yield unstable results because of the relatively low number of infection-related hospitalizations observed in the sample. The different lengths of patients' treatment episodes were accounted for by weighting costs by patients' episode length. All statistical analyses were performed using SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC).

RESULTS

Patient Characteristics

Sargramostim was found to be used relatively less frequently than filgrastim or pegfilgrastim in the context of

chemotherapy-induced neutropenia; the use of filgrastim and pegfilgrastim exceeded that of sargramostim roughly by factors of 10 and 20, respectively. Thus, to compare GM-CSF with G-CSFs in this clinical setting, a matched-cohort analysis was chosen. A total of 990 sargramostim patients who met all of the selection criteria were matched to 990 filgrastim patients and 982 pegfilgrastim patients based on gender and year of birth (not all sargramostim patients could be matched with pegfilgrastim patients). The baseline characteristics by G/GM-CSF matched cohort are summarized in Table 1. The sargramostim-filgrastim and sargramostim-pegfilgrastim matched cohorts were similar with respect to age, gender, and comorbid conditions. The sargramostim-filgrastim cohort also had similar tumor types and history of anemia.

Analysis of baseline ANC values was limited by the small number of patients with recorded values in the claims database. There were 15, 20, and 32 sargramostim, filgrastim, and pegfilgrastim patients, respectively, with documented ANC values during the period 14 days before or on the index date. With this limitation, ANC values were not significantly different among the matched cohorts, although pegfilgrastim patients had a higher mean ANC value, possibly because pegfilgrastim is usually given prophylactically, whereas sargramostim and filgrastim may be given for both treatment and prophylaxis.

The time between chemotherapy initiation and the first pegfilgrastim administration was, on average, 20 days; whereas it was 28 days and 30 days for the first sargramostim and filgrastim administration, respectively. Although it is not possible to identify accurately whether G/GM-CSF was administered prophylactically, the observation that pegfilgrastim is administered a shorter time after chemotherapy initiation is consistent with the notion that pegfilgrastim tends to be used prophylactically more often than sargramostim and filgrastim.

Among sargramostim patients, a smaller proportion had breast cancer and NHL, and a greater proportion had a history of anemia compared with pegfilgrastim patients. Although several statistically significant differences were observed with regard to the treatment episode characteristics, no systematic trends were apparent. Sargramostim patients more frequently had neutropenia at index date than both the filgrastim and pegfilgrastim cohorts analyzed in this study. The average number of chemotherapy agents used and the proportion of patients receiving myelosuppressive agents were both higher in the sargramostim cohorts than in the filgrastim cohort. The situation was reversed when comparing sargramostim to pegfilgrastim patients. The length of G/GM-CSF treatment was approximately 31 days in the sargramostim and filgrastim cohorts and approximately 58 days in the pegfilgrastim cohort.

Infection-Related Hospitalization Rates

When outcomes were compared, the sargramostim group had a lower risk of infection-related hospitalization compared with both filgrastim (univariate incidence rate ratio, 0.46; 95% CI, 0.22-0.97 [$P = .0422$]) and pegfilgrastim groups (univariate, 0.52; 95% CI, 0.17-1.98 [$P = .0628$]) (Table 2). After controlling for confounding factors, multivariate results remained similar with adjusted incidence rate ratios of 0.44 (95% CI, 0.20-0.97; $P = .0333$) and 0.44 (95% CI, 0.21-0.90; $P = .0256$) in the sargramostim versus filgrastim and sargramostim versus pegfilgrastim comparisons, respectively.

Febrile Neutropenia-Related Hospitalization Rates

Febrile neutropenia-related hospitalizations were uncommonly recorded in billing claims. There were <10 such events observed in each group (Table 2). Sargramostim-treated patients tended to have a lower febrile neutropenia-related hospitalization rate than filgrastim or pegfilgrastim; the univariate and multivariate incidence rate ratios were all less than 1, ranging from 0.58 to 0.85 ($P > .0500$). However, the low statistical power precludes conclusive analysis.

Infection-Related Hospitalization Costs

Infection-related hospitalization costs were on average 84% ($728) lower for sargramostim patients compared with filgrastim patients ($138/patient/month vs $866/patient/month; $P = .0380$) and 62% ($226) lower compared with pegfilgrastim patients ($139/patient/month vs $365/patient/month; $P = .0100$) (Figure 2). On an annualized basis, sargramostim is associated with cost reductions of $8736/patient/year ($728 $\times$ 12) compared with filgrastim and $2712/patient/year ($226 $\times$ 12) compared with

Table 1. Baseline Characteristics for the Chemotherapy-Induced Neutropenia Population

	Sargramostim (n=990)		Filgrastim (n=990)		*P*	Sargramostim (n=982)		Pegfilgrastim (n=982)		*P*
Patient characteristics										
Mean age (±SD), y	57.7	(±11.7)	57.6	(±11.6)		57.5	(±11.6)	58.6	(±11.5)	
Male, no.	415	(41.9%)	415	(41.9%)		411	(41.9%)	411	(41.9%)	
Mean Charlson comorbidity index (±SD)	5.91	(±3.29)	5.91	(±3.18)	.9778	5.93	(±3.28)	5.62	(±3.26)	.0356
Comorbid conditions, no.										
Heart disease	201	(20.3%)	182	(18.4%)	.2799	197	(20.1%)	190	(19.3%)	.6915
Renal disease	52	(5.3%)	39	(3.9%)	.1631	51	(5.2%)	33	(3.4%)	.0447
Liver disease	89	(9.0%)	95	(9.6%)	.6425	89	(9.1%)	97	(9.9%)	.5378
Tumor type, no.										
Metastases*	529	(53.4%)	535	(54.0%)	.7870	528	(53.8%)	489	(49.8%)	.0783
Localized malignancy										
Breast	288	(29.1%)	293	(29.6%)	.8052	288	(29.3%)	345	(35.1%)	.0059
Lung	233	(23.5%)	222	(22.4%)	.5570	232	(23.6%)	235	(23.9%)	.8737
NHL	160	(16.2%)	156	(15.8%)	.8062	155	(15.8%)	208	(21.2%)	.0021
History of anemia, no.	388	(39.2%)	408	(41.2%)	.3595	383	(39.0%)	324	(33.0%)	.0055
Mean baseline absolute neutrophil count (±SD)†	2185	(±1848)	2155	(±2508)	.9684	2185	(±1848)	3596	(±2699)	.0743
No. of patients	15	(1.5%)	20	(2.0%)		15	(1.5%)	32	(3.3%)	
Treatment episode characteristics										
Neutropenia diagnosis on index date, no.	644	(65.1%)	568	(57.4%)	.0005	641	(65.3%)	443	(45.1%)	<.0001
Mean no. of distinct chemotherapy drugs received (±SD)‡	2.3	(±1.1)	2.2	(±1.1)	.0092	2.3	(±1.1)	2.6	(±1.1)	<.0001
Use of myelosuppressive agents, no.§	533	(53.8%)	479	(48.4%)	.0152	527	(53.7%)	754	(76.8%)	<.0001
Distinct d on G/GM-CSF, mean (±SD)	11.2	(±15.5)	9.0	(±11.7)	.0003	11.2	(±15.5)	3.1	(±2.4)	<.0001
Days between initiation of chemotherapy and first use of G/GM-CSF, mean (±SD)	27.9	(±19.6)	29.5	(±19.4)	.0742	27.9	(±19.6)	19.9	(±20.9)	<.0001
Length of treatment episode, d, mean (±SD)	30.6	(±41.8)	31.0	(±41.0)	.8217	30.6	(±41.9)	58.4	(±42.0)	<.0001

SD indicates standard deviation; NHL, non-Hodgkin lymphoma; G/GM-CSF, granulocyte/granulocyte-macrophage–colony-stimulating factor.

*Metastases were identified based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for secondary malignancies (ICD-9-CM 196-199).

† Based on absolute neutrophil count test results occurring during the period 14 days before or on the index date.

‡ Based on the drug(s) being administered during the 60-day period preceding the index date to the end of the treatment episode (ie, end date).

§ Based on the myelosuppressive drug(s) being administered during the period 7 days before the index date to the end date.

Table 2. Hospitalizations, Incidence Rate, and Incidence Rate Ratio in the Chemotherapy-Induced Neutropenia Population: Adjusted and Unadjusted Results

Comparison Group	Outcome Event	Sargramostim		Comparison Group		Univariate		Multivariate	
		No. of Events*	Incidence Rate of Event (95% CI)	No. of Events*	Incidence Rate of Event (95% CI)	Incidence Rate Ratio (95% CI)	*P*	Adjusted Incidence Rate Ratio (95% CI)	*P*
Sargramostim vs filgrastim	Infection-related hospitalizations	10	0.12 (0.05-0.20)	22	0.26 (0.15-0.37)	0.46 (0.22-0.97)	.0422	0.44 (0.20-0.94)	.0333
	Febrile neutropenia-related hospitalizations†	4	0.05 (0.01-0.12)	7	0.08 (0.03-0.17)	0.58 (0.17-1.98)	.3837	0.61 (0.17-2.15)	.4448
Sargramostim vs pegfilgrastim	Infection-related hospitalizations	10	0.12 (0.05-0.20)	37	0.24 (0.16-0.31)	0.52 (0.26-1.04)	.0628	0.44 (0.21-0.90)	.0256
	Febrile neutropenia-related hospitalizations†	4	0.05 (0.01-0.12)	9	0.06 (0.03-0.11)	0.85 (0.26-2.75)	.7827	0.74 (0.22-2.50)	.6235

95% CI indicates 95% confidence interval.
* All events were considered.
† Febrile neutropenia was defined as at least 1 claim for neutropenia (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code: 288.0) and 1 claim for fever (ICD-9-CM code: 780.6) during the same hospitalization.

pegfilgrastim. These results indicate a statistically significant difference between the costs associated with the use of sargramostim compared with G-CSFs.

DISCUSSION

Chemotherapy-induced neutropenia and infection-related complications are major causes of morbidity for cancer patients undergoing myelosuppressive chemotherapy. Decreases in planned chemotherapy dose-intensity have been associated with inferior outcomes.[20,21] Febrile neutropenia occurs with common chemotherapy regimens in 25% to 40% of treatment-naive patients and incurs hospital stays, reduces patient quality of life, and increases medical costs.[22] The use of filgrastim and pegfilgrastim to treat and prevent chemotherapy-induced neutropenia is an established part of oncology supportive care as at least 11 randomized controlled trials have demonstrated the benefits of filgrastim and pegfilgrastim.[3,6,23,24] The use of GM-CSF to treat chemotherapy-induced neutropenia is somewhat less well-established, due to fewer placebo-controlled randomized trials.[10,12] Nonetheless, GM-CSF has been shown to have efficacy in accelerating neutrophil recovery in patients receiving induction chemotherapy for AML and in patients after autologous and allogeneic bone marrow transplantation.[25-27] This study indicates that practitioners, in light of overlapping biologic actions on neutrophil recovery, use all of the myeloid growth factors for similar indications.

Thus, the results of the current study provide new, real-world information regarding the comparative outcomes of the GM-CSF sargramostim versus the G-CSFs filgrastim and pegfilgrastim. Our primary aim was to compare the efficacy of sargramostim versus filgrastim and pegfilgrastim to reduce neutropenic complications, specifically infection-related hospitalizations, and the attendant effects on cost. These outcomes are key factors for oncologists and hematologists to consider in providing optimal supportive care in a cost-constrained healthcare environment.

We found that, although patients treated with sargramostim tended to have neutropenia diagnoses more often at treatment initiation, they experienced a 56% lower risk of infection-related hospitalization than patients treated with filgrastim or pegfilgrastim (adjusted $P < .05$ for both). Infection-related hospitalization costs exhibited

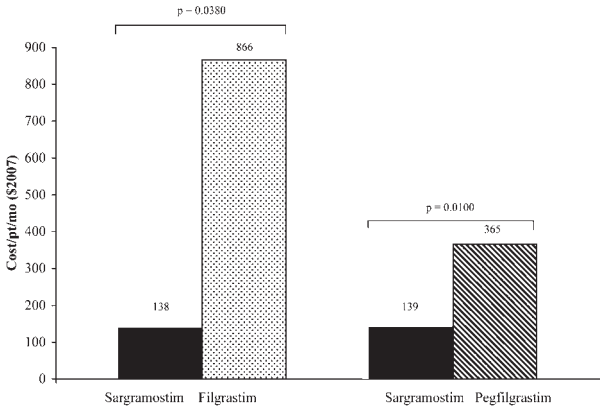

FIGURE 2. Monthly costs of infection-related hospitalization per patient per month (cost/pt/mo) are shown in the chemotherapy-induced neutropenia population. *P* values tested the null hypothesis that monthly costs of infection-related hospitalization per patient per month were equal between the 2 cohorts.

a similar trend, with sargramostim associated with 84% and 62% lower inpatient costs compared with filgrastim and pegfilgrastim, respectively.

The small number of reported cases of febrile neutropenia limited the ability to provide precise comparisons of myeloid growth factors in this respect. Whereas sargramostim patients appeared to experience fewer febrile neutropenia-related hospitalizations compared with filgrastim and pegfilgrastim, these results were not statistically significant. It is likely that cases of febrile neutropenia are generally underreported, because reimbursement rules tend to result in nonuniform coding practices regarding whether febrile neutropenia is coded as neutropenia, fever, both, or even infection.

A meta-analysis of randomized controlled trials using G-CSF in the setting of chemotherapy-induced neutropenia demonstrated a decreased mortality for the treated patients, and no similar study is available for sargramostim.[23] Indeed, few randomized controlled trials examining sargramostim exist, and only a limited number of comparative studies on filgrastim and sargramostim are available. To our knowledge, this is the first study to directly compare clinical and economic outcomes of sargramostim and pegfilgrastim in the context of chemotherapy-induced neutropenia in real-world clinical settings. Previously published studies examining sargramostim and filgrastim in chemotherapy-induced neutropenia generally found that sargramostim and filgrastim had similar clinical efficacy in terms of hospital length of stay, neutropenic fever, or intravenous antibiotic requirement.[16-18] Our study results are concordant with this literature in that febrile neutropenia-related hospitalization rates are similarly low between GM- and G-CSFs. However, we detected a significantly lower rate of infection-related hospitalization for sargramostim compared with filgrastim or pegfilgrastim. This observation may reflect the broader immune stimulating effects of GM-CSF, which may promote the immune system to combat infections.

To our knowledge, there is limited research regarding the comparative costs associated with the use of G/GM-CSF for chemotherapy-induced neutropenia. Bennett et al reported a randomized trial that compared resource utilization and costs associated with filgrastim and sargramostim in a chemotherapy-induced neutropenia setting and found that sargramostim patients had lower resource use leading to a 17% cost savings compared with filgrastim patients.[28] Whalen et al found that a formulary switch from filgrastim to sargramostim at a single US institution resulted in a 21% cost savings for the institution.[29] In contrast, our study used a large claims database that included actual cost data and reflected general clinical practice. Furthermore, although the 2 previous studies[28,29] considered a broader set of healthcare costs than our study, they are consistent with our findings demonstrating lower costs associated with sargramostim compared with the G-CSFs in the context of chemotherapy-induced neutropenia.

Because the observational design was susceptible to various biases, we attempted to control for these potential biases by carefully specifying the study design and selection criteria to ensure that the matched sargramostim-filgrastim and sargramostim-pegfilgrastim cohorts were similar and conducted multivariate analysis to control for potential confounding factors. However, such methodological measures only control for intercohort biases and do not account for potential selection biases that might arise from the population selection. Another potential limitation is the use of claims data. Claims data are subject to coding errors and different coding practices, frequently do not include needed clinical factors (eg, Eastern Cooperative Oncology Group performance status, cancer stage, neutrophil counts), and identify only services rendered

rather than services needed. This limitation likely impacted the ability to properly identify febrile neutropenia-related hospitalizations, as evidenced by relatively low frequencies observed in the data. However, because the underascertainment of neutropenia-related hospitalizations is unlikely to be related to the type of G/GM-CSF used, the comparisons made between these therapies should be valid. Also, because claims data are based on ICD-9-CM and CPT coding schemes, factors that may distribute differentially among sargramostim, filgrastim, and pegfilgrastim patients but that are either unavailable in the codes or unobservable were not adjusted for in our analysis. Moreover, because claims data do not provide information on institutions' practices, any observed differences between G/GM-CSF could not be controlled for potential heterogeneous practices across institutions. Nonetheless, an advantage of using claims data is that it permits identification of enough events, even those that are highly selected, to have sufficient statistical power for meaningful analysis. In addition, the data, derived from patients treated from a broad range of clinical environments, including both academic and community practices, reflect real-world patient management and emphasize therapies that are actually administered in a way that intention to treat analyses do not capture.

Conclusions

We believe the current study is the first to compare infection-related hospitalizations and costs of chemotherapy-induced neutropenia patients treated with sargramostim, filgrastim, and pegfilgrastim in a real-world setting. Chemotherapy-induced neutropenia patients treated with sargramostim experienced significantly lower risks of infection-related hospitalizations, which translated into lower associated costs compared with patients treated with filgrastim and pegfilgrastim. These results suggest that GM-CSF may have clinical and economic advantages over G-CSFs with respect to infection-specific endpoints.

Conflict of Interest Disclosures

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