Observational Study of the Prevalence of Febrile Neutropenia in Patients Who Received Filgrastim or Pegfilgrastim Associated With 3-4 Week Chemotherapy Regimens in Community Oncology Practices

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ABSTRACT

BACKGROUND: Colony-stimulating factors (CSFs) significantly decrease the risk of febrile neutropenia (FN), a common complication of myelosuppressive chemotherapy. Pegfilgrastim (6 mg), introduced in 2002, has a sustained duration of action, with a single dose comparable in efficacy to daily injections of filgrastim (5 µg per kg per day) for 10 to 11 days; both agents should be initiated 24 hours after completing chemotherapy.

OBJECTIVES: To (1) describe the use of pegfilgrastim and filgrastim in oncology practices throughout the United States and (2) compare their effectiveness in actual practice as measured by the outcome of febrile neutropenia in patients who received chemotherapy regimens administered every 3 to 4 weeks for breast, lung, ovarian, colon cancer, or lymphoma and who received a CSF prior to developing FN.

METHODS: Data were retrospectively obtained from the medical records of a cohort of adult patients aged 18 years or older treated in 99 community oncology practices in the United States in 2001 and 2003. Eligible patients were treated with chemotherapy every 3 to 4 weeks for breast, lung, ovarian, colon cancer, or lymphoma and were users of filgrastim in 2001 (prior to the U.S. Food and Drug Administration approval of pegfilgrastim in January 2002) or users of either filgrastim or pegfilgrastim or both CSF agents in 2003.

RESULTS: Pegfilgrastim was initiated, on average, 2.4 days (SD ±3.2) after chemotherapy in the first cycle of use and 1.9 (±3.0) days in subsequent cycles of use. In contrast, filgrastim was started on average 7.7 (±6.5) days and 4.9 (±4.6) days after chemotherapy in the first and subsequent cycles of use in 2001, increasing to 9.6 (±6.2) and 6.4 (±6.4) days in 2003. In the first cycle of CSF use, filgrastim was administered for an average of 5.2 (±3.5) days to 583 patients in 2001 and 3.7 (±2.8) days to 868 patients in 2003 (P <0.001). Among patients who received more than 1 cycle of filgrastim (n = 457 in 2001 and n = 489 in 2003; 78.4% and 56.3% of filgrastim users, respectively), the mean days of filgrastim administered in subsequent cycles was 6.0 (±3.5) in 2001 and 4.6 (±3.2) in 2003. Pegfilgrastim was administered as a single dose per chemotherapy course to 1,412 patients in 2003. Patients who received pegfilgrastim were more likely to have at least 1 myelosuppressive drug (74.8%) in the regimen compared with patients who received filgrastim in 2003 (70.0%, P = 0.013), but a greater proportion of filgrastim patients in 2003 (19.4%) had advanced-stage disease compared with pegfilgrastim patients (14.8%, P = 0.005). More patients who received filgrastim in 2003 (36.2%) had a cancer other than breast cancer or non-Hodgkin's lymphoma compared with those who received pegfilgrastim (29.5%, P = 0.001). A total of 94 of 1,451 patients (6.5%) who received filgrastim experienced FN compared with 67 of 1,412 patients (4.7%) for pegfilgrastim. The odds ratio of developing FN among patients who received filgrastim versus pegfilgrastim was 1.41 (95% confidence interval, 1.02-1.96; P = 0.040) after adjusting for patient and chemotherapy regimen characteristics.

CONCLUSION: In this retrospective study of patients treated in 99 community oncology practices, patients who received filgrastim often initiated treatment later than recommended and received fewer days per cycle than demonstrated to be effective in randomized controlled trials. Pegfilgrastim was generally initiated earlier within the course of chemotherapy compared with filgrastim, and because of its sustained duration of action, only a single injection was required. In these patients treated with a heterogeneous group of chemotherapy regimens with a broad range of risk of FN, overall, an absolute 1.8% increase in the incidence of developing FN was observed in patients who received filgrastim compared with patients who received pegfilgrastim, (absolute rates of 6.5% and 4.7%, respectively).

KEYWORDS: Adult medical oncology, Outcomes research, Growth factors, Supportive care, Febrile neutropenia, Community practice, Patient management

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What is already known about this subject

- Chemotherapy-induced neutropenia is a common side effect of cancer treatment, which leaves patients vulnerable to life-threatening infections. The risk of febrile neutropenia (FN) can vary depending on chemotherapy drug regimens and patient characteristics such as advanced age or comorbid conditions (i.e., poor renal function, diabetes).
- Randomized controlled trials have shown colony-stimulating factors (CSFs) filgrastim and pegfilgrastim significantly decrease the risk of FN by half (risk reduction [RR], 0.54 in randomized controlled trials). The absolute RR reported in the clinical trials ranged from 8% to 37%, the variation reflecting differences in the base-line risk of FN associated with the chemotherapy regimen.
- Head-to-head randomized controlled trials of pegfilgrastim versus filgrastim demonstrate that both drugs have similar efficacy; however, little is known about their relative effectiveness in clinical practice.

What this study adds

- For the first time, data are available regarding the real-world incidence of FN in chemotherapy patients treated in the community setting with filgrastim or pegfilgrastim or both CSF agents.
- In community oncology practices, patients who received filgrastim initiated treatment later and received fewer days per cycle than the timing of initiation and duration of therapy demonstrated to be effective in randomized controlled trials. In contrast, pegfilgrastim was commonly initiated within 3 days of chemotherapy.
- Among patients treated with a heterogeneous group of chemotherapy regimens with a broad range of risk of FN in community oncology practices, overall, a 1.8% overall increase in the incidence of developing FN was observed in patients who received filgrastim compared with patients who received pegfilgrastim (absolute rates of 6.5% and 4.7%, respectively) resulting in a 40% increase in the odds of FN. For every 56 patients treated in community settings with pegfilgrastim instead of filgrastim, 1 additional case of FN would be avoided.

A number of initiatives are under way to begin to measure and improve the quality of cancer care, including the American Society of Clinical Oncology's (ASCO's) Quality Oncology Practice Initiative,[1] the National Initiative for Cancer Care Quality (NICCQ),[2] and the Oncology Demonstration Project sponsored by the Centers for Medicare and Medicaid Services.[3] In addition to improving the quality of care associated with the diagnosis, staging, and cancer-related therapy, an equally important priority is to ensure that patients receive appropriate supportive care to manage both disease symptoms and treatment-related toxicity.[4-6]

Neutropenia, a marked decline in infection-fighting white blood cells, is a frequent, often serious, and sometimes fatal complication of myelosuppressive chemotherapy, which may result in chemotherapy dose reductions or delays.[7,8] In some malignancies, this may result in a poorer response to treatment and decreased survival.[7,9-13] In the United States, an estimated 60,000 patients a year are hospitalized for febrile neutropenia (FN) and neutropenia-related infections. The estimated average cost of an FN hospitalization in the United States is $13,400.[14]

By promoting hematopoietic recovery after chemotherapy, colony-stimulating factors (CSFs) reduce the incidence, duration, and severity of chemotherapy-induced neutropenia, and associated complications.[15-19] Pegfilgrastim (Neulasta) was approved by the U.S. Food and Drug Administration (FDA) in January 2002 to decrease the incidence of infection, as manifested by FN in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of FN.[20] The recommended dosage of pegfilgrastim is a single subcutaneous (SC) injection of 6 mg administered once per chemotherapy cycle. Pegfilgrastim should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy because of the potential for an increase in sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy.

Filgrastim (Neupogen) was approved by the FDA 11 years earlier, in February 1991, to decrease the incidence of infection, as manifested by FN, in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy. Filgrastim was subsequently approved by the FDA for a broader range of indications that include patients with acute myeloid leukemia receiving induction or consolidation chemotherapy, cancer patients receiving bone marrow transplant, patients undergoing peripheral blood progenitor cell collection and therapy, and patients with severe chronic neutropenia.[21] The FDA-approved label states that filgrastim should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy and continued daily for up to 2 weeks, until the absolute neutrophil count (ANC) has reached 10,000/mm^3. The duration of filgrastim therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. In the registrational clinical trials that were the basis for FDA approval for filgrastim, a median of 11 days of injections was required to achieve neutrophil recovery, defined as postnadir ANC count exceeding 10.0 x 10^9/L.[15,17,22] In randomized controlled trials, a single dose of pegfilgrastim had efficacy comparable to 10 to 11 days of filgrastim in reducing the incidence of grade IV neutropenia, defined as ANC <0.5 x 10^9/L.[16,19]

A recent population-based study in older breast cancer patients reported substantial regional variation in filgrastim use.[23] Likewise, prior studies have found substantial variation in physicians' self-reported use of CSFs for prophylaxis of FN.[24] Additionally, prescribing patterns (i.e., the timing of initiation and duration of use) for filgrastim have been shown to vary from that used in the clinical trials in several community practice studies.[25-27] It is not known if these studies are representative of U.S. prescribing patterns for filgrastim generally or if prescribing patterns changed following the commercial approval of pegfilgrastim in January 2002. Therefore, we conducted this retrospective cohort study to evaluate prescribing patterns of CSFs of filgrastim and pegfilgrastim and to assess neutropenia-related outcomes in 99 oncology practices located throughout the United States. We hypothesized that, given the need for multiple daily injections, prescribing patterns for filgrastim would vary significantly from the 10 to 14 days per cycle used in the clinical trials and, therefore, the use of pegfilgrastim with its once per chemotherapy cycle administration would result in improved patient outcomes in community practice.

Methods

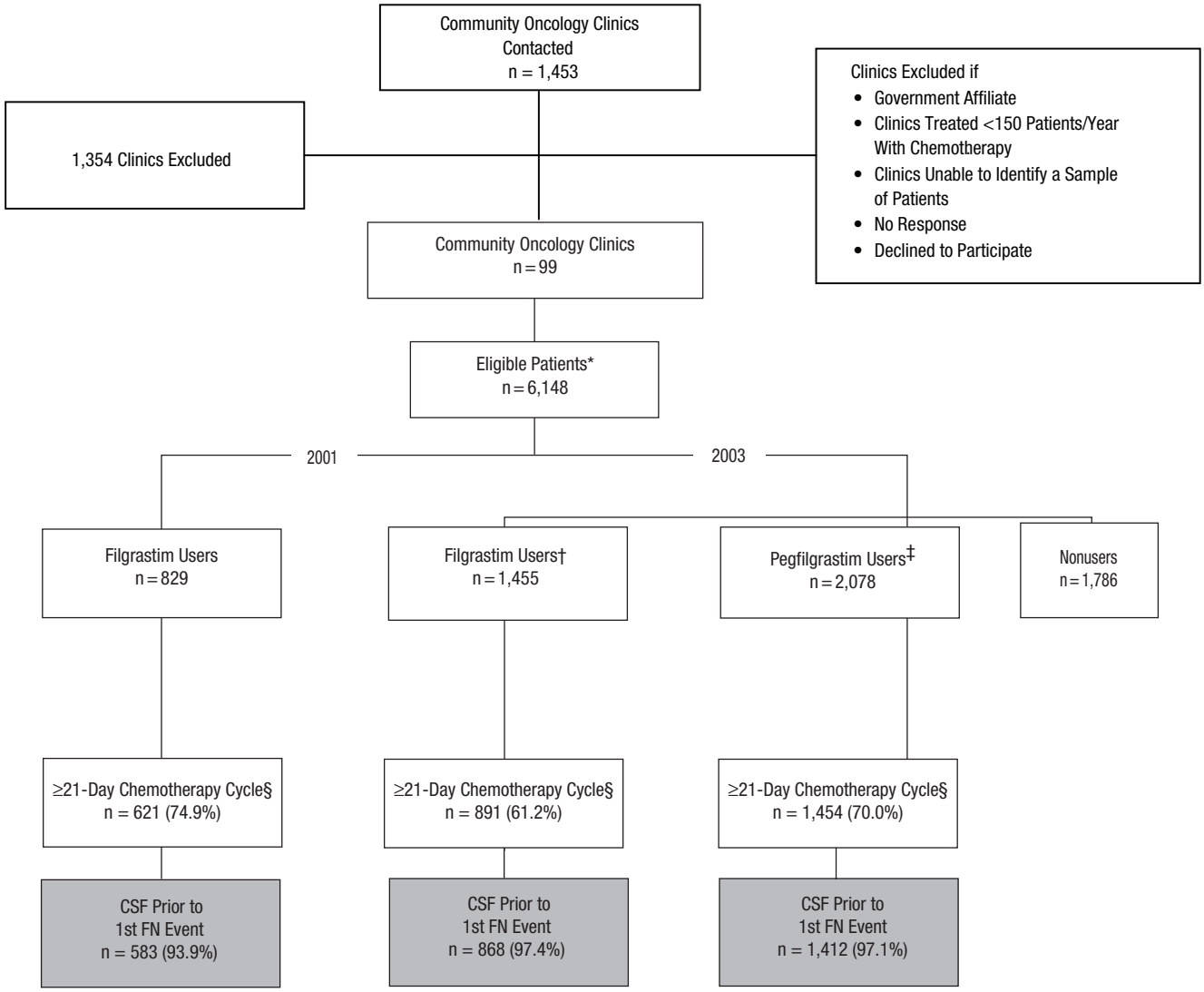
Study Sample

A 2-stage sampling procedure was used to identify a retrospective cohort of adult patients (≥18 years) with breast, lung, ovarian, or colon cancer or lymphoma (Hodgkin's and non-Hodgkin's) who initiated treatment with chemotherapy and were new users[28] of filgrastim in 2001 (prior to the FDA approval of pegfilgrastim in January 2002) or filgrastim or pegfilgrastim in 2003 (Figure 1).

Oncology practices were selected using stratified random sampling from a commercial database owned by IMS Health that contains information on prescription drug distribution by drug category within the United States.[29] A probability sample was identified from 8 of 10 strata defined by volume of chemotherapy purchases in 2003. Practices were considered ineligible if they were a government affiliate, treated <150 patients/year with chemotherapy, or were unable to identify a sample of patients. Practices that declined, did not respond, or were determined to be ineligible were replaced with another randomly selected practice (n = 1,353) until the desired sample size (n = 100) was obtained. One practice subsequently decided not to participate, resulting in a final sample of 99 practices.

The 99 practices that agreed to participate identified a consecutive sample of eligible patients using 1 of the following data sources: pharmacy records, billing records, appointment

FIGURE 1 Study Sample



** Eligible patients were treated with chemotherapy for breast, lung, ovarian, or colon cancer or lymphoma and were new users of filgrastim in 2001 (prior to the FDA approval of pegfilgrastim in January 2002) or filgrastim or pegfilgrastim in 2003. Patients could not be enrolled in a clinical trial that included a CSF (including sargramostim). A maximim of 12 patients/site were allowed in 2001 and 100 patients/site in 2003.*

† Of these 1,455 patients, 1,031 (71%) received only filgrastim, while 424 (29%) of patients in the filgrastim group received at least 1 subsequent cycle of pegfilgrastim (a total of 580 patients received both filgrastim and pegfilgrastim). The intent-to-treat analysis assigned patients to the first CSF the patients received; therefore, the 424 patients receiving both were assigned to the filgrastim group.

‡ Of these patients in the pegfilgrastim group, 1,922 (92%) received only pegfilgrastim, while 156 (8%) received at least 1 subsequent cycle of filgrastim (a total of 580 patients received both pegfilgrastim and filgrastim). The intent-to-treat analysis assigned patients to the first CSF the patients received; therefore, the 156 patients receiving both were assigned to the pegfilgrastim group.

§ To understand the effect of pegfilgrastim and filgrastim on the development of FN, analyses were limited to patients who received chemotherapy regimens that were administered every 3 to 4 weeks and who received a CSF prior to developing FN. Patients who were receiving daily or weekly chemotherapy were excluded, since they would generally not be at risk for FN, as well as patients receiving biweekly chemotherapy, as this requires CSF support.

CSF = colony stimulating factor; FDA = U.S. Food and Drug Administration; FN = febrile neutropenia.

books, or chemotherapy administration records. Patients were ineligible if they were enrolled in a clinical trial that included a CSF or if they were receiving sargramostim. For patients treated in 2001, the first 3 consecutive patients meeting the study eligibility criteria who received filgrastim at each practice in each calendar quarter were included in the study, for a total of up to 12 patients per practice (n = 829). For patients treated in 2003, each practice identified the first 25 consecutive patients treated with chemotherapy beginning with the first day of each calendar quarter, for a total of up to 100 patients per practice. Among these patients, those who received filgrastim or pegfilgrastim and every third patient not treated with a CSF were then selected for the study (n = 5,319). Of these, 1,031 received only filgrastim, 1,922 received only pegfilgrastim, 580 received both filgrastim and pegfilgrastim, and 1,786 never received a CSF.

Data Collection Procedures

Trained research staff abstracted patients' medical records from May to September 2004 for data on patient characteristics, tumor characteristics, details of chemotherapy and CSF use, laboratory data, episodes of FN, and hospitalizations for up to 8 cycles of chemotherapy. Presence of comorbid conditions was captured using a modified Charlson index that included the following: peripheral vascular disease, myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, renal disease, human immunodeficiency virus, diabetes mellitus, liver disease, connective tissue disease, dementia, and peptic ulcer disease.[30] All data collection procedures complied with the Health Insurance Portability and Accountability Act (HIPAA) regulations,[31] and the study protocol was determined to be exempt from review by the Western Institutional Review Board.

Statistical Analyses

Patients' chemotherapy treatment was characterized according to the number of chemotherapy drugs in the regimen, the planned cycle length, and whether the regimen included at least 1 of the following drugs associated with myelosuppression: cladribine, cytarabine, cyclophosphamide, docetaxel, fludarabine, ifosfamide, irinotecan, mechlorethamine, methotrexate, or topotecan. To describe the variation in use of CSFs, it was determined whether therapy was initiated before or after FN, the cycle initiated (i.e., the first cycle of chemotherapy in which a CSF was administered), the day initiated in the cycle of initiation (i.e., the first day during the cycle of chemotherapy in which a CSF was administered) and the mean day initiated in all subsequent cycles of use (i.e., the average of the first day of administration in subsequent cycles) (See Table 1 for definitions of key terms). Additionally, for filgrastim, the number of days of use was also determined (by definition, pegfilgrastim patients received only a single dose per course of chemotherapy).

TABLE 1 Definition of Key Terms

Term	Definition
Advanced disease stage	Cancer documented to have spread beyond the original tumor and lymph nodes, i.e., metastases present
ANC	Absolute neutrophil count; neutrophils are the blood cells responsible in fighting infection
ASCO guidelines for CSF therapy*	Primary prophylaxis with G-CSFs is recommended for decreasing the risk of FN in patients who have a high risk of FN based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen (risk of FN is approximately 20% or higher).
Cycle of CSF initiation	The first cycle of chemotherapy in which a CSF was administered
Day of initiation	The first day during the cycle of chemotherapy in which a CSF was administered
Subsequent cycles	Cycles of chemotherapy following the cycle of CSF initiation
Mean days of administration in subsequent cycles	The average number of days a CSF was administered in subsequent cycles.
Febrile neutropenia (FN)	Fever in the presence of neutropenia, where fever is defined as a single oral temperature of ≥38.3°C (101° F), or ≥38.0° C (100.4° F) for ≥1 hour†
Grade I neutropenia	Absolute neutrophil count ≥1.5 to <2.0 ($\times 10^9$/L)‡
Grade II neutropenia	Absolute neutrophil count ≥1.0 to <1.5 ($\times 10^9$/L)‡
Grade III neutropenia	Absolute neutrophil count ≥0.5 to <1.0 ($\times 10^9$/L)‡
Grade IV neutropenia	Absolute neutrophil count <0.5 ($\times 10^9$/L)‡
Myelosuppressive chemotherapy drugs	Examples include cladribine, cytarabine, cyclophosphamide, docetaxel, fludarabine, ifosfamide, irinotecan, mechlorethamine, methotrexate, or topotecan.
NCCN guidelines for CSF therapy§	Myeloid growth factors are recommended in first and in subsequent chemotherapy cycles for patients receiving chemotherapy regimens with a risk of FN >20%.
Neutrophil recovery	Post-nadir absolute neutrophil count exceeds 10.0 x 10^9/L.
Nonmyeloid malignancies	All cancers exclusive of those that arise from myeloid cells (e.g., leukemia); examples include breast cancer, lung cancer, and lymphoma

* *Smith TC, Khatcheressian J, Lyman GH, et al. Recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline; 2006 update. J Clin Oncol. 2006;24(19):3187-3205.*[33]

† *National Comprehensive Cancer Network. NCCN Clinical practice guidelines in oncology. Fever and neutropenia. 2005. Version 1.2005.* [32]

‡ *National Cancer Institute. Common toxicity criteria, version 2.0. Available at: http://ctep.cancer.gov/forms/CTCv20_4-30-992.pdf. Accessed January 26, 2007.*

§ *National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Myeloid growth factors. Version 1.2007.* ***Available at:*** *http://www.nccn.org/professionals/physician_gls/PDF/myeloid_growth.pdf. Accessed January 26, 2007.*[39]

ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; CSF = colony-stimulating factor; G-CSF = granulocyte-colony-stimulating factor;

Patients were considered to have experienced FN if there was documentation on any of the following in their medical records in any cycles of chemotherapy reviewed (initial and subsequent data): (1) FN, (2) temperature of ≥38.3°C with documentation of neutropenia or an absolute neutrophil count (ANC) <1.0 x 10^9L on the same day, or (3) hospitalization for FN.[32]

Since we wanted to understand the effect of pegfilgrastim and filgrastim on the development of FN, analyses were limited to patients who received chemotherapy regimens that were administered every 3 to 4 weeks and received a CSF prior to developing FN. Patients who were receiving daily or weekly chemotherapy were excluded since they would generally not be at risk for FN, as were patients receiving biweekly chemotherapy, since this requires CSF support.[33] In addition, since we were interested in comparing the effectiveness of filgrastim with pegfilgrastim when used to prevent FN, we excluded patients who had their first episode of FN prior to receiving any CSF.

We identified 580 patients who received both filgrastim and pegfilgrastim in 2003. These were patients who were started on 1 CSF type and then switched to the other. Among patients who received both CSFs in 2003, approximately 73% patients (n = 424) received filgrastim first, then were switched to pegfilgrastim. Similarly, among both users, approximately 27% (n = 156) received pegfilgrastim first, then were switched to filgrastim. For patients who received both filgrastim and pegfilgrastim, we used an intent-to-treat analysis[34] in which patients were assigned to whichever CSF treatment group they received first. Thus, our analytic sample included 583 patients treated with filgrastim in 2001, 868 patients treated with filgrastim in 2003, and 1,412 patients treated with pegfilgrastim in 2003.

Multivariable logistic regression was used to estimate the odds of developing FN in patients who received filgrastim as compared with pegfilgrastim, adjusting for their patient and chemotherapy characteristics. Interaction effects were also tested for among variables that might have a synergistic effect on the risk of developing FN (e.g., age and comorbidity). As the coefficients remained stable and the main results did not differ, only the results of our final model are reported.

Because factors that affect a patient's underlying risk of FN (e.g., chemotherapy or patient characteristics such as age or comorbid conditions) may have influenced the physician's decision to use filgrastim versus pegfilgrastim, we performed a sensitivity analysis using a propensity score approach. We used the inverse probability of treatment-weighted estimator method[35] to examine the effect of receiving filgrastim or pegfilgrastim on the risk of FN for the cohort of patients treated in 2003 (in 2001, all patients were treated with filgrastim). The propensity score was estimated using a logistic regression model of the probability of receiving pegfilgrastim versus filgrastim that included all of the patient and treatment characteristics.

Because of the potential misclassification of subjects who received both filgrastim and pegfilgrastim using an intent-to-treat approach, logistic regression was also performed after excluding patients who received both CSFs. Additionally, in order to evaluate for the effects of clustering within practices, the regression analysis was repeated using the robust variance estimation method described by Liang and Zeger that uses a generalized estimating equation (GEE) approach to account for possible correlation among data, e.g., within the same practice, in order to improve the efficiency of the estimation, e.g., of treatment effect.[36] By assuming only a functional form of marginal distribution, this method avoids the need for specifying multivariate distributions of the correlated data. GEEs have also been shown to provide consistent and asymptotically normal estimates even when correlation/covariance structures are misspecified.

Analyses were conducted using SAS version V8.2 (Cary, NC). The χ^2 test was used to test for significant differences in categorical variables and the F test for continuous variables for descriptive comparisons. All statistical tests were 2-sided.

Results

Patient Characteristics and Patterns of Care

Patient characteristics and the chemotherapy and CSF regimens are summarized in Table 2. More patients who received filgrastim in 2003 (36.2%) had a cancer other than breast cancer or non-Hodgkin's lymphoma compared with those who received pegfilgrastim (29.5%, $P = 0.001$). In addition, patients who received filgrastim in 2003 (19.4%) were more likely to have advanced cancer compared with 14.8% for pegfilgrastim in 2003 ($P = 0.005$). No differences in the mean number of chemotherapy cycles planned or mean number of drugs in the regimen were observed over time or with choice of CSF. However, patients who received pegfilgrastim were more likely to have at least 1 myelosuppressive drug in their chemotherapy regimen (74.8%) compared with patients who received filgrastim in 2003 (70.0%, $P = 0.013$).

Patients who received pegfilgrastim generally initiated treatment earlier within the course of chemotherapy compared with those receiving filgrastim (Table 2). In the first cycle in which a CSF was used, 38% of patients treated with filgrastim in 2001 received it within 3 days of chemotherapy administration, 24% within 4 to 9 days, and 38% on day 10 or later (Figure 2). In contrast, in 2003, the proportion of patients treated with filgrastim who started it on day 10 or later in the first cycle of usage increased to 52%. In subsequent cycles, the proportion of patients who initiated filgrastim within 3 days of chemotherapy administration was 39% in 2001, declining to 21% in 2003. In contrast, 86% of patients treated with pegfilgrastim received treatment within 3 days of chemotherapy in the first cycle of use, and 78% received pegfilgrastim within 3 days in subsequent cycles.

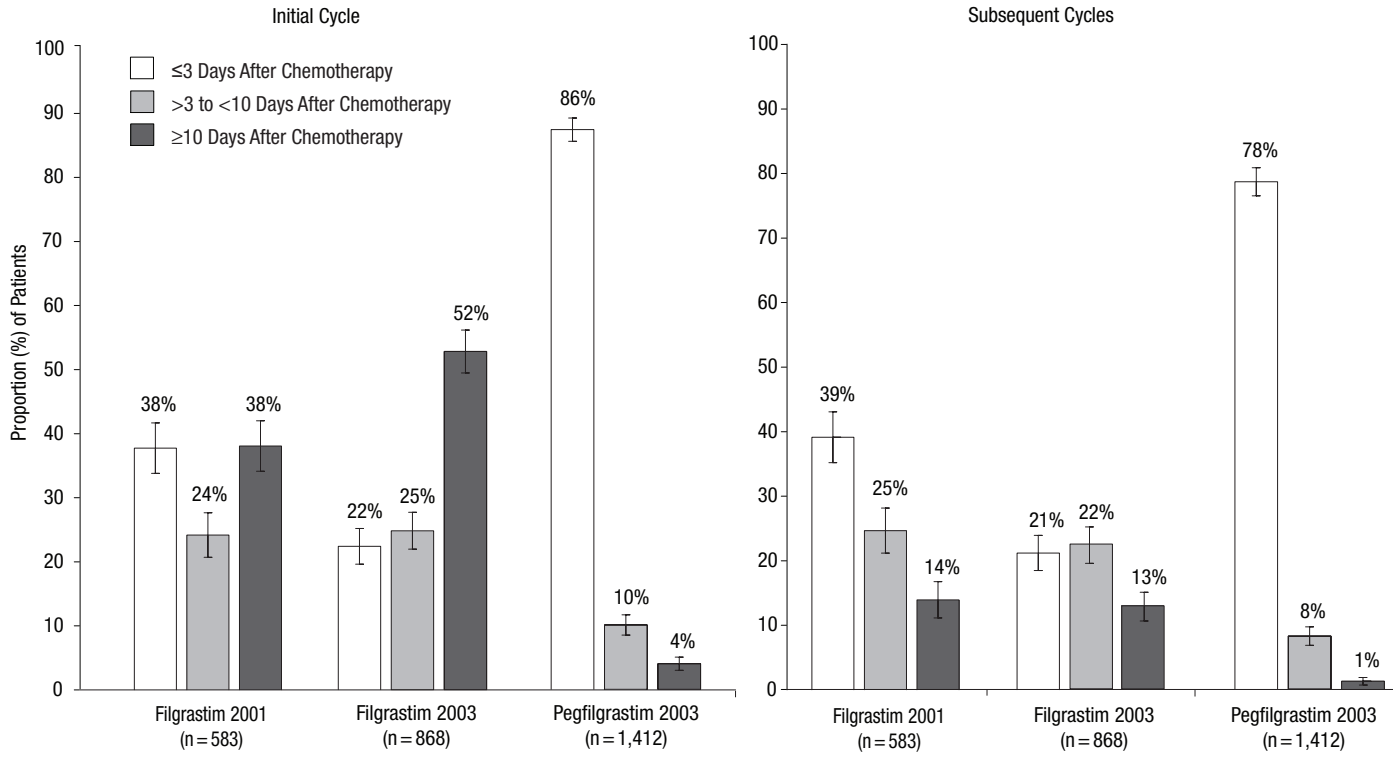
Mean days of filgrastim used also declined between 2001 and 2003. Filgrastim was administered for a mean (SD) of 5.2

TABLE 2 Patients Receiving Chemotherapy Every 3 to 4 Weeks Who Initiated Colony-Stimulating Factors Prior to Developing Febrile Neutropenia: Patient Characteristics and Patterns of Care (N = 2,863)

Patient Characteristics	2001 Filgrastim n = 583 n (%)	2003 Filgrastim n = 868 n (%)	2003 Pegfilgrastim n = 1,412 n (%)	*P* Value: Peg 2003 vs. Fil 2001	*P* Value: Peg 2003 vs. Fil 2003
Age, years				0.812	0.429
≥65	218 (37.4)	334 (38.5)	520 (36.8)		
<65	365 (62.6)	534 (61.5)	892 (63.2)		
Sex				0.790	0.400
Male	132 (22.6)	205 (23.6)	312 (22.1)		
Female	451 (77.4)	663 (76.4)	1,100 (77.9)		
Tumor				0.770	0.003
Breast	301 (51.6)	418 (48.2)	747 (52.9)	0.771*	0.001*
Lung	120 (20.6)	208 (24.0)	300 (21.2)		
NHL	106 (18.2)	136 (15.7)	248 (17.6)		
Other†	56 (9.6)	106 (12.2)	117 (8.3)		
Disease stage				0.867	0.005
Advanced	88 (15.1)	168 (19.4)	209 (14.8)		
Comorbid conditions				0.027	0.135
0 422 (72.4)	602 (69.4)	1,021 (72.3)			
1 101 (17.3)	185 (21.3)	290 (20.5)			
≥2	60 (10.3)	81 (9.3)	101 (7.2)		
Serum albumin				0.417	0.459
<3.5 g/dL	58 (9.9)	106 (12.2)	158 (11.2)		
Anemia				0.590	0.625
Hemoglobin <10 g/dL	24 (4.1)	28 (3.2)	51 (3.6)		
Baseline ANC				0.459	0.539
<1.5 x 10^9/L	8 (1.4)	11 (1.3)	14 (1.0)		
Febrile neutropenia	31 (5.3)	63 (7.3)	67 (4.7)	0.591	0.012
Patterns of Care, Mean [SD] Except Where Noted					
Characteristics of chemotherapy regimen					
Number of cycles planned	4.9 [1.6]	5.0 [1.4]	5.1 [1.5]	0.098	0.525
Number of chemotherapy drugs in regimen	2.3 [0.6]	2.3 [0.8]	2.3 [0.6]	0.039	0.188
At least 1 myelosuppressive drug in regimen, n (%)‡	424 (72.7)	608 (70.0)	1,056 (74.8)	0.339	0.013
Colony-stimulating factors (CSF)					
Chemotherapy cycle of CSF initiation, n (%)				0.004	0.108
1	322 (55.2)	537 (61.9)	848 (60.1)		
2	134 (23.0)	180 (20.7)	344 (24.4)		
3+	127 (21.8)	151 (17.4)	220 (15.6)		
Day of initiation in first cycle of use§	7.7 [6.5]	9.6 [6.2]	2.4 [3.2]	<0.001	<0.001
Day of initiation in subsequent cycles of use§	4.9 [4.6]	6.4 [6.4]	1.9 [3.0]	<0.001	<0.001
Days of administration in first cycle of use‖	5.2 [3.5]	3.7 [2.8]	1.0 [0.0]	–	–
Days of administration in subsequent cycles of use‖	6.0 [3.5]	4.6 [3.2]	1.0 [0.0]	–	–
Number of patients receiving CSFs in ≥1 subsequent cycles	457 (78.4)	489 (56.3)	1,234 (87.4)	<0.001	<0.001

Of the 868 filgrastim users in 2003, 318 (36.6%) received 1 or more subsequent cycles of pegfilgrastim and of the 1,412 pegfilgrastim users in 2003, 97 (6.9%) received 1 or more subsequent cycles of filgrastim in this intent-to-treat analysis.
P values are presented for pegfilgrastim 2003 versus filgrastim 2001 (peg 2003 vs. fil 2001) and pegfilgrastim 2003 versus filgrastim 2003 (peg 2003 vs. fil 2003).
Comparisons of days of administration are made only between filgrastim 2001 and filgrastim 2003.
The χ^2 test was used to test for significant differences in categorical variables and the F test for continuous variables. All statistical tests were 2-sided.
** P values for comparing incidence of breast cancer or NHL versus other tumor types.*
† "Other" included colon cancer, ovarian cancer, and Hodgkin's lymphoma.
‡ Myelosuppresive drug included cladribine, cytarabine, cyclophosphamide, docetaxel, fludarabine, ifosfamide, irinotecan, mechlorethamine, methotrexate, or topotecan.
§ Day of initiation refers to the first day during the cycle of chemotherapy; cycle of initiation refers to the first cycle of chemotherapy in which a CSF was administered.
‖ Days of administration was calculated for filgrastim but not pegfilgrastim since the latter requires just 1 injection per cycle.
ANC = absolute neutrophil count; NHL = non-Hodgkin's lymphoma.

FIGURE 2 *The Day of Colony-Stimulating Factor (CSF) Initiation Within the Initial and Subsequent Chemotherapy Cycles for Filgrastim in 2001 and 2003 and Pegfilgrastim in 2003*



Percentages in subsequent cycles do not add up to 100% because some patients only received 1 cycle of G-CSF.

In 2001, of 583 patients who received at least 1 cycle of filgrastim, 457 patients received filgrastim in ≥1 subsequent cycles.
In 2003, of 868 patients who received at least 1 cycle of filgrastim, 489 patients received filgrastim in ≥1 subsequent cycles.
In 2003, of 1,412 patients who received at least 1 cycle of pegfilgrastim, 1,234 patients received pegfilgrastim in ≥1 subsequent cycles.

(±3.5) days in 2001 compared with 3.7 (±2.8) days in 2003 (P <0.001) in the first cycle of usage, and 6.0 (±3.5) days versus 4.6 (±3.2) days in 2001 and 2003, respectively, in subsequent cycles of use (P <0.001) (Table 2). The proportion of patients receiving ≥8 days of filgrastim was only 9% in the first cycle and subsequent cycles of use in 2003, compared with 22% and 21% in 2001 (Figure 3).

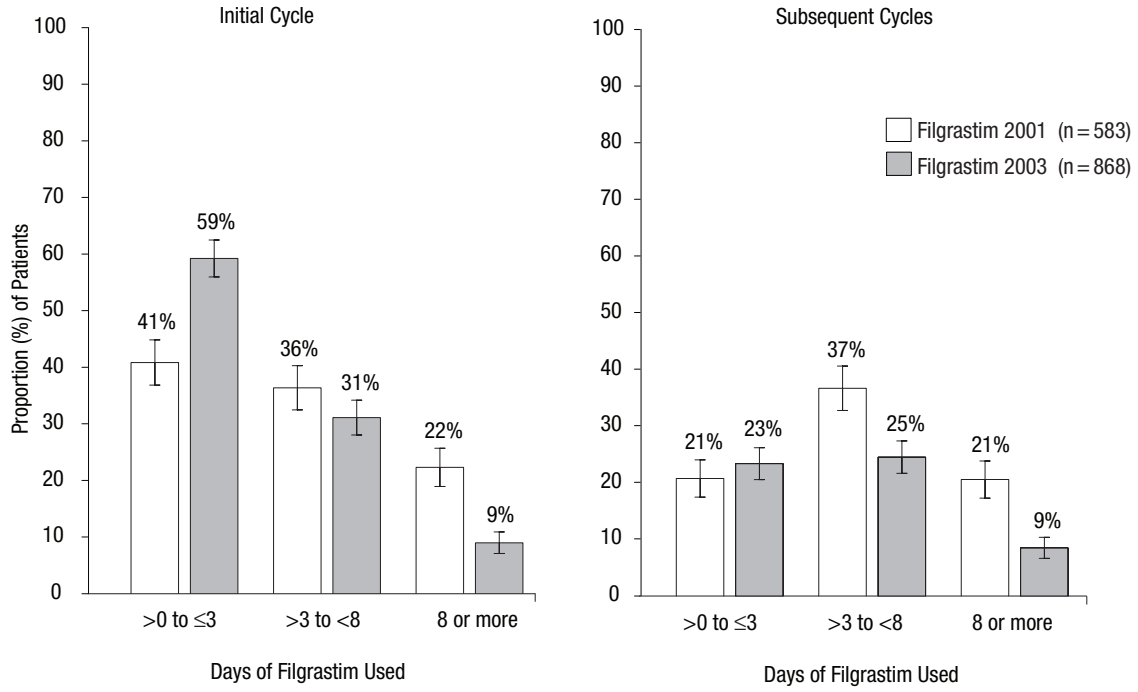
Patient Outcomes

More chemotherapy drugs in the regimen and the presence of at least 1 myelosuppressive drug were associated with a higher incidence of FN (Table 3). A low baseline serum albumin was the only patient characteristic that was significantly associated with the incidence of FN (P = 0.011).

The incidence of FN varied with the CSF received. Patients who received filgrastim had a higher incidence of FN compared with patients who received pegfilgrastim (6.5% vs. 4.7%, respectively; P = 0.044). Adjusting for patient and chemotherapy regimen characteristics, patients receiving filgrastim had an approximately 40% increase in the odds of developing FN compared with patients who received pegfilgrastim (odds ratio [OR],1.41; 95% confidence interval [CI], 1.02-1.96) (Table 4). Using a propensity score method instead of multivariate logistic regression to adjust for patient and chemotherapy regimen characteristics that predicted use of pegfilgrastim and filgrastim, the OR for developing FN in patients who received filgrastim as compared with pegfilgrastim was 1.52 (95% CI, 1.18-1.96). Excluding patients who received both pegfilgrastim and filgrastim from the analysis resulted in a modest increase in the OR for developing FN with filgrastim as compared with pegfilgrastim (OR, 1.59; 95% CI, 1.10-2.31).

Additional analysis accounting for clustering (within a given practice) yielded similar results. Adjusting for patient and chemotherapy regimen characteristics, patients receiving filgrastim were 40% more likely to experience FN than patients who received pegfilgrastim under both compound-symmetry assumption of within-cluster association (OR, 1.39; 95% CI, 1.01-1.90; P = 0.04) and independent within-cluster assumption

FIGURE 3 The Duration of Filgrastim Use in the Initial Cycle of Use and Subsequent Cycles of Use



In 2001, of 583 patients who received at least 1 cycle of filgrastim, 457 patients received filgrastim in ≥1 subsequent cycles.
In 2003, of 868 patients who received at least 1 cycle of filgrastim, 489 patients received filgrastim in ≥1 subsequent cycles.
In 2003, of 1,412 patients who received at least 1 cycle of pegfilgrastim, 1,234 patients received pegfilgrastim in ≥1 subsequent cycles.

(OR, 1.41; 95% CI, 1.03-1.93; $P = 0.03$), using a robust variance estimation method.[36]

Discussion

The objective of this study was to examine patterns of care and neutropenia-related outcomes associated with pegfilgrastim and filgrastim in oncology practices throughout the United States. In this retrospective cohort study, use of filgrastim in community practices varied significantly from its use in the registrational clinical trials, where it was always scheduled to be administered a day after the last dose of chemotherapy for a duration of 9 to 14 days.[15,17,22] Patients treated with filgrastim in these community oncology practices initiated treatment later within a chemotherapy cycle (for both the initial and subsequent cycles of use) and received shorter courses of therapy. In contrast, pegfilgrastim was initiated earlier than filgrastim in both the initial and subsequent cycles of use.

These findings are similar to other studies that have described the marked variation in the use of filgrastim.[25-27] Bennett et al. surveyed U.S. oncologists regarding the use of CSFs in 1994 and 1997.[24] They found that physicians reported using a wide variety of criteria for starting and stopping CSFs. In addition, 30% reported initiating CSF late in the cycle to treat afebrile neutropenia. In a retrospective cohort study of patients with non-Hodgkin's lymphoma, Lyman and colleagues found that among the 29.3% of patients who started a CSF in the first cycle of chemotherapy, more than half had it initiated later (more than 5 days after the start of chemotherapy) in the cycle, presumably in response to neutropenia, and more than half were treated for less than 7 days.[37] In a similar study in breast cancer patients, the median day of CSF initiation after receiving the first cycle of chemotherapy among patients who received it was 10 days.[38]

When using filgrastim, physicians appear to have a "watch and wait" approach to the management of chemotherapy-induced neutropenia, initiating therapy in response to a low white blood cell nadir, particularly in those patients who would not necessarily be considered for CSF therapy (e.g., a chemotherapy regimen with an expected risk of FN <20% and no other risk factors) according to ASCO[33] or National Comprehensive Cancer Network (NCCN)[39] guidelines. In contrast, our study indicated that pegfilgrastim was administered using a more proactive approach, with treatment initiated in the first cycle of chemotherapy in more than half of the patients and within

TABLE 3 Incidence of Febrile Neutropenia by Patient and Chemotherapy Characteristics and Colony-Stimulating Factors Received (N=2,863)

Patient Characteristics	Incidence of Febrile Neutropenia, n (%)	N (Denominator)	*P* Value
Age, years			0.773
<65	99 (5.5)	1,791	
≥65	62 (5.8)	1,072	
Sex			0.099
Male	45 (6.9)	649	
Female	116 (5.2)	2,214	
Stage			0.361
Limited or unknown	139 (5.8)	2,398	
Advanced	22 (4.7)	465	
Comorbid conditions			0.144
0	105 (5.1)	2,045	
1	37 (6.4)	576	
≥2	19 (7.9)	242	
Baseline serum albumin*			0.011
<3.5 g/dL	28 (8.7)	322	
≥3.5 g/dL	133 (5.2)	2,541	
Baseline anemia			0.067
Hemoglobin <10.0 g/dL	10 (9.7)	103	
Hemoglobin ≥10.0 g/dL	151 (5.5)	2,760	
Baseline ANC			0.103
<1.5 x 10^9/L	4 (12.1)	33	
≥1.5 x 10^9/L	157 (5.5)	2,830	
Characteristics of chemotherapy regimen			<0.0001
Number of chemotherapy drugs in regimen†			
1	8 (3.5)	227	
2	60 (3.7)	1,642	
≥3	93 (9.4)	994	
At least 1 myelosuppressive drug in regimen‡			0.0001
No	26 (3.4)	775	
Yes	135 (6.5)	2,088	
CSF received*			
Pegfilgrastim	67 (4.7)	1,412	0.044§
Filgrastim	94 (6.5)	1,451	
2001	31 (5.3)	583	
2003	63 (7.3)	868	

Filgrastim patients in 2001 and 2003; pegfilgrastim patients in 2003.
The denominator is the number of patients with a particular patient, chemotherapy, or CSF characteristic.
Incidence of febrile neutropenia refers to any febrile neutropenia event in the initial and subsequent cycles of chemotherapy reviewed. The total number of febrile neutropenia events in this entire sample is 161.
The χ^2 test was used to test for significant differences in categorical variables and the F test for continuous variables. All statistical tests were 2-sided.
** P <0.05 † P <0.001 ‡ P <0.01*
§ P value for pegfilgrastim vs filgrastim (2001 and 2003).
ANC = absolute neutrophil count; CSF = colony-stimulating factor.

TABLE 4 Odds of Febrile Neutropenia Occurrence With Use of Filgrastim Compared With Pegfilgrastim Adjusted for Patient and Chemotherapy Characteristics

	Odds Ratio	95% CI	*P* Value
CSF received			
Filgrastim	1.41	1.02-1.96	0.040
Pegfilgrastim	Reference		
Patient characteristics			
Age, years			
≥65	1.02	0.72-1.44	0.925
<65	Reference		
Stage			
Advanced	0.81	0.50-1.32	0.400
Limited or unknown*	Reference		
Comorbid conditions			
1	1.30	0.87-1.94	0.203
≥2	1.62	0.94-2.79	0.081
0	Reference		
Baseline serum albumin			
<3.5 g/dL	1.83	1.16-2.90	0.010
≥3.5 g/dL	Reference		
Baseline anemia			
Hemoglobin <10.0 g/dL	1.48	0.72-3.01	0.285
Hemoglobin ≥10.0 g/dL	Reference		
Baseline ANC			
<1.5 x 10^9/L	1.74	0.55-5.51	0.345
≥1.5 x 10^9/L	Reference		
Characteristics of chemotherapy regimen			
At least 1 myelo-suppressive drug in regimen	1.80	1.13-2.88	0.013
Number of chemotherapy drugs in regimen	1.65†	1.34-2.03	<0.001

Filgrastim patients in 2001 and 2003; pegfilgrastim patients in 2003.
Incidence of febrile neutropenia refers to any febrile neutropenia event in the initial and subsequent cycles of chemotherapy reviewed.
** Overall, 34% of patients had documentation that showed that they did not have metastases and were of limited stage (physicians often document "metastatic disease" in the medical chart but do not necessarily document the actual stage of disease).*
† OR estimate based on every 1-unit increase, i.e., 1 more drug in regimen.
ANC=absolute neutrophil count; CI=confidence interval; CSF=colony-stimulating factor.

3 days of chemotherapy 86% of the time. The burden of daily injections with filgrastim may represent a potential barrier to patients receiving all of the recommended injections of filgrastim or may have prompted physicians to recommend shorter courses of therapy.

NCCN and ASCO guidelines recommend primary prophylaxis with a CSF in the first chemotherapy cycle and in

subsequent cycles for patients receiving chemotherapy regimens with a moderate to high risk (20% or greater) of FN.[33,39] Additionally, in patients who are not necessarily candidates for primary prophylaxis, the guidelines also recommend use of CSF after FN develops or when neutropenia could result in chemotherapy dose delays or dose reductions in patients treated with curative intent. Primary prophylaxis with a CSF has been demonstrated to reduce the relative risk of FN by approximately 50%.[8] Randomized controlled trials have shown pegfilgrastim to be of similar efficacy to filgrastim.[16,19] However, we found that, among patients treated with a heterogeneous group of chemotherapy regimens with a broad range of risk of FN in community oncology practices, an overall 1.8 percentage point increase in the incidence of developing FN was observed in patients who received filgrastim compared with patients who received pegfilgrastim, (absolute rates of 6.5% and 4.7%, respectively) resulting in a 40% increase in the odds of FN. Thus, overall, for every 56 patients treated in community settings with pegfilgrastim instead of filgrastim, 1 additional case of FN would be avoided. Thus, the absolute risk reduction associated with the use of pegfilgrastim as compared with filgrastim would range from approximately 2% for a regimen with a 10% risk of FN, 4% for a regimen with a 20% risk of FN to 12% for a regimen with a 60% risk of FN. However, it is worth noting that clinical guidelines recommend consideration of prophylaxis with a CSF when the risk of FN associated with a chemotherapy regimen is less than 20% when patient characteristics place them at increased risk of dying as a result of FN or to avoid dose reduction and delays in patients treated with curative intent and not solely based upon avoidance of FN alone.[33,39]

Limitations

Several limitations should be considered when interpreting the results of this study. First, while probability sampling was used to select the participating oncology practices, the substantial nonresponse rate could limit the generalizability of our results. Second, data for this study were obtained by abstracting patients' charts and, therefore, are dependent upon the accuracy and completeness of medical record documentation. Thus, we have probably underestimated the true incidence of FN since patients who sought care in settings where care was not documented in their oncologist's chart (i.e., emergency room) are not reported. Third, our methodology may also have led to underestimation of the number of days of filgrastim use if this was not reliably documented or if patients received filgrastim outside of their oncologist's office, including self-administration of growth factors at home. Filgrastim is distributed by community pharmacies, mail order, and specialty pharmacies.

Fourth, differences in patient treatment and factors associated with risk of FN that influenced physician selection of pegfilgrastim over filgrastim could have influenced our results. For example, the most important predictor of FN is the risk associated with the chemotherapy regimen, and patients who received pegfilgrastim were more likely to be treated with myelosuppressive chemotherapy regimens so our results may underestimate the impact of pegfilgrastim on patient outcomes. On the other hand, there were minimal differences in patient characteristics; for example, more patients treated with filgrastim in 2003 had a higher proportion of advanced stage cancer compared with pegfilgrastim in 2003. However, all of these factors were adjusted for in the multivariate logistic regression analysis used in this study.

Lastly, these analyses are limited to a comparison of the outcomes of pegfilgrastim and filgrastrim and do not include chemotherapy patients who did not receive a CSF agent. This study was not intended to answer the question about the how and when CSF agents are used in chemotherapy patients with breast, lung, ovarian, or colon cancer or lymphoma.

Conclusion

Despite comparable efficacy in clinical trials,[16,19] we found that pegfilgrastim was associated with a lower incidence of FN compared with filgrastim in patients with breast, lung, ovarian, or colon cancer or lymphoma (Hodgkin's and non-Hodgkin's lymphoma) treated with chemotherapy in community practice. Difference in effectiveness of the 2 drugs may be related to how the drugs were actually used in clinical practice in contrast with their administration under optimal circumstances in clinical trials. These findings underscore the need for observational research to evaluate the effectiveness of therapy in heterogeneous patient populations treated in community practices. While all new U.S. pharmaceutical therapies undergo rigorous evaluation to demonstrate their safety and efficacy during the FDA approval process, variations in actual use and the diversity of patient populations may have a small but measurable impact on the effectiveness of medications.[40]

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Morrison served as principal author of the study. Study concept and design were contributed primarily by Morrison and Malin, with input from the coauthors. Data collection was the work of Hershman and Malin; data interpretation was primarily the work of Morrison, Malin, and Ding, with input from the coauthors. Statistical support was provided by Amgen, Inc. Writing of the manuscript and its revision were primarily the work of Morrison, Malin, and Ding, with input from the coauthors.

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