Days of Prophylactic Filgrastim Use to Reduce Febrile Neutropenia in Patients With Non-Hodgkin's Lymphoma Treated With Chemotherapy

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ABSTRACT

BACKGROUND: Filgrastim prophylaxis lessens the occurrence of febrile neutropenia in patients with non-Hodgkin's lymphoma (NHL) treated with chemotherapy, but differences in days of therapy and mode (primary or secondary) of prophylaxis may affect clinical outcomes.

OBJECTIVE: To describe the patterns of use of filgrastim prophylaxis, especially days of therapy and mode, and the possible associated incidence of febrile neutropenia in patients treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy.

METHODS: Using medical records from the Oncology Practice Pattern Study in patients treated between 1991 and 1999 at 12 sites in the United States, we studied patients with intermediate-grade NHL treated with first-line CHOP chemotherapy and prophylactic filgrastim. The number of days of prophylactic filgrastim use, mode of prophylaxis, and incidence of febrile neutropenia were evaluated. The cycles were stratified into 2 groups based on days of filgrastim prophylaxis (<7 days [Group 1] and ≥7 days [Group 2]).

RESULTS: One hundred seventy patients were treated with 652 cycles of CHOP chemotherapy with filgrastim prophylaxis. The mean days of filgrastim prophylaxis was 9.5 days (95% confidence interval [CI], 9.3-9.7 days) across all cycles, 4.7 days (95% CI, 4.5-5.0 days) across Group 1 cycles (n=73), and 10.1 days (95% CI, 9.9-10.3 days) across Group 2 cycles (n=579). Thirty-seven percent of patients were treated with primary prophylaxis; 94% of these patients' cycles were Group 2 cycles. The incidence of febrile neutropenia was 3.6% and 7.7% across cycles in patients receiving primary versus secondary prophylaxis, respectively. In patients treated with secondary prophylaxis, the incidence was 16.7% and 6.1% in Group 1 and Group 2 cycles, respectively. Multiple logistic regression modeling indicated that a lower risk of febrile neutropenia was associated with primary prophylaxis (mainly Group 2) (odds ratio [OR] 0.3; 95% CI, 0.1-0.6) and secondary prophylaxis in Group 2 (OR 0.4; 95% CI, 0.2-0.8), and lower body surface area was associated with a greater risk of febrile neutropenia (OR 1.8; 95% CI, 1.1-3.0).

CONCLUSION: Primary prophylaxis with filgrastim (mainly Group 2) and secondary prophylaxis in Group 2 (mean 10.1 days) may be associated with a lower incidence of febrile neutropenia than secondary prophylaxis in Group 1.

KEYWORDS: Non-Hodgkin's lymphoma, Febrile neutropenia, Filgrastim, Prophylaxis

Patients with cancer treated with chemotherapy often develop hematologic toxicity, including febrile neutropenia, which is a life-threatening event that may require hospitalization as well as treatment with intravenous antibiotics. As a result of febrile neutropenia, a patient's dose of chemotherapy may be delayed or reduced to enable white cell recovery and reduce the likelihood of future neutropenic events. This is particularly true in the setting of older patients with non-Hodgkin's lymphoma (NHL) treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy, who are at high risk of febrile neutropenia.^{1,2} Therefore, preventing febrile neutropenia is warranted in patients with cancer treated with cytotoxic chemotherapy, both to improve patient outcomes³ and to reduce the costs of related treatment.^{4,6}

Filgrastim is a recombinant granulocyte colony-stimulating factor that has shown efficacy in reducing the incidence and severity of chemotherapy-induced febrile neutropenia in a variety of malignancies and chemotherapy regimens.⁷⁻¹² Preventing febrile neutropenia makes it possible to deliver the cytotoxic chemotherapy on time and at doses that have been shown in clinical trials to be effective. Clinical trials have utilized approximately 10 to 11 days of filgrastim to reduce the rates of febrile neutropenia and to restore postnadir absolute neutrophil counts.^{7,8,13-15}

The efficacy of filgrastim prophylaxis has been well established in clinical trials, but less is known about its efficacy outside the clinical-trial setting. Patients treated in a clinical trial are dosed according to strict guidelines and are closely monitored throughout the study, whereas patients in a clinical-practice setting who are not on a protocol may have wide variations in their filgrastim dosing that could negatively effect outcomes. Variation in the number of days in which prophylactic filgrastim is administered in clinical practice and the impact of markedly reducing the number of days of therapy are not well documented.

We conducted a case series study to describe the association of variations in the use of prophylactic filgrastim with the incidence of febrile neutropenia in patients with NHL treated with combination chemotherapy (CHOP). We specifically investigated the clinical outcome associated with the variation in duration and mode (primary or secondary) of filgrastim prophylaxis.

Methods

Study Design and Patient Selection

This case series study analyzed data from the Oncology Practice Pattern Study (OPPS) database, described by

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TABLE 1 Patient Characteristics

Characteristics	Patients: number (%)			
	All (N=170)	Primary Filgrastim* (n=62)	Secondary Filgrastim† (n=108)	P‡
Age ≥65 years	93 (54.7)	37 (59.7)	56 (51.8)	0.409
BSA below median (1.9 m ²)	92 (54.1)	33 (53.2)	59 (54.6)	0.987
Female sex	84 (49.4)	34 (54.8)	50 (46.3)	0.361
CCI ≥1	56 (32.9)	18 (29.0)	38 (35.2)	0.514
Presence of renal disease	9 (5.3)	1 (1.6)	8 (7.4)	0.205
Presence of heart disease	22 (12.9)	11 (17.7)	11 (10.2)	0.240
Advanced stage disease (III or IV)	63 (40.4)	25 (42.4)	38 (39.2)	0.821
≥2 extranodal sites	26 (21.5)	12 (25.0)	14 (19.2)	0.592
Elevated LDH level	68 (50.0)	27 (56.3)	41 (46.6)	0.370
Presence of B symptoms	45 (26.5)	20 (32.3)	25 (23.2)	0.265
Bone marrow involvement	15 (14.2)	5 (14.7)	10 (13.9)	1.000
Histology (working formulation):				0.114
• follicular, immunoblastic (D, H), and intermediate NOS	48 (30.6)	14 (24.1)	34 (34.4)	
• small/mixed small and large cell/diffuse (E,F)	34 (21.6)	10 (17.3)	24 (24.2)	
• large cleaved or noncleaved cell/diffuse (G)	75 (47.8)	34 (58.6)	41 (41.4)	
Radiation treatment given	5 (2.9)	0 (0.0)	5 (4.6)	0.212
Planned ARDI ≤80%	19 (11.2)	7 (11.3)	12 (11.1)	1.000
Delivered ARDI ≤80%	34 (20.0)	14 (22.6)	20 (18.5)	0.661

* First prophylactic filgrastim use within the first 5 days of cycle 1.

† First prophylactic filgrastim use within the first 5 days of cycle 2 or any subsequent cycle.

‡ Primary versus secondary filgrastim, χ^2 test.

BSA=body surface area CCI=modified Charlson comorbidity index LDH=lactate dehydrogenase ARDI=average relative dose intensity

Morrison et al.¹ The OPPS database consists of data from medical records for the first course of therapy of patients treated between 1991 and 1999 at 12 diverse practice settings (2 academic cancer centers, 5 integrated hospital systems, and 5 community practices) in the United States. Patients were at least 18 years old, had intermediate-grade NHL, and had been treated with first-line CHOP chemotherapy in 21-day cycles with primary or secondary prophylactic filgrastim. Of the 577 patients with NHL who were given 3,185 cycles of CHOP (including cycles 1 through 8) in the OPPS database, 170 patients (29.5%) were given filgrastim prophylaxis in 652 cycles (20.5%). Patients were excluded if they were participating in a clinical trial, had HIV infection, were treated with concurrent radiation therapy, were switched from CHOP to another therapy, or were missing key variables. Patients with other primary invasive malignancies or who were treated with high-dose chemotherapy that required stem cell rescue were also excluded.

Study Independent Variables and Operational Definitions

Patient characteristics that were extracted from the medical records included age, sex, body surface area (BSA), comorbid con-

ditions, cancer disease stage, number of extranodal sites involved, lactate dehydrogenase (LDH) level, presence of B symptoms (ie., recurrent fever, night sweats, or the loss of >10% of body weight), bone marrow involvement, lymphoma histology, and treatment with radiation. Patient age was dichotomized as <65 years and ≥65 years, and BSA was categorized as above or below the median (1.9 m²). Comorbid conditions were classified as either 0 or ≥1, based on a modified Charlson comorbidity index (CCI).¹⁶⁻¹⁸ Additionally, heart disease and renal disease were classified as present (ICD9-CM codes 410, 411, 412, 414, 427, and 428 for heart disease; ICD9-CM codes 403, 404, 580 to 586, and 588 for renal disease) or absent. The NHL disease stage was categorized as limited (Ann Arbor stage I or II) or advanced (Ann Arbor stage III or IV),¹⁹ and the number of extranodal sites involved was classified as 0 or 1, or as ≥2. Lactate dehydrogenase levels were categorized as elevated or normal. B symptoms and bone marrow involvement were classified as present or absent. Lymphoma histology was categorized according to the Working Formulation,²⁰ which was being used by pathologists during the study period. Febrile neutropenia was documented from the patient's medical record.

FIGURE 1 Prophylactic Filgrastim Use

Group 1 received a mean of 4.7 days filgrastim prophylaxis, Group 2 a mean of 10.1 days. CI=confidence interval.

FIGURE 2 First Administration of Prophylactic Filgrastim, by Cycle

Treatment Characteristics and Outcomes

The relative dose intensity (RDI) of cyclophosphamide and doxorubicin was calculated for each patient to determine how closely the patient's dose of chemotherapy compared with that of the standard regimen. Planned RDI was calculated as the ratio of the planned first cycle dose intensity divided by the corresponding standard dose. The planned average RDI (ARDI)²¹⁻²³ was obtained by averaging the planned RDIs of cyclophosphamide and doxorubicin. Delivered ARDI was calculated in a similar manner. Planned and delivered ARDI were classified as either >80% or ≤80% of the standard dose.

Data on febrile neutropenia and hospitalization for febrile neu-

tropenia were obtained from the patient's medical record. Prophylactic filgrastim use was defined as filgrastim therapy initiated within the first 5 days of the chemotherapy cycle. Prophylactic filgrastim within cycle 1 was defined as primary prophylaxis, and prophylactic filgrastim administered for the first time after cycle 1 was defined as secondary prophylaxis. In each chemotherapy cycle in which filgrastim was administered, the cycle day of the first dose of filgrastim was recorded.

For each chemotherapy cycle in which prophylactic filgrastim was given, the number of days of filgrastim administration was recorded. Skipped days were not included in the calculation of the number of days of treatment if such interruptions occurred. Treatment days of prophylactic filgrastim in a given cycle were dichotomized into 2 groups, <7 days (Group 1) and ≥7 days (Group 2).

Statistical Methods

In this study we describe the association between the number of days of filgrastim use and the incidence of febrile neutropenia, and we also report the prophylactic use (both primary and secondary) of filgrastim. Only patient cycles of chemotherapy in which prophylactic filgrastim was administered are included in the analyses.

Two important elements of filgrastim administration are analyzed: (1) the number of days of administration, and (2) the mode of prophylaxis (primary or secondary). Days of therapy were summarized using patient cycles, and the mode of prophylaxis was assessed at the patient level. The mode of prophylaxis was categorized by first administration of filgrastim, such that all cycles in patients who were given primary prophylaxis were always classified as primary.

From a clinical perspective, ≥10 days of prophylactic filgrastim administration is considered optimal, on the basis of the results of randomized clinical trials.^{7,8,13-15} Patient cycles of therapy were stratified into 2 groups based on the empirical frequency distribution of the days of prophylactic filgrastim treatment, <7 days (Group 1) and ≥7 days (Group 2). This dichotomization was also supported by a study recently reported by Meza et al.,²⁴ in which the lower bound for the mean number of days of filgrastim therapy required for 95% of the population to achieve absolute neutrophil count recovery (mean minus 2 times standard deviation) was approximately 7 days.

The Cochran-Armitage linear trend test was used to test differences in the patterns of use (days of treatment and day of the cycle when filgrastim was started) between primary and secondary prophylactic filgrastim. Risk factors associated with a febrile neutropenic episode at the patient-cycle level were identified. As cycles are correlated within patients, inferences about risk factors for febrile neutropenia were based on simple and multiple logistic regression analysis with repeated measurements, using a generalized linear mixed model with binomial errors.²⁵ To control for different practice patterns, the site was used as the basis for the blocking procedure in the repeated measures analysis.

The separate associations between mode and days of treatment

with prophylactic filgrastim administration with the incidence of febrile neutropenia were difficult to assess since patients treated with primary prophylaxis also tended to have more days of treatment. Therefore, the reported association with days of therapy (Group 1 or Group 2) was limited to patients treated with secondary prophylaxis only. Indicators for the cross-tabulation of days of treatment (Group 1 or Group 2) and treatment mode (primary or secondary prophylaxis) were used in modeling, but because of the small number of cycles in the Group 1 with primary prophylaxis cell ($n=17$), only 3 groups were modeled: (1) Groups 1 and 2 primary prophylaxis, (2) Group 2 secondary prophylaxis, and (3) Group 1 secondary prophylaxis. The last group (Group 1 secondary prophylaxis) was the reference group for comparisons.

Results

Description of Study Population

The study population included 170 patients with intermediate-grade NHL who were treated with CHOP chemotherapy and at least one cycle of prophylactic filgrastim. Sixty-two patients (36.5%) were given primary prophylaxis, and 108 patients (63.5%) were given only secondary prophylaxis. A total of 652 chemotherapy cycles with filgrastim prophylaxis were used in the analyses, 303 cycles in patients who were given primary prophylaxis and 349 cycles in patients who were given only secondary prophylaxis.

The median patient age was 67 years (range, 26 to 85 years), and 55% of the patients were ≥ 65 years. Forty percent of the patients had stage III or IV disease (Table 1), and 78% of the patients were treated with 6 to 8 cycles of CHOP therapy. No significant differences in patient characteristics were noted between patients treated with primary prophylaxis and those treated with secondary prophylaxis.

Prophylactic Filgrastim Use

Across all cycles, the mean days of prophylactic filgrastim administration was 9.5 days (95% CI, 9.3-9.7 days; range, 1 to 18 days) (Figure 1). Filgrastim was administered for ≥ 7 days in most cycles (579 cycles Group 2 versus 73 cycles Group 1). Among Group 1 cycles, the mean days of prophylactic filgrastim therapy per cycle was 4.7 days (95% CI, 4.5-5.0 days). Among cycles in Group 2, the mean days of prophylactic filgrastim administration was 10.1 days (95% CI, 9.9-10.3 days).

Most patients (68%) were first given prophylactic filgrastim in cycle 1 or 2 of their CHOP chemotherapy (Figure 2), and about half of all prophylactic filgrastim courses were administered for 10 to 12 days (Figure 3). Overall, the number of days of filgrastim administration was similar in patients given primary prophylaxis (mean, 9.9 days; 95% CI, 9.6-10.1 days) and those who received only secondary prophylaxis (mean, 9.2 days; 95% CI, 8.9-9.5 days) (Cochran-Armitage trend test, $P=0.002$).

Figure 4 shows the distribution of the start day of filgrastim administration within the cycle, by mode of filgrastim administration (primary or secondary). Most prophylactic filgrastim treatment was initiated on cycle day 2. Primary prophylactic filgrastim

FIGURE 3 Days of Prophylactic Filgrastim Use in Cycle, by Mode of Prophylaxis

Primary prophylaxis = first prophylactic filgrastim use within the first 5 days of cycle 1, secondary prophylaxis = first use within the first 5 days of cycle 2 or any subsequent cycle.

FIGURE 4 Start Day of Prophylactic Filgrastim Within Cycle, by Mode of Prophylaxis

Primary prophylaxis = first prophylactic filgrastim use within the first 5 days of cycle 1, secondary prophylaxis = first use within the first 5 days of cycle 2 or any subsequent cycle.

tended to be initiated earlier in the cycle than did secondary prophylaxis (Cochran-Armitage trend test, $P<0.001$).

Incidence of Febrile Neutropenia and Associated Risk Factors

Univariate generalized linear mixed analysis indicated that a greater risk of febrile neutropenia was associated with <7 days of secondary prophylactic filgrastim administration in a cycle. A lower risk of febrile neutropenia was associated with primary prophylaxis (mainly Group 2) (Table 2). Other significant risk factors were BSA below the median, female sex, and limited-stage disease. In patients given only secondary prophylaxis, those in Group 2

TABLE 2 Univariate Generalized Linear Mixed-Model Estimates of Risk of FN in Cycle in 170 Patients With Intermediate-Grade NHL Treated With 652 Cycles of Prophylactic Filgrastim

Unadjusted Risk of FN in Cycle (Univariate)		
Characteristics	Odds Ratio	95% Confidence Interval
Age ≥65 years	0.946	0.633-1.412
BSA below median (1.9 m ²)	1.997	1.256-3.177
Female sex	1.878	1.203-2.934
CCI ≥1	0.633	0.387-1.035
Presence of renal disease	0.665	0.235-1.881
Presence of heart disease	0.584	0.305-1.120
Advanced-stage disease (III or IV)	0.540	0.318-0.916
≥2 extranodal sites	0.738	0.455-1.198
Elevated LDH level	1.265	0.813-1.970
Presence of B symptoms	0.784	0.476-1.290
Bone marrow involvement	0.473	0.169-1.324
Histology (working formulation)		
• Large cleaved or noncleaved cell/diffuse (G)	0.780	0.471-1.290
• Small/mixed cell diffuse (E, F)	0.965	0.557-1.670
Radiation treatment given	1.406	0.496-3.988
Planned ARDI ≤80%	1.346	0.752-2.411
Delivered ARDI ≤80%	1.080	0.648-1.799
Primary prophylactic filgrastim*	0.507	0.304-0.844
Group 1 (mean 4.7 days filgrastim treatment)	2.088	1.166-3.739

* First prophylactic filgrastim use within the first 5 days of cycle 1.

BSA=body surface area CCI=modified Charlson comorbidity index

LDH=lactate dehydrogenase ARDI=average relative dose intensity

TABLE 3 Multivariate Generalized Linear Mixed-Model Estimates of Risk of FN in Cycle in 170 Patients With Intermediate-Grade NHL Treated With 652 Cycles of Prophylactic Filgrastim

Adjusted Risk of FN in Cycle (Multiple)		
Characteristics	Odds Ratio	95% Confidence Interval
BSA below median (1.9 m ²)	1.849	1.126-3.035
Prophylactic filgrastim administration*		
• Primary prophylaxis† (mainly Group 2)	0.295	0.139-0.624
• Secondary prophylaxis‡ and Group 2§	0.433	0.225-0.834
• Secondary prophylaxis‡ and Group 1¶	1.000	—

* Reference group is patients given secondary filgrastim prophylaxis and <7 days of prophylaxis in given cycle.

† First filgrastim use within the first 5 days of cycle 1.

‡ First filgrastim use within the first 5 days of cycle 2 or any subsequent cycle.

§ ≥7 days (mean, 10.1 days) of filgrastim in given cycle.

¶ <7 days (mean, 4.7 days) of filgrastim in given cycle.

BSA=body surface area.

Cycles within site correlation (compound symmetry covariance structure)=0.220.

Discussion

This study of patients with NHL treated with CHOP chemotherapy and prophylactic filgrastim assessed practice patterns and specifically investigated the association between administering filgrastim for <7 days and the incidence of febrile neutropenia. Multivariate modeling suggested that compared with Group 1 (mean 4.7 days) secondary prophylaxis, the risk of febrile neutropenia was significantly reduced in cycles with primary prophylaxis (mainly Group 2) and for secondary prophylaxis cycles in Group 2 (mean 10.1 days). When controlling for filgrastim prophylaxis patterns, the effect of BSA below the median of 1.9 m² was significantly associated with an increased risk of febrile neutropenia.

In randomized studies, utilizing approximately 10 to 11 days of filgrastim prophylaxis significantly reduced the incidence of febrile neutropenia.^{7,8,13-15} The mean days of treatment in our study, 9.5 days, approached this target, and filgrastim was administered for at least 7 days in most of the cycles in the study. However, for the Group 1 cycles with markedly fewer days of filgrastim treatment (mean 4.7 days), the associated risk of febrile neutropenia was significantly increased. These findings are important because they show that in this sample of patients treated in clinical practice, filgrastim

had a lower incidence of febrile neutropenia than those in Group 1 (6.1% versus 16.7%) (Figure 5).

In a multivariate model of the effect of prophylactic filgrastim pattern controlling for BSA, the reference category was Group 1 cycles (mean 4.7 days) of secondary prophylaxis (Table 3). Relative to this group, a significantly lower risk of febrile neutropenia was observed for those cycles with primary prophylaxis (mainly Group 2) (OR 0.3; 95% CI, 0.1-0.6) and for secondary prophylaxis cycles in Group 2 (mean 10.1 days; OR 0.4; 95% CI, 0.2-0.8). When controlling for filgrastim prophylaxis patterns, the effect of BSA below the median of 1.9 m² remained significantly associated with an increased risk of febrile neutropenia (OR 1.8; 95% CI, 1.2-3.0).

FIGURE 5 Incidence of FN in Patients Given Primary or Secondary Prophylactic Filgrastim, by Days of Treatment

Four of 17 filgrastim administrations in Group 1 were given in cycle 1. Primary prophylaxis=first prophylactic filgrastim use within the first 5 days of cycle 1, secondary prophylaxis=first use within the first 5 days of cycle 2 or any subsequent cycle. Group 1 was given a mean of 4.7 days of filgrastim prophylaxis, Group 2 a mean of 10.1 days.

was administered for an adequate number of days in most cycles (Group 2 mean 10.1 days). However, the study results also suggest that administering filgrastim for markedly fewer days than that utilized in clinical trials may decrease the effectiveness of filgrastim prophylaxis for that cycle, thereby producing adverse effects in terms of increased incidence of febrile neutropenia. Febrile neutropenia may be life threatening, require hospitalization, and limit the dose of chemotherapy, resulting in poorer outcomes and higher treatment costs.

The risk of febrile neutropenia in primary prophylaxis cycles (mainly Group 2) in this study was significantly less than that observed in secondary cycles with a mean treatment of 4.7 days. Generally, primary prophylaxis was administered earlier in the cycle and for a longer duration than secondary prophylaxis, which may explain the difference in risk of febrile neutropenia. An alternative and more likely explanation is that patients who were treated with secondary prophylaxis either had experienced neutropenia or had clinical characteristics that indicated that they had a higher risk for neutropenic events.

Another risk factor identified for febrile neutropenia was lower BSA. This is in contrast to recent research that indicates that anthracycline dosing based on BSA does not predict the degree of neutropenia.²⁶

The study was limited by the small number of patients and by the limitations inherent in a retrospective analysis including non-random patient selection. Because reduced days of filgrastim use was observed less commonly among those who received primary prophylaxis than those who received secondary prophylaxis (only 17 cycles in 62 primary prophylaxis patients versus 56 cycles in 108 secondary prophylaxis patients), the study was limited in that it does not provide enough information about the possible shortcomings of fewer treatment days in patients receiving primary prophylaxis. Another limitation of the study was that other risk factors for febrile neutropenia were not considered, (e.g., absolute

neutrophil counts, dose and duration of CHOP therapy, prior episodes of febrile neutropenia, dose of filgrastim). Dose of filgrastim was not considered in the analysis since dosing was mostly according to the indication of 5 µg/kg and therefore considered of lesser importance than days of treatment (data not shown).

Conclusion

This historical case series study offers insight into the use of prophylactic filgrastim in clinical practice and the potentially negative clinical consequences of variations in practice patterns. Febrile neutropenia was more likely to occur in cycles with a reduced number of days of filgrastim prophylaxis. Our findings suggest that the impact of a reduced number of days of filgrastim therapy on the rates of febrile neutropenia should be investigated utilizing methods that further control for confounding variables.

DISCLOSURES

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