Supplement Policy Statement

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Supplements to the Journal of Managed Care Pharmacy are intended to support medical education and research in areas of clinical practice, health care quality improvement, or efficient administration and delivery of health benefits. The following standards are applied to all JMCP supplements to assure quality and assist readers in evaluating potential bias and determining alternate explanations for findings and results.

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2. Disclose the existence of all potential conflicts of interest among supplement contributors, including financial or personal bias.

3. Describe all drugs by generic name unless the use of the brand name is necessary to reduce the opportunity for confusion among readers.

4. Strive to report subjects of current interest to managed care pharmacists and other managed care professionals.

5. Seek and publish content that does not duplicate content in the Journal of Managed Care Pharmacy.

6. Subject all supplements to peer review.

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Pharmacoeconomics and Considerations for Injectable Products: Focus on Colony-Stimulating Factors

LEON E. COSLER, PhD, RPh

INTRODUCTION

Pharmaceutical and biotechnology companies have made tremendous efforts in the past decade in researching and developing new drug products and bringing them to market. With numerous drugs continually being introduced into the market, there is an ongoing need to systematically review these products. The drug formulary system is an established method by which health care organizations can determine which drugs are most clinically appropriate and cost effective for their patient population.1

The Pharmacy and Therapeutics (P & T) committee within a managed care organization (MCO), which consists of physicians, pharmacists, and other health care professionals, is responsible for evaluating and selecting pharmaceutical products for the formulary.1,2 The Academy of Managed Care Pharmacy (AMCP) has published guidelines to help organizations conduct their formulary review, outlining what should be submitted for the review process and how the quality and relevance of the data obtained on the drug can be improved.2 The types of data that should be presented in a formulary submission include those from clinical trials, outcome studies, meta-analyses, retrospective studies, and pharmacoeconomic models.

Since new drug products are continually entering the market, the P & T committee meets regularly to revise and update the formulary. P & T committees have traditionally focused on the safety, efficacy, and appropriateness of the drugs, but the focus has expanded to also include health economics and pharmacoeconomic data.1,2 There has been a growing demand to present all these data at product launch and to include them in the formulary review process.1

The safety and efficacy of a new drug are typically established in randomized controlled clinical trials. The appropriate dosage is also determined during these trials. The data from clinical trials form an important component of the formulary submission, especially since this information is available at product launch.

However, determining the cost-effectiveness of a new product requires pharmacoeconomics and outcomes studies in addition to safety and efficacy data. To obtain comprehensive information, MCOs may look to alternative data sources, such as observational studies, cohort studies, and administrative databases. Administrative databases generally collect data on the use of health care resources, and they can provide information on patient demographics in addition to information on health care encounters, such as doctor’s office and pharmacy visits, and costs.1 Some of the advantages and disadvantages or caveats of using administrative databases for analyses are shown in Table 1. It is important to be aware that these databases were not designed for research purposes and that they may contain incomplete or invalid data because of deficiencies in the data being captured or in edit checks.4

P

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TABLE 1 Advantages and Disadvantages or Caveats of Administrative Databases

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Advantages</th>
<th>Disadvantages, Caveats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data collection</td>
<td>• Routinely collected</td>
<td>• Differs between MCOs</td>
</tr>
<tr>
<td></td>
<td>• Easily accessible</td>
<td>• Data for billable goods and services only</td>
</tr>
<tr>
<td></td>
<td>• Can be cost effective</td>
<td>• May require a purchase price</td>
</tr>
<tr>
<td>Population</td>
<td>• All insurance beneficiaries</td>
<td>• Nonrandom patient selection (potential for bias)</td>
</tr>
<tr>
<td></td>
<td>• Large populations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Possibility of making several comparisons</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• External validity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Broad coverage</td>
<td></td>
</tr>
<tr>
<td>Data contained</td>
<td>• Inpatient and outpatient costs</td>
<td>• Charges and reimbursement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Limited number of diagnoses available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No data on severity of illness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Acute and established diagnoses not differentiated</td>
</tr>
<tr>
<td>Accuracy</td>
<td>• Accuracy related to reimbursement</td>
<td>• Coding misclassification</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Inaccurate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nonspecific</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Missing data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consistency over time may vary</td>
</tr>
</tbody>
</table>

Adapted with permission from reference 5.

Given that administrative databases are associated with reimbursement and are structured around payment items, performing a proper analysis requires translating these items into relevant clinically sound episodes of care, such as linking drugs to a disease when the pharmacy claims do not contain diagnoses. Otherwise, the results that are reported will inaccurately reflect the use of resources.

Claims databases that link pharmacy and medical data, such as in the staff model health maintenance organization, provide a better picture of the patient population and a better means of evaluating new products. However, relying on claims data alone may result in misleading and erroneous conclusions. Additional clinical information is required to accurately assess how a product is used, and much of this information is difficult to obtain or is inaccessible.

Combining data sources, such as linking pharmacy and medical claims databases or combining these data with medical chart reviews and registries, is an effective way of overcoming these limitations and thus a better way of evaluating new products. A review of patients’ medical records is a good way of checking the quality of claims data, but this may be costly and may be available for only a small population. Alternatively, disease-specific registries collect prospective clinical data on a larger population.

Registries can provide much of the clinical information that is not available in claims databases, such as the date of the initial diagnosis, disease stage, and size of the tumor. Creating such databases can be costly and difficult, but the data in them can be used to minimize or resolve the challenges that are encountered in evaluating new products and to produce reliable results.

Evaluating a combination of data from well-designed clinical trials, medical chart reviews, and prospective studies is ideal. Consolidating the information from these sources can provide a rich bank of data for evaluating use, outcomes, and clinical endpoints. The formulary review process by the P & T committee is an effective way of evaluating these products. While most of the data available and important for this review are from clinical trials, it is important to collect data from as many sources as possible and to understand how the data in those studies were obtained. While having good data is important, it is also important to evaluate the methodology and analyses to make sure that the results are interpreted correctly.

The 3 articles in this supplement discuss pharmacoeconomic and formulary considerations as they relate to colony-stimulating factors (CSFs). The clinical trials of filgrastim and pegfilgrastim and analyses of medical records and claims databases that determined the patterns of use of prophylactic filgrastim are described. This information can be useful in making decisions about the optimal use of CSFs.

DISCLOSURES

Dr. Cosler receives grant support from Amgen and is a consultant to the New York State Office of Medicaid Management. He has received honoraria and travel from Amgen for making presentations to an advisory board.

REFERENCES

Public and private payers frequently use provider claims data-bases to track health care expenditures, analyze patterns of medical resource utilization, and provide a basis for making plan-level treatment decisions (eg., drug coverage, treatment guidelines or restrictions, and medication formulary status). While claims-based analyses are increasingly used by decision makers due to low costs, rapidity of results, and large sample size, the sole reliance on claims data for making plan-level decisions is associat-ed with notable challenges, limitations, and potential biases.

The most significant limitations of claims data arise from deficiencies in the information that is available. Claims data typ-ically lack critical data such as illness severity , the indication for drug use, the criteria used in making the treatment choice, and outcomes.\(^1\)-\(^4\) In complex disease areas such as cancer, claims data present additional challenges such as a lack of information about the chemotherapy regimen used, the instances of and rea-sons for changes in the chemotherapy dose or schedule, and the cancer stage.\(^1\),\(^2\) Further, claims databases may be subject to inconsistency over time as a result of ongoing editing and changes in coding and may contain invalid data due to a lack of edit checks.\(^3\) Missing or incorrect data can introduce serious bias, producing inaccurate and misleading results. Medical record review or linking of claims and registry databases can resolve many of these discrepancies but is sometimes consid-ered too costly and difficult.\(^1\),\(^2\) Finally , all data derived from ad-ministrative databases contain a non-random patient sample, which may introduce unknown bias into an analysis.\(^3\),\(^4\) Because of these limitations, clinical guidelines and other important medical decisions should ideally be based on validated, methodologically sound data sources such as clinical trial results, medical chart reviews, or prospective studies. To illustrate the challenges and limitations of claims-based analyses compared with more methodologically rigorous techniques, we selected the use of granulocyte colony-stimulating factor (ie., filgrastim) in oncology as a case study. Filgrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever.\(^5\) In a decision-analytic model, the high costs of febrile neutropenia favored prophylactic filgrastim use compared with no use or therapeutic use.\(^6\) In randomized controlled clinical trials, fil-grastim was administered for a mean of 11 days, beginning 24 hours after chemotherapy to reach an absolute neutrophil count (ANC) of \(10 \times 10^9/L\)—the level consistent with current pre-scribing information in the chemotherapy-induced neutropenia (CIN) setting. In these trials, the costs of purchasing and adminis-tering filgrastim were partially or completely offset by a reduction in the costs of febrile neutropenia.\(^7\)

This article reports filgrastim use patterns based on analyses of

### ABSTRACT

**BACKGROUND:** Provider claims data are used to make medical analyses and decisions, but such databases typically lack important clinical information.

**OBJECTIVE:** To compare the patterns of use of filgrastim in analyses of a claims database and a medical chart review.

**METHODS:** We extracted data from the Medicare 5% sample claims database for the years 1996 through 1998 and from a medical chart review of the Oncology Practice Pattern Survey (OPPS) for the same period to determine the patterns of use of filgrastim in patients with non-Hodgkin’s lymphoma treated with cyclophosphamide, doxorubicin, vincristine, and prednisone. The analyses were restricted to the first 3 cycles of the chemotherapy.

**RESULTS:** A total of 414 patients in the Medicare database were treated with 1,360 cycles of chemotherapy. The mean duration of filgrastim use in these patients was 6.6 days. In the OPPS database, 80 patients were treated with 152 cycles of chemotherapy, with a mean duration of filgrastim use of 9.3 days.

**CONCLUSION:** The mean duration of filgrastim use in the OPPS database was greater than that in the Medicare database and was closer to that shown in clinical trials to produce optimal results (approximately 11 days). The actual use of resources may be underestimated in claims databases, owing to their limitations and potential for bias.

**KEYWORDS:** Claims database, Resource use, Medical chart review
Assessing Resource Use in Oncology Patients: A Comparison of Analyses Based on Claims Data and Medical Chart Review

the physician and outpatient files. Claims for filgrastim were identified using 2 HCFA Common Procedure Coding System (HCPCS) J-Codes (which include all non-self-administered injectable drugs): J1440 (the filgrastim 300-µg vial) and J1441 (the filgrastim 480-µg vial). Approximately 95% of filgrastim use occurred in the physician’s office setting, while 4% occurred in the hospital outpatient setting (hospital-administered medications are not reported in the Medicare SAFs).

Utilization for most patients was captured by merging the files into one analysis file containing 2.9 million claims (Figure 1). However, the records were incomplete for some patients who had either entered the analysis period after initiation of their cancer chemotherapy treatment (i.e., initiation began prior to January 1996) or exited the analysis before their cancer chemotherapy treatment ended (i.e., treatment ended after December 1998).

Medicare SAFs do not include the number of vials used or the dosage patients received from a physician-administered chemotherapy agent or supportive medication. Dose was calculated using an algorithm that assigns a dose based on the corresponding J-Code multiplied by number of units associated with the claim (eg., 2 units of J1440 = filgrastim 600 µg).

For a claims-based analysis to yield clinically meaningful results on which valid, reliable plan- or program-level decisions can be based, medically relevant time frames that accurately capture resource use patterns (eg., cycles of chemotherapy) must be defined. Three analytical approaches were considered for the claims-based analysis. These approaches were: (1) use-per-time, (2) episode-of-treatment, and (3) per-chemotherapy-cycle. The use-per-time approach involved aggregating filgrastim doses per patient and reporting the average over each year (1996, 1997, 1998) and over the 1996 to 1998 3-year period. However, this approach uses arbitrarily defined time periods, which is not considered appropriate in oncology, where treatment is typically characterized by periods of intense resource use during an episode, followed by little or no use in the interepisodic periods. The episode-of-treatment approach is clinically more appropriate than the use-per-time approach since it does capture intense resource use during an episode. Under this approach, the length of an episode of treatment (including primary and secondary prophylaxis and treatment) is defined as a period where there was a minimum of 2 months before and 2 months after any month (or contiguous month) with claims for filgrastim, where no use occurred. However, the episode-of-treatment approach failed to link filgrastim utilization to chemotherapy regimens, which is the medically appropriate

![Figure 1: Medicare 5% Analysis Process Flow Chart](image-url)

**Figure 1** Medicare 5% Analysis Process Flow Chart

<table>
<thead>
<tr>
<th>Description</th>
<th>Step 1 Using 1996, 1997, and 1998 5% samples, pulled all utilization for patients receiving one or more injections of filgrastim. The majority of utilization occurred in:</th>
<th>Item 1 Link ID 1</th>
<th>Item 2 Link ID 1</th>
<th>Item 3 Link ID 1</th>
<th>Item 4 Link ID 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare Standard Analytical Files (SAFs) Available as a 5% sample and 100% files:</td>
<td>• Physician's office (82%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hospital outpatient (12%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hospital outpatient (4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**EXAMPLE (4 records):**

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Link ID 1</th>
<th>Diagnostic trailer</th>
<th>Item 1</th>
<th>Item 2</th>
<th>Item 3</th>
<th>Item 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Step 2
Split and prepared analytical files from original physician’s office and hospital outpatient files

Demographic header

Each item represents a single claim covering many reimbursement items (services, devices or drugs).

Step 3
Merged files into one analytical file by matching patient ID and link ID numbers. Created files for patients with one or more就可以在医生的办公室场景下进行资源使用分析。这些方法是：(1) 按时间使用，(2) 治疗期，和 (3) 每个化疗周期。按时间使用方法涉及聚合在患者身上的filgrastim剂量，并报告每年(1996, 1997, 1998)和1996到1998三年的平均值。然而，这种方法使用了任意定义的时间段，这不是在肿瘤学中被认为是合适的，因为治疗通常由一段时间，即高强度资源使用时期，然后在治疗间期进行。在这个方法中，一个治疗期定义为至少两个月前和两个月后的某个月(或连续的月份)与filgrastim的使用，没有使用发生。然而，治疗期的方法未能将filgrastim的使用链接到化疗方案，这在医学上是不合适的。
A method for assessing filgrastim utilization. The per-chemotherapy-cycle approach was selected for this analysis because it linked daily filgrastim utilization to a specific chemotherapy regimen. This approach is described in greater detail below.

For the per-chemotherapy-cycle analysis, patients receiving 21-day cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy were selected for the following reasons:
- CHOP is used for both early and advanced stages of non-Hodgkin’s lymphoma (NHL)
- CHOP has moderately high CIN rates
- CHOP dose intensity is particularly significant because NHL is a curative tumor
- Prophylaxis of CIN with filgrastim can help allow for increased CHOP dose intensity.

In this analysis, an algorithm was created that assigned an index date to the first claim for CHO (cyclophosphamide, doxorubicin, vincristine, and prednisone-related claims were not found in the Medicare 5% sample database. Primary (prophylactic) filgrastim use was defined as filgrastim therapy initiated within the first 5 days of a cycle of CHOP chemotherapy. Filgrastim utilization was included in the analysis if the first claim began on or between the CHO index date (day 1 of the chemotherapy regimen) and the fifth day after the index date (day 5).

Medical Chart Review

A similar cycle-based approach as outlined above was applied to a medical chart review of patients with a diagnosis of NHL. This database included patient information abstracted from 12 community and academic oncology practice settings in the United States that participated in the OPPS between 1991 and 1999. The practice settings included 2 academic centers, 5 integrated hospital systems, and 5 community practices. Data were collected by clinical staff at each site on standard case report forms. Patients were included if they had a diagnosis of NHL, were aged at least 18 years and had received CHOP chemotherapy and filgrastim at any time between 1996 and 1998.

Results

Medicare 5% Analysis

A total of 414 cancer patients who had received a total of 1,360 cycles of CHO(P) chemotherapy were included in the analysis. Patients included in this analysis received a range of 1 to 16 cycles of CHO(P) and filgrastim therapy during the study period; however, the analysis was restricted to the first 3 cycles based on historical data showing that the largest percentage of neutropenic events in patients receiving CHO(P) therapy occur during this time. During the first 3 cycles of CHO(P), the overall mean duration of filgrastim usage per cycle was 6.6 days, approximately 4.4 days shorter than the 11 days reported in clinical trials.

OPPS

A total of 80 patients who received a total of 152 cycles of CHO(P) were included in the analysis. As in the Medicare 5% data analysis, the OPPS analysis was based on the first 3 cycles of CHO(P) therapy. Analysis of the OPPS data indicated an overall mean of 9.3 days (range, 2 to 14 days) of primary filgrastim use (Table 1).

The results of the analysis of OPPS data more closely correspond to the average 11 days duration of filgrastim therapy observed in clinical trials. These results suggest that a claims-based analysis may underestimate the actual average per-cycle duration of filgrastim use when patients are dosed consistent with filgrastim prescribing recommendations for CIN.

Discussion

This study was designed to compare 2 sources of data for analysis of resource utilization of filgrastim in the CIN setting: claims data and medical chart review. A comparison of findings from analyses based on the 2 data sources revealed consistently lower (ranging from 2.3 to 3.2 days lower) estimates of the duration of primary filgrastim per chemotherapy cycle use from the Medicare 5% data as compared with the OPPS data. The result of the Medicare 5% data analysis is a mean duration of filgrastim use per chemotherapy cycle that is approximately 4.4 days less than appropriate use consistent with the prescribing information.

The estimation of mean duration of filgrastim use in the analysis of the Medicare 5% data may have been biased from the following limitations of claims data, some of which required assumptions as noted:
- Complete information on patient, tumor, and other factors involved in making treatment decisions were not captured in the claims, thus increasing the difficulty of interpreting mean duration of filgrastim use per chemotherapy cycle from a medical perspective.
- Cancer chemotherapy regimens could not be identified; therefore, we assumed that separate claims for C, H, and O represented CHOP chemotherapy.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Per-Cycle Duration of Filgrastim Use in Patients Undergoing CHO(P) Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle</td>
<td>Medicare 5% Sample</td>
</tr>
<tr>
<td>1</td>
<td>6.3 (1-14)</td>
</tr>
<tr>
<td>2</td>
<td>6.8 (1-13)</td>
</tr>
<tr>
<td>3</td>
<td>6.9 (1-13)</td>
</tr>
<tr>
<td>All</td>
<td>6.6 (1-14)</td>
</tr>
</tbody>
</table>

*This analysis was limited to claims for C, H, and O because prednisone-related claims were not found in the Medicare 5% sample database.
†OPPS NHL patients, all ages, 1996–1998.
• The purpose of filgrastim use (primary prophylaxis or treatment) was not documented; thus, filgrastim use beginning within the first 5 days of a cycle of CHOP chemotherapy was assumed to represent primary prophylaxis use.

• Because reasons for the gaps in filgrastim therapy were absent from the claims database, gaps of 2 to 3 days were assumed to represent typical treatment interruptions, such as failure to receive filgrastim during the weekend, and were ignored when counting the duration of an episode of filgrastim use.

• Filgrastim use in other care settings such as the hospital inpatient or home health care setting was not captured by the Medicare 5% sample, thus contributing to the bias of the sample.

In a separate preliminary analysis, Chrischilles et al. (written communication, January 2003) compared filgrastim utilization from the OPPS database with corresponding Medicare claims for 1994 through 1996 present in both databases; 8 patients received primary prophylactic filgrastim (early filgrastim, defined as within 8 days after the start of the first cycle of chemotherapy) according to the OPPS database. Of these, 5 had at least one filgrastim claim in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. Utilization across databases was further examined by incorporating the start date of filgrastim use, and a match was indicated if the filgrastim start date (first use) from SEER-Medicare was within 3 days of that reported in OPPS. Of the 8 early filgrastim patients in OPPS, 4 did not match because they were hospitalized during that period, and filgrastim could not be identified from inpatient claims (there are no specific codes for filgrastim in the ICD9 procedure list used for hospital claims). Among those not hospitalized (n=4), Chrischilles et al. were able to confirm OPPS-reported early filgrastim in the Medicare claims data for 3 patients and found that while the OPPS database indicated that filgrastim was ordered for the fourth patient, a chart review was not able to confirm whether it had been administered. Hence, while Medicare claims may be valid for identifying early filgrastim use in some epidemiologic studies (e.g., factors associated with neutropenia hospitalization), claims data result in substantial underestimation of total filgrastim utilization.

Because of the limitation of the claims data and the assumptions that were required, the results of the analysis of the Medicare 5% sample may provide an underestimate of filgrastim usage on a per-chemotherapy-treatment-cycle basis. Thus, as others have shown previously,13 the results shown here strongly suggest that claims-based analyses should not serve as a sole source guide to plan-level treatment choice decisions.

**Conclusion**

This analysis shows the difficulty in analyzing claims data to accurately describe medical resource use on a per-chemotherapy-cycle basis. A comparison of the duration of filgrastim use based on analysis of claims data from the Medicare 5% sample and medical chart review (OPPS data) indicated that claims data analyses may underestimate the duration of primary filgrastim use per chemotherapy cycle due to potentially significant limitations of the databases. Although the claims-based analysis was based on Medicare claims data, the implications may be relevant to other medical claims databases. Medications such as filgrastim that are used episodically and for several indications pose unique challenges in estimating of resource use based on analysis of medical claims data as a sole source of information.

**DISCLOSURES**

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**REFERENCES**


Chemotherapy-induced neutropenia (CIN) is a serious and frequent side effect of cancer chemotherapy. As the absolute neutrophil count (ANC) drops in the days after chemotherapy, the risk of infection increases. Patients with CIN may not show the typical signs of infection since neutrophils are effectors of the inflammatory response; fever may be the only indicator. Since infection in a patient with neutropenia can be rapidly life-threatening, fever with neutropenia, or febrile neutropenia (FN), is treated as a medical emergency, typically with hospitalization and the prompt administration of intravenous antibiotics.

Patients treated with myelosuppressive chemotherapy routinely experience neutropenia and its complications during their treatment. When CIN occurs, the subsequent cycles of chemotherapy may be delayed to allow for ANC recovery, or the chemotherapy doses may be reduced in an effort to minimize the incidence of CIN in later cycles. Using practice pattern data (collected between 1993 and 2000) Link and colleagues investigated chemotherapy dose delivery in patients with breast cancer and noted that there was at least one chemotherapy dose delay or reduction in nearly half of the patients (45%). Such dose delays and dose reductions may compromise the effectiveness of treatment in patients with potentially curable malignancies such as breast cancer and non-Hodgkin’s lymphoma (NHL). Studies in these 2 tumor types have identified a dose-response relationship, with higher chemotherapy dose intensity (RDI ≥ 85% in breast cancer, RDI > 75% in NHL) being associated with improved patient survival.

Chemotherapy-induced neutropenia and FN may also have substantial economic impact on health care resources. The costs of hospitalization for CIN are high and may be even greater in older patients. Kuderer and colleagues analyzed hospital-admission data from the University HealthSystem Consortium database for the years 1995 through 2000 and found that the average cost of admissions was approximately $19,369 per hospitalization ($12,302 for solid tumors, $27,340 for hematologic malignancies). Thus, reducing the incidence of CIN has the potential to save the health care system significant economic resources.

The clinical and economic impacts of CIN and FN may be reduced by supportive therapy with hematopoietic colony-stimulating factors (CSFs) that stimulate the growth and differentiation of neutrophils. The current clinical practice guidelines of the American Society of Clinical Oncology (ASCO) for the use of CSFs recommend a “watch and wait” approach unless the chemotherapy regimen is associated with a risk of FN of 40% or higher, or the patient has one of the special circumstances outlined by ASCO. Unless these criteria are met, the guidelines recommend that prophylactic growth factors not be used until an episode of FN has occurred and thus “proved” the need for growth factors. Unfortunately, this “watch and wait” approach can result in dose delays and reductions, which can have serious consequences in
patients with potentially curable malignancies.

Delivering standard-dose chemotherapy on time is particularly important in elderly patients, who are at higher risk for hospitalization for FN than younger patients (odds ratio 2.17; 95% CI, 1.43-3.30; \( P < 0.05 \)), and in whom dose reduction is associated with poorer outcomes. Accordingly, the National Comprehensive Cancer Network recommends the routine use of growth factor support, starting in cycle 1, in older patients who are treated with myelosuppressive chemotherapy.

Filgrastim and pegfilgrastim are CSFs designed to decrease the incidence of infection, as manifested by FN, in patients with non-myeloid malignancies treated with myelosuppressive anticancer drugs. Filgrastim is administered as a daily injection throughout the expected ANC nadir, until the ANC has recovered to at least \( 10 \times 10^9/L \), the recommended end point in therapy with colony-stimulating factors. Pegfilgrastim, used once per chemotherapy cycle, is administered as a single, fixed-dose injection. This article reviews the clinical data on filgrastim and pegfilgrastim. The data show that when these CSFs are used appropriately, they are effective in reducing the risks and incidence of neutropenic complications.

### Clinical Impact of Granulocyte Colony-Stimulating Factors

#### Filgrastim

Filgrastim was approved by the U.S. Food and Drug Administration (FDA) in 1991 and has since been used in approximately 3.5 million patients. Filgrastim is indicated to decrease the incidence of infection, as manifested by FN, in patients with non-myeloid malignancies treated with myelosuppressive anticancer drugs. Based on data submitted to the FDA, the following dosing recommendations were made:

Filgrastim should be administered no sooner than 24 hours after the administration of cytotoxic chemotherapy and should be administered daily for up to 14 days, until the ANC has reached \( 10 \times 10^9/L \) after its expected nadir.

The elimination half-life of filgrastim in healthy subjects and patients with cancer is approximately 3.5 hours, which necessitates daily dosing. Owing to the short serum half-life of the drug, the serum levels of filgrastim fluctuate with daily dosing. One of the reasons for administering filgrastim to an ANC of at least \( 10 \times 10^9/L \) is that the ANC can decrease by approximately 50% within the first 48 hours after the discontinuation of daily dosing. Thus, stopping earlier may put the patient at greater risk of FN and related negative sequelae.

The safety and efficacy of filgrastim were evaluated in 2 similar phase 3 trials, one conducted in the United States and the other in Europe. Patients with small-cell lung cancer were randomized to either filgrastim or placebo daily, starting 24 hours after the completion of chemotherapy cycle 1 and continuing in each cycle. Filgrastim and placebo were given for a maximum of 14 days or until a postnadir ANC of \( 10 \times 10^9/L \). Cyclophosphamide and doxorubicin were administered on day 1 only with etoposide given on days 1, 2, and 3.

Filgrastim significantly reduced the severity and duration of CIN (Figure 1), with an earlier ANC nadir, shorter median duration of severe neutropenia (DSN) (3 versus 6 days; \( P < 0.001 \)), and a faster recovery of the ANC to its prechemotherapy value. The number of days of severe neutropenia in a cycle was also substantially less with filgrastim (median, 1 versus 6 days). Filgrastim was effective over all 6 cycles.

Data on the clinical end points in both pivotal trials are shown in Figure 2. The incidence of first-cycle FN and the overall incidence of FN were approximately 50% less with filgrastim in both studies. Patients were treated with filgrastim for approximately 11 days to achieve these outcomes. Hospitalization rates and the use of intravenous antibiotics were significantly less with filgrastim (37% versus 58%; \( P < 0.02 \), and 39% versus 58%; \( P < 0.04 \), respectively) in the European trial. The rates of culture-confirmed infections were less in the filgrastim arms in both trials, but the differences were not significant.

Dosing inconsistent with that specified in the prescribing infor-
Information for filgrastim may produce suboptimal outcomes. The start of filgrastim therapy has been delayed in clinical practice due to the potential inconvenience of daily injections and cost constraints. Koumakis and colleagues have shown that both the incidence of FN and the total duration of filgrastim therapy increase when the administration of filgrastim after chemotherapy is delayed.18 When filgrastim was given 24 hours after high-dose cyclophosphamide, the incidence of FN was 16%, and it was administered for an average of 11.5 days. When filgrastim was initiated at 96 hours, the rate of FN increased to 66%, and 15.5 days of therapy was required. Delaying filgrastim administration to more than 72 hours after chemotherapy was shown to result in more febrile episodes, antibiotic use, and higher cost.

In summary, supportive care with filgrastim significantly reduced the DSN, decreased the rate of FN and length of stay by 50%, and also decreased the use of intravenous antibiotics and the duration of their use. On average, 11 days of filgrastim support was necessary to achieve these benefits. These are important clinical measures in patients treated with myelosuppressive chemotherapy, and the appropriate use of filgrastim produces optimal outcomes.

Pegfilgrastim
Pegfilgrastim is created by the covalent attachment of a 20-kd polyethylene glycol (PEG) moiety to the N-terminal of filgrastim. Filgrastim is cleared from the body by 2 mechanisms: neutrophil-mediated clearance and excretion by the kidneys.19 The greater size of the pegfilgrastim molecule due to the addition of the PEG moiety impedes renal clearance, resulting in the longer half-life of pegfilgrastim. Neutrophil-mediated clearance is, therefore, the major route of elimination of pegfilgrastim. However, this route is less active in neutropenic patients, in whom mature neutrophils have been depleted. As the neutrophil count recovers, the elimination of pegfilgrastim is accelerated. Consequently, this self-regulated clearance mechanism allows pegfilgrastim to remain in the body during periods of neutropenia and clears it from the body upon ANC recovery. This neutrophil-mediated clearance enables treatment with a single dose of pegfilgrastim per chemotherapy cycle.

The safety and efficacy of pegfilgrastim were shown in 2 similar double-blind randomized phase 3 trials, one conducted in the United States20 and the other primarily in Europe.21 All patients had breast cancer and were treated with up to 4 cycles of adjuvant chemotherapy with doxorubicin and docetaxel. Patients were randomized to a single dose of pegfilgrastim per chemotherapy cycle (6-mg fixed dose in the European study, 100-µg/kg weight-based dose in the U.S. study) or filgrastim (5 µg/kg/d to an ANC >10 x 10⁹/L or for 14 days, whichever came first). The study drugs were started 24 hours after the completion of the chemotherapy and were continued in each subsequent chemotherapy cycle.

Data on the primary end point in these trials are shown in Figure 3. A single dose of pegfilgrastim given once per chemotherapy cycle shortened the DSN as effectively as daily filgrastim. The U.S. study found that the mean DSN in cycle 1 was 1.8 days with filgrastim and 1.7 days with pegfilgrastim; in the European study it was 1.6 days with filgrastim and 1.8 days with pegfilgrastim. The rates of FN across all chemotherapy cycles in both studies ranged from approximately 10% to 20%. The rate with pegfilgrastim and filgrastim was 13% versus 20% (P<0.05) in the U.S. trial.

Misset et al. have reported that similar chemotherapy regimens result in a 100% rate of severe neutropenia in the absence of growth factor, with a mean duration of neutropenia of 5 to 7 days and an incidence of FN of 30% to 40%.22 Thus, pegfilgrastim provides protection from CIN and FN comparable to that with filgrastim with only one dose per chemotherapy cycle.
Duration of Therapy With Filgrastim and Pegfilgrastim

The number of injections of filgrastim necessary to achieve the desired clinical end points is shown in Table 1. The clinical benefits of filgrastim relative to placebo were well established in 2 phase 3 trials, which show that optimal benefits are achieved when filgrastim is initiated 24 hours after chemotherapy and continued until the ANC has reached $10 \times 10^9/L$ after its expected nadir. This required approximately 11 daily injections of filgrastim. Similiarly, in the 4 pegfilgrastim trials, a single dose of pegfilgrastim per chemotherapy cycle was compared with daily filgrastim. As shown in Table 1, these studies established that a single dose of pegfilgrastim produces outcomes comparable to those with 11 doses of filgrastim.1,2,3,4

Meza and colleagues conducted a combined analysis of the data from the 2 pivotal pegfilgrastim trials. They determined the time to ANC recovery and the number of filgrastim injections administered in these trials. They found that by days 12 to 14, 90% of patients who had been given filgrastim had a postnadir ANC of $10 \times 10^9/L$, the recommended end point in therapy with colony-stimulating factors.3 Median time to ANC $\geq 10 \times 10^9/L$ was 11 days in all cycles, and the median time to ANC $\geq 2 \times 10^9/L$ was only 1 to 2 days less.

Conclusions

Filgrastim and pegfilgrastim are safe and effective in ameliorating CIN, the major dose-limiting toxicity of chemotherapy. Nonetheless, as evidenced in the literature, patients continue to be hospitalized for FN and to be given a lower than intended chemotherapy dose, even though maintaining the dose intensity is known to correlate with optimal clinical outcomes in certain types of cancers. The costs of treating FN and its clinical sequelae are substantial, both to patients and to the health care system.

The reasons for these suboptimal outcomes may be reactive “watch and wait” use (not using growth factor support prophylactically when it is indicated), not administering the complete course of growth factors, and delaying the initiation of growth factors.

The clinical trials for filgrastim and pegfilgrastim have shown that these CSFs significantly reduced the incidence of first-cycle FN and the overall incidence of FN, as well as the DSN, length of stay, and the use of intravenous antibiotics. Pegfilgrastim provides all the clinical benefits of daily filgrastim for CIN with a single dose per chemotherapy-cycle, replacing approximately 11 injections of filgrastim per cycle. It is possible that with this simplified once-per-chemotherapy-cycle dosing regimen for pegfilgrastim, more patients may be able to achieve positive clinical outcomes.

DISCLOSURES

Author John W. Mucenski is on speakers bureaus of Amgen, Aventis, Merck, and OrthoBiotech and on the advisory boards of Amgen, Aventis, and Genentech, with compensation. Mucenski served as principal author of this study. Critical revision of the manuscript and analysis and interpretation of data were the work of Mucenski and author Jeffrey E. Shogan.

REFERENCES


Maximizing the Outcomes in Cancer Patients Receiving Chemotherapy Through Optimal Use of Colony-Stimulating Factor


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

Methods

Study Design and Patient Selection

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

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.3-5 Therefore, preventing febrile neutropenia is warranted in patients with cancer treated with cytotoxic chemotherapy, both to improve patient outcomes and to reduce the costs of related treatment.6-8

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.9-12 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.7,13-15 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 affect 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.
Days of Prophylactic Filgrastim Use to Reduce Febrile Neutropenia in Patients With Non-Hodgkin’s Lymphoma Treated With Chemotherapy

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 conditions, cancer disease stage, number of extranodal sites involved, lactate dehydrogenase (LDH) level, presence of B symptoms (i.e., 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.

### Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (N=170)</th>
<th>Primary Filgrastim* (n=62)</th>
<th>Secondary Filgrastim† (n=108)</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 years</td>
<td>93 (54.7)</td>
<td>37 (59.7)</td>
<td>56 (51.8)</td>
<td>0.409</td>
</tr>
<tr>
<td>BSA below median (1.9 m²)</td>
<td>92 (54.1)</td>
<td>33 (53.2)</td>
<td>59 (54.6)</td>
<td>0.987</td>
</tr>
<tr>
<td>Female sex</td>
<td>84 (49.4)</td>
<td>34 (54.8)</td>
<td>50 (46.3)</td>
<td>0.361</td>
</tr>
<tr>
<td>CCI ≥1</td>
<td>56 (32.9)</td>
<td>18 (29.0)</td>
<td>38 (35.2)</td>
<td>0.514</td>
</tr>
<tr>
<td>Presence of renal disease</td>
<td>9 (5.3)</td>
<td>1 (1.6)</td>
<td>8 (7.4)</td>
<td>0.205</td>
</tr>
<tr>
<td>Presence of heart disease</td>
<td>22 (12.9)</td>
<td>11 (17.7)</td>
<td>11 (10.2)</td>
<td>0.240</td>
</tr>
<tr>
<td>Advanced stage disease (III or IV)</td>
<td>63 (40.4)</td>
<td>25 (42.4)</td>
<td>38 (35.2)</td>
<td>0.821</td>
</tr>
<tr>
<td>≥2 extranodal sites</td>
<td>26 (15.3)</td>
<td>12 (25.0)</td>
<td>14 (19.2)</td>
<td>0.592</td>
</tr>
<tr>
<td>Elevated LDH level</td>
<td>68 (50.0)</td>
<td>27 (56.3)</td>
<td>41 (46.6)</td>
<td>0.370</td>
</tr>
<tr>
<td>Presence of B symptoms</td>
<td>45 (26.5)</td>
<td>20 (32.3)</td>
<td>25 (23.2)</td>
<td>0.265</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td>15 (14.2)</td>
<td>5 (14.7)</td>
<td>10 (13.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Histology (working formulation):</td>
<td>48 (30.6)</td>
<td>14 (24.1)</td>
<td>34 (34.4)</td>
<td>0.114</td>
</tr>
<tr>
<td>• follicular, immunoblastic (D, H), and intermediate NOS</td>
<td>14 (21.6)</td>
<td>10 (17.3)</td>
<td>24 (24.2)</td>
<td></td>
</tr>
<tr>
<td>• small/mixed small and large cell/diffuse (E,F)</td>
<td>75 (47.8)</td>
<td>34 (58.6)</td>
<td>41 (41.4)</td>
<td></td>
</tr>
<tr>
<td>Radiation treatment given</td>
<td>5 (2.9)</td>
<td>0 (0.0)</td>
<td>5 (4.6)</td>
<td>0.212</td>
</tr>
<tr>
<td>Planned ARDI ≤80%</td>
<td>19 (11.2)</td>
<td>7 (11.3)</td>
<td>12 (11.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Delivered ARDI ≤80%</td>
<td>34 (20.0)</td>
<td>14 (22.6)</td>
<td>20 (18.5)</td>
<td>0.661</td>
</tr>
</tbody>
</table>

* 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, χ² test.
BSA=body surface area CCI=modified Charlson comorbidity index LDH=lactate dehydrogenase ARDI=average relative dose intensity
Days of Prophylactic Filgrastim Use to Reduce Febrile Neutropenia in Patients With Non-Hodgkin’s Lymphoma Treated With Chemotherapy

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) 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 neutropenia 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. 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., 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. 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 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...
Days of Prophylactic Filgrastim Use to Reduce Febrile Neutropenia in Patients With Non-Hodgkin’s Lymphoma Treated With Chemotherapy

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 19 m² remained significantly associated with an increased risk of febrile neutropenia (OR 1.8; 95% CI, 1.2-3.0).

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 19 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. 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

<table>
<thead>
<tr>
<th>Table 2</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted Risk of FN in Cycle (Univariate)</td>
<td></td>
</tr>
<tr>
<td>Characteristics</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>0.946</td>
</tr>
<tr>
<td>BSA below median (1.9 m²)</td>
<td>1.997</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.878</td>
</tr>
<tr>
<td>CCI ≥2</td>
<td>0.633</td>
</tr>
<tr>
<td>Presence of renal disease</td>
<td>0.665</td>
</tr>
<tr>
<td>Presence of heart disease</td>
<td>0.584</td>
</tr>
<tr>
<td>Advanced-stage disease (III or IV)</td>
<td>0.540</td>
</tr>
<tr>
<td>≥2 extranodal sites</td>
<td>0.738</td>
</tr>
<tr>
<td>Elevated LDH level</td>
<td>1.265</td>
</tr>
<tr>
<td>Presence of B symptoms</td>
<td>0.784</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td>0.473</td>
</tr>
<tr>
<td>Histology (working formulation)</td>
<td></td>
</tr>
<tr>
<td>• Large cleaved or noncleaved cell/diffuse (G)</td>
<td>0.780</td>
</tr>
<tr>
<td>• Small/mixed cell diffuse (E, F)</td>
<td>0.965</td>
</tr>
<tr>
<td>Radiation treatment given</td>
<td>1.406</td>
</tr>
<tr>
<td>Planned ARDI ≤80%</td>
<td>1.346</td>
</tr>
<tr>
<td>Delivered ARDI ≤80%</td>
<td>1.080</td>
</tr>
<tr>
<td>Primary prophylactic filgrastim*</td>
<td>0.507</td>
</tr>
<tr>
<td>Group 1 (mean 4.7 days filgrastim treatment)</td>
<td>2.088</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Table 3</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted Risk of FN in Cycle (Multiple)</td>
<td></td>
</tr>
<tr>
<td>Characteristics</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>BSA below median (1.9 m²)</td>
<td>1.849</td>
</tr>
<tr>
<td>Prophylactic filgrastim administration*</td>
<td></td>
</tr>
<tr>
<td>• Primary prophylaxis† (mainly Group 2)</td>
<td>0.295</td>
</tr>
<tr>
<td>• Secondary prophylaxis‡ and Group 2‡</td>
<td>0.433</td>
</tr>
<tr>
<td>• Secondary prophylaxis‡ and Group 1¶</td>
<td>1.000</td>
</tr>
</tbody>
</table>

* 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.
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Four of 17 filgrastim administrations in Group 1 were given in cycle 1. Primary prophylaxis—first prophylactic filgrastim use within the first 3 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 36 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

This study was supported by an unrestricted grant from Amgen and was funded as part of a larger study by authors Shane D. Scott, Elizabeth A. Chrischilles, and Brian K. Link. Authors David J. Delgado and Bradley S. Stolshek are employees and shareholders of Amgen, and Scott has received honoraria from Amgen. Scott served as principal author of this study. Study concept and design were primarily the work of Scott, Delgado, Link, and author Moshe Fridman. Drafting of the manuscript was the work of Delgado, Scott, Stolshek, and Fridman; critical revision was the work of all authors. Analysis and interpretation of data was the work of Scott, Delgado, Link, Fridman, and Chrischilles, and statistical expertise was contributed primarily by Fridman and Chrischilles.

REFERENCES

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


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Posttest Answers:

|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 1 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 2 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 3 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 4 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
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| 6 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 7 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 8 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 9 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 10 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

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1. The types of data that may be useful in a formulary submission include
   A. Safety and efficacy data from clinical trials
   B. Data from retrospective studies
   C. Prospective outcomes study data
   D. All of the above

2. Filgrastim is indicated to decrease the incidence of infection in patients who are receiving
   A. Medication for hypertension
   B. Chemotherapy for cancer
   C. Medication for epilepsy
   D. All of the above

3. Which source of data provides clinical information such as the date of the initial diagnosis, disease stage, and size of the tumor?
   A. Pharmacy claims databases
   B. Disease-specific registries
   C. Medical claims databases
   D. None of the above

4. Claims data typically lack important information such as
   A. Severity of illness
   B. Specific reason for drug use
   C. The criteria used in making the treatment choice
   D. Clinical outcomes
   E. All of the above

5. The advantage of using administrative databases is that the data are from a random patient sample
   A. True
   B. False

6. The prescribing information for filgrastim recommends administration until the postnadir absolute neutrophil count (ANC) has reached
   A. $2 \times 10^9/L$
   B. $6 \times 10^9/L$
   C. $10 \times 10^9/L$
   D. $15 \times 10^9/L$

7. Claims data analyses are sufficient as the sole source for developing treatment plans for health care organizations.
   A. True
   B. False

8. Clinical guidelines and other important medical decisions should ideally be based on validated, methodologically sound data sources such as
   A. Clinical trial results
   B. Medical chart reviews
   C. Prospective studies
   D. A and B
   E. All of the above

9. Chemotherapy-induced neutropenia (CIN) is the major dose-limiting toxicity of chemotherapy. It is important to minimize the impact of CIN because
   A. CIN is life-threatening
   B. Subsequent cycles of chemotherapy may be delayed to allow for ANC recovery
   C. Chemotherapy doses may be reduced in an effort to prevent episodes of CIN in later cycles
   D. All of the above

10. Clinical trials show that CSFs like pegfilgrastim and filgrastim
    A. Are safe but not effective in managing CIN
    B. Are effective in managing CIN, but may be toxic at high doses
    C. Are both safe and effective in managing CIN
    D. Are neither safe nor effective in managing CIN

11. Based on data submitted to the FDA (and filgrastim prescribing information), it is recommended that
    A. Filgrastim be administered no sooner than 24 hours after the administration of cytotoxic chemotherapy
    B. Filgrastim not be administered daily
    C. Filgrastim administration be continued until the ANC has reached $10 \times 10^9/L$ after its expected nadir
    D. A and C

12. Which of the following statements is false?
    A. Supportive care with filgrastim significantly reduced the duration of severe neutropenia.
    B. Supportive care with filgrastim decreased the rate of febrile neutropenia.
    C. Supportive care with filgrastim increased the use of intravenous antibiotics and the duration of their use.
    D. Supportive care with filgrastim has the potential to save health care resources while also improving patient outcomes.
13. According to findings from clinical trials, how many daily injections of filgrastim per chemotherapy cycle are required to achieve clinical benefits?
   A. Approximately 3 or 4
   B. Approximately 5 to 7
   C. Approximately 10 to 11
   D. Approximately 18 to 20

14. Pegfilgrastim provides all the clinical benefits of daily filgrastim for CIN with a single dose per chemotherapy cycle.
   A. True
   B. False

15. Which of the following statements on the economic consequences of CIN is true?
   A. The average cost of hospitalization for febrile neutropenia is higher in older patients.
   B. The cost of hospitalization varies by tumor type.
   C. Febrile neutropenia increases the costs associated with cancer.
   D. All of the above

16. Patients >65 years of age may be at
   A. Higher risk for febrile neutropenia
   B. Lower risk for febrile neutropenia
   C. The same risk for febrile neutropenia as younger patients

17. The study by Scott et al. showed that a greater risk of febrile neutropenia was associated with
   A. Lower body surface area
   B. A lack of primary prophylaxis with filgrastim
   C. Secondary prophylaxis for a shorter duration
   D. B and C
   E. All of the above

18. Scott et al. found that most CIN in patients being treated with CHOP chemotherapy occurs in
   A. Cycle 3 of chemotherapy
   B. Cycles 1 and 2 of chemotherapy
   C. All cycles of chemotherapy
   D. Cycles 4 through 7 of chemotherapy

19. The incidence of febrile neutropenia was ______ in patients treated with more days of secondary prophylaxis (mean of 10.1) than in patients treated with fewer days of secondary prophylaxis (mean of 4.7).
   A. Higher
   B. Lower

20. In the study by Scott et al. the mean duration of filgrastim prophylaxis was ______ days in patients in group 2 (patients given filgrastim for ≥7 days).
   A. 4.7
   B. 9.5
   C. 10.1
   D. 13.6
Pharmacoeconomics and Considerations for Injectable Products: Focus on Colony-Stimulating Factors

Participant’s name: _________________________ Date: ________________

Your assistance in the evaluation process is greatly appreciated. Please return this form with the posttest answers.

Scale For Questions 1–4
1. describe the sources of data available for pharmacoeconomic analyses and new product evaluation,    ____________
2. identify the challenges in analyzing the data available on colony-stimulating factors (CSFs) and in evaluating data from different sources,    ____________
3. summarize the clinical trials that established the safety and efficacy of the CSFs filgrastim and pegfilgrastim in the management of chemotherapy-induced neutropenia, and    ____________
4. evaluate practice patterns of filgrastim use and associated outcomes using real-world data.    ____________

Scale For Questions 5–7
5. What is your overall rating of this program?    ____________
6. How would you rate the pertinence of the program materials to your practice?    ____________
7. Please rate each of the following program aspects:
   a. Content    ____________
   b. Clarity    ____________
   c. Knowledge gained    ____________
8. To what degree do you anticipate changes in patient care as a result of the material presented? (circle one)
   1= No change
   2= Partial change
   3= Significant change
   4= Significant change
8. To what degree do you anticipate changes in patient care as a result of the material presented? (circle one)
   1= No change
   2= Partial change
   3= Significant change
   4= Significant change
   5= Very significant change
9. Please indicate the length of time it took to complete this program: (Circle selection)
   Hours: 1 2 3
   Minutes: 0 15 30 45
10. Please rate the difficulty factor for completing this CE program: (Circle selection) Easy Moderate Difficult
11. Please rate your willingness to recommend this program to colleagues: (Circle selection)
    Very willing  Willing  Not willing
12. Please indicate which venue you prefer for obtaining continuing education: (Circle selection)
    Written monograph  Slides  Videos  Internet-based
    Live sessions  Other: _________________________

Using the scale above for Questions 1–4, please rate how well you will be able to accomplish the following objectives based upon successful completion of the program.

Using the scale above for Questions 5–7, please indicate the number that best expresses your opinion.