

Therapeutic Insights and Review

FROM THE PUBLISHERS OF

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TARGET AUDIENCE

This educational activity is intended for pharmacists with an interest in the contemporary management of anemia.

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Contemporary Growth Factor Management: Three Institutional Perspectives

EDUCATIONAL OBJECTIVES

Upon completion of this program, participants should be able to:

- Identify the true cost of long-acting growth factors and the operational management of long-acting versus short-acting growth factors
- Describe the development and implementation of a pharmacy-initiated outpatient anemia management program
- Discuss the expanded role of the pharmacist in optimizing appropriate erythropoietic stimulating protein (ESP) utilization in the outpatient setting through guideline reinforcement
- Characterize hospital admissions for febrile neutropenia with respect to outpatient administration of filgrastim or pegfilgrastim

Growth Factor Management in Chemotherapy-Induced Anemia and Neutropenia

Robert Adamson, PharmD

BACKGROUND

Supportive care for cancer patients is designed to minimize or prevent chemotherapy-induced side effects and disease-related symptoms and complications. Two of the most profound side effects that chemotherapy patients experience are anemia and neutropenia. Chemotherapy-induced anemia management has been dramatically changed with the advent of epoetin alfa (*Procrit*) and darbepoetin alfa (*Aranesp*). Equally, chemotherapy-induced neutropenia management has been changed by the granulocyte colony-stimulating factors (G-CSFs), filgrastim (*Neupogen*) and pegfilgrastim (*Neulasta*). Due to the ability of these agents to prevent or minimize the impact of these side effects, they have become the cornerstone of adjunctive therapy for the majority of patients undergoing chemotherapy.

Darbepoetin alfa and epoetin alfa are designed to stimulate progenitor cells and thus ultimately increase red blood cell production. There have been several head-to-head studies published in abstract and manuscript form demonstrating similar hemo-

globin (Hgb) response rates for both products, with darbepoetin alfa affording the advantage of a less frequent dosing interval.^{1,2} Although, the financial implications for the use of these products are quite significant, health care professionals must consider the impact that erythropoietic stimulating proteins (ESPs) have on quality of life (QOL) for patients receiving chemotherapy and/or those with malignancy. Glaspy et al demonstrated in a study including over 2,000 patients that epoetin alfa was effective in improving QOL and functional status in patients receiving chemotherapy, most likely as a result of increased Hgb levels.³ Demetri et al concluded that patients treated with epoetin alfa had an improvement in patient reported QOL regardless of tumor type or response.⁴ Additionally, in a study of over 200 anemic patients with nonmyeloid tumors receiving multicycle chemotherapy conducted by Vadhan-Raj et al, patients receiving darbepoetin alfa demonstrated an increase in patient-reported fatigue and energy scores.⁵

Neutropenia and its associated complication of infection continues to be a significant cause of morbidity and mortality in oncology patients receiving myelosuppressive chemotherapy.⁶ Risk of infection and mortality increases with the severity and duration of the neutropenic episode and with the presence of fever.⁷ Early intervention with broad spectrum antibiotics has been shown to improve outcomes in patients with febrile neutropenia. However, a subset of these patients requires protracted hospital stays and develop severe medical complications. Prophylactic administration of a G-CSF, filgrastim (*Neupogen*) or pegfilgrastim (*Neulasta*), has been shown to shorten the neutropenic period, and reduce the incidence of febrile neutropenia by at least 50% in high-risk patients undergoing chemotherapy.⁸⁻¹¹

ECONOMIC CONSIDERATIONS

In a recent review, ESP and G-CSF products accounted for three of the top five medications hospitals purchase for outpatient departments.¹² Directors of Pharmacy often struggle with the impact that the cost and growth of these agents have on their annual budgets. Traditionally, a drug's economic impact is measured by the direct cost of the agent offering only one piece of the economic ramifications for hospitals and health systems. However, additional elements are necessary for the complete economic evaluation of a growth

factor such as the effect on patient throughput, reimbursement and cost recovery, separation of pharmacy budgets into Diagnostic Related Group (DRG) and non-DRG segments, and avoidance of neutropenic hospitalizations.

Patient throughput (the patient capacity of a given service area) is a critical variable when measuring the impact of long-acting growth factors. Historically, a patient using short-acting growth factors, epoetin alfa and filgrastim, for a standard 3-week cycle of chemotherapy might be expected to return to the clinic four times for their epoetin alfa and seven to 10 times for their filgrastim injection. This coupled with their chemotherapy administration results in 10 to 13 visits on a monthly basis. Generally, the reimbursement for a growth factor injection is 1/20 of the reimbursement for chemotherapy administration. Therefore, increasing chemotherapy administration in lieu of growth factor injections is financially desirable to health systems. With the advent of long-acting growth factors, darbepoetin alfa and pegfilgrastim, patient visits can be reduced to four times a month increasing the capacity to treat more patients with chemotherapy. These operational efficiencies were validated by both Beverage and Griffith and colleagues who found that growth factor administration is significantly reduced when long-acting agents are used.^{13,14}

A pharmacy budget is typically designed from a cost center perspective accounting only for cost of medications and not their reimbursement. Under the DRG system, hospitals are reimbursed a fixed amount for a particular disease state for their inpatient population. Due to the structure of reimbursement, hospitals are given incentives to use the most cost effective therapy. However, the outpatient arena is a non-DRG system, which allows individual drugs to be billed in order to recoup cost and a margin. A non-DRG medication's financial profile should only be evaluated by the cost recovery or margin in contrast to DRG medications, where cost is the only financial consideration. Thus, by separating these agents by their DRG classification, medications that have been traditionally viewed as expensive may now be viewed as profitable for the hospital, alleviating the administrator's directives to decrease pharmacy budgets.

Neutropenia and its clinical sequelae may result in extended hospital stays usually exceeding the DRG payment.^{15,16} Clinicians have been adminis-

tering a short-acting G-CSF to minimize or avoid febrile neutropenic admissions. In order to maximize the effectiveness of a short-acting G-CSF, patients are required to receive seven to 10 injections of filgrastim. This poses significant logistical challenges within the clinic and for patients resulting in missed doses; long-acting G-CSF (pegfilgrastim) offers the convenience of one dose per chemotherapy cycle ensuring a full-course of therapy and thus decreasing the number of febrile neutropenic admissions.^{17,18}

The last consideration is the impact long-acting growth factors have on patients and care givers. Decreasing the clinic visits can have a dramatic effect on time commitments of patients and their caregivers. Fortner et al found that 83% of all patients required assistance with transportation to and from the clinic.¹⁹ Patients and caregivers often need to take paid and unpaid time-off from work to accommodate appointments. Long-acting growth factors decrease the number of clinic visits, minimizing the impact on their day-to-day activities.

Economic concerns are a fact of modern medicine, and the analysis of operational considerations such as patient throughput, reimbursement and cost recovery, separating pharmacy budgets into DRG and non-DRG segments and avoidance of neutropenic hospitalizations will help to determine the true cost of growth factors within hospitals.

GUIDELINES FOR THE MANAGEMENT OF ANEMIA AND NEUTROPENIA

Evidence continues to evolve supporting the effective use of ESPs and G-CSFs in chemotherapy-induced anemia and neutropenia, respectively. As a result, there has been a dramatic increase in the use of these agents creating unique clinical, as well as, economic issues. Appropriate management of ESPs and G-CSFs can be achieved through the implementation of effective medication use guidelines. Usage guidelines assist in reducing errors and improving communication between team members. Guidelines ensure that each member of the health care team is adhering to the same criteria to achieve mutually agreed-upon goals. In addition, guidelines promote the most cost-effective use and administration of these agents, while preserving optimal patient outcomes.

THREE INSTITUTIONAL PERSPECTIVES

In terms of anemia management, two pharmacy

specialists describe how ESP guidelines impacted drug use in their respective oncology outpatient clinics. Ms. Niesha Griffith provides a descriptive account of the development, implementation, and current success of an outpatient anemia management program initiated at the Arthur G. James Cancer Hospital. Mr. David Baribeault provides the positive results of a medication usage evaluation (MUE) focusing on the strict enforcement of ESP guideline adherence in the oncology clinic at Boston Medical Center. In review of neutropenia management, a third pharmacy specialist, Dr. Indu Lew of St. Barnabas Health Care System, examines inpatient use of filgrastim in a select population of patients who received either filgrastim or pegfilgrastim in their outpatient oncology clinic focusing on usage patterns and hospital admission rates.

The Arthur G. James Cancer Hospital's Anemia Management Program

Niesha Griffith, MS, RPh

BACKGROUND

The Arthur G. James Cancer Hospital (hereafter referred to as “The James”) is a free-standing cancer center located on The Ohio State University campus in Columbus, OH, that offers patients an extensive, modern hospital dedicated to the detection and treatment of cancer. The James is one of just a few freestanding cancer research and treatment hospitals in the US, and the only one in Ohio. In addition to 160 inpatient beds, The James recently expanded its Bone Marrow Transplant unit to 24 beds and opened its fourth outpatient oncology clinic. The hospital is in the midst of a major expansion initiative that will double its inpatient capacity, increase outpatient facilities by 10 times, and significantly add to the Comprehensive Cancer Center's research space.

Similar to pharmacy departments at other large cancer centers, meeting the demands of rapid growth, justifying the increasing cost of drugs, and ensuring the appropriate use of medications are among the greatest challenges. With annual expenditures of over 3 million dollars and rising,

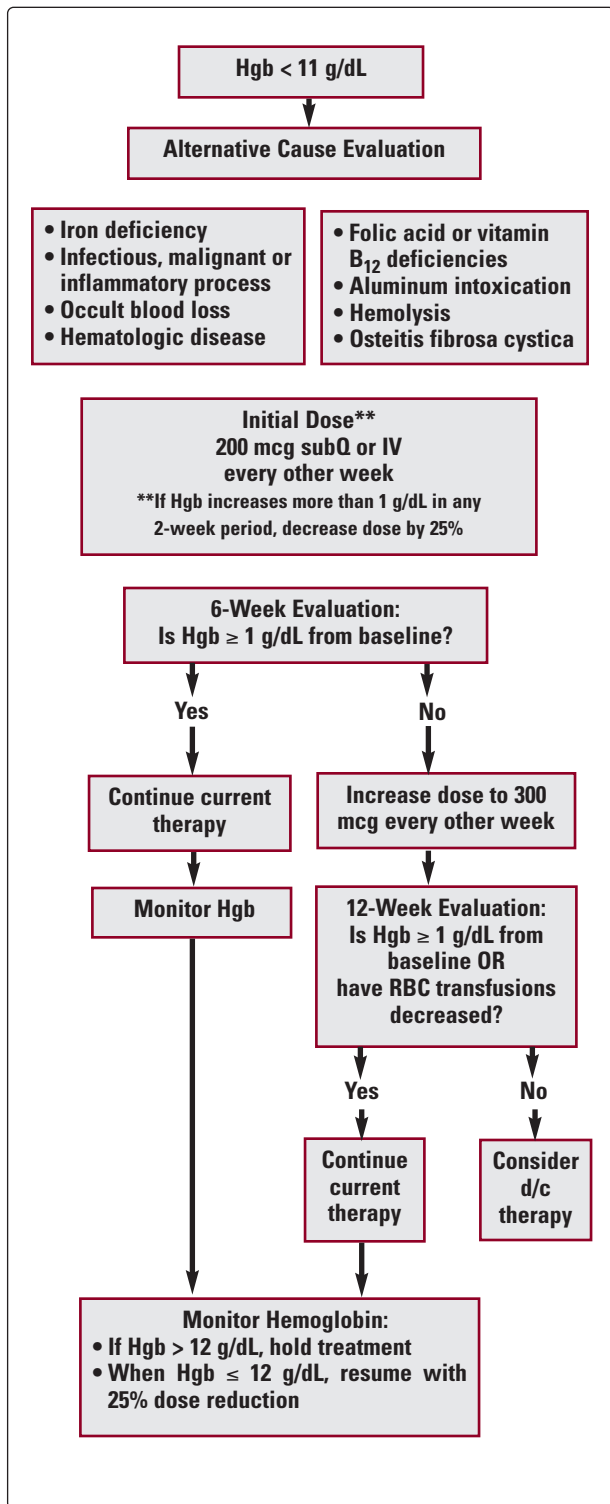


Figure 1. Clinical pathway for darbepoetin alfa in anemia associated with chemotherapy treatment in patients with nonmyeloid malignancies.

Hgb = hemoglobin; mcg = micrograms; SubQ = subcutaneously; IV = intravenously; d/c = discontinue

ESPs continue to be high on the priority list for evaluation. Despite the existence of Medication Use Evaluation (MUE) guidelines for epoetin alfa (developed in 1998) and darbepoetin alfa (developed in 2003) which include dosing and titration recommendations, as well as monitoring and adjustment parameters (see Figure 1), adherence to the guidelines continued to be identified as an area for improvement.

A pharmacy initiated review of approximately 60 outpatients receiving darbepoetin alfa for chemotherapy-induced anemia or anemia of malignancy, conducted from February to July 2003, revealed that less than 50% of patients were receiving their dose within the guideline-defined interval. In addition, Hgb responses appeared to be less than those realized in published clinical trials. Thus, it was determined that a performance improvement initiative targeting anemia management in the outpatient oncology population was warranted.

Previous initiatives to increase the appropriate use of epoetin alfa, when it was the sole formulary agent, were unsuccessful. One strategy included the use of a patient-specific tracking sheet to be completed by the nurse at each clinic visit. This tool provided the actual MUE guidelines and prompts for nursing to review the patient's current labs (specifically Hgb and HCT), to contact the physician(s) for dosing changes, and/or to hold doses per established guidelines. Nurses were also prompted at the automated distribution cabinet to complete the tracking sheet each time epoetin alfa was selected for removal.

Despite repeated educational efforts, the tracking sheets were not routinely completed. Increasing nursing responsibilities, increasing patient volume, and difficulty obtaining patient charts were identified as the major reasons for lack of success with these efforts. Consequently, patients continued to miss doses and appointments, receive unnecessary doses, and were not prescribed appropriate dose escalation and/or de-escalation.

Efforts were made to educate physicians regarding the importance of adherence to the guidelines, primarily for the clinical benefit to the patient, but also because of the significant financial implications to the institution. Information was shared at the physician faculty meetings, as well as one-on-one with the physicians who routinely prescribed ESPs. Although the physician interventions

1. Identify key players
2. Obtain “buy-in” from health care disciplines
3. Define roles of key players
4. Define process
5. Redesign operations
6. Education/in-service staff
7. Dedicate resources
8. Involve patients

Figure 2. Steps to ensure Anemia Management Program success

appeared to be unsuccessful, pharmacists and nurses were convinced it was not due to physicians actively choosing to disregard the guidelines. It was believed that appropriate adjustment of doses was often overlooked simply due to the complexity of managing oncology patients.

From these previous experiences, it appeared that a successful anemia management initiative would require a multidisciplinary approach with increased pharmacist involvement, and ongoing collaboration between pharmacists, physicians, nurses, and nurse practitioners. Goals for a collaborative program would include improved adherence to guidelines, improved Hgb response, and ultimately improved patient outcomes.

ANEMIA MANAGEMENT PROGRAM DEVELOPMENT AND IMPLEMENTATION

The development of the Anemia Management Program (AMP) required several preliminary steps to ensure its success, including: identifying of key players, obtaining the “buy-in” of physicians and other health care practitioners, defining roles of the key players, defining the process, redesigning operations, educating/in-servicing staff, dedicating resources, and involving the patients (see Figure 2).

When identifying key players, it was important to consider each group of health care professionals who were routinely involved in the care of the patients including pharmacists, physicians, nurses, and nurse practitioners. (At The James, nurse practitioners have prescriptive authority and routinely prescribe ESPs). Obtaining “buy-in” from these individuals, especially the physicians, was critical for program success. Physician “buy-in” was accomplished by meeting with the Medical Director to gain his support, then asking him to communicate information regarding the “proposed” program to the

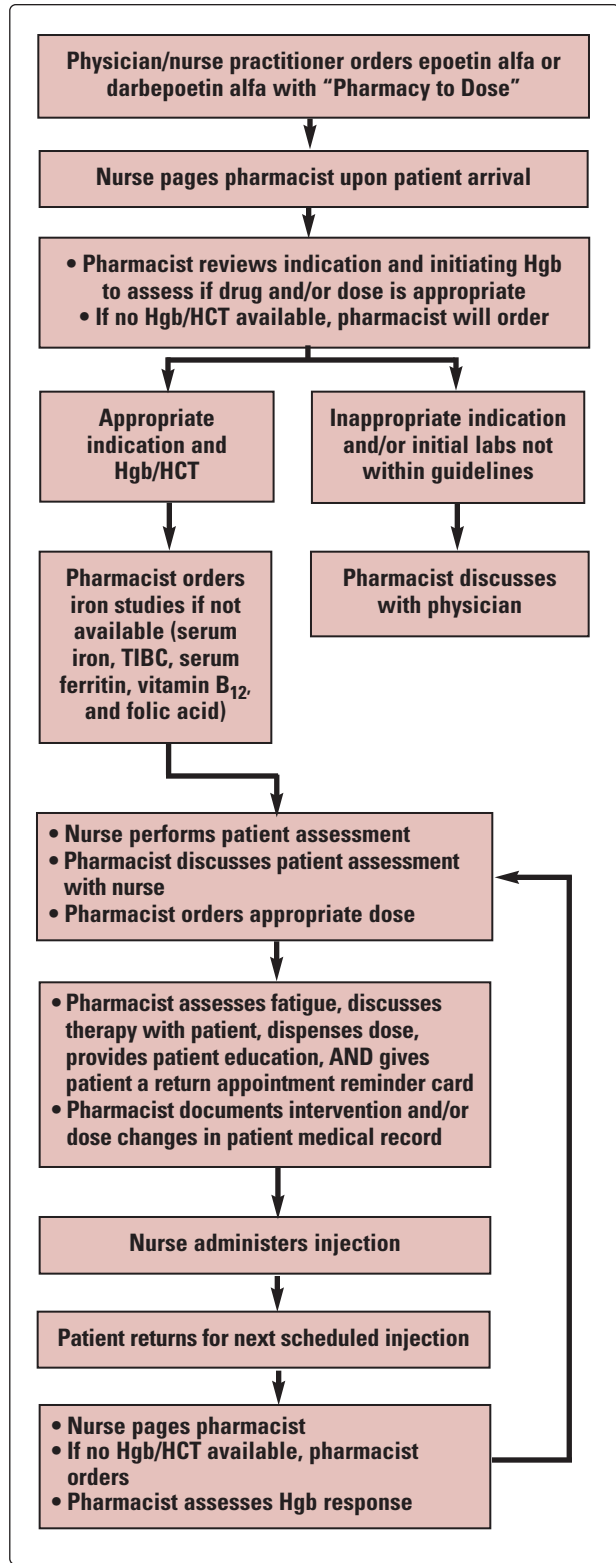


Figure 3. Anemia management process
Hgb = hemoglobin; HCT = hematocrit; TIBC = total iron binding capacity

**The James Cancer Hospital
Anemia Management Program
PATIENT REMINDER CARD**

You are currently receiving darbepoetin alfa (*Aranesp*)
injections to help prevent/treat anemia.
Your next injection is scheduled for:

Date

Time

Date

Time

Date

Time

Date

Time

**It is IMPORTANT that you receive
your injections as scheduled.
Please discuss questions or concerns about this
medication with your pharmacist or physician.**

Figure 4. Anemia Management Program patient reminder card.

entire hematology/oncology physician group. Although initial physician and nurse practitioner feedback was mostly supportive, concerns were expressed about potential delays in obtaining the ESP injections due to additional pharmacy involvement in the process.

As part of the development phase of the AMP, potential roles for each of the key players were carefully defined taking into account their current workload and responsibilities. Once this task was completed, the entire AMP process could be clearly defined. The creation of a flowchart was extremely helpful in detailing the specifics of the program (see Figure 3).

Evaluating and redesigning current clinic operational procedures, where necessary, enhanced the success of the program. Daily work-flows and processes were needed to support the new roles and responsibilities of the key players. For example, in order to ensure that pharmacists were notified of every patient who was to receive an ESP, these medications could no longer be retrieved via the automated distribution cabinets located in the outpatient oncology areas. Instead of the nursing staff obtaining the medication, they now page the pharmacist

upon the patient's arrival for an ESP injection and then proceed with the initial patient assessment. The pharmacist completes the tracking sheet (previously described) alleviating some of the documentation burden from the nursing staff and allowing more time for direct patient care activities. The completed tracking forms are maintained in notebooks in the pharmacy area instead of patient charts providing ready access to dosing and lab history information prior to the patient visits. To ensure all patients receive the same information regarding anemia and their therapy, the pharmacist now has the opportunity to counsel each patient. Topics covered include a brief overview of anemia, etiology, treatment, and monitoring parameters, as well as the importance of receiving injections as scheduled. The pharmacist is available to address any questions posed by the patients or the nursing staff. ESP injections continue to be administered by the nursing staff.

In regards to educational initiatives, initial education regarding the AMP was provided to all of the pharmacists and nursing staff who routinely work in the outpatient oncology areas. Appropriate and timely communication with the physician/nurse practitioner staff was also necessary. Physicians and nurse practitioners were initially introduced to the program via an E-mail communication from the Medical Director which delineated program specifics and their individual responsibilities. In addition to this written notice, a personal interaction took place with each physician and nurse practitioner when the pharmacist received a new ESP order, providing an additional opportunity to further detail the program and answer any pending questions.

Since pharmacy possessed such an integral role in the implementation and maintenance of the AMP, adequate personnel resources needed to be available. Current pharmacy staffing in the outpatient oncology clinic was unable to support this new service; thus, additional resources were initially provided by pharmacy residents.

The involvement of the pharmacist in anemia management was intended to provide increased counseling opportunities, to ensure the dissemination of consistent and appropriate information, and to help patients become more proactive in their care. In addition, to enhance medication adherence, patients also receive a "reminder card" providing the date of their next visit(s) (see Figure 4).

Program Success

The AMP was initiated in August 2003 and its

success was evident during the first month. All physicians and nurse practitioners writing for ESPs elected to have their patients managed by the AMP, although each physician and nurse practitioner still retained the option to individually manage difficult or unique patients without placing them in the program. Patients were found to be responsive and appreciative of the information and services provided by the pharmacist. As pharmacists assumed the responsibility of completing the tracking forms, there was an improvement in data capture and medical necessity documentation. In addition, this improvement in data capture permitted an accurate ESP analysis/comparison of the two agents, epoetin alfa and darbepoetin alfa. The analysis assisted in the selection of a preferred ESP agent, darbepoetin alfa (*Aranesp*), a decision which was based upon efficacy, safety, cost, and throughput considerations.

The most critical success attributed to the AMP was an increase in adherence to the MUE guidelines. During the initial evaluation, 47% (26/53) of patients received at least one dose of darbepoetin alfa outside of the guideline specified dosing interval while post-AMP data (August to November 2003) demonstrated that only 30% (10/30) of patients received any doses outside of the specified interval. In addition, prior to the AMP, approximately 75% of the patients meeting the guideline criteria for titration were actually appropriately titrated, while post-AMP data demonstrated that 92% of patients who required a titration received the dose changes according to the guidelines. The ultimate test of the AMP will be to determine whether Hgb and/or transfusion outcomes are affected by this new process.

Expanded Role of the Pharmacist

Based on the initial success of the program, including patient feedback and overwhelming support of both physicians and nurse practitioners, an additional pharmacist position was approved to support the AMP. Since the inception of the AMP, the role of the pharmacist in the outpatient oncology clinic has continued to expand. In addition to clinical and educational responsibilities, the AMP pharmacist plays a key role in monitoring the economic components of the program and focusing on issues associated with reimbursement. For example, all pharmacists in the outpatient oncology areas are familiar with the Medicare Local and National Coverage Decisions for medications prescribed in

the clinic. Pharmacist-initiated interventions are performed, when necessary, to avoid financial losses to the institution. Such interventions include educating practitioners regarding reimbursement criteria for medications (when they are prescribed outside of reimbursable indications) and gathering pertinent literature for petitioning the Medicare Fiscal Intermediary to add a new indication for use when appropriate clinical evidence exists to support it. This expanded role could prove particularly beneficial for institutions that are struggling with an increase in off-label uses of medications.

CONCLUSION

The involvement of a pharmacist in the management of anemia can provide numerous benefits to the patient, clinic staff, and institution by enhancing program success from a clinical, as well as, an economic perspective. The continued success of the AMP at The James will depend upon its ability to continue to do both.

Boston Medical Center: Improved Adherence to ESP Guidelines Through Pharmacy Interventions

David Baribeault, RPh, BCOP

BACKGROUND

Boston Medical Center is a 547-bed, private, non-profit academic center located in Boston, MA. The mission of the Boston Medical Center is to provide high-quality care to all people of the community, regardless of their ability to pay, and to do it in a cost-effective manner. As such, Boston Medical Center is the largest safety-net hospital in all of New England. The oncology clinic at Boston Medical Center serves a diverse population with similarly diverse needs. Approximately 10,000 patients are treated each year in the oncology clinic.

EVALUATION

It is common practice at Boston Medical Center to develop evidence-based guidelines for the prescribing and administration of high-risk and high-cost drugs. These guidelines are the result of

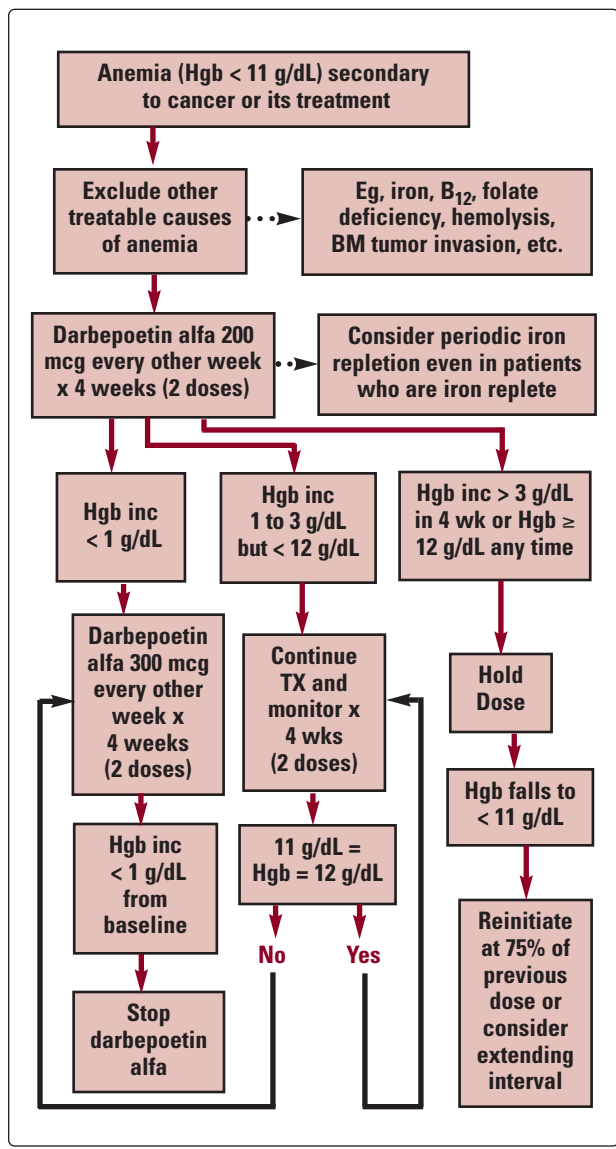


Figure 5. Darbepoetin alfa usage guidelines.
 Hgb = hemoglobin; BM = bone marrow; inc = increase; TX = treatment

a collaborative effort between the pharmacy department and the thought leaders for the other health care disciplines involved with the use of the selected agent(s). ESP usage guidelines have been approved at our center and are described in Figure 5. Consensus for these guidelines was achieved from multiple disciplines including pharmacy, hematology, oncology, nephrology, orthopedics, and infectious disease. In August 2002, coincident with a formulary change from epoetin alfa to darbepoetin alfa, the Pharmacy Department at Boston Medical Center conducted

Table 1. ESP MUE Demographics: The Boston Medical Center

Variable	Value	
	Pre-enforcement MUE	Post-enforcement MUE
Number of patients	67	67
Sex, no. (%)		
Male	28 (41.8)	24 (35.6)
Female	39 (58.2)	42 (64.4)
Cancer diagnosis, no. (%)		
AL amyloidosis	2 (3)	2 (3)
Bladder	0 (0)	1 (1.5)
Breast	19 (28.4)	15 (22.4)
Cervical	1 (1.5)	2 (3)
Cholangio-carcinoma	2 (3)	0 (0)
CLL	1 (1.5)	0 (0)
Colorectal	5 (7.5)	4 (6)
Esophageal	1 (1.5)	3 (4.5)
Gastric	2 (3)	3 (4.5)
Head and neck	2 (3)	3 (4.5)
Hodgkin disease	1 (1.5)	0 (0)
Kaposi's sarcoma	2 (3)	0 (0)
Non-Hodgkin lymphoma	2 (3)	4 (6)
Lung		
Non-small cell	12 (17.9)	13 (19.4)
Small cell	0 (0)	2 (3)
Melanoma	0 (0)	1 (1.5)
Multiple myeloma	6 (9)	7 (10.4)
MDS	7 (10.4)	1 (1.5)
Ovarian	4 (6)	0 (0)
Pancreatic	1 (1.5)	1 (1.5)
Prostate	0 (0)	4 (6)
Age, years mean	60.3	61.7

ESP = erythropoietic stimulating protein, MUE = medication use evaluation, CLL = chronic lymphocytic anemia, MDS = myelodysplastic syndrome

a prospective MUE to assess ESP usage guideline adherence. This evaluation was conducted in anemia treatment-naïve patients who were followed prospectively for a 16-week treatment period.

The elements of practice evaluated in this MUE were many, diversified, and included the following: demographic information (tumor type and chemotherapy regimen), Hgb value at therapy initiation, initial dose, and schedule of darbepoetin alfa administration, baseline iron status evaluation and repletion, dose escalation rate (includ-

Table 2. ESP MUE Results: The Boston Medical Center

<i>Elements</i>	<i>Pre-enforcement (N = 67)*</i>	<i>Post-enforcement (N = 67)*</i>
Initiation of therapy when Hgb is < 10 g/dL	50%	80%
Initial assessment of iron deficiency	40%	60%
Ongoing assessment of iron depletion during stimulated erythropoiesis	17%	10%
Dose escalation of darbepoetin alfa after 4 weeks in the absence of clinical response	13%	70%
Discontinuation of therapy after an additional 4 weeks in the absence of response		< 10%
Hematopoietic response rate	Approximately 52%	70%

ESP = erythropoietic stimulating protein; Hgb = hemoglobin
 *ESP treatment naïve patients with anemia of malignancy

ing an analysis of appropriateness of dose escalation), and the number of darbepoetin doses administered. In an effort to correlate practice patterns with efficiency of therapy, the mean change in Hgb was also assessed.

MUE Results (Pre-enforcement)

In all, 67 consecutive patients were evaluated, correlating with the number of treatment naïve patients in whom erythropoietic therapy was initiated between August 2002 and February 2003. The demographics for this group were quite diverse and are available in Table 1. Upon review of the data, we found that physicians were adherent to our guidelines in many areas. However, there was a lack of adherence to MUE elements crucial (in our opinion) to the achievement of optimal clinical outcomes, such as a decrease in transfusion requirements and the attainment of a Hgb between 11 and 12 g/dL. Specifically, these elements were as follows: the initiation of therapy when Hgb is less than 10 g/dL, initial assessment of iron deficiency, repletion of overt iron deficiency, dose escalation of darbepoetin alfa after 4 weeks in the absence of clinical response, and discontinuation of therapy after an additional 4 weeks in the absence of clinical response. Interestingly, over the 16-week treatment period, we observed a hematopoietic response rate and mean change in Hgb in our cohort that was very similar to the responses reported both in randomized clinical trials and in subsequently published MUE data.

When prescribers were educated about the

guidelines, but not forced to adhere to them, we found that treatment outside the guidelines was quite commonplace. Specifically, we observed that treatment initiation occurred when Hgb levels were less than 10 g/dL in only 50% of patients. Although the guidelines were very clear about ruling out other causes of anemia (ie, deficiencies in iron, folic acid, or cyanocobalamin), baseline assessments of these causes were obtained in less than 40% of cases. Ongoing assessment of iron depletion, related to stimulated erythropoiesis, was only found in 17% of cases. Most disturbing was the low percentage of patients offered the benefit of a dose escalation in the event of an inadequate clinical response after 4 weeks. The initial Hgb response rate of our patient population was expected and was consistent with the published literature related to the treatment of malignancy-associated anemia with ESPs (approximately 52%). However, only 13% of the patients, who had an inadequate Hgb response, underwent darbepoetin dose escalation from 200 to 300 mcg every other week. Although treatment was not maximized through the benefit of a dose escalation, neither was treatment discontinued. Non-responders received an average of 8.9 doses (18 weeks) of darbepoetin treatment in the absence of a targeted Hgb response (see Table 2).

MUE Results (Post-enforcement)

As a result of the poor adherence to ESP usage guidelines observed in our initial MUE, the Pharmacy Department was granted authority to

more strictly enforce these guidelines. Moving forward, the Pharmacy and Therapeutics Committee decided that exceptions to the guidelines could only be made after a consultation occurred between the pharmacy clinical specialist in hematology/oncology and the ordering physician. To observe the impact of this change, we conducted another MUE (post-enforcement) including the next 67 consecutive ESP treatment naïve patients with anemia of malignancy. The criteria evaluated in the second MUE were identical to the first MUE (pre-enforcement).

Strict enforcement of the ESP usage guidelines resulted in dramatic changes in therapy and a modest improvement in the overall hematopoietic response rate. Patients did not have treatment initiated until their baseline Hgb fell below 10 g/dL more than 80% of the time. In patients for whom therapy was considered, baseline assessments of nutritional status were conducted nearly 60% of the time. For patients who did not experience a 1 g/dL increase in Hgb above the baseline after 4 weeks, dose escalation to darbepoetin 300 mcg every other week occurred 70% of the time. Of note, only 40% of participating patients required dose escalation. In patients who did not experience a 1 g/dL increase in Hgb despite a dose escalation, therapy was only discontinued in less than one in 10. Ongoing assessment of iron stores was still suboptimal as only approximately 10% of patients had these tests performed. Our overall hematopoietic response rate (including patients who required dose modification) was increased to 70% (see Table 2).

CONCLUSION

Implementation and strict enforcement of ESP usage guidelines proved to be very effective methods of delivering appropriate therapy to our patient population. Through our MUEs, we were able to assess the effectiveness of these guidelines and initiate changes that will further optimize ESP therapy in patients with anemia of malignancy. For example, we are currently assessing the possibility of baseline iron repletion, as well as, periodic iron supplementation to diminish the rate of iron body store depletion caused by stimulated erythropoiesis.

Although ESP usage guidelines are very effective tools in optimizing ESP therapy, scrutiny and diligence are required to ensure a high-rate of adherence, so patients actually receive the care necessary

to achieve the target Hgb in a rapid and cost-effective fashion. When guideline adherence is managed and enforced by pharmacists, ongoing assessments of medication use and outcomes are essential in order to provide optimal anemia management.

Saint Barnabas Health Care System: Impact of Outpatient G-CSF Administration on Inpatient G-CSF Usage

Indu Lew, PharmD

BACKGROUND

Prior to the availability of the long-acting granulocyte colony stimulating factor (G-CSF), pegfilgrastim (*Neulasta*), at-risk patients were given the shorter acting G-CSF, filgrastim (*Neupogen*), on an outpatient basis to prevent or reduce the incidence of chemotherapy-induced neutropenia. However, a proportion of these patients still developed febrile neutropenia requiring hospitalization and continued to receive filgrastim as inpatients until their white blood cell (WBC) counts normalized. Now, with the availability of pegfilgrastim, complete G-CSF therapy can be given in the outpatient clinic as one injection per chemotherapy cycle vs seven to 10 daily injections of filgrastim. Theoretically, outpatient pegfilgrastim therapy should preclude the use of inpatient filgrastim in febrile neutropenia.

Evaluation

The Saint Barnabas Medical Center is a 645-bed tertiary acute care teaching hospital and the largest inpatient facility of the multihospital Saint Barnabas Health Care System located in West Orange, NJ. A MUE was conducted at this institution with the primary objective to describe the inpatient use of filgrastim for febrile neutropenia in patients who received either filgrastim or pegfilgrastim in the outpatient clinic as an adjunct to chemotherapy. A secondary objective was to examine hospital admissions for febrile neutropenia with respect to outpatient administration of filgrastim or pegfilgrastim.

METHODS

This was a single-center, retrospective chart review in a tertiary acute care hospital. Sequential records of outpatients receiving either filgrastim or pegfilgrastim were identified using the hospital's billing database, *Trendstar*. These patients were then cross-matched with the inpatient hospital billing database for the presence of a febrile neutropenia admission. The evaluation included the records of adult patients (at least 18 years of age) who were treated with myelosuppressive chemotherapy and initiated on filgrastim or pegfilgrastim support during the first or subsequent chemotherapy cycles for breast cancer, cervical cancer, colon cancer, Hodgkin lymphoma, intermediate- or high-grade non-Hodgkin lymphoma, small cell or non-small cell lung cancer, or ovarian cancer. Patients were excluded if their treatment was initiated outside the study identification time period, participating in a filgrastim or pegfilgrastim study, or if they were pregnant. Two different evaluation time periods were selected based on the availability of pegfilgrastim: January to December 2001 (prior to the availability of pegfilgrastim) and January 2003 to June 2004 (post-availability of pegfilgrastim). The first time period included only patients given filgrastim in an outpatient setting (Cohort I). The second time period included subjects given either filgrastim (Cohort II) or pegfilgrastim (Cohort III) in the outpatient setting.

Neutropenia grade was measured prior to the administration of a G-CSF in the outpatient setting and on the first day of hospital admission. Neutropenia was determined using the National Cancer Institute grading.²⁰

RESULTS

A total of 1,438 patients were treated with outpatient chemotherapy during the identified study periods. Among those, 261 (18.2%) were admitted for the management of febrile neutropenia. In Cohort I and II, 107 and 102 patients (respectively), received adjunctive prophylaxis with filgrastim, and the remaining 52 patients (Cohort III) receiving adjunctive prophylaxis with pegfilgrastim. Demographic characteristics of included patients were comparable for sex, age, payer type, and discharge status among the three cohorts. Cancer types among the cohorts were equally matched with the exception of ovarian cancer being greater in Cohort III and colon cancer was greater in Cohorts I and II. The majority of out-

patients experienced febrile neutropenia in chemotherapy cycle two through four despite primary and secondary prophylaxis with G-CSFs. The number of G-CSF doses administered in the outpatient setting varied between each cohort. Of the 10 recommended doses included in a course of filgrastim therapy, Cohorts I and II received only an average of 3.8 and 4.8 doses, respectively. Cohort III received a single injection of pegfilgrastim, representing a full-course of therapy (see Figure 6).

The timing of administration of G-CSFs with respect to chemotherapy has evolved significantly over the last several years at our institution. In Cohort I (2001), the timing of filgrastim administration following chemotherapy was somewhat erratic, starting at day-0 and extending at times to day-12. In Cohorts II and III (2003 to 2004), therapy with filgrastim and pegfilgrastim became standardized with administration isolated to the first several days after chemotherapy. Further distinctions in timing of G-CSF administration were seen between Cohort II and Cohort III with those in Cohort II receiving filgrastim up to day-4 post chemotherapy; whereas, patients in Cohort III receiving pegfilgrastim almost exclusively on day-1 following chemotherapy (see Figure 7).

All patients in Cohorts I and II, admitted for febrile neutropenia, received filgrastim as inpatients and were given an average of 6.6 and 6.3 days of therapy, respectively. However, 78% of patients in Cohort III received filgrastim as inpa-

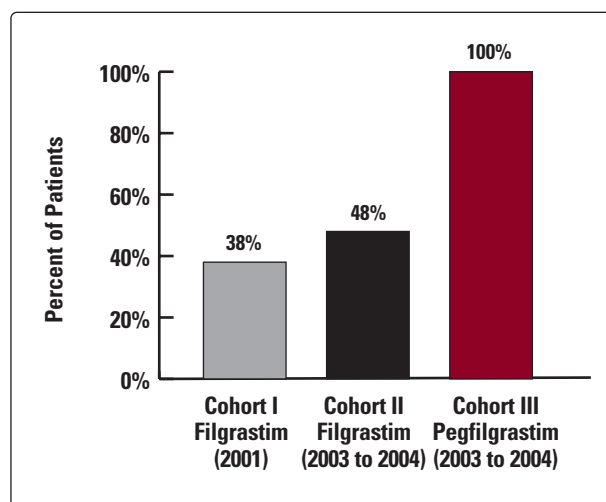


Figure 6. Percent of total outpatient G-CSF regimen received by patient.

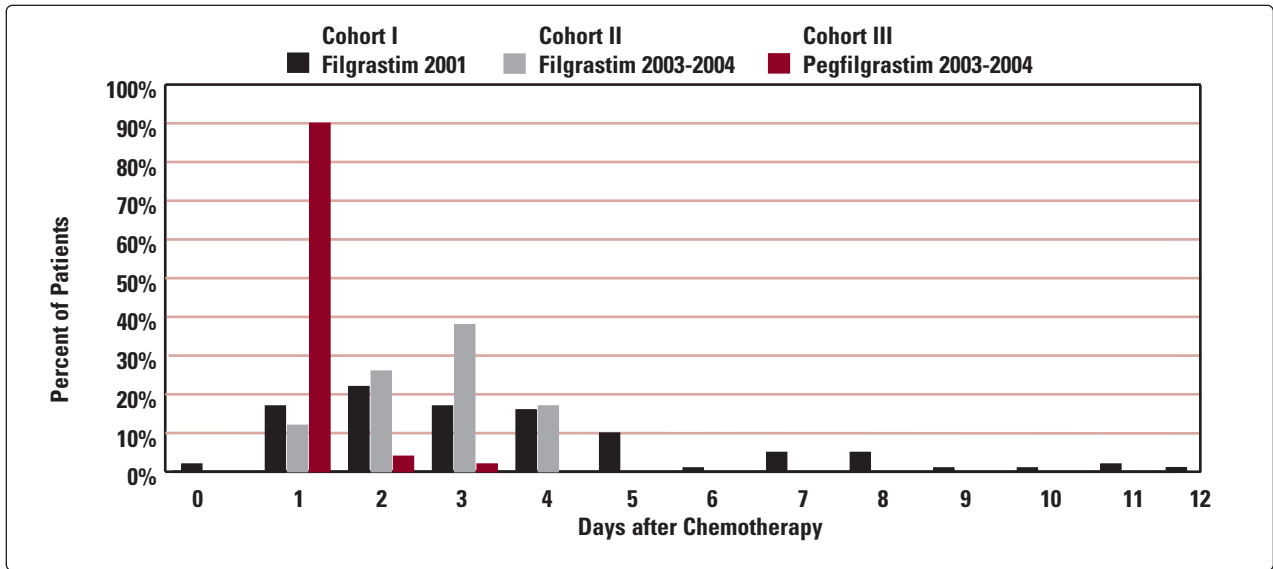


Figure 7. Outpatient administration of G-CSF following chemotherapy.

tients and were given an average of 2.3 days of therapy (see Figure 8). The differences observed in inpatient use of filgrastim extended into per-patient costs of G-CSF therapy, which were reduced in Cohort III (\$837) compared to those in Cohorts I (\$2,402) and II (\$2,293). These costs were calculated using AWP pricing for a 480 mcg vial of filgrastim therapy.

Our secondary objective, the rate of hospital admissions for febrile neutropenia, was significantly reduced among patients in Cohort III, compared to those in Cohorts I and II. Patients in Cohort III had an estimated 68% lower hospital admission rate compared to Cohort I and an estimated 59% lower rate compared to Cohort II.

DISCUSSION

The primary objective of this study was to characterize the inpatient use of filgrastim following outpatient administration of either filgrastim or pegfilgrastim. It was hypothesized that outpatient administration of the long-acting G-CSF, pegfilgrastim, would preclude any inpatient use of filgrastim. This hypothesis was realized in only 22% of patients in Cohort III (patients who received pegfilgrastim on an outpatient basis). However, when comparing inpatient use of filgrastim between the cohorts, it was observed that patients in Cohort III received significantly less days of inpatient filgrastim therapy (2.3), compared to those in Cohorts I and II (6.6 and 6.3, respective-

ly) (see Figure 8).

The secondary objective of this evaluation was to characterize hospital admissions for febrile neutropenia with respect to outpatient prophylaxis with filgrastim or pegfilgrastim. The premise was that hospital admissions for chemotherapy-induced febrile neutropenia were predicated on two factors including the timing of G-CSF administration post chemotherapy and compliance with the full-course G-CSF therapy. The rate of hospital admissions for febrile neutropenia was significantly reduced among patients in Cohort III, compared to those in Cohorts I and II. The severity of neutropenia in Cohort I may be attributable to the wide variation in timing of filgrastim administration following chemotherapy which was not as extensive in Cohort II (see Figure 7). According to the National Comprehensive Cancer Network Guidelines, therapy with G-CSFs should be initiated 24 to 72 hours post chemotherapy.²¹

Literature has demonstrated that the number of doses needed for a full-course of filgrastim therapy ranges from seven to 11 doses.²²⁻²⁵ Patients included in Cohorts I and II did not receive a full-course of G-CSF therapy, which potentially may have led to an increased incidence of chemotherapy-induced febrile neutropenia admissions. Patients in Cohort III received a full-course pegfilgrastim therapy, which may explain the decrease in the febrile neutropenia admission rate (see Figure 6).

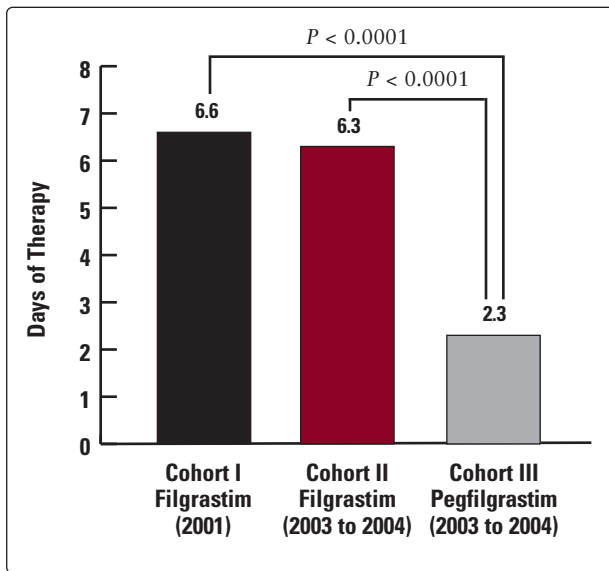


Figure 8. Inpatient days of filgrastim therapy.

CONCLUSION

This study illustrates the need to develop operational procedures in institutions reconciling outpatient G-CSF administration with inpatient filgrastim use. This process will ensure that patients receiving full-course G-CSF therapy in the outpatient setting will not subsequently receive inpatient filgrastim therapy upon admission for febrile neutropenia. In addition, reductions in chemotherapy-induced neutropenic hospitalizations can be achieved with all G-CSF agents provided that full-course therapy is completed. However, based on the differences seen between the cohorts in the completion of the total G-CSF regimen, it appears that patients are more likely to comply with a full-course of pegfilgrastim than with filgrastim. Further prospective trials involving larger patient populations are needed to better quantify the use of inpatient filgrastim therapy with respect to outpatient G-CSF administration, as well to comprehensively evaluate the impact of pegfilgrastim on the hospital admission rate for febrile neutropenia.

Improving Patient Care and Health Care Value

In the management of chemotherapy-induced anemia and neutropenia, the ESPs (*Procrit* and *Aranesp*) and the G-CSFs (*Neupogen* and *Neulasta*)

have become the cornerstone of adjunctive therapy for the majority of patients undergoing chemotherapy. Due to the increased use of these agents, they account for three of the top five medication expenditures in hospital outpatient clinics.

In order to ensure that patients receive the maximum clinical benefit of ESPs and G-CSFs, the implementation of medication usage guidelines is strongly recommended. In addition, strict adherence to these guidelines will ensure that these agents are prescribed in the most cost-effective manner. The two initial institutional perspectives provided in this article demonstrate that the appropriate use of ESPs can be greatly enhanced through the successful implementation of medication use guidelines. To ensure guideline success, the initial development should be directed by a multidisciplinary clinical team and the implementation guided by a comprehensive, well-planned process. Guideline adherence is greatly improved by the presence of a clinical pharmacist in the outpatient setting.

In addition to guideline development, a thorough MUE program should exist within an institution to measure the success of current guidelines and identify new opportunities for guideline refinement and development. The final perspective included in this article describes a G-CSF MUE, which identified significant opportunities to improve both clinical and financial outcomes with filgrastim and pegfilgrastim in the in- and outpatient settings.

The management of anemia and neutropenia of malignancy can be effectively optimized through education, medication usage guidelines, an ongoing MUE program, and timely economic assessments. Pharmacists play an integral role in each component of anemia and neutropenia management, further ensuring enhanced patient outcomes.

Disclosures

Robert Adamson received educational grants from Amgen and Ortho McNeil.

Niesha Griffith is a speaker and advisory board member for Amgen.

David Baribeault is a consultant for Amgen.

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Gordon J. Vanscoy — no disclosures.

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CONTINUING EDUCATION POST-TEST

1. In review of outpatient expenditures, which of the following drug classes are included in the top-five annual expenditures:
 - A. Serotonin receptor antagonists
 - B. Erythropoietic stimulating proteins
 - C. Granulocyte colony stimulating factors
 - D. Platinum-based chemotherapeutic agents
 - E. B and C

2. The use of using long-acting growth factors in outpatient clinics is associated with the following:
 - A. An increase in throughput
 - B. An increase in the number of clinic visits per patient
 - C. An increase in medication adherence
 - D. An increase in the burden to the care-givers
 - E. A and C

3. The implementation of an anemia-management program requires all of the following essential steps to ensure success except:
 - A. Identify key players
 - B. Redesign operations
 - C. Involve only pharmacists in program development
 - D. Educate/in-service staff

4. When darbepoetin usage guidelines were strictly enforced at the Boston Medical Center, there was an improvement in all of the following MUE elements except:
 - A. Initiation of therapy when Hgb is less than 10 g/dL
 - B. Initial assessment of iron deficiency
 - C. Ongoing assessment of iron depletion
 - D. Dose escalation of darbepoetin alpha after 4 weeks in the absence of clinical response

5. According to the G-CSF MUE conducted by Dr. Indu Lew, inpatient days of filgrastim therapy were significantly reduced when:
 - A. Patients received pegfilgrastim in the outpatient setting
 - B. Patients received filgrastim in the outpatient setting
 - C. Patients received antibiotics and no G-CSF doses in the outpatient setting
 - D. A and B

POST-TEST ANSWER FORM/EVALUATION FORM

University Pharmacotherapy Associates, LLC, respects and appreciates your opinions. To assist us in the evaluation the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minute to complete this evaluation form. Please note: a statement of credit is issued only upon receipt and successful completion of the evaluation form.

Please answer the following questions by circling the appropriate rating:

5 = Outstanding 4 = Good 3 = Satisfactory 2 = Fair 1 = Poor

Extent to which program activities met the identified objectives

Upon completion of this activity, the participant should be able to:

- | | | | | | |
|---|---|---|---|---|---|
| • Identify the true cost of long-acting growth factors and the operational management of long-acting vs short-acting growth factors | 5 | 4 | 3 | 2 | 1 |
| • Describe the development and implementation of a pharmacy-initiated outpatient anemia management program | 5 | 4 | 3 | 2 | 1 |

(continued on next page)

- Discuss the expanded role of the pharmacist in optimizing appropriate erythropoietic stimulating protein (ESP) use in the outpatient setting through guideline reinforcement 5 4 3 2 1
- Characterize hospital admissions for febrile neutropenia with respect to outpatient administration of filgrastim or pegfilgrastim 5 4 3 2 1

Overall effectiveness of the activity

Objectives were related to overall purpose/goals(s) of activity	5	4	3	2	1
Related to my practice needs	5	4	3	2	1
Will influence how I practice	5	4	3	2	1
Will help me improve patient care	5	4	3	2	1
Stimulated my intellectual curiosity	5	4	3	2	1
Overall quality of materials	5	4	3	2	1
Overall, the activity met my expectations	5	4	3	2	1
Avoided commercial bias or influence	5	4	3	2	1
Will the information presented cause you to make any changes in your practice?	<input type="checkbox"/> Yes		<input type="checkbox"/> No		
How committed are you to making these changes?	5	4	3	2	1

Please list any other topics that would be of interest to you for future educational activities.

Additional comments about this activity:

To obtain a statement of credit for 1.0 contact hour (0.1 CEU) of ACPE credit, you must complete the post-test answer form/evaluation form and mail or fax to UPA. At least 4 of 5 answers must be correct to obtain a statement of credit.

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 4. _____ 5. _____

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