

Impact of Long-Acting Growth Factors on Practice Dynamics and Patient Satisfaction

Roy A. Beveridge, M.D., Robert M. Rifkin, M.D., Ronald J. Moleski, Pharm.D., Gary Milkovich, B.S., John F. Reitan, Pharm.D., Thomas A. Paivanas, M.H.S.A., and R. Jake Jacobs, M.P.A.

Objective. To quantify time expended, patient satisfaction, and economics associated with short-acting (sargramostim, epoetin alfa) and long-acting (darbepoetin alfa, pegfilgrastim) growth factors.

Design. Retrospective resource utilization and prospective two-phase observational study.

Methods. During week 1, time-motion measurements related to patient treatment and drug preparation were collected for scheduling; check-in; phlebotomy; laboratory; and drug preparation, administration, and recording. Drug utilization for one chemotherapy cycle during weeks 2 and 3 was assessed for sargramostim, pegfilgrastim, epoetin alfa, darbepoetin alfa, sargramostim plus epoetin alfa, and pegfilgrastim plus darbepoetin alfa. Patients completed a satisfaction survey.

Results. Among 140 patients (mean age 58 yrs), mean chemotherapy cycle duration was 19 days. A total of 268 events were observed. Mean total staff time/patient visit for drug administration was 22.1 minutes, with most time spent on scheduling (5.5 min) and drug preparation, administration, recording (5.2 min). For sargramostim only versus pegfilgrastim only, pegfilgrastim resulted in a 37% reduction ($p<0.01$) in all visits and an 85% reduction ($p<0.01$) in mean number of doses. For epoetin alfa only versus darbepoetin alfa only, darbepoetin alfa resulted in a 48% reduction ($p<0.01$) in mean number of doses. The most common dosage of epoetin alfa was 40,000 U/week (63.6%) and that of darbepoetin alfa was 200 μg every other week (92%), but complete blood counts were obtained weekly. For pegfilgrastim plus darbepoetin alfa versus sargramostim plus epoetin alfa, a 45% reduction ($p<0.01$) in total visits and a 77% reduction ($p<0.01$) in mean number of doses were noted in the former group. In 69 patients converted to long-acting drugs, 65 actual hours for a single treatment cycle were saved. For patients receiving pegfilgrastim plus darbepoetin alfa, there was a 45% reduction in total clinic visits, 77% reduction in doses, and staff time savings of 1.9 hours/patient/cycle of chemotherapy. Fifty-four patients completed the survey and trended toward neutral in their responses, with moderate disagreement that receiving injections is painful.

Conclusion. Long-acting growth factors resulted in significant time savings for staff and providers by reducing the number of necessary office visits for drug administration. These time savings can significantly improve the quality of life for patients, as well as nurses, physicians, and caregivers.

Key Words: Darbepoetin alfa, long-acting growth factors, resource utilization. (Pharmacotherapy 2003;23(12 Pt 2):101S–109S)

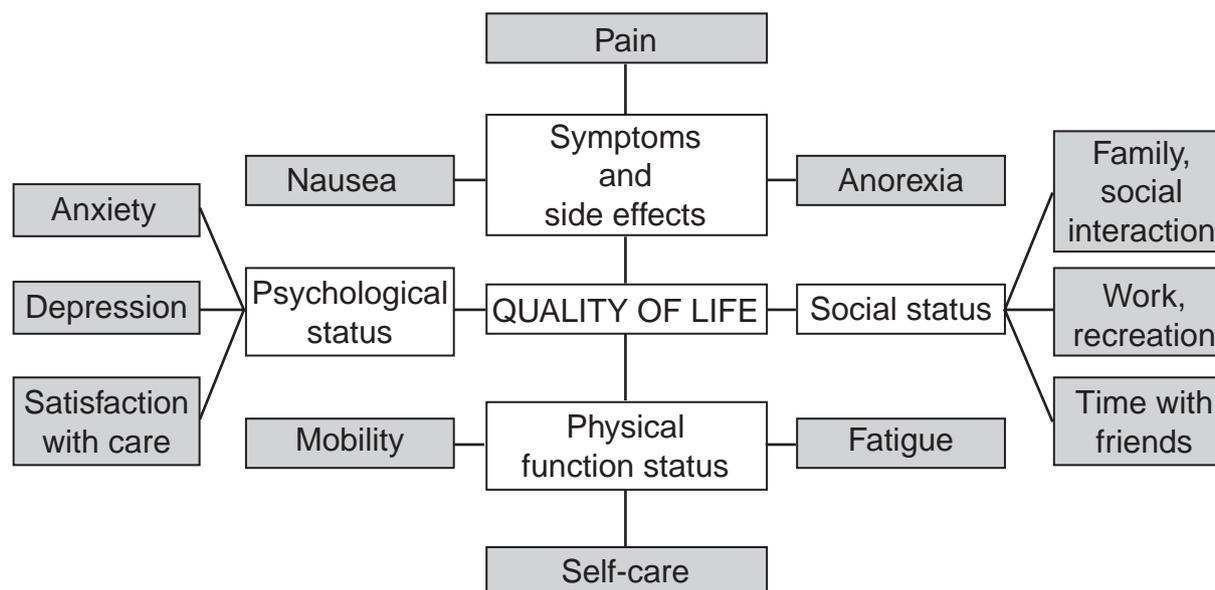


Figure 1. Construct of quality of life.

Anemia is the most common hematologic abnormality in patients with cancer, whether or not they are actively receiving chemo- and/or radiation therapy. Estimates place the prevalence of anemia at 35–95%.^{1–3} Cancer-related anemia often is associated with many debilitating symptoms, decreased health outcomes, decreased ability to comply with recommended therapy, and lower quality of life.^{4–7} Fatigue, a frequent symptom of anemia, affects physical function and quality of life (Figure 1).⁸ This impacts other aspects in the patient's day-to-day activities, including social interactions, work and/or recreation, and time for social activities.

The Fatigue Coalition, a multidisciplinary group including representatives with expertise in oncology, human immunodeficiency virus, neurology, psychometrics, psychiatry, and patient advocacy, confirmed that two thirds of patients with cancer experience daily fatigue or fatigue that significantly affects their daily routines.^{9–11} The impact of the fatigue experienced by patients

with cancer was pervasive in both activities of daily living and in personal and social interactions. As such, methods to simplify the already complicated and difficult lifestyle of a patient with cancer are needed to ease the daily strains. The economic impact of fatigue to the patient is significant. It can change employment status, increase caregiver time off from work, reduce overall work hours, and increase unpaid family and medical leave time to help the patient with fatigue.

Until the early 1990s, blood transfusion was the only option for treatment of symptomatic anemia. Safety concerns, limited supply, and potential adverse effects of blood transfusion created a need for a safer alternative. The advent of recombinant growth factors has changed the treatment of patients with cancer and chronic anemia and is now the mainstay of treating a patient with cancer-related anemia.

Several recombinant products of erythropoietin are commercially available worldwide. Epoetin alfa, the most frequently used erythropoiesis-stimulating growth factor thus far, usually is administered as a weekly subcutaneous injection, starting at 40,000 U/dose. Erythropoietin therapy is effective in correcting anemia in patients with cancer, and studies have consistently shown improvements in hemoglobin levels and quality-of-life measures when patients with cancer-related anemia are treated with epoetin alfa.^{7, 12–16}

From Inova Fairfax Hospital, Fairfax, Virginia (Dr. Beveridge); Rocky Mountain Cancer Center, Denver, Colorado (Dr. Rifkin); RJM Marketing and Research Associates, LLC, Guilford, Connecticut (Drs. Moleski and Reitan, and Mr. Milkovich); Thomas A. Paivanas and Associates, Annandale, Virginia (Mr. Paivanas); and Capitol Outcomes Research, Alexandria, Virginia (Mr. Jacobs).

Address reprint requests to Roy A. Beveridge, M.D., Inova Fairfax Hospital, Fairfax Northern Virginia Hematology Oncology, PC, 8503 Arlington Boulevard, Suite 400, Fairfax, VA 22031; e-mail: Roy.Beveridge@usoncology.com.

Darbepoetin alfa is a modified recombinant form of erythropoietin, with two more glycosylation sites that allow the addition of more sialic acid residues to the molecule. The increase in sialic acid residues increases the half-life of darbepoetin alfa 3-fold compared with that of epoetin alfa. This increase in half-life has been confirmed in patients with cancer¹⁷⁻¹⁹ and those with chronic renal failure.²⁰ The feasibility of administering darbepoetin alfa less frequently was confirmed¹⁷ and found to be clinically effective in increasing hemoglobin levels when administered every 3 weeks.²¹ A randomized controlled trial of darbepoetin alfa (administered once/wk) compared with epoetin alfa (administered 3 times/week) in patients undergoing hemodialysis showed that darbepoetin alfa can maintain hemoglobin levels at least as effectively as epoetin alfa, with less-frequent dosing.²² Administering recombinant erythropoietin to patients with cancer has a significant effect on both hemoglobin levels and patient quality of life. Epoetin alfa has proved safe, with a very acceptable toxicity profile, and newer formulations, such as darbepoetin alfa, have the advantage of a longer half-life, allowing less-frequent administration.

Another significant dose-limiting toxicity of chemotherapy is neutropenia. The risk of infection increases as the severity of neutropenia increases. Febrile neutropenia significantly affects quality of life, causes delays in chemotherapy administration, and significantly increases the cost of treatment. The cost of hospitalization for a single episode of febrile neutropenia was estimated to be \$19,000, with a 10.9% mortality rate.²³

Granulocyte colony-stimulating factor (G-CSF), one of the major regulators of neutrophil maturation in the bone marrow, promotes differentiation of cells in the neutrophilic lineage and speeds development of fully mature neutrophils from stem cells. The level of G-CSF is inversely proportional to the peripheral neutrophil count and increases in response to inflammatory and infectious processes. After G-CSF administration, a left shift in cell maturation rapidly occurs in the bone marrow, and hyperplasia of myeloid cells occurs at different stages of development.

Filgrastim, a short-acting recombinant G-CSF, and sargramostim, a short-acting recombinant granulocyte-macrophage colony-stimulating factor are usually administered as a single daily subcutaneous injection. Pegfilgrastim is a

polyethylene glycol form of filgrastim, has a longer half-life than that of filgrastim, and has been shown to be effective in increasing neutrophil counts.²⁴ Pegfilgrastim, which is given as a single injection after chemotherapy, has been evaluated in patients with non-small cell lung cancer and those with breast cancer and has been shown to be at least as effective as filgrastim in increasing neutrophil counts, with a comparable toxicity profile.^{25,26}

Erythropoietin and filgrastim have been used in patients with cancer for more than a decade. These relatively short-acting agents require multiple daily injections that necessitate many visits by patients to an oncology clinic during each chemotherapy cycle solely for the administration of growth factor. In addition to the inconvenience for patients and their caregivers, frequent clinic visits for growth factor administration require time, effort, and preparation of injections by health care providers. The advent of long-acting growth factors—pegfilgrastim and darbepoetin alfa—may impact practice dynamics and patient satisfaction.

Methods

A three-phase, 4-week study was conducted at two large oncology practices in Denver, Colorado, and Fairfax, Virginia. The study design was approved by a local institutional review board. Both practices use erythropoietic-stimulating agents, epoetin alfa (Procrit; Ortho Biotech, Raritan, NJ) and darbepoetin alfa (Aranesp; Amgen, Thousand Oaks, CA), and colony-stimulating factors, sargramostim (Leukine; Berlex, Wayne, NJ) and pegfilgrastim (Neulasta; Amgen) routinely in patients undergoing chemotherapy and adhere to the American Society of Clinical Oncology guidelines for growth factor use.²⁷

Time-motion measures for all aspects of growth factor use were conducted during week 1 by investigators through observation of clinic functions. The amount of time to conduct events for each of the following categories was recorded for five separate events on standardized case report forms: patient scheduling; patient check-in; phlebotomy; laboratory; and growth factor preparation, administration, and recording. Time measurements began and ended based on predefined steps within each event. These steps were identified from prior observations of these functions in each practice.

Table 1. Baseline Demographics and Characteristics of the 140 Patients

Characteristic	Sargramostim	Pegfilgrastim	Epoetin alfa	Darbepoetin alfa	Sargramostim + Epoetin alfa	Pegfilgrastim + Darbepoetin alfa
No. of patients	22	25	30	32	19	12
Mean age (yrs)	51	55	60	60	62	57
M/F	10/12	11/14	7/23	4/28	10/9	4/8
Primary tumor site						
Breast	7	7	10	18	2	2
Lung	6	1	13	10	7	3
Lymphoma	1	9	1	2	4	4
Ovarian	1	3	6	2	2	2
Sarcoma	7	5	0	0	4	1
Primary Insurer						
Medicare	6	5	8	13	7	1
Private	16	20	22	19	12	11

A retrospective chart review of growth factor utilization for a single chemotherapy cycle occurred during weeks 2 and 3, and patients were grouped into the following categories: patients who received sargramostim only, pegfilgrastim only, epoetin alfa only, darbepoetin alfa only, sargramostim plus epoetin alfa (short-acting growth factors), or pegfilgrastim plus darbepoetin alfa (long-acting growth factors). Patient records were reviewed consecutively in reverse chronologic order from January 1–December 31, 2002, for patients who had their chemotherapy cycle started and completed during the January 1–October 31, 2002 interval. All records for each growth factor category were flagged and reviewed for the following inclusion criteria: male and female patients aged 18 years or older who were receiving chemotherapy for solid tumor types, had chemotherapy cycles of 7–28 days, received at least one dose of growth factor in the clinic, and had complete documentation of growth factor and laboratory testing data for the cycle reviewed. Day 0 of a cycle was considered the day chemotherapy was started, and the end of the cycle was when the next round of chemotherapy was administered or when 28 days had elapsed before the next round of chemotherapy. Baseline demographic data were collected, as were therapy-specific data.

A patient satisfaction survey was completed during weeks 2, 3, and 4 by patients who required a clinic visit for growth factor administration, were fluent in English, and had sufficient capacity to understand the questions. The survey quantified satisfaction with the use of growth factors and estimated the amount of time devoted to the visit, out-of-pocket expenses, time

involved for travel to and from the clinic, and waiting time. Patients also were queried about time lost from activities they would have been able to participate in (e.g., going to work or engaging in housekeeping activities, hobbies, relaxation) had they not been required to come to the clinic for a growth factor injection.

Statistical Analysis

The mean, standard deviations, 95% and 99% confidence intervals, medians, ranges, and interquartile ranges were calculated for clinic staff time required for each of the five categories related to growth factor administration activities.

Differences between the two centers were assessed with the Student *t* test, when data were normally distributed, or the Wilcoxon rank sum (Mann-Whitney) test, when the data were not normally distributed. The normality of each distribution was determined by using the Kolmogorov-Smirnov D-statistic test.

Growth factor utilization was calculated on a per-cycle basis. Within each pair, imbalances in baseline characteristics were examined by using a χ^2 or Fisher exact test. If no imbalances were detected, differences between long-acting and short-acting growth factor groups were analyzed with the Student *t* test or Wilcoxon rank sum test. If differences were found at a *p* value less than 0.05, analyses of covariance models were used to determine independent effects.

Results

Baseline demographics and clinical characteristics of the 140 patients are summarized in Table 1. The mean age of the patients was 58 years, and

the mean chemotherapy cycle duration was 19 days (median 21 days).

Time-Motion Assessment

A total of 268 events were observed; a summary of the mean time for each category is listed in Table 2. Mean total clinic staff time/patient visit for growth factor administration was 22.1 minutes, with the most time spent on patient scheduling (mean 5.5 min) and preparation, administration, and recording of growth factor use (mean 5.2 min). Using single-dose vials to prepare growth factor injections, the staff took a mean of 5.7 minutes compared with a mean of 4.8 minutes if prefilled syringes were used.

Growth Factor Utilization

When comparing the sargramostim (short-acting growth factor)-only group with the pegfilgrastim (long-acting growth factor)-only group, use of pegfilgrastim resulted in a 37% reduction ($p < 0.01$) in all visits, attributed primarily to reduction in growth factor administration and laboratory testing visits; there was an 85% reduction ($p < 0.01$) in the mean number of doses administered (Table 3). When comparing the epoetin alfa-only group with the darbepoetin alfa-only group, there was a 48% reduction ($p < 0.01$) in the mean number of doses administered. The change in visits was negligible, due primarily to the continued practice of bringing patients to the clinic during the “no growth factor” weeks for determination of complete blood count. The most common once-weekly dose of epoetin alfa was 40,000 U (63.6%), whereas 35% of doses were 60,000 U. Ninety-two percent of darbepoetin alfa doses

Table 2. Time-Motion Assessments

Category	No. of Events (N=268)	Staff Time (min) ^a
Patient scheduling	40	5.5
Patient check-in	46	2.4
Phlebotomy	52	4.5
Laboratory	47	4.5
Growth factor preparation, administration, recording		
Prefilled syringe	42	4.8
Single-dose vials	41	5.7
All	83	5.2
Total processing time/visit		22.1 ^b

^aData are means.

^bDoes not include times for full pharmacy activity, back-office activity (e.g., billing and accounting), phone consultations, patient counseling, and other activities during a typical visit.

were 200 µg administered every other week; however, complete blood counts were obtained weekly. When comparing the combination groups, there was a 45% reduction ($p < 0.01$) in total visits and a 77% reduction ($p < 0.01$) in mean number of doses administered.

Patient Satisfaction and Time Utilization Survey

Fifty-four patients completed the satisfaction and time utilization survey. The study did not address patients’ insurance deductibles.

Forty-seven patients (87%) came to the clinic from home, whereas the remainder came from a work environment. Fifty-one patients (94%) traveled to the clinic in their own car and traveled a mean one-way distance of 12 miles, with a mean travel time of 27 minutes. The total time spent preparing for the clinic visit, including round-trip travel and time spent at the clinic, was 125 minutes (2.1 hrs; Table 4).

Table 3. Growth Factor Utilization

Variable	Sargramostim Only	Pegfilgrastim Only	Epoetin alfa Only	Darbepoetin alfa Only	Sargramostim + Epoetin alfa	Pegfilgrastim + Darbepoetin alfa
No. of visits						
All	11.5 ± 5.3	7.2 ± 3.8 ^a	4.0 ± 1.5	3.8 ± 2.7	11.6 ± 5.5	6.4 ± 2.8 ^b
Chemotherapy	4.0 ± 2.7	4.4 ± 2.9	2.5 ± 1.0	2.6 ± 2.3	3.9 ± 3.8	4.3 ± 3.2
CBC and/or GF	7.5 ± 3.5	2.8 ± 1.7 ^a	1.5 ± 1.4	1.2 ± 1.3	7.6 ± 5.2	2.2 ± 2.0 ^b
No. of CBC determinations	5.5 ± 3.1	4.2 ± 2.5	3.5 ± 1.1	3.0 ± 1.6	5.5 ± 2.0	2.4 ± 0.7
No. of GF doses	6.5 ± 3.2	1.0 ± 0.2 ^a	2.5 ± 1.1	1.3 ± 0.5 ^c	10.6 ± 5.6	2.4 ± 0.7 ^b
GF dose	427 ± 248 µg	6.2 ± 1.2 mg	45.2 ± 26 U	214 ± 88 µg		

CBC = complete blood count; GF = growth factor.

Data are mean ± SD.

^a $p < 0.01$ for sargramostim only vs pegfilgrastim only.

^b $p < 0.01$ for sargramostim + epoetin alfa vs pegfilgrastim + darbepoetin alfa.

^c $p < 0.01$ for epoetin alfa only vs darbepoetin alfa only.

Table 5 summarizes the results from the section of the survey that evaluated patient satisfaction statements based on a scale of 1–5 (1 = strongly disagree, 5 = strongly agree). Patients were neutral concerning most of the statements. Patients tended toward neutral when asked about convenience of coming to the physician office, desirability of shot avoidance, and willingness to pay extra for fewer shots. There was moderate disagreement that receiving injections is a painful experience, and the mean score from the two sites differed: site 1 had a mean score of 1.3, and site 2 had a mean score of 2.3.

Time Utilization

The clinic staff witnessed a time savings with the use of long-acting growth factors. Actual time saved was 1.6 hours/chemotherapy cycle for pegfilgrastim only, 0.1 hour for darbepoetin alfa only, and 1.9 hours for pegfilgrastim plus darbepoetin alfa. Patients also had time saved: 9.0 hours saved/chemotherapy cycle with pegfilgrastim, 0.4 hour saved with darbepoetin alfa, and 10.9 hours with pegfilgrastim plus darbepoetin alfa.

Of 69 patients who were converted to long-acting growth factors (pegfilgrastim, darbepoetin alfa), there was a saving of 65.0 actual hours for a single treatment cycle (Table 6). If the remaining 71 patients in this study who were receiving short-acting agents (sargramostim, epoetin alfa) were converted to their long-acting counterparts, the potential savings would be an additional 199.4 visits and 73.4 hours for a total of 138.4 hours saved/single treatment cycle.

Table 4. Patient Travel Time Utilization and Expense

Variable	Patient Response
	(N=54) No. (%)
Travel to clinic	
From home	47 (87)
From work	7 (13)
Travel mode	
Automobile	51 (94)
Walking	2 (4)
Public transit	1 (2)
	Mean
Time (min)	
At clinic	31
For one-way travel	27
Preparing for visit	40
Distance one way (miles)	12
Costs (\$)	
Parking	0.00
Tolls	0.02
Public transit	0.30
Lost work (hrs)	
Patient	0.11
Other	0.15
Copayment (\$)	
All patients	4.46
Only patients with copayment	12.78

Discussion

Clinic visits for growth factor administration are associated with significant time devoted to activities surrounding the injection for both office staff and patients. Each clinic visit requires 22 minutes of clinic staff time for activities such as patient scheduling, patient check-in, phlebotomy, laboratory processing, and drug

Table 5. Patient Satisfaction

Statement	No. Responding (N=54)	Mean Score ^a
It is inconvenient to have to come to the office just for a shot.	39	2.5
I have better things to do than drive to the office multiple times a week for injections.	23	2.4
I prefer to come to the office multiple times during the week for shots so my doctor can follow my condition more closely.	32	3.5
If I could reduce my trips to the office to once every 2 or 3 weeks instead of daily, it would greatly improve my satisfaction with my therapy.	23	3.4
Receiving shots is a painful experience.	54	1.8
If I could avoid shots, it would greatly improve my comfort and satisfaction.	54	2.7
I would be willing to pay an additional fee if I could have one shot per cycle, rather than having to come to the office every day.	32	2.6

^aOn a scale of 1–5, where 1 = strongly disagree and 5 = strongly agree.

Table 6. Resource Reduction in Patients Converted to Long-Acting Growth Factors

Patient Group	No. of Patients	No. of Visits Reduced/Patient	Total No. of Visits Reduced	Total Time Saved (hrs)
Converted to pegfilgrastim	25	4.3	107.5	39.6
Converted to darbepoetin alfa	32	0.2	6.4	2.4
Converted to pegfilgrastim + darbepoetin alfa	12	5.2	62.4	23.0
Totals	69		176.3	65.0

preparation and injection. The times measured in this study are conservative and do not account for actual total time spent during a visit and do not take into account time used for pharmacy fulfillment, accounting, billing, travel from room to room, and patient counseling. The total time the clinic staff actually spent managing growth factor administration, therefore, exceeds 22 minutes.

Use of pegfilgrastim was associated with a 37% reduction in total clinic visits and an 85% reduction in total number of doses administered. Based on the average of 22.1 minutes saved/growth factor administration, a reduction of clinic visits will result in 95 minutes (1.6 hrs) saved/patient/cycle when pegfilgrastim is used. The reduced number of clinic visits associated with darbepoetin alfa administration reduced the time commitment/cycle for both clinic staff and patients. Patients receiving darbepoetin alfa experienced only a modest reduction in number of total clinic visits when compared with patients receiving epoetin alfa. However, the average number of doses/cycle was reduced by 50% when darbepoetin alfa was used. The lack of a significant difference in total visits is attributable to the fact that patients still were scheduled for at least one clinic visit/week for complete blood count determination, even during weeks when growth factor was not administered. Possibly, clinic staff scheduled patients based on a prior routine established with weekly epoetin alfa administration. If visits that were only for complete blood count determination had been eliminated, the result would have been greater avoidance of office visits and a more significant time savings. With the advent of long-acting growth factors, health care providers should reevaluate the need for routine weekly complete blood count determinations in certain patients, as this would result in significantly fewer clinic visits.

By using long-acting growth factors, clinic staff could reduce total visits by conducting laboratory

determinations only on days when growth factor is administered. They also should review past processes, modify those processes, and participate in an education program to fully capitalize on the advantages of the long-acting agents.

For patients who received both pegfilgrastim and darbepoetin alfa, there was a 45% reduction in total clinic visits, a 77% reduction in growth factor doses, and a clinic staff time savings of 1.9 hours/patient/cycle. In combination, the time savings exceeded that of pegfilgrastim alone and acknowledges the impact of using darbepoetin alfa. Based on these data, a typical oncology clinic would save 47.5 hours and reduce growth factor administration visits by 130/cycle for every 25 patients treated with combination growth factor therapy. These time savings are likely to have a significant impact on workload reduction and time consumption for nurses, technicians, and other physician extenders.

Freeing up significant time will allow clinic personnel greater flexibility in scheduling, decrease burnout, enable scheduling of new patients for evaluation, and shorten time of referral to the oncology clinic for patients in urgent need. Typically, in these two practices, the waiting time for an initial referral can be 2–3 weeks. These time savings will likely enable treatment of additional patients and potentially offer a positive financial impact for the oncology practice. A reduction in clinic visits affords patients more time for other activities and less time taken from work, while improving compliance with treatment and laboratory testing schedules.

In addition to the improved quality of life for staff and patients, it is possible that several clinical advantages may be achieved with long-acting growth factors. Compliance has been an issue when administering daily injections, especially of sargramostim. Patients might miss doses of growth factor when therapy extends over a weekend or is scheduled for a holiday.

Not all oncology practices are open on weekends and holidays, and patients must either skip doses or go to a local emergency room to receive growth factor injections. The advantage of having fewer injections, especially when administering only one/cycle will likely improve compliance in these patients. Improved compliance may well result in better clinical outcome and fewer adverse events such as extreme fatigue and febrile neutropenia.

The reduction in visits afforded by long-acting growth factors also will offer a significant financial advantage for those patients with copayment responsibilities. When analyzing only patients with a copayment, the number of visits/cycle was reduced by 4.3 visits. For a patient who has a \$20 copayment, this represents a reduction of out-of-pocket expenses of \$86/cycle. It was also subsequently discovered that some of the patients interviewed were not aware of their responsibility for copayment until their claims were processed by the practice and payers.

Summary

The use of long-acting growth factors, darbepoetin alfa and pegfilgrastim, resulted in a significant time savings for office staff and providers by reducing the number of necessary office visits for growth factor administration. In a large busy practice, these time savings allow health care providers to provide better, more efficient patient care, and significantly improve the quality of life for nurses, physicians, caregivers, and, most important, their patients.

Acknowledgment

The authors gratefully acknowledge the assistance of Susan Reitan, R.N., and Lisa Lynch, R.N.

References

- Bron D, Meuleman N, Mascaux C. Biological basis of anemia. *Semin Oncol* 2001;28:S1-6.
- Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. *J Natl Cancer Inst* 1999;91:1616-34.
- Harrison LB, Sasha D, White C, Ramdeen B. Radiotherapy-associated anemia: the scope of the problem. *Oncologist* 2000;5:S1-7.
- Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer* 2001;91:2214-21.
- Fein DA, Lee WR, Hanlon AL, et al. Pretreatment hemoglobin level influences local control and survival of T1-T2 squamous cell carcinomas of the glottic larynx. *J Clin Oncol* 1995;13:2077-83.
- Lee WR, Berkey B, Marcial V, et al. Anemia is associated with decreased survival and increased locoregional failure in patients with locally advanced head and neck carcinoma: a secondary analysis of RTOG 85-27. *Int J Radiat Oncol Biol Phys* 1998;42:1069-75.
- Littlewood TJ, Bajetta E, Nortier JW, Vercammen E, Rapoport B, for the Epoetin alfa Study Group. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2001;19:2865-74.
- Tchekmedyian NS, Hickman M, Siau J, Greco A, Aisner J. Treatment of cancer anorexia with megestrol acetate: impact on quality of life. *Oncology (Huntingt)* 1990;4:185-92, 194.
- Curt GA. The impact of fatigue on patients with cancer: overview of FATIGUE 1 and 2. *Oncologist* 2000;5:S9-12.
- Curt GA, Breitbart W, Cella D, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the fatigue coalition. *Oncologist* 2000;5:353-60.
- Vogelzang NJ, Breitbart W, Cella D, et al. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. The fatigue coalition. *Semin Hematol* 1997;34:4-12.
- Cascinu S, Fedeli A, Del Ferro E, et al. Recombinant human erythropoietin treatment in cisplatin-associated anemia: a randomized, double blind trial with placebo. *J Clin Oncol* 1994;12:1058-62.
- Demetri GD, Kris M, Wade J, Degos L, Cella D. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. Procrit study group. *J Clin Oncol* 1998;16:3412-25.
- Glaspj J, Bukowski R, Steinberg D, et al. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. *J Clin Oncol* 1997;15:1218-34.
- Henry DH, Abels RI. Recombinant human erythropoietin in the treatment of chemotherapy-induced anemia: results of double-blind and open-label follow-up studies. *Semin Oncol* 1994;21:21-8.
- Patton J, Camp M, Kuzur M, et al. Epoetin alfa 60,000 U once weekly followed by 120,000 U every 3 weeks to maintain levels in anemic cancer patients receiving chemotherapy]. Presented at the annual meeting the American Society of Clinical Oncology, Orlando, Florida, May 18-21, 2002.
- Glaspj J, Singh Jadeja J, Justice G, et al. A dose-finding and safety study of novel erythropoiesis stimulating protein (NESP) for the treatment of anaemia in patients receiving multicycle chemotherapy. *Br J Cancer* 2001;84(suppl 1):17-23.
- Heatherington AC, Schuller J, Mercer AJ. Pharmacokinetics of novel erythropoiesis stimulating protein (NESP) in cancer patients: preliminary report. *Br J Cancer* 2001;84(suppl 1):11-16.
- Smith RE Jr, Jaiyesimi IA, Meza LA, et al. Novel erythropoiesis stimulating protein (NESP) for the treatment of anaemia of chronic disease associated with cancer. *Br J Cancer* 2001;84(suppl 1):24-30.
- Macdougall IC, Gray SJ, Elston O, et al. Pharmacokinetics of novel erythropoiesis stimulating protein compared with epoetin alfa in dialysis patients. *J Am Soc Nephrol* 1999;10:2392-5.
- Kotasek D, Albertson M, Mackey J, et al. Randomized, double-blind, placebo-controlled, dose-finding study of darbepoetin alfa administered once every 3 (Q3W) or 4 (Q4W) weeks in patients with solid tumors. Presented at the annual meeting of the American Society of Clinical Oncology, Orlando, Florida, May 18-21, 2002.
- Nissenson AR, Swan SK, Lindberg JS, et al. Randomized, controlled trial of darbepoetin alfa for the treatment of anemia in hemodialysis patients. *Am J Kidney Dis* 2002;40:110-18.
- Kuderer N, Cosler L, Crawford J, et al. Cost and mortality associated with febrile neutropenia in adult cancer patients. Presented at the annual meeting of the American Society of Clinical Oncology, Orlando, Florida, May 18-21, 2002.
- Molineux G, Kinstler O, Briddell B, et al. A new form of filgrastim with sustained duration in vivo and enhanced ability

- to mobilize PBPC in both mice and humans. *Exp Hematol* 1999;27:1724–34.
25. Johnston E, Crawford J, Blackwell S, et al. Randomized dose-escalating study of SD/01 compared with daily filgrastim in patients receiving chemotherapy. *J Clin Oncol* 2000;18:2522–8.
 26. Holmes FA, O'Shaughnessy JA, Vukelja S, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. *J Clin Oncol* 2002;20:727–31.
 27. Rizzo JD, Lichtin AE, Woolf SH, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *J Clin Oncol* 2002;20:4083–107.

Guidelines for Using Darbepoetin alfa in Patients with Chemotherapy-Induced Anemia

Michael Bloomfield, B.S., George Jaresko, Pharm.D., John Zarek, B.S., and Nicki Dozier, Pharm.D.

Anemia is an undertreated but common complication of cancer and is associated with debilitating symptoms that impair the patient's ability to perform daily functions of life. Treatment with darbepoetin alfa, a novel erythropoiesis-stimulating protein, is appropriate for chemotherapy-induced anemia. Guidelines on darbepoetin alfa therapy will assist clinicians in its appropriate application. Other causes of anemia in patients with cancer should be investigated and corrected before therapy with darbepoetin alfa is begun. Patients with hemoglobin levels below 11 g/dl are candidates for immediate therapy. For patients receiving chemotherapy who have declining hemoglobin levels but less severe anemia (< 12 but ≥ 11 g/dl), the decision to treat immediately should be determined by the clinical circumstances. The preferred initial dosage for darbepoetin alfa is 200 μg every 2 weeks; 100 $\mu\text{g}/\text{week}$ is an acceptable alternative. Dosages should be titrated to maintain hemoglobin levels at or near 12 g/dl. Reasons for failure to respond to darbepoetin alfa should be investigated before discontinuing therapy. Clinicians should consider discontinuing therapy if the hemoglobin level has not increased by 1 g/dl or more at 6–8 weeks after appropriate dosage adjustments or the number of red blood cell transfusions has not decreased.

Key Words: Darbepoetin alfa, chemotherapy-induced anemia, treatment guidelines.

(Pharmacotherapy 2003;23(12 Pt 2):110S–118S)

Anemia is an undertreated, common complication of cancer, occurring in more than 50% of patients. The debilitating symptoms of anemia contribute to a reduced quality of life (QOL) and impair the patient's ability to function normally.

From Department of Pharmacy Services, Winship Cancer Institute of Emory University, Atlanta, Georgia (Mr. Bloomfield); the College of Pharmacy, University of Southern California, Los Angeles, California (Dr. Jaresko); Cardinal Health Swedish Medical Center, Seattle, Washington (Mr. Zarek); and Virginia Oncology Associates—US Oncology (Dr. Dozier).

RJM Marketing & Research Associates, LLC, held an advisory board in October of 2002 on behalf of Amgen, Inc. The purpose of this advisory board was to develop guidelines for the treatment of chemotherapy-induced anemia, and the results are reflected in this article.

Address reprint requests to Michael Bloomfield, B.S., Department of Pharmacy Services, Winship Cancer Institute of Emory University, 1365-C Clifton Road NE, Atlanta, GA 30322.

In certain circumstances, it also can adversely affect disease and treatment outcomes.¹

Controlled clinical trials have shown that erythropoiesis-stimulating proteins effectively increase hemoglobin levels in more than 50% of patients with cancer who are receiving chemotherapy.² Increases in hemoglobin levels not only improve the physical symptoms of extreme fatigue associated with anemia but also are closely correlated with improvements in objective QOL measures.³

Despite strong evidence of the benefit of treating chemotherapy-induced anemia, 50–70% of patients with anemia do not receive erythropoietin therapy.¹ Historically, clinicians have intervened only when the hemoglobin level decreased below 8 g/dl.⁴ However, improvement of even mild anemia can improve health-related QOL.⁵

Darbepoetin alfa (Aranesp; Amgen Inc., Thousand Oaks, CA) is a new erythropoiesis-stimulating protein, closely related to human erythropoietin. Its prolonged half-life allows for less frequent dosing regimens, which has important implications for the QOL of patients with cancer, as well as for resource utilization.⁶ The integration of darbepoetin alfa into clinical practices may overcome some of the limitations of current erythropoietin therapy and improve the management of chemotherapy-related anemia.⁴

The Need for Guidelines for Darbepoetin alfa Therapy

Because of the high prevalence of clinically significant chemotherapy-induced anemia and its impact on QOL and clinical outcomes, a systematic approach to managing anemia with

erythropoiesis-stimulating proteins is important.¹ Although physicians may be familiar with guidelines for the erythropoietic protein epoetin alfa,^{7,8} darbepoetin alfa is a novel protein, different from earlier agents.

An advisory panel of experts met in November 2002 to develop guidelines and recommendations for darbepoetin alfa therapy in patients with chemotherapy-induced anemia and to provide guidance on questions frequently asked when administering this agent. The panel made evidence-based recommendations when clinical data were available. When controlled clinical trials were lacking, other recommendations were made by panel consensus, based on expert opinion and best clinical practices. The results of this meeting are summarized below. Figure 1 illustrates the guidelines, while Appendix 1 summarizes the recommendations discussed below.

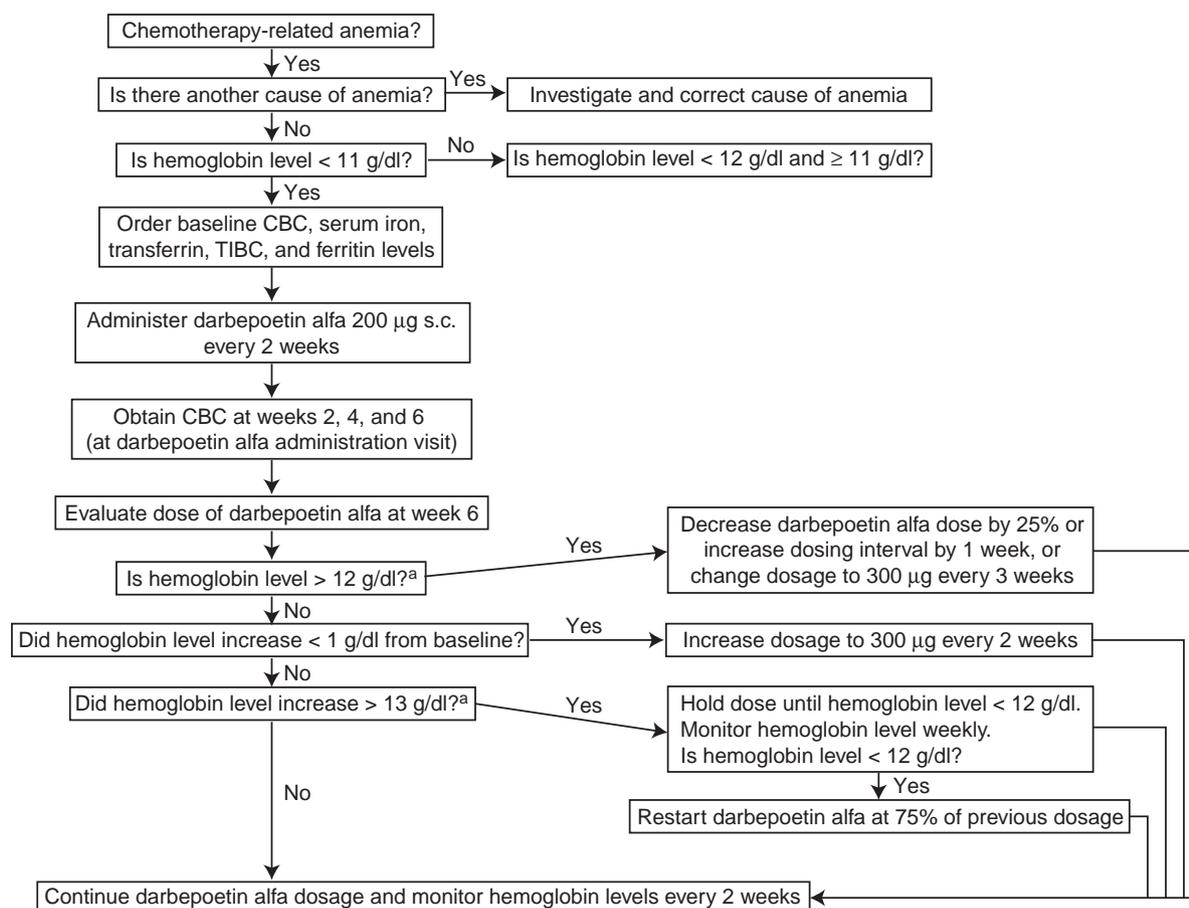


Figure 1. Guideline algorithm for darbepoetin alfa treatment in patients with chemotherapy-related anemia. CBC = complete blood count; TIBC = total iron-binding capacity. ^aBlood transfusions will increase hemoglobin levels transiently; carefully evaluate anemia before adjusting darbepoetin alfa dosage.

What Is the Framework for Using These Guidelines?

Recommendation

The guidelines should be clear, consistent, and easily implemented in all health care settings.

Discussion

Because darbepoetin alfa is administered in a wide range of health care settings, the guidelines should be consistent and applicable to research as well as community-practice settings. They should take into account patients who begin therapy in the hospital and are then treated on an outpatient basis, as well as those who receive darbepoetin alfa as outpatients but may be admitted to the hospital. Recommendations should be evidence based whenever possible. Finally, it is noted that these guidelines are based on currently available data and experience and, as with all guidelines, should be updated on an ongoing basis.

Who Should Receive Darbepoetin alfa and What Is the Evidence for Treatment?

Recommendation

Darbepoetin alfa should be given for the treatment of chemotherapy-induced anemia. Because the etiology of anemia in patients with cancer is multifactorial, other causes of anemia should be ruled out before therapy with darbepoetin alfa is instituted.

Discussion

Initially, studies of darbepoetin alfa assessed its safety and efficacy for the correction of anemia in adult patients with dialysis-dependent or non-dialysis-dependent chronic renal failure. In general, after 4 weeks of treatment, mean hemoglobin level increased from baseline by 1 g/dl.⁹ Based on its efficacy and safety, darbepoetin alfa was approved in September 2001 for the treatment of anemia associated with chronic renal failure, in patients undergoing dialysis and those not undergoing dialysis.^{9, 10}

The safety and efficacy of darbepoetin alfa in reducing the requirement for red blood cell transfusions in patients undergoing chemotherapy also was assessed in several trials.^{6, 11-13} In July 2002, darbepoetin alfa was approved for the treatment of anemia in patients with nonmyeloid malignancies in whom anemia is due to the effect

of concomitantly administered chemotherapy.

One group of authors compared recombinant human erythropoietin (epoetin alfa, r-HuEPO) with darbepoetin alfa in anemic patients with solid tumors who were receiving chemotherapy.¹¹ Thirty-five patients received epoetin alfa 40,000 U/week (a 33% increase from the standard dosage of 3 times/wk), and 141 received darbepoetin alfa 3.0, 5.0, or 9.0 µg/kg every 2 weeks (approximately double the weekly dose). Dosage increases were allowed for those who did not respond to epoetin alfa but not for those in the darbepoetin alfa group. Data showed that darbepoetin alfa 3.0 µg/kg was equivalent to epoetin alfa 40,000 U/week. The higher doses of darbepoetin alfa (weekly and every other week) resulted in higher hematopoietic response rates, faster times to response, greater changes in hemoglobin levels from baseline, and greater reductions in the number of red blood cell transfusions. Similar cumulative weekly and every-other-week doses of darbepoetin alfa resulted in similar response rates and incremental increases in hemoglobin level. The authors concluded that darbepoetin alfa every other week was as effective as once-weekly dosing.¹¹

A large-scale clinical trial, Successful Outcomes in Anemia Research (SOAR), confirmed that darbepoetin alfa dosed once every 2 weeks is as effective as once-weekly dosing.^{14, 15} One group of authors¹⁴ reported on an interim analysis of darbepoetin alfa 200 µg (equivalent to 3.0 µg/kg) in 1173 patients with nonmyeloid cancer who were undergoing multicycle chemotherapy and found a 1.7-g/dl increase ($p < 0.001$ vs baseline) in hemoglobin level in the intent-to-treat analysis and a 2.1-g/dl increase ($p < 0.001$ vs baseline) in an analysis based on available data. After 16 weeks of darbepoetin alfa every 2 weeks, 71% of patients had an increase in hemoglobin level of 2 g/dl or more and 84% had a hematopoietic response (increase in hemoglobin level of ≥ 2 g/dl, or a hemoglobin level of ≥ 12 g/dl).¹⁴ These responses were similar across all tumor types.¹⁴ Patients receiving darbepoetin alfa every 2 weeks reported an improvement in Functional Assessment of Cancer Therapy (FACT)-Fatigue subscale scores ($p < 0.001$) and Energy Numerical Rating grade ($p < 0.001$).¹⁵

When Should Treatment with Darbepoetin alfa Be Considered?

Recommendation

Patients with hemoglobin levels less than 11 g/dl are candidates for immediate therapy with

darbepoetin alfa. Darbepoetin alfa therapy in patients with less severe anemia (hemoglobin level ≥ 11 but < 12 g/dl) should be determined by the clinical circumstances.

Discussion

The use of strict hemoglobin levels to define anemia and the need for treatment in patients with cancer misses individuals who can benefit from erythropoietin therapy. A functional definition, such as insufficient red blood cells to provide adequate tissue oxygenation, may be more relevant, especially in the presence of the underlying disease and comorbid conditions. For example, a patient with lung cancer and chronic obstructive pulmonary disease might be considered anemic based on associated symptoms despite normal hemoglobin levels. Also, symptoms vary with different degrees of anemia, and symptom severity differs among individual patients. For example, elderly patients with comorbid conditions may experience more severe symptoms than those of younger patients.¹

For patients receiving chemotherapy who have declining hemoglobin levels but less severe anemia (< 12 but ≥ 11 g/dl), the decision to begin therapy immediately or to wait until levels decrease to 11 g/dl is controversial. The decision to treat should be determined by the clinical circumstances. Immediate treatment is reasonable in patients who have hemoglobin levels of greater than or equal to 11 but less than 12 g/dl and symptoms of chest pain, dyspnea on exertion, and/or comorbidities, such as a cardiac history or chronic pulmonary disease. Optimal QOL improvements occur at hemoglobin levels maintained in the range of 11–12 g/dl; therefore, starting treatment when hemoglobin levels decrease below 11 g/dl, even in asymptomatic patients, is reasonable. Whether the patient is continuing to receive radiation therapy or chemotherapy is also a consideration in determining when to begin treatment.

Treatment of chemotherapy-associated anemia with erythropoietic-stimulating proteins significantly improves hemoglobin levels, which improves energy and activity levels, and QOL measures.^{15–17} One group of authors¹⁷ compared hemoglobin response rates (defined as an increase in hemoglobin level of ≥ 2 g/dl) in 375 patients with initial hemoglobin levels of 10.5 g/dl or less and in those with hemoglobin levels of greater than 10.5 but less than or equal to 12 g/dl. In this study, 68.5% of patients with lower

hemoglobin levels responded to erythropoietin therapy, whereas 80% of patients with higher hemoglobin levels at the time of enrollment had improvements in hemoglobin responses.¹⁷

Treatment of anemia in cancer also has implications for the psychological state of patients, and improvements are correlated with the hemoglobin level. For example, anxiety and depression scores improve when anemia-related fatigue scores improve.¹⁸ In one study,¹⁹ little improvement was noted in QOL measures when hemoglobin levels were increased to 10 g/dl, a common target. The greatest incremental benefit in QOL was seen when hemoglobin level increased from 11 to 12 g/dl.¹⁹

Using the Linear Analog Scale Assessment and the more disease-specific FACT-Anemia instrument, a group of authors³ found that patients who had increases in hemoglobin level of 2 g/dl or more reported statistically significant improvements in scores on these measures of QOL. The relationship was nonlinear, and the maximum QOL gains occurred at a hemoglobin level of 12 g/dl (range 11–13 g/dl),³ precisely the level below which tissue hypoxia in healthy subjects upregulates endogenous erythropoietin release.¹

What Tests Should Be Performed Before Starting Darbepoetin alfa?

Recommendation

Because the etiology of anemia in patients with cancer is multifactorial, clinicians should treat all correctable causes of anemia before starting therapy. Evaluating the nutritional status, looking for occult bleeding, and assessing comorbid or coexistent disease that can be treated should be done before starting therapy with darbepoetin alfa. Baseline tests should include a complete blood count to determine hemoglobin and hematocrit values, serum iron levels, transferrin saturation, total iron-binding capacity, and ferritin level. There is no need to obtain or monitor erythropoietin levels.

Discussion

To identify causes of anemia other than chemotherapy or underlying hematopoietic malignancy, relevant diagnostic testing should be done. Determining the patient's iron stores before beginning therapy with darbepoetin alfa is important because treatment will not be successful in the presence of an iron deficiency. In addition, periodic monitoring of iron stores

may help in determining the reason for failure to respond.⁸ Erythropoietin levels in patients with cancer are typically low, and studies have shown that those levels are not predictive of a response to therapy²⁰; therefore, they need not be monitored.

What Are the Recommended Dosing Schedules for Initial Therapy?

Recommendation

The preferred initial regimen for darbepoetin alfa is a fixed dose of 200 µg subcutaneously every 2 weeks; 100 µg weekly is an acceptable alternative. Clinicians should be mindful of where the patient begins therapy (in the hospital or as an outpatient) when considering the initial dose and instruct the patient on appropriate follow-up to ensure consistency of the dosing regimen when transitioning from hospital to outpatient care.

Discussion

Because of the distinctively characteristic pharmacokinetics of darbepoetin alfa, several aspects of dosing have to be considered. These include fixed versus weight-based dosing, the relative equivalence of subcutaneous versus intravenous doses, and once-weekly versus every-other-week dosing. The setting in which therapy is started is also important when considering the dosing regimen because of the need for continuity between inpatient and outpatient therapy.

The structure of darbepoetin alfa has the addition of sialic acid side chains that result in approximately a 3-fold greater elimination half-life than that of epoetin alfa.²¹ Thus, the half-life of darbepoetin alfa is increased and allows for less frequent dosing. In patients undergoing dialysis, the mean terminal half-life of intravenous darbepoetin alfa was 25.3 hours compared with 8.5 hours for epoetin alfa. After subcutaneous administration, it was 48.8 hours for darbepoetin alfa.²² After subcutaneous administration in patients with cancer, the peak concentrations occur at 90 hours (range 71–123 hrs).⁹ Darbepoetin alfa administered either intravenously or subcutaneously once/week or every other week is as effective as epoetin alfa treatment administered 3 times/week.²²

The recommendation for a starting dosage of 200 µg every other week is supported by the results of an investigation¹¹ that validated the

minimally effective dosage indicated in the prescribing information for darbepoetin alfa.⁹ The recommended minimally effective dosage is 1.5 µg/kg/week; therefore, 200 µg every other week is well within this dosage. Hospital inpatient dosing protocols may elect the 100-µg/week dosage as an alternative. Also, some physicians are more comfortable with a weekly dosing schedule.

One group of authors²³ used data from 547 patients as a simulation model to assess the feasibility of administering darbepoetin alfa as a fixed dosage of 200 µg every 2 weeks rather than a weight-based dosage. There was a higher mean hemoglobin change from baseline at the lowest body weight (< 45 kg) and slight decreases in hemoglobin response with increasing body weight. The lowest change in hemoglobin level was at the highest weights (> 95 kg). However, at the central portion of the weight curve (45–95 kg), which represented 90% of the population, hemoglobin responses with the weight-based dosage and the fixed dosage were within 2 g/dl of a change from baseline. The researchers concluded that a fixed dosage of 200 µg every 2 weeks is as effective as a weight-based dosage of 3 µg/kg every 2 weeks.^{23,24}

The results of a recent drug usage evaluation (reported in abstract form) of darbepoetin alfa in anemic patients undergoing chemotherapy support a fixed dosage of 200 µg every 2 weeks.²⁵ In this report, a chart review was conducted to evaluate darbepoetin alfa therapy in anemic patients with nonmyeloid malignancies. Patients with hemoglobin levels less than 11 g/dl or hematocrit value less than 33% were either switched from epoetin alfa or had never received darbepoetin alfa. All patients received a fixed dosage of 200 µg every 2 weeks. During darbepoetin alfa treatment, 296 patients (77%) required 200 µg or less and the remainder required 200–300 µg every 2 weeks. The authors concluded that darbepoetin alfa at a fixed dosage of 200 µg every 2 weeks is effective for chemotherapy-associated anemia in patients who had been switched from epoetin alfa and in those who had never received an erythropoietic-stimulating protein previously.²⁵

How Can Continuity of Dosing Be Maintained When Discharging the Patient from the Hospital?

Recommendation

Patients should be given clear instructions

about follow-up and be discharged to receive the appropriate dose at the proper interval.

Discussion

It is important to consider the need for continuity between hospital dosing regimens and outpatient therapy when the patient begins treatment with darbepoetin alfa. A reliable system for ensuring continuity of care in the hospital and after discharge should be instituted so that appropriate dosing schedules are maintained. To ensure that patients do not miss a dose, they should be discharged from the hospital with a clear understanding of and proper instructions for when to follow up with their own physicians. For example, if they received 100 µg in the hospital, they should be instructed to follow up with their physician the next week to receive the next dose of darbepoetin alfa. At that point, they can start the every-other-week dosing schedule. It is imperative to have continuity of care from the inpatient setting to the outpatient arena so that consistent therapy can be maintained.

How Do Hemoglobin Levels and/or Symptoms Affect the Decision to Start Darbepoetin alfa Therapy?

Recommendation

Dosages should be titrated to maintain hemoglobin levels at or near 12 g/dl. Starting therapy when the hemoglobin level is less than 11 g/dl is appropriate. There are no data supporting an additional benefit of normalizing hemoglobin levels to greater than 12 g/dl. In patients with decreasing hemoglobin levels but less severe anemia (hemoglobin levels of ≥ 11 but < 12 g/dl), the decision to start darbepoetin alfa immediately or wait until a further decline in hemoglobin level is determined by clinical circumstances. For patients with comorbid conditions that either contribute to or are adversely affected by anemia, immediate treatment with darbepoetin alfa should be considered.

How Often Should Laboratory Tests Be Monitored?

Recommendation

Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, and ferritin levels should be performed. However,

evidence specifying the optimum timing or periodicity of testing is lacking. Patients should be monitored routinely based on hemoglobin levels, symptoms, signs, and the potential of the intended treatment regimen to induce anemia. Initially, hemoglobin levels should be monitored every 2 weeks when starting therapy. Thereafter, they can be obtained at reasonable intervals but not more frequently than every 2 weeks. Blood pressure should be monitored routinely.

Discussion

Periodic monitoring allows for correction of iron deficiency and can enhance the effectiveness of darbepoetin alfa therapy. Also, monitoring can detect the emergence of nonresponse to therapy.

In patients receiving initial therapy with an agent, hemoglobin levels typically are monitored every other week. When a response is observed, the physician can consider less frequent monitoring.

Physicians may decide the frequency of monitoring patients based on signs and symptoms of anemia. This is especially true if patients are receiving a chemotherapy regimen known to exacerbate anemia when hemoglobin levels may continue to decline.

Patients being monitored for initial responses to therapy whose hemoglobin levels have increased 2 g/dl or more before 6 weeks should continue to receive darbepoetin alfa at the same dosage if they are currently or will soon receive chemotherapy that is anticipated to reduce hemoglobin levels.

How Should Dosages Be Adjusted Based on Hemoglobin Levels?

Recommendations

Dosage adjustments are based on an observed response after 6 weeks of therapy. If interim hemoglobin levels do not reflect the expected response, the dosage should not be adjusted until after the initial 6-week period. After this period, laboratory workup can be performed every 2 weeks and the dosage adjusted until the hemoglobin is stabilized at around 12 g/dl. Many physicians feel comfortable obtaining hemoglobin levels at the same time the patient is scheduled for chemotherapy.

The use of blood transfusions is also a factor when adjusting darbepoetin alfa dosages. If the patient has received red blood cell transfusions, the hemoglobin levels may be increased more than normal. Dosage adjustments of darbepoetin

alfa should be considered carefully. Higher than anticipated hemoglobin levels, which are a transient effect of the transfusion, might cause the physician to lower the dosage inappropriately or discontinue darbepoetin alfa therapy.

For patients who fail to respond to an escalated dosage, further adjustments should be delayed for at least 4–6 weeks. For patients whose hemoglobin level increases more than 2 g/dl in 2 weeks, consider decreasing the dose or increasing the interval between doses. At hemoglobin levels greater than 12 g/dl, the dose should be decreased by 25% or the interval increased by a week. Practitioners may choose to increase the dosing interval to 300 µg every 3 weeks.

Discussion

Many chemotherapy regimens are administered once every 3 weeks, and matching the erythropoiesis-stimulating agent would facilitate treatment. One study²⁶ examined the feasibility of administering darbepoetin alfa every 3 or 4 weeks. Darbepoetin alfa doses ranging from 4.5–15 µg/kg were administered to patients after each chemotherapy dose. At 12 weeks of follow-up, the mean increase in hemoglobin level was 2.6 g/dl, and the hematopoietic response was 51% for patients administered darbepoetin alfa 4.5 µg/kg every 3 weeks.²⁶

The dosage should be adjusted for each person to achieve the targeted hemoglobin level. If there is a less than 1.0-g/dl increase in hemoglobin level after 6 weeks of therapy, the dose can be increased from 200 to 300 µg. If the hemoglobin level increases more than 1 g/dl in a 2-week period or if the hemoglobin level exceeds 12 g/dl, the dose should be reduced by approximately 25%. If the hemoglobin level is greater than 13 g/dl, darbepoetin alfa should be withheld temporarily until the hemoglobin level decreases to 12 g/dl and restarted at approximately 75% of the previous dose.

What Are the Differences in Approach to Patients Who Fail to Respond to Initial Therapy and Those with a Declining Hemoglobin Level Who Are Receiving Maintenance Darbepoetin alfa?

Recommendation

When the hemoglobin level is declining, there is a need to distinguish between nonresponse to initial therapy and a declining hemoglobin level in a patient receiving maintenance therapy with a previous good response.

Discussion

If the patient has no response at 6 weeks to an initial dosage of 200 µg every 2 weeks, increase the dosage by 50% or to 300 µg every 2 weeks and reassess the patient 2 weeks later.

In patients who have been well maintained by receiving 200 µg every 2 weeks for a prolonged period of time but whose hemoglobin level declines after a disease recurrence and multiple cycles of chemotherapy, some physicians may choose to increase the dosage to 300 µg every 2 weeks.

When Should Therapy Be Discontinued in Patients Who Fail to Respond?

Recommendation

Consider discontinuing therapy if the hemoglobin level has not increased by more than 1 g/dl 6–8 weeks after appropriate dosage adjustments or the number of red blood cell transfusions has not decreased.

Discussion

When patients have failed to respond to therapy (typically a lack of a 1–2-g/dl increase in hemoglobin level) and have had a dosage escalation, they should be reevaluated 6–8 weeks after the dosage escalation. If there is still no response, continuing therapy beyond 6–8 weeks does not appear to be beneficial. Waiting for 8 weeks to discontinue therapy also assumes that causes for a lack of response have been investigated (the patient is not iron depleted and does not have a tumor progression). In the absence of identifiable causes for a lack of response (such as continued platinum-based chemotherapy), there is no evidence at this time that further dosage increases will result in a response.

When to discontinue therapy, however, also depends on a clinical definition of nonresponse. If, for example, the patient has had a 0.5-g/dl increase in the hemoglobin level and is feeling better, increasing the dosage might be considered. If the dosage has been increased to 300 µg every 2 weeks and there is still no response and transfusions are still required, consider discontinuing therapy. There is no evidence to support a defined period of time to make a determination of whether to continue the same dosage, to increase it, or to discontinue therapy.

When Should Therapy Be Discontinued in Patients Who Respond?

Recommendation

Therapy with darbepoetin alfa can be discontinued when chemotherapy has been completed, hemoglobin level is stable, and no additional blood transfusions have been needed.

Conclusions

Anemia is an undertreated but common complication of cancer and is associated with debilitating symptoms that impair the patient's ability to perform daily functions of life. Despite evidence of the benefit of erythropoietin therapy for chemotherapy-induced anemia, most patients do not receive treatment. Darbepoetin alfa is a novel erythropoiesis-stimulating protein that is different from previous agents; therefore, guidelines for its use are needed.

Patients with hemoglobin levels less than 11 g/dl are candidates for immediate treatment with darbepoetin alfa. In patients with less severe anemia, the decision to begin treatment is based on the clinical situation. The preferred initial dosage is 200 µg every 2 weeks; 100 µg once/week is an acceptable alternative. Dosages should be titrated to maintain the hemoglobin level at or near 12 g/dl. For patients who fail to respond within 6–8 weeks after appropriate dosage adjustments, discontinuing therapy should be considered. For patients who have had a good response, darbepoetin alfa therapy can be discontinued when chemotherapy is completed, the hemoglobin is stable, and no further blood transfusions are needed.

References

1. Smith RE Jr, Tchekmedyian S. Practitioners' practical model for managing cancer-related anemia. *Oncology* 2002;16(suppl 9):55–63.
2. Glaspy JA, Tchekmedyian NS. Darbepoetin alfa administered every 2 weeks alleviates anemia in cancer patients receiving chemotherapy. *Oncology* 2002;16(suppl 10):23–9.
3. Crawford J, Cella D, Cleeland CS, et al. Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. *Cancer* 2002;95:888–95.
4. Langer CJ, Choy H, Glaspy JA, Colowick A. Standards of care for anemia management in oncology: focus on lung cancer. *Cancer* 2002;95:613–23.
5. Henry DH. Optimizing the treatment of anemia in cancer patients: the role of a new erythropoietic agent. *Oncology* 2002;16(suppl 10):9–12.
6. Glaspy JA. Overcoming barriers to erythropoietic therapy: characteristics of darbepoetin alfa and potential advances in scheduling, dosing, and dose-efficiency. *Oncology* 2002;16(suppl 9):71–7.
7. National Comprehensive Cancer Network. NCCN practice guidelines in oncology: cancer and treatment-related anemia, version 1. Jenkintown, PA: National Comprehensive Cancer Network, 2002.
8. Rizzo JD, Lichtin AE, Woolf SH, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *J Clin Oncol* 2002;20:1–25.
9. Amgen Inc. Aranesp (darbepoetin alfa) package insert. Thousand Oaks, CA; 2002.
10. Joy MS. Darbepoetin alfa: a novel erythropoiesis-stimulating protein. *Ann Pharmacother* 2002;36:1183–92.
11. Glaspy JA, Jadeja J, Justice G, Kessler J, Richards D, for the Darbepoetin alfa 980290 Study Group. Darbepoetin alfa administered every 2 weeks alleviates anemia (with no loss of dose efficiency) in patients with solid tumors [abstr]. *Blood* 2001;98:298a.
12. Hedenus M, Hansen S, Taylor K, et al. Randomized, dose-finding study of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies. *Br J Haematol* 2002;119:79–86.
13. Vansteenkiste J, Pirker R, Massuti B, et al. Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. *J Natl Cancer Inst* 2002;94:1211–20.
14. Blayney DW, Spiridonidis H, Fesen MR, et al. Darbepoetin alfa every 2 weeks to treat chemotherapy-induced anemia: experience in a randomized, open-label study [abstr]. *Proc Am Soc Clin Oncol* 2003;22:747a.
15. Vadhan-Raj S, Schreiber F, Thomas LC, et al. Every-2-week darbepoetin alfa improves fatigue and energy rating scores in cancer patients (pts) undergoing chemotherapy [abstr]. *Proc Am Soc Clin Oncol* 2003;22:732a.
16. Glaspy J, Bukowski R, Steinberg D, Taylor C, Tchekmedyian S, Vadhan-Raj S. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. Procrit study group. *J Clin Oncol* 1997;15:1218–34.
17. Littlewood TJ, Bajetta E, Nortier JW, Vercaemmen E, Rapoport B, for the Epoetin alfa Study Group. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2001;19:2865–74.
18. Kallich JD, Tchekmedyian NS, Damiano AM, Shi J, Black JT, Erder MH. Psychological outcomes associated with anemia-related fatigue in cancer patients. *Oncology* 2002;16(suppl 10):117–24.
19. Cleeland CS, Demetri GD, Glaspy J, et al. Identifying hemoglobin level for optimal quality of life: results of an incremental analysis [abstr]. *Proc Am Soc Clin Oncol* 1999;18:574a.
20. Demetri GD, Kris M, Wade J, Degos L, Cella D. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. Procrit study group. *J Clin Oncol* 1998;16:3412–25.
21. Heatherington AC, Schuller J, Mercer AJ. Pharmacokinetics of novel erythropoiesis stimulating protein (NESP) in cancer patients: preliminary report. *Br J Cancer* 2001;84(suppl 1):11–16.
22. Maccougall IC. An overview of the efficacy and safety of novel erythropoiesis stimulating protein (NESP). *Nephrol Dial Transplant* 2001;16(suppl 3):14–21.
23. Jumbe N, Yao B, Rovetti R, Rossi G, Heatherington AC. Clinical trial simulation of a 200-µg fixed dose of darbepoetin alfa in chemotherapy-induced anemia. *Oncology* 2002;16(suppl 10):37–43.
24. Horl WH, Holzer H, Mayer GJ, for the Osterreichische Aranesp Studiengruppe. Treatment of renal anemia with darbepoetin alfa: results of an Austrian multicenter study. *Wien Klin Wochenschr* 2002;114:967–71.
25. Thames W, Yao B, Scheifele A, Alley JL. Drug use evaluation (DUE) of darbepoetin alfa in anemic patients undergoing

- chemotherapy supports a fixed dose of 200 µg given every 2 weeks (Q2W) [abstr]. Proc Am Soc Clin Oncol 2003; 22:546a.
26. Kotasek D, Albertson M, Mackey J. Randomized, double-blind, placebo-controlled, dose-finding study of darbepoetin alfa administered once every 3 (Q3W) or 4 (Q4W) weeks in patients with solid tumors [abstr]. Proc Am Soc Clin Oncol 2002;21:356a.

Appendix 1. Recommendations for Darbepoetin alfa Therapy

- Guidelines should be clear, consistent, and easily implemented in all health care settings.
 - Darbepoetin alfa should be administered for chemotherapy-induced anemia. Other causes of anemia in patients with cancer should be investigated and corrected before therapy with darbepoetin alfa begins.
 - Patients with hemoglobin levels less than 11 g/dl are candidates for immediate therapy with darbepoetin alfa.
 - For patients receiving chemotherapy who have declining hemoglobin levels but less severe anemia (< 12 but ≥ 11 g/dl), the decision to treat immediately should be determined by the clinical circumstances.
 - The preferred initial dosage for darbepoetin alfa is 200 µg every 2 weeks; 100 µg/week is an acceptable alternative.
 - Dosages should be titrated to maintain hemoglobin levels at or near 12 g/dl.
 - The patient should be instructed on appropriate follow-up when transitioning from the hospital to outpatient therapy to ensure consistency of the dosing regimen.
 - Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, and ferritin levels should be performed.
 - Hemoglobin level should be monitored every 2 weeks when starting therapy; thereafter, it can be done at reasonable intervals but not more frequently than every 2 weeks.
 - Dosages should not be adjusted until 6 weeks after therapy is started. After the initial period, laboratory workup is performed every 2 weeks and the dosage adjusted until the hemoglobin level is stabilized around 12 g/dl.
 - For patients whose hemoglobin level increases more than 2 g/dl in 2 weeks, consider decreasing the dose or increasing the interval between doses.
 - Reasons for failure to respond should be investigated before discontinuing therapy.
 - If the dosage has been escalated, consider discontinuing therapy if the hemoglobin level has not increased by 1 g/dl or more at 6–8 weeks after the dosage adjustment, or the number of red blood cell transfusions has not decreased.
 - Therapy with darbepoetin alfa can be discontinued when chemotherapy has been completed, the hemoglobin level is stable, and additional blood transfusions are not needed.
-

Considerations in Darbepoetin alfa Cost and Reimbursement: A Model for Pharmacy Managers

Ernest R. Anderson, Jr., M.S., and Gene Gibson, Pharm.D.

With health care administrators focusing on the financial aspects of patient care, pharmacy budget managers must be able to evaluate all financial implications of drugs under formulary review. Clinical considerations, dosing equivalency, direct and indirect costs, payer mix, and reimbursement level are issues that should be considered by a multidisciplinary team. A pharmacoeconomic evaluation of darbepoetin alfa compared with epoetin alfa is presented as a model to help pharmacy budget managers address these issues and develop an evaluation of two high-cost drugs to determine which would be the better agent to have on their formulary.

Key Words: Darbepoetin alfa, pharmacoeconomics, reimbursement analysis. (Pharmacotherapy 2003;23(12 Pt 2):119S–124S)

Health care systems face significant challenges today, including limited reimbursement for services provided,¹ personnel shortages (most notably in nursing),¹ continued high demand for inpatient care,¹ and the skyrocketing costs of medical malpractice insurance.² These problems in health care are of national concern and drive health care administrators to focus on the financial aspects of patient care. Thus, pharmacy budget managers must be able to evaluate astutely all of the financial implications of drugs under formulary review. This evaluation is best accomplished by means of a pharmacoeconomic study of the agents under consideration.

Darbepoetin alfa is a new erythropoiesis-stimulating protein.³ A thorough evaluation of darbepoetin alfa as it compares with epoetin alfa

can serve as a model for the pharmacoeconomic analysis of these drugs. Clinical considerations, dosing equivalency, direct and indirect costs, payer mix, and reimbursement level should all be considered by a multidisciplinary team of clinical staff, financial managers, and pharmacy managers. We focus on the pharmacoeconomic evaluation of darbepoetin alfa in an effort to guide pharmacy budget managers as they attempt to address these issues and develop pharmacoeconomic evaluations of costly drugs at their institutions.

Clinical Issues

Erythropoiesis-stimulating protein therapy alleviates mild-to-severe anemia as well as fatigue related to cancer and myelotoxic chemotherapy regimens in patients with cancer.⁴ Epoetin alfa has been administered for more than a decade to reduce the need for red blood cell transfusions and improve quality of life in patients with anemia.^{4–6} However, this drug must be given either 3 times/week or once/week. In addition, up to 40% of patients with cancer do not respond adequately to epoetin alfa.⁷ These factors, coupled with the high cost of the drug, may explain why only 20–30% of patients with a hemoglobin level less than 10 g/dl are treated for anemia in the United States.⁸ Darbepoetin alfa is

From the Department of Pharmacy Services, Lahey Clinic Medical Center, Burlington, Massachusetts (Mr. Anderson); the Center of Managed Pharmaceutical and Economic Outcomes, and the Department of Pharmacy, University of Pennsylvania, Philadelphia, Pennsylvania (Dr. Gibson).

RJM Marketing & Research Associates, LLC, held an advisory board in November of 2002 on behalf of Amgen, Inc. The purpose of this advisory board was to develop a pharmacoeconomic model for the economic evaluation of chemotherapy-induced anemia, and the results are reflected in this article.

Address reprint requests to Ernest R. Anderson, Jr., M.S., Department of Pharmacy Services, Lahey Clinic Medical Center, 41 Mall Road, Burlington, MA 01805.

Table 1. Acquisition Cost for Darbepoetin alfa and Epoetin alfa

Dosage	Cost/Week (\$) ^a
Darbepoetin alfa	
2.25 µg/kg/wk (70 kg) = 160 µg	574.56
4.50 µg/kg/wk (70 kg) = 320 µg	1167.00 (325 µg) ^b
100 µg/wk	359.10
200 µg q2wks	359.10
Epoetin alfa	
40,000 U/wk	414.04
60,000 U/wk	621.05

^aWeighted average cost.^bAdjusted to accommodate unit sizes.

a highly potent erythropoiesis-stimulating drug with a longer half-life than that of epoetin alfa and is effective when given once every 1–3 weeks.⁸

Darbepoetin alfa dosing, response rate, and rate of response should be considered in a pharmacoeconomic analysis of this agent. Several clinical studies have evaluated every-2-week administration, with doses ranging from 3.0–5.0 µg/kg.^{9–12} Darbepoetin alfa administered every 2 weeks at double the dose used once/week can decrease the number of visits to the clinic, reduce the number of injections necessary, increase the overall quality of life for the patient, and does not exhibit a loss of efficacy that was observed when epoetin alfa administration was reduced from 10,000 U 3 times/week to 40,000 U once/week.

When comparing agents or evaluating the costs of a single agent, one must select a single dose and regimen for each product studied based on clinical efficacy, prescribing patterns, and drug costs and reimbursements (Table 1). Although darbepoetin alfa 200 µg administered every 2 weeks is as efficacious in increasing hemoglobin levels as is epoetin alfa 40,000 U administered weekly, the cost of darbepoetin alfa is less than that of epoetin alfa at these dosages. The direct cost of darbepoetin alfa 200 µg every 2 weeks results in the same cost as 100 µg administered weekly. However, every-2-week dosing results in an impact on indirect costs such as time and inconvenience and an impact on quality of life and clinic resources such as staff time and supplies. Thus, dosing issues include clinical questions of efficacy and safety, as well as concerns of direct and indirect costs. In addition, acquisition costs and reimbursement levels are a necessary component of the decision-making process regarding product and dosage selection.

Drug Reimbursement in Ambulatory Clinics

Pharmacy budget managers are under pressure to contain drug costs, independent of concerns with patient outcomes.¹³ In general, health care resource allocation is divided into “silos” that prohibit consideration of potential cost savings or even reimbursement when considering direct costs. Overall societal benefit of treatment is simply beyond the scope of health care budgets.¹³ Minimally, pharmacy budget managers must obtain reimbursement data for high-cost drugs. This information typically is contained in a separate silo from the pharmacy expense budget and may not be shared routinely with the budget managers. However, this information is critical to justify budget expenses and make knowledgeable formulary recommendations.

Budget Review Process

Several steps can be taken by pharmacy budget managers to determine the impact of drugs on the overall budget. First, one should review drug costs. The focus should be on high-cost drugs, which will account for a disproportionate share of drug expenses. Because the reimbursement systems for inpatient drugs are more limited than those for outpatient drugs, only outpatient drugs will be considered in this discussion. Next, one should compare projected annual costs of these agents to the actual costs incurred the previous year. Any agents with increasing costs require further scrutiny. Finally, a full accounting of financial data and third-party reimbursement for the high-cost agents should be evaluated.

Third-Party Reimbursement

Drug charges should be reviewed to ensure that billing is adequate to cover costs. Parenteral products should have a drug charge (Health Care Financing Administration Common Procedural Coding System codes), an infusion charge (Q0081), a facility charge, and a professional charge. If charging is incomplete or inconsistent, nursing and pharmacy systems must be modified to improve the process. Reimbursement systems differ with each third party. For example, Medicare uses ambulatory payment classifications (APCs) to determine reimbursement amounts in specific drug quantity increments. Health maintenance organizations may include drug charges within a capitation payment or may pay drug charges separately.

Table 2. Weighted Average Cost and Reimbursement Analysis, Net Payment, and Net Profit of Darbepoetin alfa Based on a Sampling of Various Drug Plans

	Charge (\$) ^a	Collection Rate (%) ^b	Payment (\$)	Payer Mix (%) ^c	Weighted Payment (\$)
Weighted average cost analysis					
Insurance A	1464.04	37.07	542.73	11	59.70
Insurance B	1464.04	39.33	575.77	7	40.30
Insurance C	1464.04	68.48	1002.57	2	20.05
Insurance D	1464.04	62.11	909.38	11	100.03
Insurance E	1464.04	45.85	671.26	6	40.28
Medicare ^d	Fee schedule	Fee schedule	474.00	33	156.42
Medicaid	1464.04	41.05	601.06	2	12.02
Insurance F	1464.04	62.11	909.38	15	136.41
Self-pay	1464.04	100	1464.04	1	14.64
Insurance G	1464.04	29.97	438.77	12	52.65
Totals				100	632.50
Summary of net payment					
Weighted average payment by payer		632.50			
Reductions					
Free care	3.49%	51.09			
Bad debt	2.31%	33.82			
UCC pool	1.38%	20.20			
Totals		105.11			
Adjusted net payment/dose		527.39			
Summary of estimated net profit					
Adjusted net payment/dose		527.39			
Average cost/dose ^e		488.01			
Estimated net profit/dose		39.38			

UCC = uncompensated care pool.

^aBased on a cost of \$488.01 with a 3.0 markup.^bBased on sample data as of September 30, 2001. This analysis does not include the administrative payment for each injection, cost for each injection, or rebates.^cSample payer mix.^dThis collection rate is based on the calculated reimbursement under ambulatory payment classifications as of April 1, 2002.^eBased on darbepoetin alfa 200 µg every 2 wks.

High-Cost-Drug Reimbursement Analysis

Reimbursement data for each high-cost drug can be analyzed by calculating the payment and weighted average from each contracted third-party organization on the basis of the payer mix within the institution (Tables 2 and 3). Note that functional equivalents were determined for darbepoetin alfa based on epoetin alfa reimbursement by Medicare. This analysis will demonstrate the profit margin for each agent evaluated on the basis of payer mix and collection rates. An adjusted net payment can be determined by subtracting free care and bad debt. Note that overhead, salary, clinic professional charges, facility charges, and drug rebates are not included in this analysis. Using this model, one institution saved \$488,422 by using darbepoetin alfa as the erythropoiesis-stimulating agent of choice (Table 4).

Medicare reimbursement for certain drugs, including darbepoetin alfa and epoetin alfa, has been reduced. Drugs that were not available in 1996, which is the base year for APCs, were granted temporary "pass-through" status. This meant that they would be reimbursed temporarily at 95% of average wholesale price. In April 2002, pass-through drugs and devices were recategorized into other APCs. Overall, this resulted in an average reduction in drug reimbursement of 19%. Sole-source drug reimbursement (e.g., darbepoetin alfa) was reduced the least, with multisource agents (e.g., epoetin alfa) reduced more and multisource with generic competition reduced most significantly. Currently, Medicare reimbursement for darbepoetin alfa as a fraction of acquisition cost will exceed that of epoetin alfa.

Effective January 2003, the Centers for Medicare and Medicaid determined the

Table 3. Weighted Average Cost and Reimbursement Analysis, Net Payment, and Net Profit of Epoetin alfa Based on a Sampling of Various Drug Plans

	Charge (\$) ^a	Collection Rate (%) ^b	Payment (\$)	Payer Mix (%) ^c	Weighted Payment (\$)
Weighted average cost analysis					
Insurance A	1113.00	37.07	412.60	11	45.39
Insurance B	1113.00	39.33	437.71	7	30.64
Insurance C	1113.00	68.48	762.18	2	15.24
Insurance D	1113.00	62.11	691.34	11	76.05
Insurance E	1113.00	45.85	510.31	6	30.62
Medicare ^d	Fee schedule	Fee schedule	364.00	33	120.12
Medicaid	1113.00	41.05	456.94	2	9.14
Insurance F	1113.00	62.11	691.34	15	103.70
Self-pay	1113.00	100	1113.00	1	11.13
Insurance G	1113.00	29.97	333.57	12	40.03
Totals				100	482.06
Summary of net payment					
Weighted average payment by payer		482.06			
Reductions					
Free care	3.49%	38.84			
Bad debt	2.31%	25.71			
UCC pool	1.38%	15.36			
Totals		79.91			
Adjusted net payment/dose		402.15			
Summary of estimated net profit					
Adjusted net payment/dose		402.15			
Average cost/dose ^e		371.00			
Estimated net profit/dose		31.15			

UCC = uncompensated care pool.

^aBased on a cost of \$371.00 with a 3.0 markup.^bBased on sample data as of September 30, 2001. This analysis does not include the administrative payment for each injection, cost for each injection, or rebates.^cSample payer mix.^dThe collection rate is based on the calculated reimbursement under ambulatory payment classifications as of April 1, 2002.^eBased on epoetin alfa 40,000 U every week.**Table 4. Comparison of Equivalent Doses of Darbepoetin alfa (200 µg every 2 wks) and Epoetin alfa (40,000 U every wk) at One Institution During a 2-Week Period**

Drug	Cost/Equivalent Dose (\$)	Profit Margin/Dose (\$)	Annual Total Doses	Annual Cost (\$)	Annual Profit Margin (\$)
Darbepoetin alfa	488.01	39.37	1923	938,443.23	75,708.51
Epoetin alfa	742.00	31.14	1923	1,426,866.00	59,882.22
Variance	253.99	-8.23		488,422.77	-15,826.29

functional equivalency of epoetin alfa and darbepoetin alfa. Medicare spent considerable dollars for epoetin alfa in 2002, and reimbursement for epoetin alfa was reduced in 2003 after it had spent 2–3 years on the pass-through list. Had darbepoetin alfa maintained its status as a new drug, the reimbursement rate would have been 95% of average wholesale price; however, the Centers for Medicare and Medicaid determined darbepoetin alfa to be reimbursed at

a rate similar to that of epoetin alfa, by using a functional dose equivalency of 260 U of epoetin alfa to 1 µg of darbepoetin. Epoetin alfa is paid at \$9.10/1000 U, and darbepoetin alfa is paid at \$2.37/1 µg.

Pharmacoeconomic Analysis

Pharmacoeconomic studies may be conducted in several different ways, depending on the objectives of the analysis and the type of data

Table 5. Pharmacoeconomic Evaluation of Darbepoetin alfa versus Epoetin alfa

Cost	Comment
Direct	
Drug acquisition	
Indirect	
Laboratory monitoring, drug preparation, and administration time	May be greater with epoetin alfa because of more frequent dosing
Opportunity	
Additional resources required to care for patient because of drug administration	May be reduced with darbepoetin alfa because of reduced dosing frequency

available. To obtain an overall understanding of broad issues related to a drug, economic modeling can be used. Existing clinical and epidemiologic treatment data are evaluated. Current literature, institution-specific data, or a combination may be used. A retrospective study may be used to determine actual trends in drug use in an institution. For example, a study to determine the dosing trends of epoetin alfa or darbepoetin alfa may be conducted. A medication or drug use evaluation is a prospective or retrospective study of drug use trends and may encompass a range of data such as dose, regimen, laboratory monitoring, and clinical and/or humanistic outcomes. Finally, a pharmacoeconomic analysis published in the literature may provide sufficient information to determine the best agent for an institution. However, a pharmacoeconomic analysis conducted in a different health care system or in another country may not represent prescribing patterns in another system. Therefore, literature data must be selected and applied cautiously.¹⁴

An economic model designed to assist in formulary decisions or drug usage guidelines will include very specific data and will exclude other information that usually may be seen in an economic model. An institution-specific model will use clinical information that emanates from the medical staff's actual practices and recommendations. For example, the medical staff's prescribing patterns of epoetin alfa as well as consensus on the appropriate dosage of darbepoetin alfa will assist in cost and reimbursement comparisons. The model will include specific acquisition cost, known as direct cost, and reimbursement analysis with projections for the upcoming year. These data will depend on payer mix, dosage, and administration regimen. Indirect costs related to

more frequent epoetin alfa dosing and monitoring related to nursing time for drug preparation and administration, as well as laboratory-related costs, should be included and quantified. Opportunity costs refer to the opportunities that cannot be realized because of the use of the agent. For example, nursing time to administer epoetin alfa detracts from the ability of nursing staff to participate in other billable activities; however, this does yield an injection charge. Conversely, epoetin alfa and darbepoetin alfa can reduce the need for a blood transfusion,³ which will reduce costs and the need for additional patient evaluation (Table 5).

Other issues that are considered in broader pharmacoeconomic analyses include patient pain and suffering, indirect costs due to time off from work or school to seek care or serve as a caregiver, transportation costs, and societal costs related to premature loss of life or function.

Summary

To compare two high-cost drugs to determine which would be a better agent to have on formulary, a thorough pharmacoeconomic analysis should be conducted. To do this, pharmacy budget managers can take several steps to ensure that all pertinent issues are considered:

- Work with financial and clinical staff at your institution to gather data and develop a model.
- Develop a consensus regarding dosing based on the literature and current usage.
- Determine current costs, reimbursement, and payer mix.
- Ensure that appropriate and consistent charging for drugs is ongoing.
 - a. Place drug in Charge Master before obtaining agent.
 - b. Ensure that the medical staff charges for all aspects of drug administration.
 - c. Ensure appropriate follow-up on unpaid charges.
- Develop an institution-specific model of costs and reimbursement for both drugs based on previous year's data as well as projections to elucidate the most cost-effective product. When accounting for costs, both direct and indirect costs should be considered.
- Routinely reevaluate cost and reimbursement of high-cost drugs.

Careful analysis of pertinent data on darbepoetin alfa and epoetin alfa should reveal the financial impact of each agent on the

institution and help guide formulary and clinical use decisions.

Addendum

Since the drafting of this manuscript, on October 31, 2003, the Centers for Medicare and Medicaid Services (CMS) published the revised hospital reimbursement rates for epoetin alfa and darbepoetin alfa for the 2004 under the Outpatient Prospective Payment System (OPPS). The following represents the changes from from 2003 to 2004 that become effective on January 1, 2004:

Growth Factor	2003 Rate	2004 Rate	% Change
Darbepoetin alfa	\$2.37/μg	\$3.24/μg	37%
Epoetin alfa	\$9.10/1000 U	\$9.83/1000 U	8%

These revised reimbursement rates should be used when conducting pharmacoeconomic analyses.

References

1. Bodenheimer TS, Grumbach K. Understanding health policy, 3rd ed. New York: McGraw-Hill; 2002.
2. Korcok M. Malpractice fee hikes mean some U.S. MDs can't afford to work. *Can Med Assoc J* 2003;168:472.
3. Valley AW. Overview of cancer-related anemia: focus on the potential role of darbepoetin alfa. *Pharmacotherapy* 2002;22(9 pt 2):S150-9.
4. Rizzo JD, Lichtin AE, Woolf SH, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *J Clin Oncol* 2002;20:1-25.
5. Crawford J, Cella D, Cleeland CS, et al. Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. *Cancer* 2002;95:888-95.
6. Scott SD. Dose conversion from recombinant human erythropoietin to darbepoetin alfa: recommendations from clinical studies. *Pharmacotherapy* 2002;22(9 pt 2):S160-5.
7. Zamboni WC, Stewart CF. An overview of the pharmacokinetic disposition of darbepoetin alfa. *Pharmacotherapy* 2002;22(9 pt 2):S133-40.
8. Glaspy JA. Overcoming barriers to erythropoietic therapy. *Oncology* 2002;16:S71-7.
9. Amgen Inc. Aranesp (darbepoetin alfa) package insert. Thousand Oaks, CA; 2002.
10. Mirtsching B, Charu V, Vadhan-Raj S, et al. Every-2-week darbepoetin alfa is comparable to rHuEPO in treating chemotherapy-induced anemia: results of a combined analysis. *Oncology* 2002;16:S31-6.
11. Glaspy JA, Tchekmedyian NS. Darbepoetin alfa administered every 2 weeks alleviates anemia in cancer patients receiving chemotherapy. *Oncology* 2002;16(10 suppl 11):23-9.
12. Glaspy JA, Jadeja JS, Justice G, et al. Darbepoetin alfa given every 1 to 2 weeks alleviates anaemia associated with cancer chemotherapy. *Br J Cancer* 2002;87:268-76.
13. Trueman P, Drummond M, Hutton J. Developing guidance for budget impact analysis. *Pharmacoeconomics* 2001;19:609-21.
14. Sanchez LA. Applied pharmacoeconomics: evaluation and use of pharmacoeconomic data from literature. *Am J Health-Syst Pharm* 1999;56:1630-40.