Effects of Darbepoetin Alfa Administered Every Two Weeks on Hemoglobin and Quality of Life of Patients Receiving Chemotherapy

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Purpose/Objectives: To review the effects on hemoglobin and quality of life of an every-two-week (Q2W) regimen of the erythropoietic agent darbepoetin alfa for treating patients with chemotherapy-induced anemia.

Data Sources: Published articles and abstracts.

Data Synthesis: Darbepoetin alfa Q2W increases hemoglobin in patients with chemotherapy-associated anemia and is well tolerated. Increased hemoglobin is associated with improvements in fatigue and energy level. A starting dose of darbepoetin alfa 3.0 mcg/kg (approximately 200 mcg for an average 70 kg patient) Q2W produces a similar level of response to recombinant human erythropoietin.

Conclusions: Darbepoetin alfa effectively treats chemotherapy-associated anemia with fewer clinic visits and fewer injections than are required with conventional erythropoietic therapy.

Implications for Nursing: The less-frequent dosing schedule of darbepoetin alfa can simplify anemia management for nurses and other clinic staff, and it offers patients greater freedom in their day-to-day activities, less dependence on caregivers, and less injection-associated discomfort.

Key Points . . .

- The erythropoietic agent darbepoetin alfa is effective and well tolerated when dosed every two weeks (Q2W), improving hemoglobin levels and reducing fatigue.
- Darbepoetin alfa dosed Q2W has similar efficacy to widely used weekly and three-times-weekly regimens of epoetin alfa.
- Darbepoetin alfa can improve patients' quality of life, directly through relief of anemia symptoms and indirectly through reduction of the frequency of injections and thus the number of clinic visits.

Goal for CE Enrollees:

To enhance nurses' knowledge about the effects of darbepoetin alfa given every two weeks on hemoglobin and quality of life in patients with chemotherapy-induced anemia.

Objectives for CE Enrollees:

On completion of this CE, the participant will be able to

1. Discuss the impact of chemotherapy-induced anemia on patients with cancer.
2. Outline the current evidence about the use of darbepoetin alfa in the treatment of chemotherapy-induced anemia.
3. Compare the use of epoetin alfa and darbepoetin alfa in the treatment of patients with chemotherapy-induced anemia.

In recent years, much attention has been focused on anemia in patients with cancer and its effect on their health-related quality of life (QOL). Anemia is highly prevalent in patients with cancer, either as a result of the cancer itself or as a consequence of treatments, be they chemotherapy, radiation, or surgery (Groopman & Itri, 1999; Johnston & Crawford, 1998; Mercadante, Gebbia, Marrazzo, & Filosto, 2000; Tchekmedyian, 2002). More than half of all patients with cancer may be affected by anemia (Gillespie, 2002; Johnston & Crawford). In addition to myelosuppressive or nephrotoxic chemotherapy, underlying causes of anemia in patients with cancer include destruction or displacement of bone marrow, bleeding, nutritional deficiencies, and chronic anemia of cancer (Erslev, 2000; Mercadante et al.). Hemolytic anemia also may occur in lymphoproliferative disorders, such as chronic lymphocytic leukemia and lymphoma, because of the destruction of red blood cells (RBCs) through an inappropriate autoimmune response (Montserrat, Bosch, & Rozman, 1997).

Anemia is associated with a range of debilitating symptoms, in particular fatigue (Cella, 1998, 2002; Curt, 2000; Holzner et al., 2002; Ludwig & Pecorelli, 2000). Fatigue can have significant effects on patients' QOL. For example, it can reduce

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a patient's ability to work and increase the assistance required from informal caregivers (Berndt et al., 2002), such as family members or spouses. Fatigue also may result in considerable distress for patients. Of the most frequent symptoms reported by patients with cancer in a survey of those attending an ambulatory care center, lack of energy was cited as the most severe, and 50% of patients reported symptom distress related to their disease and treatment (Singer & Patel, 2002). The negative effects of fatigue on QOL may be long-term. One study found that patients experiencing greater fatigue during chemotherapy for breast cancer had lower social functioning, vitality, and general health and more pain one year later (Byar & Berger, 2003). In addition to fatigue, patients with anemia also may experience dizziness, headache, chest pain, shortness of breath, and decreased motivation (Cella, 1998), all of which reduce well-being and affect the ability to continue with life as normal.

The high prevalence and impact of anemia in patients with cancer are especially of concern to those providing care and treatment. Despite the increasing evidence of the benefits of managing anemia, the condition still is under-recognized and undertreated in patients with cancer (Gillespie, 2002; Mock & Olsen, 2003). Studies have suggested that more than half of patients with cancer-related anemia do not receive any treatment for it (Lawless, Wilson-Royalty, & Meyers, 2000; Ludwig, Birgegard, Barrett-Lee, & Krzakowski, 2002). Oncology nurses are involved closely with symptom identification and treatment planning. Nurses must not only understand the implications of anemia in patients with cancer, but also intervene on their behalf by raising awareness among patients and healthcare providers about the significant impact of anemia on QOL and the need for appropriate monitoring. Educational resources now are more readily available to help healthcare providers achieve that goal (Buchsel, Murphy, & Newton, 2002). Nurses also can help ensure that the care plan developed to manage patients' anemia addresses their needs and enables them to maximize their QOL.

Management options for anemia in patients with cancer currently include RBC transfusions and erythropoietic agents, such as recombinant human erythropoietin (rHuEPO) (e.g., epoetin alfa and epoetin beta [Procrit®, Ortho Biotech Products, L.P., Bridgewater, NJ; NeoRecormon®, F. Hoffman-La Roche Ltd., Basel, Switzerland]) or darbepoetin alfa (Aranesp®, Amgen Inc., Thousand Oaks, CA). Because RBC transfusions are associated with several risks, including infection, immunosuppression, and adverse hemolytic reactions (Mercadante et al., 2000; Tchekmedyian, 2001), patients may be reluctant to receive allogeneic transfusions (Lee et al., 1998). Consequently, the use of erythropoietic agents is increasing in anemia management. However, a need exists for more convenient dosing schedules to minimize the frequency of clinic visits for patients requiring treatment for anemia. This review evaluates the evidence supporting the effectiveness of darbepoetin alfa administered every two weeks (Q2W) for the treatment of chemotherapy-induced anemia and its effects on health-related QOL.

Managing Chemotherapy-Induced Anemia With Erythropoietic Agents

Erythropoietic agents correct anemia by stimulating the production of RBCs (erythropoiesis) in the same way as endogenous human erythropoietin (EPO), the hormone that regulates erythropoiesis. EPO is produced primarily in the kidneys in response to hypoxia (Mercadante et al., 2000). In patients with cancer, the number of RBC progenitor cells may be decreased, or a blunted response may exist to EPO or decreased EPO production relative to the degree of anemia (Erslev, 2000; Mercadante et al.; Miller, Jones, Piantadosi, Abeloff, & Spivak, 1990). Erythropoietic therapy can restore RBC levels, thereby alleviating anemia and its symptoms and improving patients' QOL (Buchsel et al., 2002; Cella, 2002; Cleeland et al., 2003; Crawford et al., 2002; Demetri, Kris, Wade, Degos, & Cella, 1998; Gabrilove et al., 2001; Glaspy et al., 1997, 2002; Littlewood, Bajetta, Nortier, Vercammen, & Rapoport, 2001; Quirt et al., 2001; Vadhan-Raj et al., 2003).

Although recent reports of clinical trials of epoetin alfa and epoetin beta have suggested that erythropoietic treatment may be associated with adverse outcomes in some patients (Henke et al., 2003; Leyland-Jones, 2003; Wun et al., 2003), a large body of evidence supports the safe use of these agents. A three-times-weekly (TIW) schedule of epoetin alfa had been used widely because of the drug's relatively short half-life (four to eight hours) (Abels, 1993; Demetri et al., 1998; Glaspy et al., 1997; Kunikane et al., 2001; Littlewood et al., 2001; Ortho Biotech Products, L.P., 2000; Osterborg et al., 2002). More recently, a weekly schedule of 40,000 U epoetin alfa was shown to be equally effective in patients with chemotherapy-induced anemia (Gabrilove et al., 2001) and now commonly is used in clinical practice in the United States (Rizzo et al., 2002).

Darbepoetin alfa was approved by the U.S. Food and Drug Administration in July 2002 for the treatment of anemia in patients with nonmyeloid malignancies in which anemia is associated with concomitantly administered chemotherapy. Darbepoetin alfa is a unique erythropoietic agent that acts in the same way as endogenous EPO and rHuEPO but has an approximately threefold longer half-life than rHuEPO (Egrie, Dwyer, Browne, Hitz, & Lykos, 2003), allowing less-frequent dosing (Amgen Inc., 2002). Additionally, the longer half-life permits administration in a variety of schedules, including once weekly (QW) and Q2W (Glaspy & Tchekmedyian, 2002; Vadhan-Raj et al., 2003; Vansteenkiste et al., 2002). Studies are under way to investigate the use of darbepoetin alfa every three weeks, and data so far suggest that this also is an effective regimen (Kotasek et al., 2003). The Q2W dosing regimen, however, has been used in the largest number of patients in clinical studies (Vadhan-Raj et al.) and has been adopted widely in clinical practice (Boccia, Davidson, Tomita, Green, & Smith, 2003; Schwartzberg et al., 2003; Thames, Yao, Scheifele, & Alley, 2003).

Hematologic Effects of Darbepoetin Alfa Administered Every Two Weeks

Dose-Finding Studies

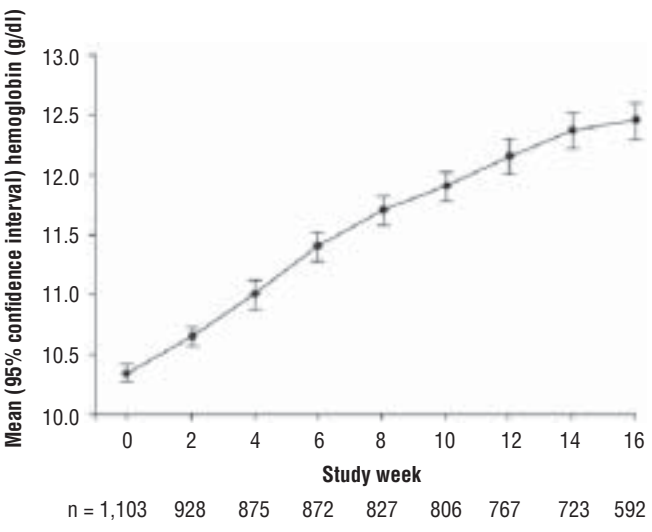
In a dose-finding study of darbepoetin alfa, a variety of QW and Q2W doses were evaluated (Glaspy et al., 2002). The study established that the minimum effective weekly dose of darbepoetin alfa is 1.5 mcg/kg. In addition, the study showed that the dosing interval of darbepoetin alfa could be extended from QW to Q2W with no requirement for an

increased weekly dose (i.e., 3 mcg/kg Q2W was equivalent to 1.5 mcg/kg QW).

Weight-Based Dosing Studies

The largest study of darbepoetin alfa Q2W in the management of chemotherapy-induced anemia that has been published to date was an ongoing, 16-week, open-label, community-based study of 1,173 patients (Vadhan-Raj et al., 2003). The study was designed to develop a screening tool to assess functional capacity in patients with nonmyeloid malignancies and anemia (hemoglobin ≤ 11.0 g/dl) receiving chemotherapy. Patients currently receiving chemotherapy, with at least eight additional weeks of treatment planned, received darbepoetin alfa 3.0 mcg/kg Q2W for a total of eight doses (16 weeks of treatment and observation). After three doses, if hemoglobin levels had not increased by ≥ 1.0 g/dl from baseline, the darbepoetin alfa dose was increased to 5.0 mcg/kg Q2W. In the interim analysis of this study, the hematologic effects of darbepoetin alfa were evaluated, and the relationship between hemoglobin level and patient-reported fatigue scores was investigated.

As shown in Figure 1, hemoglobin increased over time during the study. The mean increase in hemoglobin from baseline to the end of treatment was 2.1 g/dl for patients who received the full 16 weeks of therapy. Seventy-one percent of patients had a hemoglobin response (an increase in hemoglobin of ≥ 2.0 g/dl from baseline in the absence of an RBC transfusion), and 84% of patients had a hematopoietic response (hemoglobin response or hemoglobin correction to ≥ 12.0 g/dl) during the treatment period (Kaplan-Meier estimates of proportion) (Vadhan-Raj et al., 2003). Thus, the majority of patients treated with darbepoetin alfa Q2W experienced a correction of or clinically meaningful improvement in hemoglobin level.



Note. Hemoglobin values within 28 days of a red blood cell transfusion were excluded; other missing data were not input (available data method). Observations were taken at the end of the week, indicated in the x axis (i.e., week 4 is after four weeks on study or after two doses of the study drug).

Figure 1. Mean Hemoglobin Concentration by Time for All Patients

Note. From "Assessment of Hematologic Effects and Fatigue in Cancer Patients With Chemotherapy-Induced Anemia Given Darbepoetin Alfa Every Two Weeks," by S. Vadhan-Raj, B. Mirtsching, V. Charu, D. Terry, G. Rossi, D. Tomita, et al., 2003, *Journal of Supportive Oncology, 1,* p. 135. Copyright 2003 by BioLink Communications, Inc. Reprinted with permission.

Fixed-Dosing Studies

Early data from studies of patients treated in clinical practice and from clinical trial simulation suggest that a fixed dose of darbepoetin alfa 200 mcg Q2W (equivalent to 3.0 mcg/kg based on an average patient weight of 70 kg) would be equally effective in most patients (Jumbe, Yao, Rovetti, Rossi, & Heatherington, 2002; Thames et al., 2003). In a phase IV, open-label, community-based clinical study, anemic patients (hemoglobin ≤ 11.0 g/dl) with nonmyeloid malignancies (N = 1,127) received darbepoetin alfa 200 mcg Q2W for as long as 24 weeks, with dose escalation to 300 mcg Q2W after four weeks if hemoglobin increased < 1.0 g/dl from baseline (Gabrilove et al., 2003). In an interim analysis of data through week 13 of the study, 65% of evaluable patients achieved a hematopoietic response, and the incidence of RBC transfusions decreased by 40% from months 1 through 3. Several chart reviews also have confirmed the effectiveness of this fixed dose of darbepoetin alfa Q2W in clinical practice (Reeves, Wallace, & Patton, 2003; Schwartzberg et al., 2003).

Measuring the Effects of Darbepoetin Alfa Given Every Two Weeks on Health-Related Quality of Life

Fatigue

In addition to increasing patients' hemoglobin levels, treatment with darbepoetin alfa Q2W also can improve QOL. Fatigue, one of the most incapacitating symptoms of anemia, can be assessed using the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) questionnaire (Cella, 1998; Yellen, Cella, Webster, Blendowski, & Kaplan, 1997), which is administered to patients at baseline and during treatment with darbepoetin alfa. As part of the FACT-F, patients are asked to indicate how true statements such as "I feel fatigued," "I have energy," and "I need help doing my usual activities" were for them during the previous seven days.

The maximum score on the FACT-F is 52 points, which indicates that no fatigue is present. The average FACT-F score for the U.S. population is about 44 points, compared with an average of 40 points for the nonanemic cancer population and an average of 24 points for the anemic cancer population (Cella, Lai, Chang, Peterman, & Slavin, 2002). In the large, community-based study of darbepoetin alfa (Vadhan-Raj et al., 2003), the mean FACT-F score at baseline was 26 points. Cella, Eton, Lai, Peterman, and Merkel (2002) have established that an increase of more than three points on the FACT-F subscale represents a clinically important improvement in fatigue. In the Vadhan-Raj et al. study, after eight weeks of treatment with darbepoetin alfa (four doses), the mean FACT-F score had increased by 4.6 points, indicating that, on average, a meaningful improvement in fatigue had occurred. After 16 weeks, the mean score improved by 6.8 points, indicating substantial improvement in fatigue on average. On an individual patient basis, 61% of patients in the study experienced a clinically important reduction in fatigue after treatment with darbepoetin alfa (Vadhan-Raj et al.).

As shown in Figure 2, improvement in fatigue is associated closely with increases in hemoglobin, such that the greatest

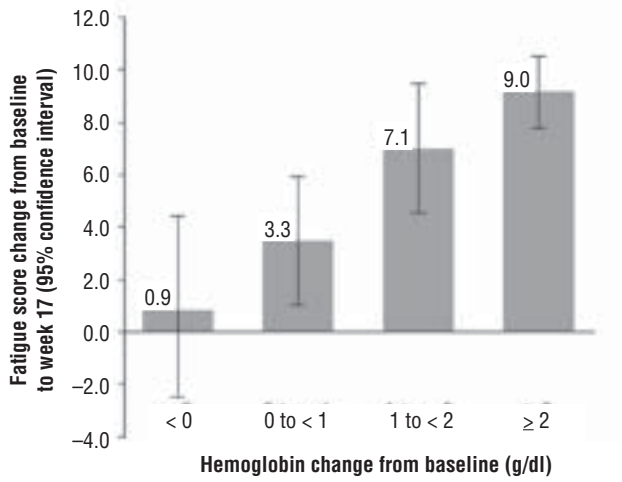


Figure 2. The Relationship Between Fatigue Score and Hemoglobin Change

Note. From "Assessment of Hematologic Effects and Fatigue in Cancer Patients With Chemotherapy-Induced Anemia Given Darbepoetin Alfa Every Two Weeks," by S. Vadhan-Raj, B. Mirtsching, V. Charu, D. Terry, G. Rossi, D. Tomita, et al., 2003, *Journal of Supportive Oncology, 1,* p. 137. Copyright 2003 by BioLink Communications, Inc. Reprinted with permission.

relief in fatigue occurred in patients with the highest increase in hemoglobin (Glaspy et al., 2002; Vadhan-Raj et al., 2003). Of note, patients did not need to have moderate to severe anemia (hemoglobin < 10.0 g/dl) to experience a reduction in fatigue; even patients with only mild anemia (hemoglobin ≥ 10.0 g/dl) at baseline had noticeable improvements in their fatigue symptoms.

Energy Level

Energy levels were assessed in patients treated with darbepoetin alfa Q2W using the Energy Numerical Rating Grade, a self-reported visual analog scale developed for use in studies of darbepoetin alfa. Patients record their energy levels over the previous four weeks on a scale of 1–10 (Vadhan-Raj et al., 2003). The score then was converted to a 0–100 scale to allow comparisons with published results of similar scales. Mean increases from baselines of 7.3 and 12.5 points, respectively, from a mean baseline score of 45.4 points were observed after 8 and 16 weeks of treatment with darbepoetin alfa. Thus, patients treated with darbepoetin alfa experienced an improvement in their energy levels of almost 30% on average after 16 weeks.

Symptom Burden

In the study of darbepoetin alfa administered as a fixed dose of 200 mcg Q2W, a new tool for assessing the impact of symptoms in patients with cancer, the M.D. Anderson Symptom Inventory was used (Cleeland et al., 2000). This also was developed and validated to measure symptom severity and its interference with functional capacity; it includes 19 questions, 13 relating to core symptoms and 6 to symptom interference with life activities. Five symptoms thought to be associated with anemia (fatigue, distress, sleep disturbances, lack of appetite, and pain) were prespecified for analysis in the protocol. In an interim analysis, change in these symptoms after 12 weeks of treatment with darbepoetin alfa was analyzed (Cleeland et al., 2003). Fatigue, distress, sleep disturbance, and lack of appetite scores all improved from baseline, indicating decreased symptom severity. Analysis of the fatigue scores by change in hemoglobin suggests that improvement in fatigue was related strongly to an increase in hemoglobin levels.

Safety of Darbepoetin Alfa Every Two Weeks

Darbepoetin alfa Q2W has been well tolerated in clinical studies, with the reported adverse events typical for a population of patients with cancer receiving chemotherapy (Glaspy & Tchekmedyian, 2002; Kotasek et al., 2003; Vadhan-Raj et al., 2003; Vansteenkiste et al., 2002). In an open-label study of patients with nonmyeloid malignancies, the only adverse event considered to be related to treatment and occurring in more than 1% of patients was injection-site pain (in 2% of patients) (Vadhan-Raj et al.). No antibodies to darbepoetin alfa have been detected in clinical studies, and no clinical symptoms or sequelae suggesting the presence of neutralizing antibodies have been observed (Glaspy & Tchekmedyian; Kotasek et al.; Vadhan-Raj et al.; Vansteenkiste et al., 2002). The safety profiles of darbepoetin alfa and epoetin alfa are similar (Amgen Inc., 2002; Glaspy et al., 2002; Mirtsching et al., 2003). No detriment to survival or disease progression has been reported to date in clinical trials of darbepoetin alfa (Hedenus et al., 2003; Vansteenkiste et al., 2002; Vansteenkiste, Tomita, Rossi, & Pirker, 2004).

Comparison of Darbepoetin Alfa Every Two Weeks and Epoetin Alfa

Epoetin alfa is used widely to treat chemotherapy-induced anemia in patients with cancer and is effective in increasing hemoglobin levels, decreasing transfusion requirements, and improving energy levels and QOL (Buchsel et al., 2002; Cella, 2002; Crawford et al., 2002; Demetri et al., 1998; Gabrilove et al., 2001; Glaspy et al., 1997; Littlewood et al., 2001; Quirt et al., 2001). Nurses should understand how darbepoetin alfa administered Q2W compares with epoetin alfa in terms of efficacy and convenience to patients and their caregivers. The relative cost of the two treatments also is of interest, as it may be a factor when healthcare providers are considering the options for anemia management.

Comparison of Hematologic Efficacy

Darbepoetin alfa Q2W demonstrated similar efficacy to the epoetin alfa QW control group in an early dose-finding study (see Table 1) (Glaspy & Tchekmedyian, 2002). Because this comparison was based on small numbers of patients, Mirtsching et al. (2003) performed a larger analysis combining data from three studies of darbepoetin alfa to obtain a larger sample size for comparison. The meta-analysis confirmed the similar efficacy and safety of darbepoetin alfa at a starting dose of 3.0 mcg/kg Q2W (N = 1,206) and epoetin alfa at a starting dose of 150 U/kg TIW or 40,000 U QW (N = 115). Both treatments had a similar rate of RBC transfusion: 15% for the darbepoetin alfa group and 14% for the epoetin alfa group.

Table 1. Comparison of Efficacy Results for Darbepoetin Alfa and Epoetin Alfa

Variable	Epoetin Alfa (40,000 U QW)[a]	Darbepoetin Alfa (mcg/kg Q2W) 3.0	Darbepoetin Alfa (mcg/kg Q2W) 5.0
Number of patients included in analysis	32	33	31
Proportion[b] achieving hemoglobin response (95% confidence interval)	60% (40%–79%)	60% (39%–80%)	79% (56%–100%)
Proportion[b] achieving hemoglobin correction (95% confidence interval)	53% (35%–72%)	57% (36%–79%)	62% (44%–80%)
Number of patients included in analysis	30	30	30
Red blood cell transfusion incidence from week 5 to the end of the treatment phase (95% confidence interval)	36% (0%–87%)	4% (0%–11%)	22% (6%–37%)

[a] Increased to 60,000 U QW at week 6 in patients with an inadequate initial response

[b] Kaplan-Meier proportion

Q2W—every two weeks; QW—once weekly

Note. From "Darbepoetin Alfa Administered Every Two Weeks Alleviates Anemia in Cancer Patients Receiving Chemotherapy," by J.A. Glaspy, & N.S. Tchekmedyian, 2002, *Oncology, 16*(10, Suppl. 11), p. 28. Copyright 2002 by PRR, Inc. Reprinted with permission.

The results of the large, community-based study of darbepoetin alfa Q2W (Amgen Inc., data on file; Vadhan-Raj et al., 2003) also can be benchmarked against results of similarly designed studies of epoetin alfa given TIW or QW (Demetri et al., 1998; Gabrilove et al., 2001; Glaspy et al., 1997) (see Table 2). Hemoglobin response, hematopoietic response, change in hemoglobin, and incidence of transfusions were similar for darbepoetin alfa and epoetin alfa across all studies.

To directly analyze the similar findings seen with darbepoetin alfa Q2W and epoetin alfa QW treatment regimens, three comparative trials have been conducted, each in patients with a specific tumor type (breast, lung, or gynecologic cancer). In the trials, anemic patients (hemoglobin ≤ 11.0 g/dl) were randomized in a 1:1 ratio to receive either darbepoetin alfa 200 mcg Q2W or epoetin alfa 40,000 U QW for as long as 16 weeks. Dose increases to 300 mcg Q2W for darbepoetin alfa and 60,000 U QW for epoetin alfa were allowed for patients who did not have at least a 1.0 g/dl increase in hemoglobin after four weeks of treatment. Final analysis of data from pooled findings of the three studies suggests that both treatment regimens appear to achieve comparable outcomes (Schwartzberg et al., 2004). The mean change in hemoglobin from baseline to the end of treatment was 1.4 g/dl for patients receiving darbepoetin alfa and 1.5 g/dl for those receiving epoetin alfa, with a similar proportion of patients in both treatment groups requiring an RBC transfusion during the study (16% and 17%, respectively) Data on the effects of the two agents on QOL in these comparative studies have not yet been published. However, the studies were designed to validate the Patient Satisfaction Questionnaire for Anemia (PSQ-An) tool. This was found to be valid, feasible, and reliable, although future studies need to be conducted with the PSQ-An to assess the impact of anemia on patients and caregivers.

A line of evidence supporting the comparable hematologic effects of the two agents comes from recent retrospective chart reviews of patients with chemotherapy-induced anemia treated at hospitals and community centers throughout the United States (Boccia et al., 2003; Patton, Reeves, & Wallace, 2003; Reeves et al., 2003; Schwartzberg et al., 2003). The chart reviews indicated that the most common doses of the two agents used in community practice (darbepoetin alfa 200 mcg Q2W and epoetin alfa 40,000 U QW) are associated with similar changes in hemoglobin and similar rates of RBC transfusion, with a similar frequency of dose increase.

Relative Cost of Darbepoetin Alfa and Epoetin Alfa

To examine and compare the costs associated with two therapies of equivalent effectiveness, a cost-minimization analysis can be performed (Bootman, Townsend, & McGhan, 1996). A simple cost-minimization model was designed (see Table 3) using assumptions based on the data from Schwartzberg et al.'s (2003) retrospective chart review. Costs related to treatment are based only on acquisition costs and are calculated using the average wholesale prices for both products: $4.99 per mcg for darbepoetin alfa and $13.36 per 1,000 units for epoetin alfa, from the December 2003 Red Book (Red Book™, 2003). Assuming that the effectiveness of darbepoetin alfa 200 mcg Q2W and epoetin alfa 40,000 U QW are the same, and that a dose escalation occurs for both treatments in 15% of patients at week 7 (to darbepoetin alfa 300 mcg Q2W or epoetin alfa 60,000 U QW), the average cost savings over 16 weeks of therapy using darbepoetin alfa for 100 patients, based on the model, would be $592.95, or approximately 7%.

Table 2. Efficacy of Darbepoetin Alfa and Epoetin Alfa in Community-Based Studies

Variable	Darbepoetin Alfa: Vadhan-Raj et al., 2003; Amgen Inc., data on file	Darbepoetin Alfa: Glaspy et al., 1997	Epoetin Alfa: Demetri et al., 1998	Epoetin Alfa: Gabrilove et al., 2001
Sample size	1,173	2,030	2,289	2,964
Proportion achieving hemoglobin response	58%	53.4%	NR	NR
Proportion achieving hematopoietic response	71%	NR	61%	68%
Mean change in hemoglobin after 16 weeks	2.1 g/dl	1.8 g/dl	2.0 g/dl	1.8 g/dl

NR—not reported

Table 3. Estimated Acquisition Costs for Darbepoetin Alfa Every Two Weeks and Epoetin Alfa Every Week for 100 Patients Over 16 Weeks of Treatment

	Darbepoetin Alfa					Epoetin Alfa				
	Dosed Every Other Week (mcg)					Dosed Once Weekly (U)				
Week	No Dose Escalation (n = 85)	Dose Escalation (n = 15)	Total Dose	Total Cost	Average Cost Per Patient	No Dose Escalation (n = 85)	Dose Escalation (n = 15)	Total Dose	Total Cost	Average Cost Per Patient
1	200	200	20,000	$99,800	$998.00	40,000	40,000	4,000,000	$53,440	$534.40
2						40,000	40,000	4,000,000	$53,440	$534.40
3	200	200	20,000	$99,800	$998.00	40,000	40,000	4,000,000	$53,440	$534.40
4						40,000	40,000	4,000,000	$53,440	$534.40
5	200	200	20,000	$99,800	$998.00	40,000	40,000	4,000,000	$53,440	$534.40
6						40,000	40,000	4,000,000	$53,440	$534.40
7	200	300	21,500	$107,285	$1,072.85	40,000	60,000	4,300,000	$57,448	$574.48
8						40,000	60,000	4,300,000	$57,448	$574.48
9	200	300	21,500	$107,285	$1,072.85	40,000	60,000	4,300,000	$57,448	$574.48
10						40,000	60,000	4,300,000	$57,448	$574.48
11	200	300	21,500	$107,285	$1,072.85	40,000	60,000	4,300,000	$57,448	$574.48
12						40,000	60,000	4,300,000	$57,448	$574.48
13	200	300	21,500	$107,285	$1,072.85	40,000	60,000	4,300,000	$57,448	$574.48
14						40,000	60,000	4,300,000	$57,448	$574.48
15	200	300	21,500	$107,285	$1,072.85	40,000	60,000	4,300,000	$57,448	$574.48
16						40,000	60,000	4,300,000	$57,448	$574.48
Total costs				**$835,825**	**$8,358.25**				**$895,120**	**$8,951.20**

Discussion

Erythropoietic Therapy Improves Quality of Life

A discernible need exists to treat anemia in patients receiving chemotherapy. Management of chemotherapy-induced anemia has been shown to be one of only two interventions that have consistent, positive effects on patients' fatigue levels (the other is aerobic exercise) (Nail, 2002). The use of erythropoietic agents improves patients' overall health-related QOL, by decreasing fatigue and increasing energy levels, as cited in the studies reviewed for this article. In an analysis of data from two additional clinical trials in which patients with chemotherapy-induced anemia were treated with erythropoietic therapy, a clinically important reduction in fatigue (as measured by the FACT-F questionnaire) was associated with a reduction in levels of depression and anxiety (Amorajabi, Tchekmedyian, & Kallich, 2003; Tchekmedyian, Kallich, McDermott, Fayers, & Erder, 2003).

Benefits of Less-Frequent Dosing of Erythropoietic Agents

Patients with cancer receive multiple treatments for the primary disease and as supportive therapy. However, frequent clinic visits to receive treatment may be a burden for patients and caregivers. The time and expense involved may mean that patients have to take leave from work, change or cancel social functions, and neglect household responsibilities. Often, difficulties with transportation are cited in connection with clinic visits (Haithcox, Ramnes, Lee, Lu, & Lyman, 2003; Moore, 2002). Out-of-pocket expenses are an added burden (Meehan et al., 2002). Anemic patients experiencing fatigue may find frequent clinic visits particularly taxing because they place an extra burden on already-depleted energy levels (Moore, Fortner, & Okon, 2003). Frequent visits may have psychological effects, reinforcing patients' self-perception as "patients with cancer" and causing increased anxiety and even depression (Moore; Moore et al.). Caregivers also may be placed under additional strain; for example, they may need to take repeated time off work to accompany patients to the clinic (Moore; Haithcox et al.).

Those closely involved with patients are likely to appreciate the advantages of treatment that reduces the number of injections, as long as the effectiveness of the treatment is not impaired. Patients also indicate this preference. In an observational study of patients with cancer receiving supportive therapy, most patients expressed a wish for longer-acting treatment that would require fewer injections (Haithcox et al., 2003). Recent data also have confirmed that the use of long-acting growth factors to treat cancer-associated anemia and neutropenia results in significant time savings for clinic staff as a consequence of fewer clinic visits required (Beveridge et al., 2003).

Role of Nurses in Anemia Management

Given the impact of multiple clinic visits, a need exists to minimize the number of trips required for cancer treatment and its associated complications, when possible, to optimize patients' QOL. Many visits may be solely to receive supportive therapy (Haithcox et al., 2003), so a treatment for anemia that permits less-frequent dosing clearly is desirable. As indicated in this review, darbepoetin alfa appears to offer the opportunity to manage anemia in patients with cancer effectively and with fewer clinic visits, without adversely affecting the efficacy of hematopoietic supportive care.

Because oncology nurses play an important role in detecting chemotherapy-induced anemia, they should be aware of the treatment options available to develop and maximize

effective management strategies for the symptoms associated with this condition. Darbepoetin alfa, with a longer half-life than epoetin alfa, enables Q2W dosing and has the potential to substantially improve the health-related QOL of patients with chemotherapy-induced anemia, directly through relief of the symptoms of anemia and indirectly through reduction of the number of clinic visits and injections. This treatment adds greater flexibility to the management of anemia and increases the therapeutic options available to patients and healthcare providers. Given the favorable outcomes seen in the majority of those treated with darbepoetin alfa Q2W, "less is more" in improving the QOL of patients with chemotherapy-induced anemia.

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References

Abels, R. (1993). Erythropoietin for anaemia in cancer patients. *European Journal of Cancer, 29A*(Suppl. 2), S2–S8.

Amgen Inc. (2002). *Aranesp® (darbepoetin alfa)* [Prescribing information]. Thousand Oaks, CA: Author.

Amorajabi, M., Tchekmedyian, S., & Kallich, J. (2003, May). Patient-reported depression and anxiety in patients with cancer improves following reduction in anemia-related fatigue with darbepoetin alfa therapy [Abstract 118]. Poster presented at the 28th Annual Congress of the Oncology Nursing Society, Denver, CO.

Berndt, E., Kallich, J., Xu, X., Erder, M.H., Lee, H., & Glaspy, J. (2002). Reductions in anemia and fatigue are associated with improvements in productivity [Abstract 3454]. *Blood, 100,* 876a.

Beveridge, R.A., Rifkin, R.M., Moleski, R.J., Milkovich, G., Reitan, J.F., Paivanas, T.A., et al. (2003). Impact of long-acting growth factors on practice dynamics and patient satisfaction. *Pharmacotherapy, 23*(12, Pt. 2), 101S–109S.

Boccia, R., Davidson, S., Tomita, D., Green, L., & Smith, R.E. (2003). Usage and clinical outcomes of erythropoietic proteins for the treatment of chemotherapy-induced anemia (CIA): Clinical Evaluation of Anemia Response (CLEAR), a multicenter, retrospective cohort study [Abstract 2761]. *Blood, 102,* 748a.

Bootman, J.L., Townsend, R.J., & McGhan, W.F. (Eds.). (1996). *Principles of pharmacoeconomics*. Cincinnati, OH: H. Whitney Books.

Buchsel, P.C., Murphy, B.J., & Newton, S.A. (2002). Epoetin alfa: Current and future indications and nursing implications. *Clinical Journal of Oncology Nursing, 6,* 261–267.

Byar, K., & Berger, A. (2003, May). Women receiving adjuvant chemotherapy for breast cancer: Impact on quality of life and fatigue [Abstract 142]. Poster presented at the 28th Annual Congress of the Oncology Nursing Society, Denver, CO.

Cella, D. (1998). Factors influencing quality of life in cancer patients: Anemia and fatigue. *Seminars in Oncology, 25*(3, Suppl. 7), 43–46.

Cella, D. (2002). The effects of anemia and anemia treatment on the quality of life of people with cancer. *Oncology, 16*(9, Suppl. 10), 125–132.

Cella, D., Eton, D.T., Lai, J.S., Peterman, A.H., & Merkel, D.E. (2002). Combining anchor and distribution-based methods to derive minimal clinically meaningful differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *Journal of Pain and Symptom Management, 24,* 547–561.

Cella, D., Lai, J.S., Chang, C.H., Peterman, A., & Slavin, M. (2002). Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer, 94,* 528–538.

Cleeland, C.S., Gabrilove, J., Crawford, J., Mendes, E., Lubeck, D., Tomita, D., et al. (2003). Assessing symptom burden using the M.D. Anderson Symptom Inventory (MDASI) in patients with chemotherapy-induced anemia: Early results of a multicenter, open-label study of patients treated with darbepoetin alfa 200 mcg every two weeks [Abstract 2765]. *Blood, 102,* 749a.

Cleeland, C.S., Mendoza, T.R., Wang, X.S., Chou, C., Harle, M.T., Morrissey, M., et al. (2000). Assessing symptom distress in cancer patients: The M.D. Anderson Symptom Inventory. *Cancer, 89,* 1634–1646.

Crawford, J., Demetri, G.D., Gabrilove, J.L., Blasi, M.V., Sarokhan, B.J., & Glaspy, J. (2002). Clinical benefits of epoetin alfa therapy in patients with lung cancer. *Clinical Lung Cancer, 3,* 180–190.

Curt, G.A. (2000). Impact of fatigue on quality of life in oncology patients. *Seminars in Hematology, 37*(4, Suppl. 6), 14–17.

Demetri, G.D., Kris, M., Wade, J., Degos, L., & Cella, D. (1998). 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. *Journal of Clinical Oncology, 16,* 3412–3425.

Egrie, J.C., Dwyer, E., Browne, J.K., Hitz, A., & Lykos, M.A. (2003). Darbepoetin alfa has a longer circulating half-life and greater in vivo potency than recombinant human erythropoietin. *Experimental Hematology, 31,* 290–299.

Erslev, A.J. (2000). Erythropoietin and anemia of cancer. *European Journal of Haematology, 64,* 353–358.

Gabrilove, J., Crawford, J., Swan, F., Mendes, E., Tomita, D., Colowick, A., et al. (2003). A multicenter study to assess the effects of darbepoetin alfa 200 mcg every two weeks (Q2W) in patients with nonmyeloid malignancies receiving chemotherapy: Early results of the SURPASS study [Abstract 3778]. *Blood, 102,* 19b.

Gabrilove, J.L., Cleeland, C.S., Livingston, R.B., Sarokhan, B., Winer, E., & Einhorn, L.H. (2001). Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: Improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. *Journal of Clinical Oncology, 19,* 2875–2882.

Gillespie, T.W. (2002). Effects of cancer-related anemia on clinical and quality of life outcomes. *Clinical Journal of Oncology Nursing, 6,* 206–211.

Glaspy, J., Bukowski, R., Steinberg, D., Taylor, C., Tchekmedyian, S., & Vadhan-Raj, S. (1997). Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. *Journal of Clinical Oncology, 15,* 1218–1234.

Glaspy, J.A., Jadeja, J.S., Justice, G., Kessler, J., Richards, D., Schwartzberg, L., et al. (2002). Darbepoetin alfa given every one or two weeks alleviates anaemia associated with cancer chemotherapy. *British Journal of Cancer, 87,* 268–276.

Glaspy, J.A., & Tchekmedyian, N.S. (2002). Darbepoetin alfa administered every two weeks alleviates anemia in cancer patients receiving chemotherapy. *Oncology, 16*(10, Suppl. 11), 23–29.

Groopman, J.E., & Itri, L.M. (1999). Chemotherapy-induced anemia in adults: Incidence and treatment. *Journal of the National Cancer Institute, 91,* 1616–1634.

Haithcox, S., Ramnes, C., Lee, H., Lu, J., & Lyman, G.H. (2003). The impact of frequent injections for hematopoietic growth factor support in patients receiving chemotherapy: An observational study. *BMC Nursing, 2*(1), 2.

Hedenus, M., Adriansson, M., San Miguel, J., Kramer, M.H., Schipperus, M.R., Juvonen, E., et al. (2003). Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: A randomized, double-blind, placebo-controlled study. *British Journal of Haematology, 122,* 394–403.

Henke, M., Laszig, R., Rube, C., Schafer, U., Haase, K.D., Schilcher, B., et al.

(2003). Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: Randomised, double-blind, placebo-controlled trial. *Lancet, 362,* 1255–1260.

Holzner, B., Kemmler, G., Greil, R., Kopp, M., Zeimet, A., Raderer, M., et al. (2002). The impact of hemoglobin levels on fatigue and quality of life in cancer patients. *Annals of Oncology, 13,* 965–973.

Johnston, E., & Crawford, J. (1998). The hematologic support of the cancer patient. In A. Berger, R.K. Portenoy, & D.E. Weissman (Eds.), *Principles and practices of supportive oncology* (pp. 549–569). Philadelphia: Lippincott-Raven.

Jumbe, N., Yao, B., Rovetti, R., Rossi, G., & Heatherington, A. (2002). Clinical trial simulation of a 200-mcg fixed dose of darbepoetin alfa in chemotherapy-induced anemia. *Oncology, 16*(10, Suppl. 11), 37–44.

Kotasek, D., Steger, G., Faught, W., Underhill, C., Poulsen, E., Colowick, A.B., et al. (2003). Darbepoetin alfa administered every three weeks alleviates anaemia in patients with solid tumours receiving chemotherapy: Results of a double-blind, placebo-controlled, randomised study. *European Journal of Cancer, 39,* 2026–2034.

Kunikane, H., Watanabe, K., Fukuoka, M., Saijo, N., Furuse, K., Ikegami, H., et al. (2001). Double-blind randomized control trial of the effect of recombinant human erythropoietin on chemotherapy-induced anemia in patients with non-small cell lung cancer. *International Journal of Clinical Oncology, 6,* 296–301.

Lawless, G., Wilson-Royalty, M., & Meyers, J. (2000). Epoetin alfa practice pattern usage in community practice sites [Abstract 5446]. *Blood, 96,* 390b.

Lee, S.J., Liljas, B., Churchill, W.H., Popovsky, M.A., Stowell, C.P., Cannon, M.E., et al. (1998). Perceptions and preferences of autologous blood donors. *Transfusion, 38,* 757–763.

Leyland-Jones, B. (2003). Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncology, 4,* 459–460.

Littlewood, T.J., Bajetta, E., Nortier, J.W., Vercammen, E., & Rapoport, B. (2001). 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. *Journal of Clinical Oncology, 19,* 2865–2874.

Ludwig, H., Birgegard, G., Barrett-Lee, P.J., & Krzakowski, M. (2002). Prevalence and management of anemia in patients (pts) with hematologic malignancies (HMs) and solid tumors (STs): Results from the European Cancer Anaemia Survey (ECAS) [Abstract 884]. *Blood, 100,* 234a.

Ludwig, H., & Pecorelli, S. (2000). Suboptimal hemoglobin levels: Do they impact patients and their therapy? Audience responses. *Seminars in Oncology, 27*(2, Suppl. 4), 18–19.

Meehan, K.R., Tchekmedyian, S., Smith, R.E., Jr., Kleinman, L., Fitzmaurice, T., & Kallich, J.D. (2002). An activity based costing estimate of anemia correction activities in an oncology practice [Abstract 5595]. *Blood, 100,* 502b.

Mercadante, S., Gebbia, V., Marrazzo, A., & Filosto, S. (2000). Anaemia in cancer: Pathophysiology and treatment. *Cancer Treatment Reviews, 26,* 303–311.

Miller, C.B., Jones, R.J., Piantadosi, S., Abeloff, M.D., & Spivak, J.L. (1990). Decreased erythropoietin response in patients with the anemia of cancer. *New England Journal of Medicine, 322,* 1689–1692.

Mirtsching, B.C., Beck, J.T., Charu, V., Nazha, N.T., Tchekmedyian, N.S., Ghazal, H., et al. (2003). Darbepoetin alfa administered every two weeks (Q2W) reduces chemotherapy-induced anemia (CIA) to the same extent as recombinant human erythropoietin (rHuEPO) but with less-frequent dosing [Abstract 2944]. *Proceedings of the American Society of Clinical Oncology, 22,* 732.

Mock, V., & Olsen, M. (2003). Current management of fatigue and anemia in patients with cancer. *Seminars in Oncology Nursing, 19*(4, Suppl. 2), 36–41.

Montserrat, E., Bosch, F., & Rozman, C. (1997). B-cell chronic lymphocytic leukemia: Recent progress in biology, diagnosis, and therapy. *Annals of Oncology, 8*(Suppl. 1), 93–101.

Moore, K. (2002, July). Impact of medical visits on the patient and caregiver: Every day counts. *Point of Care Perspectives,* 1–4.

Moore, K., Fortner, B., & Okon, T. (2003, May). The impact of medical visits on patients with cancer [Abstract 73]. Poster presented at the 28th Annual Congress of the Oncology Nursing Society, Denver, CO.

Nail, L.M. (2002). Fatigue in patients with cancer. *Oncology Nursing Forum, 29,* 537–544.

Ortho Biotech Products, L.P. (2000). *Procrit® (epoetin alfa)* [Prescribing information]. Bridgewater, NJ: Author.

Osterborg, A., Brandberg, Y., Molostova, V., Iosava, G., Abdulkadyrov, K., Hedenus, M., et al. (2002). Randomized, double-blind, placebo-controlled trial of recombinant human erythropoietin, epoetin beta, in hematologic malignancies. *Journal of Clinical Oncology, 20,* 2486–2494.

Patton, J., Reeves, T., & Wallace, J.F. (2003, May). Darbepoetin alfa 200 mcg every two weeks (Q2W) and epoetin alfa 40,000 U every week (QW) in chemotherapy-induced anemia patients result in similar initial hemoglobin outcomes. Presented at the International Society for Pharmacoeconomics and Outcomes Research 8th Annual International Meeting, Arlington, VA.

Quirt, I., Robeson, C., Lau, C.Y., Kovacs, M., Burdette-Radoux, S., Dolan, S., et al. (2001). Epoetin alfa therapy increases hemoglobin levels and improves quality of life in patients with cancer-related anemia who are not receiving chemotherapy and patients with anemia who are receiving chemotherapy. *Journal of Clinical Oncology, 19,* 4126–4134.

Red Book™. (2003, December). Thomson Micromedex. Greenwood Village, CO: Author.

Reeves, T.J., Wallace, J.F., & Patton, J.F. (2003, December). Darbepoetin alfa is comparable to epoetin alfa for chemotherapy induced anemia in clinical practice [Abstract P-500]. Presented at the 38th American Society of Health-System Pharmacists Annual Midyear Clinical Meeting, New Orleans, LA.

Rizzo, J.D., Lichtin, A.E., Woolf, S.H., Seidenfeld, J., Bennett, C.L., Cella, D., et al. (2002). 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. *Blood, 100,* 2303–2320.

Schwartzberg, L., Shiffman, R., Tomita, D., Stolshek, B., Rossi, G., & Adamson, R. (2003). A multicenter retrospective cohort study of practice patterns and clinical outcomes of the use of darbepoetin alfa and epoetin alfa for chemotherapy-induced anemia. *Clinical Therapeutics, 25,* 2781–2796.

Schwartzberg, L.S., Yee, L.K., Senecal, F.M., Charu, V., Tomita, D., Wallace, J., et al. (2004). A randomized comparison of every-two-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia in patients with breast, lung or gynecologic cancer. *Oncologist, 9,* 696–707.

Singer, M., & Patel, A. (2002, April). Improving symptom management in an ambulatory oncology clinic [Abstract 32]. Podium session presented at the 27th Annual Congress of the Oncology Nursing Society, Washington, DC.

Tchekmedyian, N.S. (2001). New frontiers in oncology supportive care: Anemia management. *Primary Care and Cancer, 21,* 9–12.

Tchekmedyian, N.S. (2002). Anemia in cancer patients: Significance, epidemiology, and current therapy. *Oncology, 16*(9, Suppl. 10), 17–24.

Tchekmedyian, N.S., Kallich, J., McDermott, A., Fayers, P., & Erder, M.H. (2003). The relationship between psychologic distress and cancer-related fatigue. *Cancer, 98,* 198–203.

Thames, W., Yao, B., Scheifele, A., & Alley, J.L. (2003). Drug use evaluation (DUE) of darbepoetin alfa in anemic patients undergoing chemotherapy supports a fixed dose of 200 mcg Q2W given every two weeks (Q2W) [Abstract 2196]. *Proceedings of the American Society of Clinical Oncology, 22,* 546.

Vadhan-Raj, S., Mirtsching, B., Charu, V., Terry, D., Rossi, G., Tomita, D., et al. (2003). Assessment of hematologic effects and fatigue in cancer patients with chemotherapy-induced anemia given darbepoetin alfa every two weeks. *Journal of Supportive Oncology, 1,* 131–138.

Vansteenkiste, J., Pirker, R., Massuti, B., Barata, F., Font, A., Fiegl, M., et al. (2002). Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. *Journal of the National Cancer Institute, 94,* 1211–1220.

Vansteenkiste, J., Tomita, D., Rossi, G., & Pirker, R. (2004). Darbepoetin alfa in lung cancer patients on chemotherapy: A retrospective comparison of outcomes in patients with mild versus moderate-to-severe anaemia at baseline. *Supportive Care in Cancer, 12,* 253–262.

Wun, T., Law, L., Harvey, D., Sieracki, B., Scudder, S.A., & Ryu, J.K. (2003). Increased incidence of symptomatic venous thrombosis in patients with cervical carcinoma treated with concurrent chemotherapy, radiation, and erythropoietin. *Cancer, 98,* 1514–1520.

Yellen, S.B., Cella, D.F., Webster, K., Blendowski, C., & Kaplan, E. (1997). Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *Journal of Pain and Symptom Management, 13,* 63–74.

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