Darbepoetin alfa: An Effective Treatment with Flexible and Simplified Dosing for Anemia in Patients with Cancer

James G. Stevenson, Pharm.D., and James J. Natale, Pharm.D.

Anemia is common in patients with cancer or myelodysplastic syndrome. Erythropoietic therapy offers an effective way to manage anemia by increasing hemoglobin levels, decreasing transfusion requirements, and alleviating symptoms. We reviewed data showing the feasibility and effectiveness of treatment with the erythropoiesis-stimulating protein darbepoetin alfa at extended dosing intervals to treat anemia in patients with cancer receiving multicycle chemotherapy. We also explored the darbepoetin alfa's potential for treating anemia in patients with myelodysplastic syndrome. Data from clinical studies and drug therapy evaluations confirm that darbepoetin alfa administered weekly, every 2 weeks, and every 3 weeks corrects and maintains hemoglobin levels in patients with chemotherapy-induced anemia. In addition, the data demonstrate that both weight-based and fixed dosing with darbepoetin alfa are effective, and that early intervention to treat anemia has clinical benefits. Darbepoetin alfa also is an effective treatment for anemia in patients with cancer not receiving chemotherapy, at extended dosing intervals of at least 3 weeks. Extended dosing for anemia treatment can provide benefits for patients, caregivers, and clinicians because it reduces the number of clinic visits needed and permits synchronizing anemia treatment with chemotherapy cycles. Data from recent studies suggest that darbepoetin alfa is effective for treating anemia in patients with myelodysplastic syndrome; this potential use is being investigated further in ongoing studies. Thus, darbepoetin alfa is an attractive therapy option for patients with chemotherapy- or cancer-induced anemia. It allows increased flexibility and simplified dosing and may offer some benefit in the treatment of anemia in patients with myelodysplastic syndrome.

Key Words: darbepoetin alfa, anemia, cancer, chemotherapy, myelodysplastic syndrome, MDS.

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OUTLINE

Anemia in patients with cancer can be treated effectively with erythropoiesis-stimulating proteins, such as recombinant human erythropoietin (rHuEPO; epoetin alfa and epoetin beta) and darbepoetin alfa. However, despite the treatment benefits, anemia in this patient population remains an undertreated condition.[1, 2] The symptoms of anemia, including fatigue, lethargy, reduced functional and cognitive capacity, and weakness, all have a considerable impact on health-related quality of life.[3–7] In addition to these negative effects, fatigue, in particular, may result in additional loss of work productivity in patients with cancer.[8] Thus, effective treatment of anemia in this patient population is important from several perspectives.

Both rHuEPO and darbepoetin alfa stimulate erythropoiesis by the same mechanism as endogenous erythropoietin. By binding to the erythropoietin receptor,[9] these agents effectively increase and maintain hemoglobin levels and reduce the need for transfusions. Recombinant human erythropoietin has a relatively short half-life (4–8 hrs). For treatment of anemia in patients with cancer receiving concomitant chemotherapy, the starting dosage of epoetin alfa approved by the United States Food and Drug Administration (FDA) is 150 units/kg 3 times/week or 40,000 units/week.[10] However, darbepoetin alfa has two additional carbohydrate chains, resulting in an extended half-life compared with rHuEPO, which creates the potential for less frequent dosing.[9, 11] The initial FDA-approved dosage of darbepoetin alfa for patients with chemotherapy-induced anemia was 2.25 µg/kg/week,[12, 13] and recently, 500 µg every 3 weeks was approved.[13]

Patients, their caregivers, and clinicians could benefit from anemia treatment administered less frequently. Clinic visits can be a considerable burden for patients and caregivers in terms of time, impact on daily life, and cost,[14–16] so reducing the number of visits would be beneficial. A survey of patients with cancer receiving anemia treatment found that approximately 2 hours for patients and 1 hour for their caregivers was required for each visit.[15] Visits to the clinic for anemia treatment can adversely affect patients and caregivers in many ways, such as taking time off from work, changing or canceling social functions or vacations, and failing to accomplish household responsibilities.[14, 15] For patients experiencing anemia-related fatigue, clinic visits may further deplete already low energy reserves.[14] Also, visits may involve out-of-pocket expenses for patients and their accompanying caregivers.[16]

Less frequent dosing could also reduce the time clinicians spend preparing and administering injections, thereby increasing the efficiency of their clinics through better use of resources. Time-and-motion data confirm that when long-acting growth factors are administered to treat cancer-associated anemia and neutropenia, fewer clinic visits result in significant time savings for clinic staff.[17] Because many chemotherapy regimens are administered in 3-week cycles (Figure 1),[18] less frequent administration of anemia treatment could be synchronized with the chemotherapy cycles.

The benefits of darbepoetin alfa in the management of cancer- and chemotherapy-related anemia have become clearer with additional data from clinical trials and increased clinical experience.

Etiology of Anemia in Patients with Cancer or Myelodysplastic Syndrome

Anemia, a common complication among patients with cancer (Figure 2),[18, 19] may occur as a result of cancer treatment, or as a direct or indirect effect of the malignancy itself.[20, 21] Chemotherapy is a frequent cause of anemia through a range of mechanisms, including stem cell death, blockage of hematopoietic factors, and damage to mature hematopoietic cells.[20] Patients may also develop anemia even if they are not receiving chemotherapy. Other causes of anemia

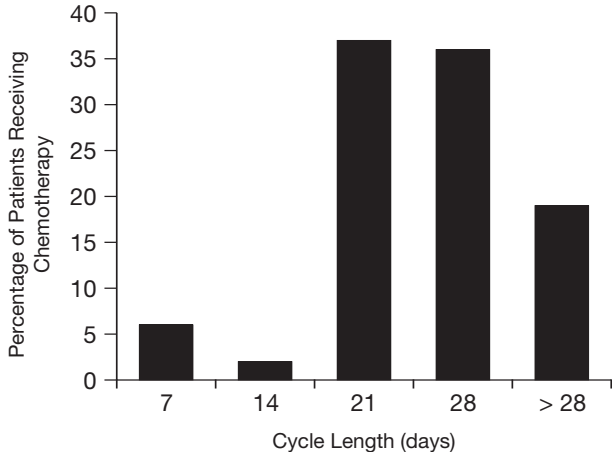

Figure 1. Distribution of patients receiving chemotherapy in the United States during 2000 by cycle length. Most chemotherapy regimens were estimated to be administered in 3–4-week cycles. (From reference 18 with permission.)

in patients with cancer are chronic blood loss, hemolysis, and displacement of bone marrow due to invasion by the tumor.[20, 21] Another cause may be the release of cytokines such as interferons, interleukin-1, and tumor necrosis factor-α by the immune and inflammatory system in response to the malignancy.[22, 23] Increased levels of these cytokines can produce effects that contribute to the development of chronic anemia of cancer, such as reduced life span of red blood cells, inadequate erythropoietin production or utilization, and impaired iron utilization.[22]

Myelodysplastic syndrome is a neoplastic clonal stem cell disorder characterized by bone marrow failure and a tendency to progress to acute myelogenous leukemia.[24] Cytopenia, particularly anemia, is the most common clinical manifestation, and myelodysplastic syndrome is a frequent cause of anemia in the elderly. Anemia in patients with myelodysplastic syndrome results from ineffective hematopoiesis, thought to be caused by increased intramedullary apoptosis, although the exact contributing mechanisms remain unknown.[25]

Guidelines for Erythropoietic Treatment in Patients with Cancer

Given the impact of anemia in patients with cancer, treatment guidelines concerning erythropoietic therapy in this population have been established, such as those from the American Society of Clinical Oncology–American Society of Hematology.[26] These guidelines recommend erythropoietic treatment for patients with chemotherapy-associated anemia and hemoglobin levels of 10 g/dl or less. For patients with hemoglobin levels of greater than 10 g/dl but less than 12 g/dl, these guidelines recommend that deciding whether to administer epoetin alfa is based on the patient's clinical manifestation of anemia.

Similarly, the European Organization for Research and Treatment of Cancer recommends erythropoietic therapy for patients whose hemoglobin level is 9–10 g/dl.[27] Therapy should be based on anemia-related symptoms both in patients with cancer receiving chemotherapy and/or radiotherapy and in those not receiving these treatments. The National Comprehensive Cancer Network's evidence-based practice guidelines for treating cancer- and treatment-related anemia recommend considering appropriate treatment after a patient's hemoglobin level decreases to 11 g/dl or less.[28]

Regardless of which recommendations are used on when to start erythropoietic therapy, all of these guidelines support a similar target hemoglobin concentration. The American Society of Clinical Oncology–American Society of Hematology and the National Comprehensive Cancer Network recommend a target hemoglobin concentration of 12 g/dl, and the European Organization for Research and Treatment of Cancer recommends maintaining a concentration of 12–13 g/dl.

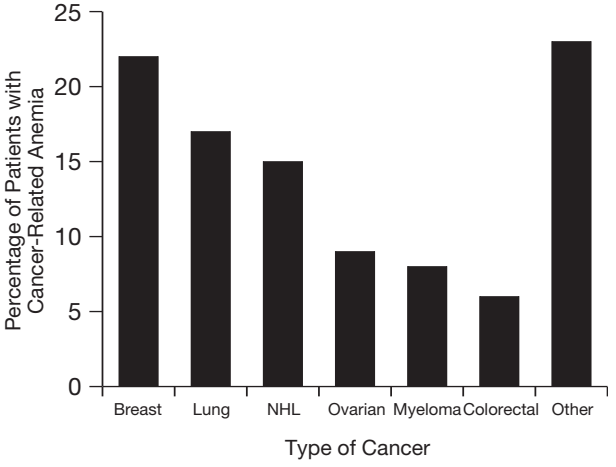

Figure 2. Distribution of patients with cancer-related anemia in the United States during 2000 by the most common types of cancer associated with chemotherapy- and cancer-related anemia. NHL = non-Hodgkin's lymphoma. (From reference 18 with permission.)

Darbepoetin alfa

Chemotherapy-Induced Anemia

Establishing the Efficacy of Darbepoetin alfa Once/Week and Every 2 Weeks

A 2002 active-controlled study involving patients receiving multicycle chemotherapy and subcutaneous darbepoetin alfa 0.5–8.0 μg/kg/week for 12 weeks demonstrated that weekly administration raised hemoglobin levels.[29] Mean change in hemoglobin level was 1.4 g/dl in the 0.5-μg/kg/week cohort and 2.75 g/dl in the 8.0-μg/kg/week cohort. A dose-response relationship was apparent with doses up to 4.5 μg/kg. Based on this study's findings, the minimum effective dose with respect to reducing blood transfusions was 1.5 μg/kg/week.[12]

The efficacy of a weekly regimen was confirmed in a large, double-blind, placebo-controlled phase III study of 320 patients receiving chemotherapy

Table 1. Summary of Retrospective Cohort Studies of Darbepoetin alfa in Clinical Practice

	Darbepoetin alfa		Epoetin alfa	
No. of Patients	Most Common Initial Dosage (% of patients receiving this dosage)	Percentage of Patients Who Required Dosage Increase[a]	Most Common Initial Dosage (% of patients receiving this dosage)	Percentage of Patients Who Required Dosage Increase[a]
1391[37]	200 µg every 2 wks (75.2)	11.4	40,000 units/wk (74.2)	14.0
2785[38]	200 µg every 2 wks (61.0)	22.0	40,000 units/wk (72.0)	23.0
408[39]	100 µg/wk (49.0)	16.0	40,000 units/wk (86.0)	24.0

[a]These patients refer to those who had received the most common initial dosage.

for lung cancer.[30] Significantly fewer patients receiving darbepoetin alfa 2.25 µg/kg/week than those receiving placebo required red blood cell transfusions from week 5 to the end of the treatment phase (27% [95% confidence interval (CI) 20–35%] vs 52% [95% CI 44–66%], p<0.001). Furthermore, a greater proportion of patients in the darbepoetin alfa group had a hematopoietic response (defined as an increase in hemoglobin level of at least 2 g/dl, or achieving a hemoglobin level of at least 12 g/dl in the absence of a red blood cell transfusion in the previous 28 days). Hematopoietic response in the darbepoetin alfa and placebo groups was 66% (95% CI 58–74%) and 24% (95% CI 16–31%), respectively (p<0.001).

Early dose-finding data also provided the first evidence that extending the frequency of darbepoetin alfa administration from every week to every 2 weeks does not reduce efficacy.[29] Across a range of doses, the proportion of patients with a hematopoietic response was similar when twice the weekly dose was administered once every 2 weeks. Results from a multicenter, open-label, noncomparative study confirmed that darbepoetin alfa can alleviate chemotherapy-induced anemia when given every 2 weeks.[31, 32] Over the 16-week study period, patients with nonmyeloid malignancies and anemia (baseline hemoglobin level ≤ 11 g/dl) receiving multicycle chemotherapy were given eight doses of subcutaneous darbepoetin alfa 3.0 µg/kg every 2 weeks. Interim results showed a rapid and steady increase in hemoglobin level (Figure 3).

Final data were presented for all 1558 patients enrolled in the study. Mean change in hemoglobin level was 1.7 g/dl (95% CI 1.6–1.8). Over 70% of patients achieved a hematopoietic response (increase in hemoglobin level ≥ 2 g/dl or achieving a hemoglobin level ≥ 12 g/dl in the absence of a red blood cell transfusion in the previous 28 days). Overall, 19% (95% CI 17–21%) of patients required a red blood cell transfusion.[32] The results of this study, with darbepoetin alfa administered every 2 weeks, are similar to those seen with commonly used rHuEPO dosing regimens, such as 10,000 units 3 times/week or 40,000 units once/week, in large community-based studies of epoetin alfa.[31, 33–35]

Potential for Fixed Dosing

Recent studies have demonstrated that darbepoetin alfa administered using fixed rather than weight-based dosing may simplify anemia management.[36–39] A drug use evaluation, conducted by the US Oncology Network, suggested that a fixed dose of darbepoetin alfa 200 µg every 2 weeks is effective in treating chemotherapy-induced anemia in patients naïve to erythropoietic therapy, and in maintaining hemoglobin levels in patients previously stabilized with epoetin alfa.[36] Additional retrospective cohort studies confirmed that a

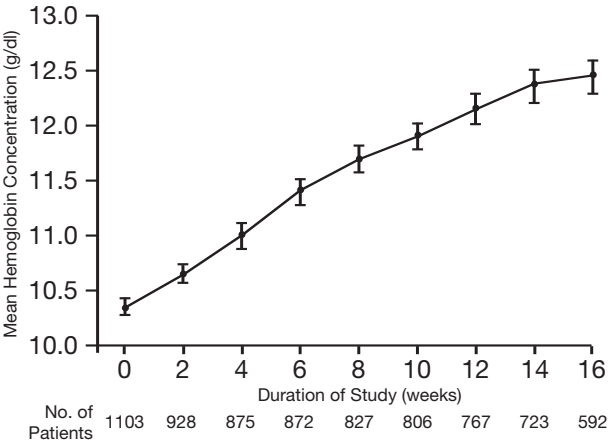

Figure 3. Mean hemoglobin concentrations (with 95% confidence intervals) in patients with cancer receiving chemotherapy who were given eight doses of subcutaneous darbepoetin alfa 3.0 µg/kg every 2 weeks. (From reference 31 with permission.)

fixed dose of darbepoetin alfa 200 µg every 2 weeks is effective in treating anemia in patients receiving chemotherapy.[37–39] The rates of dose escalation in these studies were comparable to rates seen with epoetin alfa (Table 1).

Comparison of Darbepoetin alfa Every 2 Weeks with Epoetin alfa Once/Week

Several head-to-head comparison studies assessed the relative efficacy of darbepoetin alfa every 2 weeks and epoetin alfa once/week. In one study, patients with anemia who had breast, lung, or gynecologic cancer and were receiving multicycle chemotherapy were randomized to receive darbepoetin alfa 200 µg every 2 weeks or epoetin alfa 40,000 units/week for up to 16 weeks.[40] Doses were increased (frequencies remained the same) to darbepoetin alfa 300 µg and epoetin alfa 60,000 units after 4 weeks if hemoglobin levels had increased less than 1 g/dl from baseline.

In a combined analysis incorporating these three tumor types and a total of 312 patients, the rate of red blood cell transfusions over the treatment period was similar in both groups, with 16% and 17% in the darbepoetin alfa and epoetin alfa groups, respectively. The hematopoietic response at the end of treatment (the proportion of patients whose hemoglobin increased by ≥ 2 g/dl or who achieved a hemoglobin concentration ≥ 12 g/dl) was similar, with 69% and 72% in the darbepoetin alfa and epoetin alfa groups, respectively.

The target hemoglobin concentration range was 11–13 g/dl, and similar proportions of patients in both treatment groups achieved a hemoglobin level of at least 11 g/dl, with 82% and 86% for the darbepoetin alfa and epoetin alfa groups, respectively. Of these patients, 81% and 75% maintained levels within the target range. Thus, both treatments appeared to have comparable efficacy in improving and maintaining hemoglobin concentrations as well as reducing transfusion requirements.

Another study involved 358 patients with anemia (hemoglobin concentration ≤ 11.0 g/dl) who had solid tumors and were scheduled to receive chemotherapy for at least 12 weeks.[41] Patients in this study were also randomized to receive darbepoetin alfa 200 µg every 2 weeks or epoetin alfa 40,000 units/week for 16 weeks. Doses were increased to darbepoetin alfa 300 µg after 6 weeks and to epoetin alfa 60,000 units after 4 weeks if hemoglobin levels had increased by less than 1 g/dl. In an analysis based on data for the first 305 patients who completed 4 weeks of study treatment, the proportion of patients whose hemoglobin concentration increased by at least 1 g/dl in the first 4 weeks of treatment was 32.5% and 47.0% for those receiving darbepoetin alfa and epoetin alfa, respectively (p=0.0078). (Levels obtained within 28 days of a transfusion were excluded from this analysis.)

For 318 study patients at risk of needing a transfusion from week 5 to the end of the study, transfusions were required in 17.8% and 12.9% in the darbepoetin alfa and epoetin alfa groups, respectively (p=0.2936). The proportion of patients whose hemoglobin levels increased by at least 2 g/dl by the end of the study was 41.8% and 57.7% in the respective groups (p=0.004). These results differ from those of previous and subsequent studies of these two treatments; however, this may reflect different dosage escalation and reduction used for each treatment during the study. Hematopoietic response rates were not evaluated.

A larger study involved 1220 patients with nonmyeloid malignancies who were scheduled to receive at least 8 weeks of chemotherapy.[42] Again, patients were randomized to receive darbepoetin alfa 200 µg every 2 weeks or epoetin alfa 40,000 units/week for up to 16 weeks. A total of 1209 patients received at least one dose of study drug and were included in the primary analysis data set. From week 5 to the end of treatment, 21% (95% CI 17–24%) of patients receiving darbepoetin alfa also received a red blood cell transfusion, compared with 16% (95% CI 12–19%) of those receiving epoetin alfa. The upper limit of the 95% CI of the difference between groups was 10.8%, which is below the prespecified noninferiority margin of 11.5%. Thus, noninferiority regarding transfusion was demonstrated with darbepoetin alfa 200 µg every 2 weeks compared with epoetin alfa 40,000 units/week. A similar proportion of patients in both treatment groups achieved the target hemoglobin concentration range (11–13 g/dl), with 80% and 86% in the darbepoetin alfa and epoetin alfa groups, respectively.

In a recent review of darbepoetin alfa (1087 patients) versus epoetin alfa (1415 patients), analysis of trials did not show a significant difference between the two treatments in hemoglobin response, transfusion reduction, or thromboembolic events.[43] In addition, comparative analysis produced no conclusions about quality of life, tumor response and progression,

survival, or adverse outcomes other than thromboembolic events.

Extended Dosing Intervals

A two-part, randomized, double-blind, dose-finding study investigated the efficacy of administering darbepoetin alfa every 3 weeks in 249 patients with anemia (hemoglobin level ≤ 11.0 g/dl) who had cancer and were receiving multicycle chemotherapy.[44] In part A of the study, patients were randomized in a 4:1 ratio to receive up to 12 weeks of placebo or subcutaneous darbepoetin alfa at one of six doses ranging from 4.5–15.0 µg/kg every 3 weeks. In part B, patients who completed part A and continued receiving chemotherapy could choose whether to continue receiving open-label darbepoetin alfa every 3 weeks for up to 12 more weeks.

Hematopoietic response rates ranged from 51% (95% CI 33–70%) in the darbepoetin alfa 4.5-µg/kg group to 71% (95% CI 52–91%) in the 12-µg/kg group. No further increase was seen in the proportion of patients achieving a hematopoietic response with darbepoetin alfa doses greater than 12 µg/kg every 3 weeks. Fewer patients in the darbepoetin alfa groups than in the placebo group required red blood cell transfusions from week 5 to the end of the treatment phase. Transfusion rates in the darbepoetin alfa groups ranged from 19% (95% CI 6–32%) to 30% (95% CI 16–44%) compared with 46% (95% CI 32–61%) in the placebo group. No significant differences in transfusion rates were observed between the darbepoetin alfa groups.

In another randomized trial, 81 patients with anemia (hemoglobin levels 9–11 g/dl) who had cancer and were receiving chemotherapy every 3 weeks were randomized to receive darbepoetin alfa 6.75 µg/kg every 3 weeks either 1 week before each chemotherapy cycle (asynchronous) or on the same day as chemotherapy (synchronous) for up to 16 weeks.[45] With either schedule, darbepoetin alfa administered once/chemotherapy cycle was effective in treating chemotherapy-induced anemia. After 6 weeks of therapy, the mean increase in hemoglobin concentration was 1.0 g/dl (95% CI 0.6–1.3) with asynchronous darbepoetin alfa administration (43 patients) and 1.0 g/dl (95% CI 0.6–1.5) with synchronous administration (38 patients).

As with the every-2-week darbepoetin alfa regimen, the every-3-week schedule also may be further simplified with fixed dosing. Results from a randomized clinical study indicated that a fixed dose of 300 µg every 3 weeks is effective in treating both mild and moderate chemotherapy-induced anemia.[46] Other recent studies have also demonstrated that fixed dosing of darbepoetin alfa every 3 weeks in patients with chemotherapy-induced anemia is effective for achieving and maintaining hemoglobin at a level consistent with the evidence-based guidelines.[47–49]

One analysis involved data for 1493 patients with chemotherapy-induced anemia (hemoglobin < 11 g/dl) who had completed 16 weeks of treatment with darbepoetin alfa 300 µg every 3 weeks.[47] After 6 weeks, this could be increased to 500 µg every 3 weeks if the hemoglobin level remained below 10 g/dl and the increase from baseline was less than 1 g/dl. Most patients (79% [95% CI 77–81%]) achieved and maintained the target hemoglobin concentration of 11 g/dl or greater. When results were stratified by baseline hemoglobin concentration, a greater proportion of patients with a baseline concentration of at least 10 g/dl versus less than 10 g/dl achieved the target hemoglobin concentration (87% [95% CI 85–90%] vs 66% [95% CI 61–70%]). However, similar proportions of patients in both groups (73% and 71%, respectively) then maintained levels of 11–13 g/dl.

A subset analysis of patients in the study who had breast cancer confirmed that darbepoetin alfa every 3 weeks increased and maintained hemoglobin concentrations of 11–13 g/dl in this patient population.[50] Again, similar proportions of patients with baseline hemoglobin levels 10 g/dl or greater and less than 10 g/dl maintained levels within the target range (92% [95% CI 88–95%] and 80% [95% CI 71–89%], respectively).

In another large study, 705 patients with anemia (hemoglobin < 11 g/dl) who had non-myeloid malignancies and were receiving chemotherapy were randomized to receive darbepoetin alfa 500 µg every 3 weeks or 2.25 µg/kg once/week for 15 weeks.[48] The proportion of patients achieving the target hemoglobin concentration of at least 11 g/dl was similar in both groups (84% [95% CI 81–88%] and 77% [95% CI 72–81%], respectively, adjusted Kaplan-Meier proportions). The rate of blood transfusions from week 5 to the end of the treatment phase was also similar in both groups. Of those receiving darbepoetin alfa every 3 weeks, 23% (95% CI 19–28%) required a transfusion, compared with 30% (95% CI 25–30%) of the weekly treatment group (unadjusted Kaplan-Meier estimates). Because the upper limit of the 95% CI for the between-

group difference was below the prespecified noninferiority margin of 12.5%, the every-3-week treatment was considered comparable to weekly treatment with respect to transfusion rate.

An exploratory analysis of data from this study investigated the effect of reduced or withheld doses of darbepoetin alfa on hemoglobin levels.[51] Results confirmed that the starting dosage of darbepoetin alfa 500 µg every 3 weeks, with dose reductions of 25–50% as required, effectively maintained hemoglobin concentrations in the study population. A similar proportion of patients in the every-3-week and weekly treatment groups required a dose reduction (74% [95% CI 69–80%] and 75% [95% CI 70–80%], respectively), primarily because their hemoglobin levels increased by 1 g/dl or greater in a 2-week period. The average weekly doses over the entire study period were 129.6 and 113.0 µg for the every-3-week and weekly treatment groups, respectively. The safety profiles of both treatments were similar, with no increase in cardiovascular or thromboembolic events associated with rapid increases in hemoglobin concentrations.

The effectiveness of darbepoetin alfa every 3 weeks for treating chemotherapy-induced anemia was confirmed by a recent placebo-controlled study involving patients with nonmyeloid malignancies.[49] In this study, 386 patients with anemia (hemoglobin < 11 g/dl) receiving chemotherapy were randomized to receive darbepoetin alfa 300 µg or placebo every 3 weeks. Dose-adjustment rules during the study allowed for an increase to darbepoetin alfa 500 µg every 3 weeks or a decrease in dose depending on hemoglobin concentration. In the darbepoetin alfa group, 24% of patients received a dose increase, and the average weekly dose was 94.6 µg every 3 weeks.

The proportion of patients achieving the hemoglobin concentration target range of 11–13 g/dl from week 5 to the end of the treatment period was significantly higher in the group receiving darbepoetin alfa every 3 weeks versus placebo (82% [95% CI 76–88%] vs 48% [95% CI 41–56%], p<0.001). The rate of blood transfusions during the treatment period was also significantly lower with darbepoetin alfa versus placebo (24% [95% CI 18–30%] vs 41% [95% CI 34–49%], p<0.001).

Benefits of Early Intervention

There has been considerable debate as to when anemia treatment should be started in patients with cancer receiving chemotherapy, and few studies have addressed this issue. However, a recent systematic review of trials of erythropoietic therapy in patients with chemotherapy-induced anemia suggested a clinical benefit from early intervention.[52] The benefit was seen when hemoglobin concentrations were 10 g/dl or greater, with reduced relative risk of blood transfusion and reduced risk of a decrease in hemoglobin concentration to less than 10 g/dl. Thus, early intervention with erythropoietic therapy in patients undergoing chemotherapy is likely to reduce the risk of severe symptomatic anemia, with its associated detrimental effects on health status and quality of life.

Results from a trial of fixed every-3-week dosing confirmed that treatment with darbepoetin alfa in patients with mild anemia can help prevent progression of the anemia to more severe levels.[46] Patients with chemotherapy-induced anemia and baseline hemoglobin levels of 10.5–12 g/dl were randomized in a 1:1 ratio to early intervention with darbepoetin alfa (immediate therapy) or late intervention (not treated until hemoglobin concentration dropped to ≤ 10 g/dl). In both groups, a fixed dose of 300 µg every 3 weeks was given for up to 23 weeks.

Data through week 17 for 201 evaluable patients were reported. In the early intervention group, 29% (95% CI 19–38%) of patients progressed to moderate anemia (hemoglobin < 10 g/dl), compared with 65% (95% CI 55–75%) in the late intervention group (p<0.0001). The early intervention group maintained an average hemoglobin level in the target range of 11–12 g/dl. The late intervention group required darbepoetin alfa after a median of 4.5 weeks (95% CI 3–6) to increase hemoglobin concentrations.

Anemia of Cancer

A multicenter, dose- and schedule-finding, open-label study in patients with nonmyeloid malignancies who were not receiving chemotherapy was conducted to determine the efficacy of darbepoetin alfa in this population.[53] Initially, 102 patients received subcutaneous darbepoetin alfa for 12 weeks at escalating doses of 0.5, 1.0, 2.25, or 4.5 µg/kg/week. Results demonstrated a significant increase in hemoglobin concentration; at least 70% (95% CI 53–88%) of patients with chronic anemia of cancer in each dose cohort achieved a hematopoietic response.

After completion of the once-weekly schedule, different patient cohorts were enrolled in double-blind, placebo-controlled studies of darbepoetin

alfa every 3 weeks and every 4 weeks. Eighty-six patients were randomized in a 3:1 ratio to receive treatment for 12 weeks with subcutaneous darbepoetin alfa 6.75 µg/kg every 3 weeks, 6.75 µg/kg every 4 weeks, or 10 µg/kg every 4 weeks, or placebo every 3 or 4 weeks. This treatment period was followed by an optional 12-week, open-label, darbepoetin alfa treatment phase. In this phase, patients in the darbepoetin alfa group continued to receive their study dosage, and those who previously received placebo were given the darbepoetin alfa dosage for which they had previously served as the control. A 4-week observation period followed the last dose.

During the 12-week blinded phase, a hematopoietic response occurred in 60% (95% CI 36–83%) and 70% (95% CI 50–91%) of patients who received darbepoetin alfa every 3 weeks and every 4 weeks, respectively, compared with only 10% (95% CI 0–24%) of those who received placebo (Figure 4). Also during this phase, the mean increase in hemoglobin level in each cohort receiving darbepoetin alfa was at least 1.0 g/dl, whereas the mean concentration in the placebo group remained unchanged. In patients who continued receiving darbepoetin alfa every 3 and 4 weeks in the open-label phase, hemoglobin levels were maintained for another 12 weeks. Overall, hemoglobin response rates were at least comparable to those observed in similar patient populations who received epoetin alfa 3 times/week in other studies.[54, 55]

Data from another multicenter study confirmed the efficacy of darbepoetin alfa administered at extended intervals to patients with anemia (hemoglobin ≤ 11 g/dl) who had cancer and were not receiving chemotherapy or radiotherapy.[56] Patients were randomized in a 4:1 ratio to receive darbepoetin alfa 3.0 µg/kg every 2 weeks for 21 weeks, or to a 12-week observation period followed by 9 weeks of treatment with the same dosage of darbepoetin alfa (the control group).

Data from the first 170 patients enrolled were analyzed through the comparative phase (the first 12 wks) of the study. Mean baseline hemoglobin level was 10.2 g/dl in the darbepoetin alfa group and 10.3 g/dl in the control group. Mean change from baseline in hemoglobin level was 2.1 g/dl (95% CI 1.8–2.4) in the darbepoetin alfa group compared with the much smaller change in the control group of 0.3 g/dl (95% CI 0.0–0.6). A hematopoietic response (increase of ≥ 2 g/dl in hemoglobin level and/or achieving a hemoglobin level of ≥ 12 g/dl) was seen in 81% (95% CI 72–91%) of patients in the darbepoetin alfa group compared with 27% (95% CI 10–44%) of controls.

These studies demonstrate the ability of darbepoetin alfa administered at extended dosing frequencies to increase and maintain the hemoglobin concentrations of patients with chronic anemia of cancer.

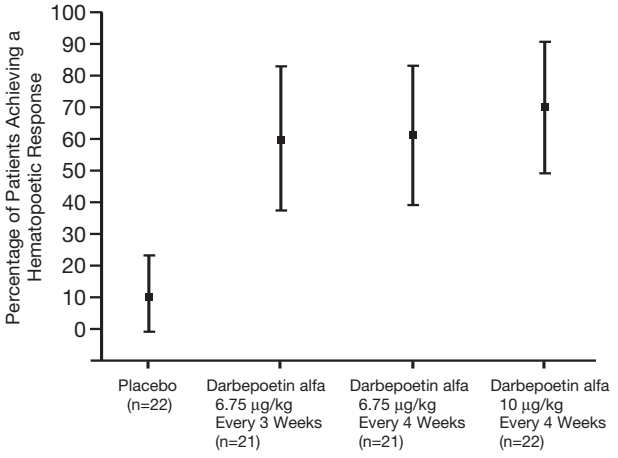

Figure 4. Mean percentages (with 95% confidence intervals) of patients with cancer-related anemia who achieved a hematopoietic response during administration of darbepoetin alfa every 3 or 4 weeks compared with those who received placebo. (From reference 53 with permission.)

Myelodysplastic Syndrome

Given the proven effectiveness of darbepoetin alfa in treating cancer- and chemotherapy-related anemia, its potential in the management of anemia in patients with myelodysplastic syndrome also is being explored. Numerous studies have been performed in patients with low- and intermediate-risk myelodysplastic syndrome.[57–63]

In one study, patients with anemia who had myelodysplastic syndrome (hemoglobin level ≤ 10 g/dl or transfusion dependent) and had not received previous erythropoietic therapy were administered subcutaneous darbepoetin alfa at a starting dose of 4.5 µg/kg/week.[58] In preliminary results, five of 10 evaluable patients showed a major erythroid response (increase in hemoglobin of > 2 g/dl in those whose pretreatment level was < 11 g/dl, or transfusion independence in those previously transfusion dependent, according to the International Working Group response criteria[57]). These patients received darbepoetin alfa 4.5 µg/kg/week, 9.0 µg/kg/week, or 9.0 µg/kg/week plus granulocyte colony-stimulating factor 2.5

µg/kg twice/week. Darbepoetin alfa was generally well tolerated.

In another small study, 12 patients with low- and intermediate-risk myelodysplastic syndrome and hemoglobin levels below 11 g/dl received subcutaneous darbepoetin alfa for 6 months at a starting dose of 150 µg/week.[59] This weekly dose was increased to 300 µg in nonresponders. Overall, seven (58%) patients had a complete response to treatment (hemoglobin concentration increase of ≥ 2 g/dl or a level of 12 g/dl, with no red blood cell transfusions). In addition, a trend seemed apparent toward reduction in apoptotic cells associated with treatment response. No adverse effects associated with darbepoetin treatment were observed.

Similar erythroid response rates using the International Working Group criteria[57] were observed in another study involving patients with low-risk myelodysplastic syndrome and anemia (transfusion required or hemoglobin level < 10 g/dl).[60] Patients received darbepoetin alfa 300 µg/week for at least 12 weeks. Of 40 evaluable patients, 24 (60%) responded at 12 weeks. Nineteen patients experienced a major erythroid response (hemoglobin increase of > 2 g/dl in patients with pretreatment levels < 11 g/dl, or transfusion independence in those previously transfusion dependent), and five patients had a minor erythroid response (hemoglobin increase of 1–2 g/dl in patients with pretreatment levels of < 11 g/dl, or 50% decrease in transfusion requirements in those who were transfusion dependent). Two additional patients responded after 12 additional weeks of treatment with darbepoetin alfa plus granulocyte colony-stimulating factor 100 µg 3 times/week. No adverse effects were observed.

Factors predicting a response to darbepoetin alfa treatment were explored in a study involving 37 patients with anemia who had low-to-intermediate risk myelodysplastic syndrome.[61] After at least 12 weeks of treatment with darbepoetin alfa 150 µg/week, 15 (41%) patients achieved an erythroid response (13 major and 2 minor, according to the International Working Group criteria[57]). Multivariate analysis found that a baseline serum level of endogenous erythropoietin below 100 IU/L, limited or no need for transfusions, no excess blasts, and hypoplastic bone marrow significantly predicted a response.

A retrospective chart review examining the impact of switching treatments in patients with myelodysplastic syndrome stabilized with epoetin alfa to darbepoetin alfa 200 µg every 2 weeks found comparable clinical outcomes with both treatments.[62] Using the International Working Group definitions,[57] a major erythroid response was observed in 27% (95% CI 15–39%) of the 62 patients treated with darbepoetin alfa and in 19% (95% CI 7–30%) of the 50 treated with epoetin alfa. A minor response was observed in 46% (95% CI 33–59%) and 47% (95% CI 31–63%) of the patients, respectively. A similar proportion of patients in both treatment groups required a red blood cell transfusion, with 8% (95% CI 1–15%) and 12% (95%, CI 3–22%), respectively.

A recent open-label clinical study explored the use of darbepoetin alfa at extended dosing intervals to treat anemia in patients with low- or intermediate-1–risk myelodysplastic syndrome.[63] In this study, myelodysplastic syndrome was defined using the criteria of the International Prognostic Scoring System[64] and the French-American-British Cooperative Group.[65] Patients with anemia (hemoglobin level ≤ 11 g/dl) received darbepoetin alfa 500 µg every 3 weeks for 13 weeks. In an interim analysis based on data for 100 patients, of 63 patients naïve to erythropoietic therapy, 77% (95% CI 66–88%) had an overall erythroid response (major plus minor, defined according the International Working Group criteria.[57]) and 47% (95% CI 34–60%) had a major response. Of 37 patients who had previously received erythropoietic therapy, 36% (95% CI 20–53%) had an overall erythroid response and 21% (95% CI 7–35%) had a major response. The proportion of patients who had versus had not received previous erythropoietic therapy who required a transfusion during the study period was 32% (95% CI 17–48%) versus 17% (95% CI 8–27%).

Taken together, the results of these small studies suggest that darbepoetin alfa is effective in treating anemia in patients with myelodysplastic syndrome. However, larger, randomized studies are needed to confirm these findings and to delineate the proper dosing schedule.

Safety Profile

In clinical studies involving patients with cancer, adverse events reported for those receiving darbepoetin alfa were comparable to those reported for patients receiving placebo,[44] or were generally consistent with adverse events expected in the populations studied.[44, 53] Dosage adjustment may be necessary to minimize the

risk of rapid increases in hemoglobin concentrations or in achieving excessive concentrations. A pooled analysis of data from five randomized trials attempted to define what constitutes an excessive rate of rise in hemoglobin concentration.[66] Results suggested that an increase of 2 g/dl in 28 days may be associated with an increased risk of thrombotic events in patients receiving darbepoetin alfa versus placebo. However, no significant differences in the exposure-adjusted rate of embolism or thrombosis events were observed between extended-interval (every 3 wks) and weekly administration. Based on the results of studies so far, darbepoetin alfa also appears well tolerated in patients who have myelodysplastic syndrome, with no or few treatment-associated adverse effects observed.[58–61, 63]

Two trials involved patients with anemia who had breast cancer[67] and head and neck cancer[68] who were treated with rHuEPO (epoetin alfa and epoetin beta). The reported data from these trials have raised concerns regarding the safety of erythropoietic treatment (particularly regarding occurrence of thrombotic events) and its impact on overall survival in patients with cancer. However, the Oncology Drug Advisory Committee of the FDA concluded that current dosage recommendations for erythropoietic therapy are adequate to minimize the risk of thrombotic events, although further research into its effect on overall and progression-free patient survival is warranted.[69]

A meta-analysis of data from four randomized, placebo-controlled trials involving patients with chemotherapy-induced anemia indicated that treatment with darbepoetin alfa is associated with both a reduced risk of need for blood transfusions and improved hematologic and hematopoietic responses.[70] In addition, the findings indicated that a negative effect on survival is unlikely in this patient population.

Conclusion

Early and adequate management of anemia in patients with cancer or myelodysplastic syndrome is important to help ameliorate adverse effects of the anemia. Evidence indicates that darbepoetin alfa and epoetin alfa are equally effective in treating anemia in these patient populations. However, data from clinical trials, drug use evaluations, and retrospective cohort studies suggest that darbepoetin alfa has the potential to improve the management of chemotherapy- and cancer-related anemia through a more flexible dosing schedule compared with epoetin alfa. Studies are under way to determine whether epoetin alfa can be administered effectively at extended intervals.

The studies reviewed in this article confirm that darbepoetin alfa administered at extended dosing intervals (every 2, 3, or 4 wks) corrects and maintains hemoglobin concentrations in patients with chemotherapy- and cancer-related anemia, and that early intervention in patients with mild anemia has clinical benefits. The extended dosing intervals possible with darbepoetin alfa are expected to decrease the burden on patients and their caregivers regarding the number of clinic visits required for anemia management. Less frequent administration also could reduce the time clinicians spend preparing and administering anemia treatment. Time-and-motion data confirm that reducing the number of clinic visits required to treat cancer-associated anemia and neutropenia by using long-acting growth factors results in significant time savings for clinic staff. Many chemotherapy regimens are administered in a 3-week cycle. Thus, administering darbepoetin alfa every 3 weeks may also represent an opportunity for health care providers to synchronize anemia treatment in patients receiving chemotherapy by permitting darbepoetin alfa administration once/cycle.

Although the original FDA-approved dosage of darbepoetin alfa for patients with chemotherapy-induced anemia is 2.25 µg/kg/week, the minimum effective weekly dose has been identified as 1.5 µg/kg/week. As the studies described have shown, the equivalent dosages of 3.0 µg/kg every 2 weeks and 4.5 µg/kg every 3 weeks are equally effective in this population. The FDA has approved only one fixed-dose regimen: darbepoetin alfa 500 µg every 3 weeks. However, 74% of patients starting treatment at this dose needed a dose reduction.

Further investigations showed similar results with fixed darbepoetin alfa doses of approximately 100 µg/week, 200 µg every 2 weeks, and 300 µg every 3 weeks. Therefore, trials comparing fixed darbepoetin alfa doses of 300 µg and 500 µg every 3 weeks are planned. No data are available yet regarding a fixed dose for patients with chronic anemia of cancer. However, these findings suggest that in the future, management of anemia in patients with cancer may be further simplified by the introduction of fixed dosing for darbepoetin alfa.

Data from both prospective and retrospective studies suggest that darbepoetin alfa is effective

in maintaining hemoglobin concentrations in patients with myelodysplastic syndrome who were previously stabilized with other erythropoietic therapies. Trials have also shown encouraging initial results in treating de novo patients with myelodysplastic syndrome with darbepoetin alfa. In these trials, a substantial proportion of patients showed correction of hemoglobin concentrations or an erythroid response (as defined by the International Working Group criteria). Although darbepoetin alfa is not licensed for administration in patients with myelodysplastic syndrome, its potential for this indication is being explored in continuing trials.

Darbepoetin alfa offers an attractive therapy option for patients with chemotherapy- or cancer-induced anemia. It has the potential of increased flexibility and simple administration, and it may offer an effective treatment for anemia in patients with myelodysplastic syndrome.

Addendum

On January 26, 2007, after submission of this manuscript but before publication, Amgen Inc. (Thousand Oaks, CA), the manufacturer of darbepoetin alfa, posted a safety alert on the FDA's Web site (www.fda.gov) regarding the use of darbepoetin in patients with cancer who are not receiving concurrent chemotherapy. A large, phase III, multicenter, randomized, placebo-controlled study, sponsored by Amgen (not published at the time of publication of this article), showed that darbepoetin was ineffective in reducing red blood cell transfusions in patients with cancer who have anemia that is not due to concurrent chemotherapy. In addition, this study found a higher mortality rate in patients receiving darbepoetin. The study compared darbepoetin with placebo in patients with active malignant disease who were not receiving or expected to receive chemotherapy or radiation therapy. The study failed to meet its primary end point of reducing red blood cell transfusions in the darbepoetin group. In addition, more deaths occurred in the darbepoetin treatment group compared with the placebo group.

The study treatment period was 16 weeks, with an additional 16-week extension study comparing the safety and efficacy of darbepoetin versus placebo. The target hemoglobin level in the darbepoetin group was 12 g/dl. A total of 989 patients with hemoglobin levels below 11 g/dl, who had active cancer, and who were not receiving myelosuppressive chemotherapy or radiotherapy, were enrolled. Approximately 60% of the patients enrolled had advanced (stage IV) disease. Analysis of the initial 16-week treatment period did not show a statistically significant effect on the primary efficacy end point (hazard ratio 0.89, 95% CI 0.65–1.22), with a frequency of red blood cell transfusions of 24% in the placebo group versus 18% in the darbepoetin group (p=0.15). In addition, more deaths were reported in the darbepoetin group (136/515 patients [26%]) than in the placebo group (94/470 [20%]). With median survival follow-up of 4.3 months, the absolute number of deaths was greater in the darbepoetin group compared with those in the placebo group (250/515 patients [49%] vs 216/470 patients [46%]; hazard ratio 1.25, 95% CI 1.04–1.51).

Although the studies referenced in our article found that darbepoetin treatment improves hemoglobin levels in patients with anemia of cancer who are not receiving concomitant chemotherapy, this new study raises concern about the potential role of darbepoetin in this population.

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