A Randomized Controlled Trial of Darbepoetin Alfa Administered as a Fixed or Weight-Based Dose Using a Front-Loading Schedule in Patients with Anemia Who Have Nonmyeloid Malignancies

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BACKGROUND. The effect of using fixed versus weight-based doses for erythropoietic agents has not been reported previously. To investigate this issue, the authors conducted a randomized Phase II study of darbepoetin alfa administered as either a fixed dose or a weight-based dose using an accelerated correction and maintenance dosing regimen (*front-loading*).

METHODS. During the correction phase, patients with anemia (hemoglobin < 11.0 g/dL) who had nonmyeloid malignancies and who were receiving chemotherapy were given darbepoetin alfa at a fixed dose of 325 μg ($n = 122$) or at a weight-based dose of 4.5 μg/kg ($n = 120$) once weekly until they achieved a hemoglobin concentration ≥ 12.0 g/dL. Patients then received darbepoetin alfa (325 μg or 4.5 μg/kg) once every 3 weeks for the remainder of the 16-week treatment period (maintenance phase).

RESULTS. Darbepoetin alfa resulted in high Kaplan–Meier rates of hematopoietic response ($\geq$ 2 g/dL increase from the baseline level or a hemoglobin level $\geq$ 12 g/dL) in both the fixed-dose group (86%; 95% confidence interval [95% CI], 78–

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94%) and the weight-based dose group (84%; 95% CI, 76–92%). The median time to hematopoietic response was 34 days (95% CI, 28–44 days) for the fixed-dose group and 36 days (95% CI, 30–45 days) for the weight-based dose group. Hemoglobin concentrations were maintained at target levels for up to 16 weeks in both groups. Darbepoetin alfa was well tolerated, and no clinically significant differences between fixed doses and weight-based doses were observed.

CONCLUSIONS. Darbepoetin alfa was effective when administered as either a fixed dose or a weight-based dose using a front-loading approach to rapidly correct anemia and effectively maintain hemoglobin levels in patients with anemia who had malignant disease. ***Cancer* 2004;100:859–68.**

KEYWORDS: anemia, cancer, erythropoietin, dose administration.

Anemia is a frequent and significant complication of malignant disease or chemotherapy and can contribute to increased morbidity and reduced quality of life.[1] The introduction of erythropoietic agents has provided an effective treatment option for patients with chemotherapy-induced anemia, resulting in increased hemoglobin concentrations and reduced red blood cell (RBC) transfusion requirements.[2–4] In addition, previous studies in the oncologic setting have demonstrated that patients who had hemoglobin concentrations $>$ 12 g/dL had significantly less fatigue and better physical and functional well-being compared with patients who had lower hemoglobin concentrations.[5]

Darbepoetin alfa is an a erythropoietic agent with a unique amino acid sequence, greater sialic acid content, longer terminal half-life, and greater biologic activity compared with epoetin,[6,7] allowing less frequent administration with a similar efficacy and safety profile.[8–10] Dose-finding studies of darbepoetin alfa in patients with nonmyeloid malignancies who were receiving chemotherapy indicated that, although the dose of darbepoetin alfa that appeared to result in outcomes that were comparable to outcomes in an epoetin alfa control arm (in terms of hemoglobin concentrations and transfusions) was 1.5 μg/kg per week, maximum responsiveness was observed at a dose of 4.5 μg/kg per week.[8] At that dose, the percentage of patients who achieved a hematopoietic response (i.e., an increase $\geq$ 2.0 g/dL in hemoglobin from the baseline level or a concentration $\geq$ 12.0 g/dL in the absence of RBC transfusions) was 84%, which was achieved in a median of 6 weeks. Darbepoetin alfa, with its threefold longer half-life compared with epoetin,[7] also has exhibited efficacy in the treatment of anemia in this patient population when administered once every 3 weeks,[11] a common schedule for many chemotherapy regimens.

More recently, a pilot study suggested that improved dosing of darbepoetin alfa may be possible with *front-loading*, an accelerated correction and maintenance dosing regimen.[12] In that randomized active-controlled study, patients initially received darbepoetin alfa 4.5 μg/kg once weekly, followed by lower/less frequent maintenance doses (e.g., 3.0 μg/kg every 2 weeks). The results of that study indicated that front-loaded doses of darbepoetin alfa safely and effectively corrected anemia and appeared to decrease the time to hemoglobin response relative to treatment with epoetin, with associated improvements in patient-reported outcomes for symptoms such as fatigue. The results of that study, in combination with the feasibility of every-3-weeks dosing, suggested that darbepoetin alfa could be administered using a correction dose (4.5 μg/kg every week) to achieve a rapid response followed by a more convenient, every-3-weeks maintenance dose (4.5 μg/kg every 3 weeks). Consequently, this dosing approach was evaluated in the current study.

The use of fixed doses could further optimize the administration of darbepoetin alfa. Although no randomized studies are available that provide a direct comparison of fixed and weight-based dosing regimens of darbepoetin alfa or epoetin,[13] the convenience of fixed dosing has been recognized by the oncology community. Because of the excellent safety profile of these agents, fixed dosing of darbepoetin alfa (200 μg every 2 weeks) and epoetin alfa (40,000 units [U] once weekly) have been adopted in current practice. In a community-based study of epoetin alfa administered at a starting dose of 40,000 U per week, a hematopoietic response rate of 68% was observed, although 33% of patients required a dose increase to 60,000 U per week after 4 weeks of treatment.[14] The mean change in hemoglobin from the baseline level to the end of treatment was 1.8 g/dL (based on available data, including values influenced by RBC transfusions). However, that study did not include a control group, thus precluding any comparisons with weight-based doses of epoetin alfa. Comparisons between

studies of erythropoietic agents are complicated further by differing methods of evaluating changes in hemoglobin reported in the literature (e.g., intent-to-treat [ITT] vs. available data and inclusion/exclusion of values influenced by RBC transfusions).

Detailed pharmacokinetic/pharmacodynamic (PK/PD) modeling of darbepoetin alfa has suggested that, over the weight range of a typical oncology population, weight is not a primary determinant of the efficacy of this molecule.[15] To evaluate this hypothesis further, we studied the impact of fixed dosing versus weight-based dosing of darbepoetin alfa in a randomized Phase II study of patients with anemia who had nonmyeloid malignancies and who were receiving chemotherapy. A front-loading dosing approach was used to provide further information on the efficacy and safety of this darbepoetin alfa dosing strategy.

MATERIALS AND METHODS

Patients

The Institutional Review Board for each of the 31 participating centers in the United States approved the study, and all patients provided written informed consent before any study-specific procedures were done. Men or women age $\geq$ 18 years who had a nonmyeloid malignancy and at least 12 additional, planned weeks of chemotherapy were eligible to participate in the study. Patients were required to have anemia (hemoglobin concentration $\leq$ 11.0 g/dL) primarily due to malignant disease or chemotherapy, an Eastern Cooperative Oncology Group performance status of 0 to 2, and adequate renal and liver function (serum creatinine and bilirubin levels $<$ 2 times the central laboratory upper limit of normal).

Patients were excluded from the study if they had significant central nervous system, cardiac, or inflammatory diseases or any known primary hematologic disorders that could cause anemia. To ensure a stable baseline hemoglobin value (i.e., not resulting from transfusions or erythropoietic therapy), patients were not to have received epoetin or $>$ 2 RBC transfusions within 4 weeks, or any RBC transfusion within 2 weeks, before their first dose of darbepoetin alfa.

Study Design

The current investigation was a multicenter, randomized, open-label Phase II study of darbepoetin alfa conducted in patients with nonmyeloid malignancies who were receiving multicycle chemotherapy. After a screening period, eligible patients were randomized by a central computerized system to receive darbepoetin alfa administered subcutaneously as a fixed/unit dose (μg) or a weight-based dose (μg/kg) for 16 weeks. Randomization was stratified by patient weight ($<$ 55 kg vs. from 55 kg to $<$ 90 kg vs. $\geq$ 90 kg) and baseline hemoglobin concentration ($<$ 10.0 g/dL vs. $\geq$ 10.0 g/dL). The 16-week treatment period consisted of a correction phase and a maintenance phase. During the correction phase, patients received darbepoetin alfa (325 μg as a fixed dose or 4.5 μg/kg) every week until a hemoglobin concentration of $\geq$ 12.0 g/dL was achieved in the absence of an RBC transfusion in the previous 28 days (defined as a hemoglobin correction). After achieving a hemoglobin correction, patients received darbepoetin alfa (325 μg as a fixed dose or 4.5 μg/kg) at a reduced dosing frequency of every 3 weeks for the remainder of the 16-week treatment period (maintenance phase). The study duration of 16 weeks was chosen because it is a common treatment duration for patients with chemotherapy-induced anemia and was anticipated to provide enough time to evaluate the impact of the every-3-weeks maintenance schedule.

The study drug was to be withheld if a patient's hemoglobin value increased to $>$ 15.0 g/dL for men or $>$ 14.0 g/dL for women and was to be reinstated at a lower dose (200 μg or 3.0 μg/kg every 3 weeks) once the hemoglobin concentration decreased to $\leq$ 13.0 g/dL. Iron therapy and RBC transfusion policies were left to the discretion of the investigators, although transfusions were recommended for patients with hemoglobin concentrations $\leq$ 8.0 g/dL. Patients completed a 4-week follow-up evaluation after the last dose of study drug.

Study Drug

Darbepoetin alfa (Aranesp; Amgen Inc., Thousand Oaks, CA) was supplied in vials as a clear, colorless, sterile protein solution containing 500 or 1000 μg/mL darbepoetin alfa.

Study Endpoints

The main objective of the current study was to evaluate the impact of fixed dosing versus weight-based dosing on the efficacy and safety of darbepoetin alfa. The primary measures of efficacy were the percentage of patients achieving a hematopoietic response (an increase of $\geq$ 2.0 g/dL in hemoglobin concentration from baseline or a concentration $\geq$ 12.0 g/dL in the absence of RBC transfusions within the previous 28 days) and the time required to achieve a hematopoietic response. Because patients were to receive maintenance treatment once a hemoglobin concentration $\geq$12.0 g/dL was achieved, hematopoietic response was chosen as the primary endpoint, because it allowed patients who reached a hemoglobin concentration of 12.0 g/dL in the absence of a 2.0-g/dL increase from

baseline to be counted as achieving the therapeutic objective.

The efficacy of fixed dosing versus weight-based dosing also was assessed by comparing hemoglobin profiles over time in each treatment group, excluding hemoglobin values within 28 days of an RBC transfusion. In addition, the percentage of patients receiving RBC transfusions and the average number of units transfused were evaluated from Week 5 to the end of the treatment period, consistent with previous studies of erythropoietic agents.[2,4,16]

An additional objective of the current study was evaluation of the efficacy and safety of darbepoetin alfa administered using a front-loading dosing approach. To assess the efficacy of this approach, the percentage of patients who achieved a hemoglobin correction (hemoglobin concentration $\geq$ 12.0 g/dL in the absence of an RBC transfusion in the previous 28 days) was calculated. The median time to correction also was calculated. Hemoglobin concentrations were evaluated during both the correction phase and the maintenance phase, excluding hemoglobin values within 28 days of an RBC transfusion. To evaluate the effectiveness of dosing every 3 weeks for maintaining stable hemoglobin concentrations, the proportion of patients with average hemoglobin concentrations $\geq$ 11.0 g/dL during the maintenance phase in the absence of RBC transfusions was calculated.

Baseline weight and hemoglobin concentrations were identified prospectively as important independent factors that had the potential to affect the endpoints in the current study. Thus, exploratory analyses of efficacy by quartiles of baseline weight and with weight as a continuous covariate were conducted. Exploratory analyses of efficacy by baseline hemoglobin category ($<$ 10 g/dL and $\geq$ 10 g/dL) also were conducted. Safety was assessed by summarizing the incidence of adverse events by treatment group and by evaluating the potential formation of antibodies resulting from darbepoetin alfa administration.

Statistical Analysis

The estimated sample size of 240 patients (120 patients per treatment group) was based on previous studies of darbepoetin alfa in which approximately 70–75% of patients achieved a hematopoietic response, with a lower 95% confidence interval (95% CI) limit of 65–68%. The sample size of 120 patients randomized per treatment group provided for a 95% CI around the expected point estimates of $\pm$ 8.5% (based on the large-sample normal approximation to the binomial distribution), which, in the current Phase II study, was considered sufficient for assessing any major differences in efficacy between the two dosing approaches.

All randomized patients who received at least 1 dose of study drug (ITT analysis set) were included in the analyses of efficacy and safety, with the exception of analyses of transfusion endpoints from Week 5 to the end of the treatment period. For these endpoints, only patients who completed the first 4 weeks of treatment were included in the analyses. In addition, the analysis of the proportion of patients with average hemoglobin values $\geq$ 11.0 g/dL during the maintenance phase included those patients who received at least 1 dose of darbepoetin alfa during the maintenance phase and had at least 4 evaluable hemoglobin concentrations after hemoglobin correction.

For calculating the proportion of patients who achieved a hematopoietic response or a hemoglobin correction during treatment or for patients who required transfusions, Kaplan–Meier (K–M) estimates were provided. This method was chosen because it accounts for patient attrition from the study and enables an estimate to be made of the median time to event adjusted for varying lengths of exposure. The K–M proportions were calculated by subtracting the K–M estimate of the survivor function from 1.0; 95% CIs were calculated using the Greenwood estimate of variance. Differences between treatment groups were calculated using weighted K–M estimates to account for the stratification factor of baseline hemoglobin concentration. In addition, hemoglobin measurements taken within 28 days after an RBC transfusion were excluded from the analysis, so that the immediate effects of the transfusion would not confound the effects of study drug. Where indicated, an ITT method of analysis was used in which hemoglobin values taken within 28 days after an RBC transfusion were supplied using the last available pretransfusion value (last value carried forward); missing data also were imputed using the last available value carried forward. Analyses were conducted with and without adjustment for baseline hemoglobin concentration and weight. Because the results of these analyses were similar, only the unadjusted results are presented (except where noted).

RESULTS

Patient Demographics and Disposition

Overall, 243 patients were randomized into the study. One patient (in the weight-based dose group) withdrew from the study before receiving study drug and was excluded from the efficacy and safety analyses. Thus, 122 patients were evaluated in the fixed-dose group (325 μg), and 120 patients were evaluated in the weight-based dose group (4.5 μg/kg).

TABLE 1
Baseline Demographic and Clinical Characteristics

Characteristic	Darbepoetin alfa dose	
	325 μg	4.5 μg/kg
All patients	122	120
Gender, no. of patients (%)		
Male	44 (36)	37 (31)
Female	78 (64)	83 (69)
Age (yrs)		
Mean ± SD	63.2 ± 13.3	60.4 ± 13.3
Weight (kg)		
Median	72	71
Range	40–132	49–133
Primary tumor type, no. of patients (%)		
Breast	30 (25)	33 (28)
Gastrointestinal	22 (18)	14 (12)
Genitourinary	9 (7)	8 (7)
Gynecologic	14 (11)	14 (12)
Lung	17 (14)	23 (19)
Lymphoproliferative	14 (11)	14 (12)
Other	16 (13)	14 (12)
ECOG performance status, no. of patients (%)		
0	32 (26)	40 (33)
1	77 (63)	62 (52)
2	11 (9)	18 (15)
Unknown	2 (2)	0 (0)
Hemoglobin concentration		
Mean ± SD (g/dL)	10.2 ± 1.0	10.2 ± 0.9
Concentration ≥ 10.0 g/dL	84 (69)	79 (66)
Serum endogenous EPO (mU/mL)		
No. of patients	119	116
Median	40.1	37.1
Range	6.5–1338.3	4.9–1253.4
Ferritin (μg/L)		
No. of patients	121	118
Median	241.2	328.3
Range	5.0–2470.0	10.0–2487.0
Transferrin saturation (%)		
No. of patients	113	111
Median	20.0	23.0
Range	3.0–96.0	6.0–93.0

SD: standard deviation; EPO: erythropoietin; mU: milliunits; ECOG: Eastern Cooperative Oncology Group.

Patient baseline demographic and clinical characteristics generally were balanced well between treatment groups (Table 1). The median body weight for patients who received fixed doses of darbepoetin alfa was 72 kg (range, 40–132 kg), consistent with the range anticipated for this patient population. The median weight was similar in the weight-based dose group. When adjusted for baseline weight, the median dose of darbepoetin alfa at baseline in the fixed-dose group (4.5 μg/kg) was the same as that of the weight-based dose group, and the range of doses (2.5–8.1 μg/kg) was consistent with the range for baseline weight.

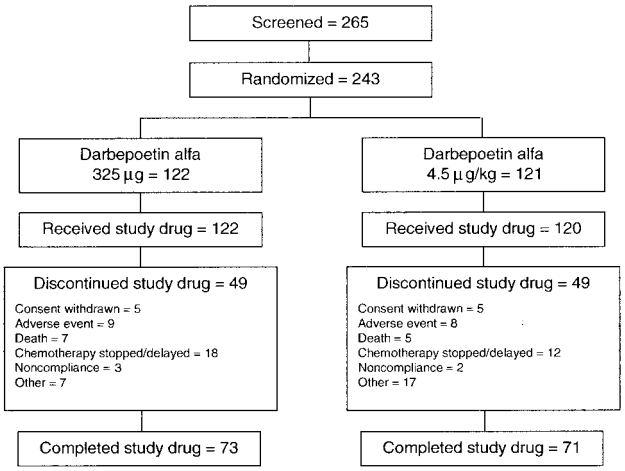

FIGURE 1. Patient disposition data.

The most common primary tumor type in both treatment groups was breast malignancy. The mean hemoglobin concentration at baseline was 10.2 g/dL in both treatment groups. Most patients (69% in the fixed-dose group and 66% in the weight-based dose group) had a hemoglobin concentration ≥ 10.0 g/dL at baseline. Endogenous erythropoietin concentrations appeared to be suppressed relative to the degree of anemia observed, as expected in this population. Iron indices (despite broad inclusion criteria) indicated that, in general, patients were iron replete. Only 1 patient (in the fixed-dose group) had a serum ferritin level < 10 μg/L and a transferrin saturation < 15% at baseline.

Overall, 144 patients (59%) completed study drug treatment, with 73 patients in the fixed-dose group and 71 in the weight-based dose group (Fig. 1). The most frequent reason for discontinuing treatment was a delay in or discontinuation of chemotherapy, as expected in this population.

Efficacy of Fixed Dosing versus Weight-Based Dosing

Hematopoietic response

The percentages of patients achieving a hematopoietic response (an increase of ≥ 2.0 g/dL in hemoglobin concentration from baseline or a concentration ≥ 12.0 g/dL in the absence of RBC transfusions within the previous 28 days) were similar in the fixed-dose group (K–M estimate, 86%; 95% CI, 78–94%) and the weight-based dose group (K–M estimate, 84%; 95% CI, 76–92%) (Table 2). The difference between treatment groups adjusted for weight and baseline hemoglobin level was 2% (95% CI, −8–12%), indicating that the maximum estimated difference in hematopoietic re-

TABLE 2
Hematopoietic Response Data

Characteristic	Darbepoetin alfa dose	
	325 μg	4.5 μg/kg
All patients	122	120
Patients who achieved a hematopoietic response		
Percentage[a] (95% CI)	86 (78–94)	84 (76–92)
Difference in percentages (95% CI)	—	2 (−8–12)

CI: confidence interval.
[a] Estimated using the Kaplan–Meier method.

sponse rate for the fixed-dose group relative to the weight-based dose group was −8%. The median time required to achieve a hematopoietic response was 34 days (95% CI, 28−44 days) for patients receiving darbepoetin alfa as a fixed dose and 36 days (95% CI, 30−45 days) for patients receiving darbepoetin alfa as a weight-based dose (Fig. 2). After approximately 2 months, > 70% of patients had achieved a hematopoietic response in both treatment groups.

Despite a broad range in actual dose per kg in the fixed dose group, when the data were analyzed by baseline weight, no trend indicating an effect of weight on the efficacy of darbepoetin alfa was observed for patients receiving fixed doses (Fig. 3). Furthermore, the response rate observed in the weight-based dose group was comparable to that achieved with fixed dosing within each weight quartile. An additional analysis using Cox proportional hazards modeling showed that weight was not a significant prognostic factor for hematopoietic response (relative risk, 1.005; 95% CI, 0.996–1.01).

Hemoglobin concentration over time

The mean hemoglobin concentrations over time are shown by treatment group in Figure 4. No notable differences were observed between patients receiving fixed or weight-based doses of darbepoetin alfa. As with regard to hematopoietic response, additional analyses investigating the impact of weight on the change in hemoglobin were performed. No trend indicating an effect of weight on the efficacy of darbepoetin alfa was observed for patients receiving fixed doses, and the change in hemoglobin concentration appeared to be comparable between treatment groups within each weight quartile (data not shown). Further analyses of hemoglobin concentrations during the correction and maintenance phases of the study are provided below.

RBC transfusions

A similar percentage of patients received RBC transfusions from Week 5 to the end of the treatment period in the fixed-dose group (19%; 95% CI, 11–27%) and the weight-based dose group (16%; 95% CI, 9–23%). The mean (± standard error) number of units of RBCs transfused was 0.6 (± 0.1) in the fixed-dose group and 0.4 (± 0.1) in the weight-based dose group. Additional analyses by weight quartile revealed findings consistent with those observed for similar analyses of the hemoglobin endpoints (data not shown).

Efficacy of Front-Loading

Correction phase

According to the front-loading design, patients received darbepoetin alfa every week during the correction phase until they achieved hemoglobin correction (i.e., a hemoglobin concentration ≥ 12.0 g/dL in the absence of RBC transfusion in the previous 28 days). High percentages of patients achieved hemoglobin correction in the fixed-dose group (K–M estimate, 81%; 95% CI, 73–90%) and in the weight-based dose group (K–M estimate, 81%; 95% CI, 73–89). The median time to correction was 42 days (95% CI, 29–52 days) in the fixed-dose group and 42 days (95% CI, 33–50 days) in the weight-based dose group.

Most patients in the current study (67%) had a baseline hemoglobin concentration ≥ 10.0 g/dL and thus could not achieve an increase of 2.0 g/dL before reaching a value of ≥ 12.0 g/dL and entering the maintenance phase of the study. Because clinical outcomes were similar between the weight-based and fixed-dose groups, the data from both treatment groups were pooled to allow an evaluation of the change in hemoglobin by baseline hemoglobin category. These analyses indicated that the average hemoglobin change during the correction phase was greater for the group of patients with a baseline hemoglobin concentration < 10.0 g/dL compared with the group of patients with higher baseline hemoglobin concentrations (Fig. 5). After 4 weeks of treatment, the mean changes in hemoglobin concentrations using available data were 1.6 g/dL for patients with baseline concentrations < 10.0 g/dL and 1.0 g/dL for patients with baseline concentrations ≥ 10.0 g/dL; corresponding values using an ITT analysis were 0.8 g/dL and 0.9 g/dL, respectively (Table 3). After 8 weeks of treatment, the mean changes in hemoglobin concentrations using available data were 2.7 g/dL for patients with baseline concentrations < 10.0 g/dL and 1.4 g/dL for patients with baseline concentrations ≥ 10.0 g/dL; corresponding values using an ITT analysis were 1.5 g/dL and 1.1 g/dL, respectively. The difference be-

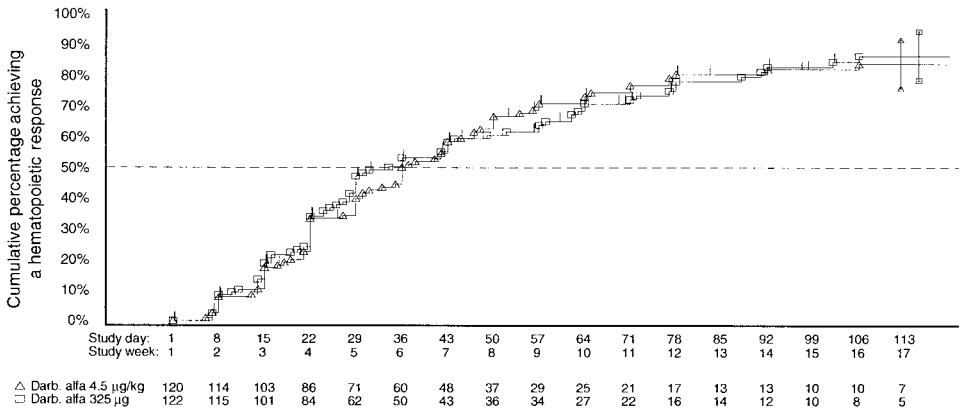

FIGURE 2. Time to hematopoietic response during the treatment period for patients who received darbepoetin (Darb.) alfa. Ninety-five percent confidence intervals (error bars) are displayed for the cumulative percentages of patients who achieved hematopoietic responses by the end of 16 weeks. Vertical bars represent censored patients. Numbers in the bottom two rows represent the risk set at the start of each time point.

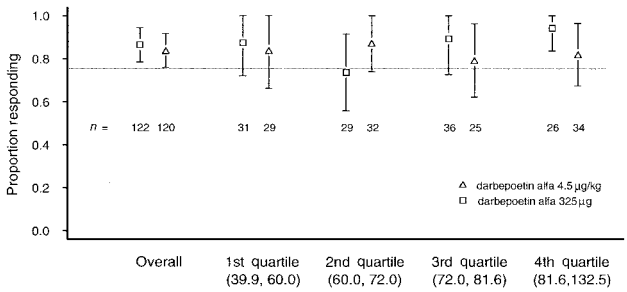

FIGURE 3. Rates of hematopoietic response (with 95% confidence intervals [error bars]) to treatment with darbepoetin alfa by quartile of baseline weight.

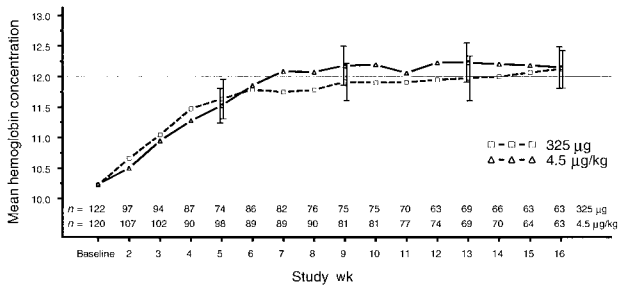

FIGURE 4. Mean hemoglobin concentrations (with 95% confidence intervals [error bars]) over time by treatment group. Hemoglobin concentrations that were determined within 28 days of red blood cell transfusions were excluded. ITT Analysis set (available data, no imputation).

tween hemoglobin strata was a result of the large number of patients with baseline hemoglobin values $\geq$ 10.0 g/dL who entered the every-3-weeks maintenance phase during the first 2 months of treatment rather than a differential responsiveness to therapy between these strata.

Every-3-Weeks Maintenance Phase

Overall, most patients achieved hemoglobin correction and were eligible for every-3-weeks maintenance therapy. The median duration of maintenance therapy

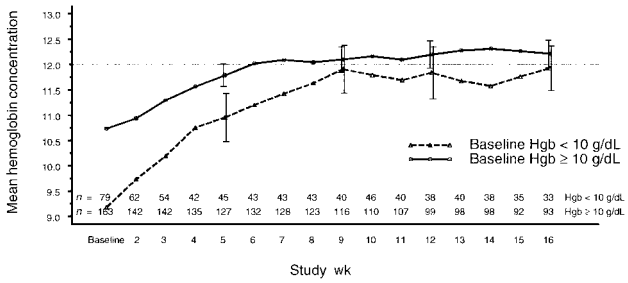

FIGURE 5. Mean hemoglobin (Hgb) concentrations (with 95% confidence intervals [error bars]) over time by baseline hemoglobin category. Hgb concentrations that were determined within 28 days of red blood cell transfusions were excluded. ITT Analysis set (available data, no imputation).

was 77 days (i.e., 11 weeks). Despite the reduction in darbepoetin alfa dosing frequency to once every 3 weeks for patients who achieved hemoglobin correction, no reduction in mean hemoglobin concentration was observed at the end of the maintenance phase. The mean monthly hemoglobin concentrations during the maintenance phase are shown in Figure 6. Darbepoetin alfa administered every 3 weeks maintained target hemoglobin concentrations effectively through the end of the 16-week treatment period. Although patients in both groups had isolated hemoglobin values $<$ 12.0 g/dL after switching to every-3-weeks maintenance, the mean change in hemoglobin concentration during the maintenance phase was only -0.28 g/dL (95% CI, -0.59–0.03 g/dL) in the fixed-dose group and -0.14 g/dL (95% CI, -0.41–0.13 g/dL) in the weight-based dose group. In addition, 96% of patients in the fixed-dose group and 95% of patients in the weight-based dose group had an average hemoglobin concentration $\geq$ 11.0 g/dL in the absence of RBC transfusions during the maintenance phase.

Safety Results

The types of adverse events reported in the current study were consistent with those observed previously

TABLE 3
Changes in Hemoglobin Levels by Baseline Hemoglobin Category

	Baseline Hgb concentration			
	<10.0 g/dL		≥10.0 g/dL	
Characteristic	No. of patients	Mean (95% CI)	No. of patients	Mean (95% CI)
Baseline Hgb concentration (g/dL)	79	9.2 (9.0–9.3)	163	10.7 (10.7–10.8)
Change in Hgb after 4 weeks (g/dL)				
Intent-to-treat	79	0.8 (0.5–1.2)	163	0.9 (0.7–1.1)
Available data	45	1.6 (1.2–2.1)	126	1.0 (0.8–1.3)
Change in Hgb after 8 weeks (g/dL)				
Intent-to-treat	79	1.5 (1.1–1.9)	163	1.1 (0.9–1.4)
Available data	40	2.7 (2.2–3.1)	116	1.4 (1.1–1.6)

Hgb: hemoglobin; CI: confidence interval.

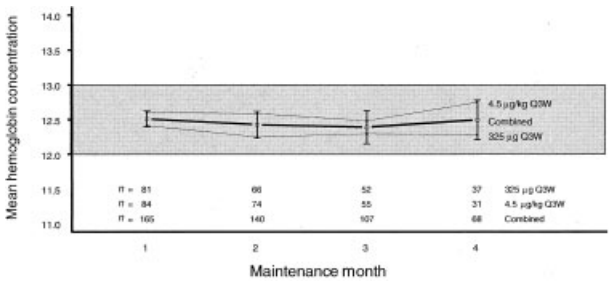

FIGURE 6. Mean hemoglobin concentrations (with 95% confidence intervals [error bars] for combined estimates) during the darbepoetin alfa every-3-weeks (Q3W) maintenance phase. Patients entered the maintenance phase when they achieved a hemoglobin concentration ≥ 12.0 g/dL. Hemoglobin concentrations that were determined within 28 days of red blood cell transfusions were excluded. ITT Analysis set (available data, no imputation).

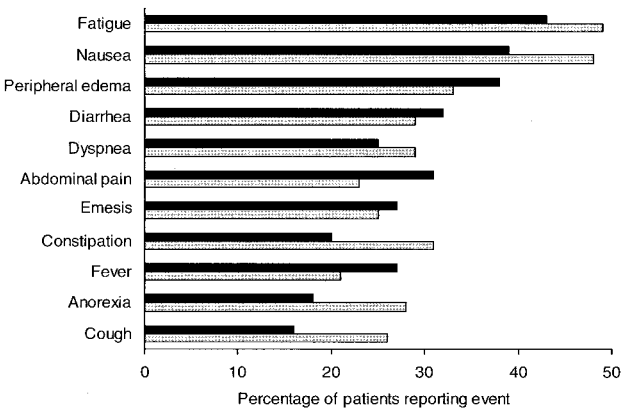

FIGURE 7. Adverse events observed in at least 25% of patients who received darbepoetin alfa 325 μg (black bars; $n = 122$) or 4.5 μg/kg (gray bars; $n = 120$).

in clinical trials of darbepoetin alfa[17] and generally were associated with malignant disease and the toxic effects of chemotherapy. Figure 7 shows the incidence of adverse events that occurred in at least 25% of patients in either treatment group. In general, the safety profile of darbepoetin alfa was similar between the fixed-dose and weight-based dose groups. No safety issues associated with weight were observed for patients who received fixed doses of darbepoetin alfa.

Thirteen patients (11%) in the fixed-dose group and 11 patients (9%) in the weight-based group died during the study or within 30 days after the last dose of study drug. Most deaths were attributed to progressive disease, and none were considered related to darbepoetin alfa by the investigators. The incidence of discontinuations from study due to adverse events was similar for the fixed-dose group (6%) and the weight-based dose group (7%). No evidence of neutralizing antibodies to darbepoetin alfa was detected for any patient.

DISCUSSION

A wide variety of literature provides compelling, empiric evidence that the almost universal practice of administering convenient, fixed doses of erythropoietic therapy is effective and safe.[3,14] However, despite > 10 years of clinical experience with erythropoietic therapies in cancer patients, no formal randomized trials evaluating the impact of administering these agents as a fixed dose, rather than the licensed weight-based dose, have been performed. This point has been raised by the American Society of Hematology/American Society of Clinical Oncology Guidelines Committee in their evidence-based guidelines for the management of chemotherapy-induced anemia.[13] The current Phase II trial was designed to provide a direct, randomized comparison of the effectiveness and safety of darbepoetin alfa administered by a fixed dosing regimen versus a standard, weight-based dosing

regimen. A high rate of hematopoietic response was observed regardless of whether darbepoetin alfa was administered as a fixed dose (K–M estimate, 86%) or as a weight-based dose (K–M estimate, 84%). No difference in the rate of hematopoietic response between treatment groups was observed for any baseline weight category evaluated, including the heaviest 25% of patients. The robustness of this conclusion was confirmed in a sensitivity analysis of weight as a continuous variable in a Cox proportional hazards model, which did not show that weight was a significant prognostic factor for hematopoietic response (relative risk, 1.005; 95% CI, 0.996–1.01). Further sensitivity analyses (not shown) on other efficacy endpoints supported these findings. The results indicate that the efficacy profile of darbepoetin alfa is not affected if a fixed-dose regimen is employed. This finding is consistent with PK/PD modeling of data on darbepoetin alfa from previous studies, which indicate that weight is not a primary determinant of the efficacy of this molecule.[15]

No notable difference in the safety profile of darbepoetin alfa was observed between the fixed-dose group and the weight-based dose group in this study. The most frequently reported adverse events were consistent with those observed commonly in patients with cancer who are receiving chemotherapy and with the adverse events reported previously for darbepoetin alfa in this population.[17] Potential issues regarding the safety of using fixed doses in patients with lower body weights do not appear to be of concern with darbepoetin alfa. These results are not surprising, because no dose-response effects have been observed for adverse events in previous studies of darbepoetin alfa in patients with nonmyeloid malignancies.[8,11]

The results of the current study also provide further information regarding front-loading, the accelerated correction and maintenance regimen for darbepoetin alfa, which initially was evaluated in a randomized, open-label, active-controlled pilot study.[12] In that pilot study, 2 of 3 darbepoetin alfa front-loading groups had a median time to hemoglobin response (defined as an increase of $\geq$ 2.0 g/dL in hemoglobin concentration from baseline in the absence of RBC transfusions) of 50 days (i.e., at Week 8); in contrast, the median time to hemoglobin response could not be estimated for the epoetin alfa control group because only 49% (K–M estimate) of the patients in that group had responses during the 12-week study. These results suggest that administration of darbepoetin alfa using an accelerated correction and maintenance regimen may improve the rate of response relative to conventional doses of epoetin. In the current study, a rapid time to response (34–36 days) was observed, and a high percentage of patients achieved the hemoglobin target of 12.0 g/dL with the weekly darbepoetin alfa correction dose and were able to maintain target hemoglobin concentrations from the time of correction until the end of the study with a less frequent dose (every 3 weeks) of approximately 300 μg.

In clinical practice, the utility of an accelerated correction approach may be limited to patients with moderate-to-severe anemia at baseline, particularly if patients are asymptomatic. Therefore, we presented an analysis stratified by baseline hemoglobin concentration to assess the impact of front-loading in patients with baseline hemoglobin values $<$ 10.0 g/dL. These patients had a substantial and rapid increase in hemoglobin over the first 2 months of treatment before entering the every-3-weeks maintenance phase. Because the target hemoglobin level was 12.0 g/dL, the change in hemoglobin levels for patients with mild anemia at baseline was less compared with patients who initiated therapy at lower hemoglobin levels; however, the rapid attainment of target hemoglobin levels in this group enabled the use of a convenient, every-3-weeks dosing schedule for most of the 4-month treatment period.

The current study had a number of limitations. With regard to the primary question of the impact of fixed versus weight-based doses of darbepoetin alfa, the study had limited sample sizes at the extremes of weight. Although the results are supportive of the current approach used with erythropoietic proteins, the results cannot exclude absolutely the possibility of a slight difference in effectiveness for patients at the extremes of the weight distribution. However, a major impact of weight is unlikely, because no evidence of a trend toward decreased effectiveness in higher weight patients was observed. A further limitation of the current study relates to the assessment of front-loading. Whereas the data appear compelling with respect to the rapidity of response and are consistent with the findings of Glaspy et al.,[12] the lack of a standard control group limits any definitive conclusions regarding the relative benefit of this approach. It is noteworthy that the data from the current study show that every-3-weeks maintenance dosing with darbepoetin alfa is effective in patients with malignant disease who continue to receive multicycle chemotherapy. These findings support further investigation of the potential benefits of the accelerated correction approach with darbepoetin alfa in studies designed to provide a direct comparison with current standard therapy (either epoetin alfa 40,000 U every week or darbepoetin alfa 200 μg every 2 weeks). It is noteworthy that while the current study did not include an assessment of pa-

tient-reported outcomes, a comparative study of this nature should include an assessment of the relative benefit of accelerated anemia correction with regard to improvements in symptom burden and patient-reported quality of life to demonstrate the clinical benefit of an accelerated correction strategy.

In conclusion, darbepoetin alfa can be administered as a fixed dose or a weight-based dose for the treatment of chemotherapy-induced anemia in patients with nonmyeloid malignancies. The use of a fixed-dose regimen could simplify the administration of darbepoetin alfa in this population. In addition, darbepoetin alfa administered using a front-loading approach results in rapid correction of anemia with dosing every week and effective hemoglobin maintenance with dosing every 3 weeks.

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