A Randomized, Active-Control, Pilot Trial of Front-Loaded Dosing Regimens of Darbepoetin-alfa for the Treatment of Patients with Anemia during Chemotherapy for Malignant Disease

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BACKGROUND. Anemia in patients receiving chemotherapy can be ameliorated with recombinant human erythropoietin (rHuEPO), which is administered one to three times per week. Darbepoetin α, a new erythropoietic agent, has longer serum residence time, allowing it to be administered less frequently.

METHODS. Patients ($n = 127$) were randomized to receive study drug for 12 weeks: either rHuEPO 40,000 U with escalations to 60,000 U for nonresponders or darbepoetin α at doses of 4.5 μg/kg per week until hemoglobin concentration $\geq$ 12 g/dL, then 1.5 μg/kg per week (Group 1); 4.5 μg/kg per week for 4 weeks, then 2.25 μg/kg per week for 8 weeks (Group 2); or 4.5 μg/kg per week for 4 weeks, then 3.0 μg/kg every 2 weeks (Group 3). Efficacy was measured using the mean change in hemoglobin level, the proportion of patients achieving a hemoglobin response, the time to response, and the mean change in Functional Assessment of Cancer Therapy-Fatigue Scale scores. Safety was assessed by reports of adverse events.

RESULTS. Overall, after 4 weeks of treatment, the mean change (95% confidence interval [95%CI]) in hemoglobin concentration was 0.53 g/dL (95%CI, 0.05–1.02 g/dL), 0.70 g/dL (95%CI, 0.11–1.29 g/dL), and 0.90 g/dL (95%CI, 0.47–1.33 g/dL) in darbepoetin α Groups 1, 2, and 3, respectively, and 0.39 g/dL (95%CI, $-$ 0.22–1.00 g/dL) in the rHuEPO group. By the end of the study, the mean change (95%CI) in hemoglobin concentration was 1.35 g/dL (95%CI, 0.67–2.02 g/dL), 1.35 g/dL (95%CI, 0.57–2.12 g/dL), and 1.28 g/dL (95%CI, 0.84–1.73 g/dL) in darbepoetin α Groups 1, 2, and 3, respectively, and 1.03 g/dL (95%CI, 0.53–1.53 g/dL) in the rHuEPO group. The early erythropoietic response in patients who were treated with darbepoetin α was associated with an early and maintained reduction in patient-reported fatigue. The adverse event profile was comparable with all doses of darbepoetin α and rHuEPO.

CONCLUSIONS. Darbepoetin α, given as a front-loaded dose for 4 weeks and followed by lower and/or less frequent doses, appears to be efficacious and may decrease the time to response relative to treatment with rHuEPO. ***Cancer* 2003;97: 1312–20.** *© 2003 American Cancer Society.*

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Patients with malignant disease frequently are anemic, particularly during chemotherapy. This anemia is multifactorial but is sustained in part by the relative deficiency in endogenous erythropoietin associated with chronic disease.[1] In randomized clinical trials, it has been shown that treatment with recombinant human erythropoietin

(rHuEPO) decreases the incidence of red blood cell transfusions and improves the quality of life in patients receiving chemotherapy.[2,3] The recognition of these benefits for patients has led to the increasing use of rHuEPO in the setting of chemotherapy for patients with malignant disease. Current clinical practice emulates the manner in which rHuEPO has been administered in published studies, wherein a predetermined starting dose (usually 10,000 U three times weekly or 40,000 U once per week) is administered for 6–8 weeks, with a dose increase at that time if the patient has not had a hematopoietic response (usually defined as an increase < 1 g/dL in hemoglobin concentration).[4] With this approach, 50–65% of patients ultimately will meet the criteria for benefit from therapy during a 12–16-week trial.[4–6] The current approach to rHuEPO administration during chemotherapy, in which doses that do not necessarily produce the highest response rate or the most rapid response are administered for several weeks before initial nonresponders are treated with a potentially effective dose, may not be the most beneficial for patients (i.e., minimizing the time a patient is at risk of transfusion and/or the time taken to provide relief from the symptoms of anemia) or may not be the most cost-effective way to use these agents.

Darbepoetin α is a new erythropoietic agent that was generated by site-directed mutagenesis of the erythropoietin gene.[7] The resulting molecule has an increased number of glycosylation sites and carbohydrate content that results in an increase in serum half-life and residence time and, thus, increased in vivo activity.[8,9] In patients with malignant disease who are receiving chemotherapy, darbepoetin α therapy is effective in increasing hemoglobin values when administered weekly, every 2 weeks, or every 3 weeks.[10–12] Moreover, when a given weekly dose is doubled and administered every 2 weeks, the observed response is not diminished, suggesting that, at dosing intervals of up to once every 2 weeks, there is no apparent loss of dose efficiency with darbepoetin α.[13]

Studies of darbepoetin α in patients with chronic anemia from malignant disease and with anemia associated with chemotherapy for malignant disease have shown that, in both clinical settings, there is a correlation between darbepoetin α dose and both the proportion of patients who meet the criteria for response and the rate at which that response occurs.[10–12,14] In patients with malignant disease who are receiving chemotherapy, the lowest dose at which the maximum response and the most rapid responses were observed was 4.5 μg/kg per week. At this dose, despite no allowance for dose increase, the mean change in hemoglobin from baseline to week 12 was 1.87 g/dL for the darbepoetin α group compared with 1.14 g/dL for patients in the rHuEPO (150 U/kg three times weekly) control group, who were allowed to have their dose doubled at Week 8 for an inadequate initial response. In addition, hemoglobin response rates of 76% and a median time to response of 43 days were observed for the group receiving darbepoetin α 4.5 μg/kg per week.[15] Patients who were treated with darbepoetin α at doses of 1.5 μg/kg per week or 3.0 μg/kg every other week had changes in hemoglobin concentrations of 1.07 g/dL and 1.23 g/dL, respectively.

The data not only suggest that darbepoetin α can be administered less frequently compared with rHuEPO but also that higher doses of darbepoetin α (e.g., 4.5 μg/kg per week) appear to result in increased effectiveness compared with rHuEPO as it is used currently. Using the development of novel, *front-loaded* dosing schedules for darbepoetin α, an effective strategy for both enhancing patient well being and improving the cost effectiveness of this agent in this setting was postulated. The strategy, in which higher doses are used initially with the intent to decrease doses or extend the dosing interval later during the maintenance phase of therapy, may represent an approach that allows for the optimal efficacy profile of this agent to be achieved at a lower total dose requirment over the entire treatment period.

The objective of this pilot study was to determine the feasibility and safety of various front-loaded dosing schedules and to explore their relative effects on various measures of hematologic response. These pilot data could then be used in the design of large, randomized trials aimed at establishing the superiority of front-loaded dosing strategies.

MATERIALS AND METHODS

Patients

The study protocol was approved by the Institutional Review Boards of participating medical centers, and all patients provided written, informed consent before any study-related procedures were done. Patients were eligible for the study if they met the following inclusion criteria: age $\geq$ 18 years, diagnosed with a solid tumor and scheduled to receive cyclic chemotherapy for at least 12 weeks after study enrollment. Patients also were required to have anemia (hemoglobin concentration $\leq$ 11.0 g/dL), an Eastern Cooperative Oncology Group performance status of 0–2, adequate iron stores (transferrin saturation $\geq$ 15% or ferritin $\geq$ 10 μg/L, and an adequate renal function (serum creatinine concentration, $\leq$ 2 mg/dL). Patients were excluded if they had received $>$ 2 units of transfused red blood cells during the preceding 4 weeks,

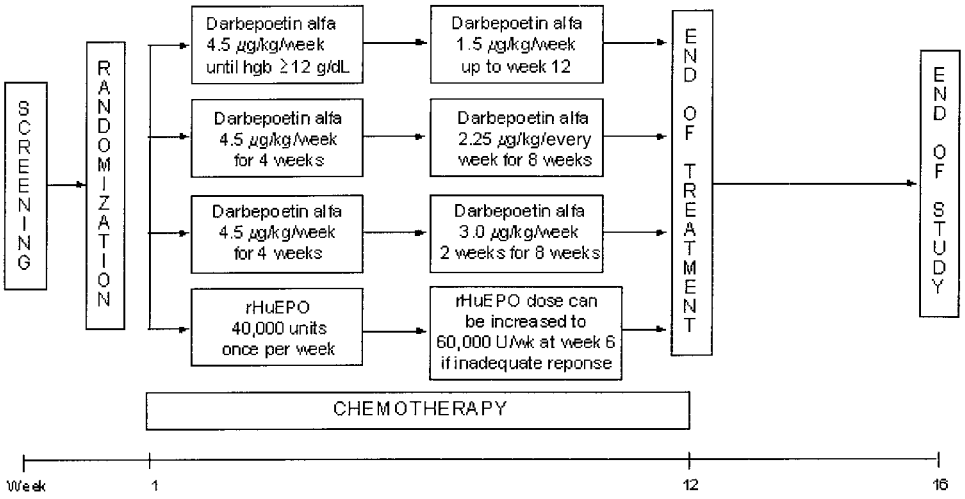

FIGURE 1. The study design. Patients were randomized in a 1:1:1:1 ratio. Study drug was to be withheld if hemoglobin increased to $>$ 15.0 g/dL for men or $>$ 14.0 g/dL for women. Once hemoglobin reached a level $\leq$ 13.0 g/dL, study drug was reinstated at 75% of the withheld dose. The recombinant human erythropoietin (rHuEPO) dose could be increased to 60,000 U per week at Week 6 if the increase in the hemoglobin level was $<$ 1.0 g/dL in the absence of a red blood cell transfusion.

any red cell transfusion during the preceding 16 days, or therapy with rHuEPO during the preceding 8 weeks.

Study Drugs

Darbepoetin α (Aranesp®; Amgen Inc., Thousand Oaks, CA) was supplied as a clear, colorless, sterile protein solution containing 500 μg/mL darbepoetin α. Darbepoetin α initially was administered in the clinic at a dose of 4.5 μg/kg per week, followed by either 1.5 μg/kg per week, 2.25 μg/kg per week, 3.0 μg/kg every 2 weeks. Commercially available rHuEPO (Procrit®; Ortho Biotech, Raritan, NJ) was obtained by the study centers and was administered in a fashion emulating current practice,[4] initially at 40,000 U with a dose increase to 60,000 U in patients with an inadequate initial response (defined as a $<$ 1 g/dL increase in hemoglobin by Study Week 6). All study drug administration was done by subcutaneous injection.

Study Design

This dose-finding and schedule-finding study was multicenter, randomized, active-controlled, and open-label in design (Fig. 1). After eligibility screening, patients were randomized in a 1:1:1:1 ratio to one of four treatment groups. Groups 1, 2, and 3 were treated with front-loaded darbepoetin α dosing schedules with 4.5 μg/kg per week administered for the first 4 weeks. For patients in Group 1, this dose was continued until a hemoglobin concentration of 12.0 g/dL was achieved, at which point, a maintenance dose of 1.5 μg/kg per week was used. Patients in Groups 2 and 3 received front-loaded darbepoetin α dosing for a fixed interval of 4 weeks, at which point, lower maintenance doses were begun independent of hematologic response. The maintenance dose in Group 2 was darbepoetin α 2.25 μg/kg per week and 3.0 μg/kg every 2 weeks in Group 3. Patients in Group 4 served as an active control group, reflecting current practice; these patients received rHuEPO 40,000 U with a dose increase to 60,000 U if an increase $\geq$ 1 g/dL in hemoglobin concentration was not observed after Day 35 (Week 6) of therapy.

Patients could have study drug administration stopped if they experienced a dose-limiting toxicity. Doses of darbepoetin α or rHuEPO were to be withheld for hemoglobin concentrations $>$ 15.0 g/dL in men or $>$ 14.0 g/dL in women. Study drug was to be reinstated at 75% of the dose once the hemoglobin concentration decreased to $\leq$ 13.0 g/dL. Patients were allowed to receive red blood cell transfusions if their hemoglobin concentrations decreased to $\leq$ 8.0 g/dL or as medically indicated.

Hemoglobin levels, the Functional Assessment of Cancer Therapy (FACT) quality-of-life measure (FACT-An), and adverse events were measured and recorded weekly. The FACT-An contains six scales that measure different domains of quality of life.[16] We report the FACT-Fatigue (FACT-F) Scale scores. The FACT-F Scale assesses patient perceptions of fatigue and associated sequelae, including their functional ability to engage in activities of daily life. A sample size of approximately 30 patients per study group (120 patients total) was planned prospectively, because it was believed that this number was sufficient to provide preliminary efficacy results.

Efficacy Endpoints

The efficacy endpoints were the mean change in hemoglobin concentration, the proportion of patients achieving a hemoglobin response (i.e., an increase $\geq$ 2.0 g/dL over baseline in the absence of a red blood cell transfusion over the past 28 days) measured after 4 weeks and

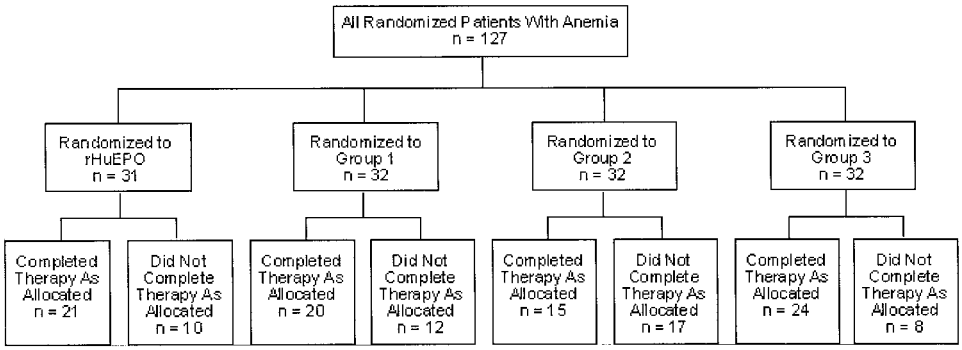

FIGURE 2. Trial profile outlining the participants' flow through the study. rHuEPO: recombinant human erythropoietin.

12 weeks of treatment, and time to hemoglobin response. Mean changes in FACT-F Scale scores from baseline were measured at Weeks 4, 6, 8, 10, and 12.

Safety Endpoints

Safety was assessed by summarizing reports of adverse events. All adverse events were grouped according to the body system affected and by preferred term within body system according to a modified World Health Organization adverse reaction term dictionary. Samples for antibody assessment were collected before the first dose of study drug and monthly throughout the study. The seroreactivity of all samples was evaluated using a standard solution-phase radioimmunoprecipitation screening assay (limit of detection, 10 ng/mL).

Statistical Analysis

Statistical analyses were conducted using the intent-to-treat analysis set (i.e., all patients who were randomized to receive the study drug and who received at least one dose) and are presented by treatment group. Because this pilot study was designed to provide preliminary data on front-loaded dosing, no formal statistical comparisons among the study groups were planned. Baseline demographic and clinical characteristics were summarized by the mean ± standard deviation for continuous measures and the number and percentage for categoric measures. The changes in hemoglobin concentrations after 4 weeks and 12 weeks of treatment were summarized by the mean and 95% confidence interval (95%CI) values; hemoglobin values that were missing or that occurred within 28 days of a red blood cell transfusion were replaced with the last available value not within 28 days of a red blood cell transfusion (sensitivity analyses that calculated the change after 4 weeks only for patients with no missing hemoglobin values after 4 weeks and the change after 12 weeks only for patients who completed the 12-week treatment phase were performed to explore the potential of the *last value carried forward* approach to underestimate the change in hemoglobin). The proportion of patients who achieved a hemoglobin response during the 12-week treatment phase was estimated by subtracting the Kaplan–Meier estimate of the survivor function from 1 at each of these time points; 95%CIs were calculated by using a Greenwood estimate of the variance. Time to hemoglobin response was summarized using the Kaplan–Meier estimate of the median. FACT-F Scale scores were summarized using the mean with 95%CIs for all darbepoetin α patients combined and for all rHuEPO patients in the intent-to-treat analysis set who completed the FACT-F at baseline and at least once between Week 5 and the end of treatment. Missing FACT-F Scale scores were imputed by using the last value carried forward. Adverse events that occurred in > 15% of either the all patients in the darbepoetin α groups or all patients in the rHuEPO group were summarized with the odds ratio (all darbepoetin α groups to the rHuEPO group) along with the 95% CI.

RESULTS

Patient Demographics and Disposition

A total of 122 patients received at least 1 dose of study drug (92 patients received darbepoetin α, and 30 patients received rHuEPO) (Fig. 2). Baseline demographic and clinical characteristics of patients are summarized in Table 1. The treatment groups were comparable with the exception of lower mean baseline hemoglobin concentrations and lower baseline serum erythropoietin concentrations in darbepoetin α Group 1 and a larger proportion of women in the darbepoetin α cohorts. The larger proportion of women in these cohorts was not due to an imbalance of patients with breast carcinoma or gynecologic malignancies but resulted in a lower average body weight in this treatment group compared with the rHuEPO group. The most common chemotherapy regimens administered during the study (i.e., used by > 15% of patients) were carboplatin, paclitaxel, docetaxel, and gemcitabine hydrochloride.

The proportion of patients who completed 12 weeks of study drug treatment was similar for the

TABLE 1
Baseline Demographic and Clinical Characteristics for All Patients Enrolled in the Clinical Trial: Intent-to-Treat Population

Characteristic	rHuEPO (n = 30 patients)[b]	Darbepoetin α[a]			
		Group 1 (n = 32 patients)	Group 2 (n = 30 patients)	Group 3 (n = 30 patients)	All
Age (yrs)					
Mean	63.5	60.5	66.4	62.7	63.2
SD	8.7	14.1	12.7	13.2	13.4
Gender (%)					
Men	13 (43)	10 (31)	7 (23)	6 (20)	23 (20)
Women	17 (57)	22 (69)	23 (77)	24 (80)	69 (75)
Primary disease (%)					
Breast	8 (27)	9 (28)	4 (13)	11 (37)	24 (26)
Lung	8 (27)	9 (28)	11 (37)	3 (10)	23 (25)
GI	5 (17)	8 (25)	6 (20)	5 (17)	19 (21)
GYN	4 (13)	3 (9)	6 (20)	5 (17)	14 (15)
GU	4 (13)	1 (3)	1 (3)	2 (7)	4 (4)
Other	1 (3)	2 (6)	2 (7)	4 (13)	8 (9)
ECOG status (%)					
0	9 (30)	9 (28)	6 (20)	11 (37)	26 (28)
1	18 (60)	20 (63)	21 (70)	13 (43)	54 (59)
2	3 (10)	3 (9)	3 (10)	6 (20)	12 (13)
Weight (kg)					
Mean	83.4	71.7	69.6	72.4	71.3
SD	24.2	15.9	15.7	14.6	15.3
Hemoglobin (g/dL)					
Mean	9.84	9.54	9.90	9.90	9.77
SD	0.83	1.12	1.02	0.99	1.05
Endogenous EPO (mU/mL)					
Mean	56.4	219.9	83.3	96.5	134.2
SD	50.5	738.5	132.6	235.4	457.4
Ferritin (μg/L)					
Mean	415.2	441.2	357.0	563.5	453.6
SD	332.7	384.9	379.5	684.6	502.8

rHuEPO: recombinant human erythropoietin; SD: standard deviation; GI: gastrointestinal; GYN: gynecologic; GU: genitourinary; ECOG: Eastern Cooperative Oncology Group; EPO: erythropoietin.
[a] Darbepoetin α doses: Group 1, 4.5 μg/kg per week until hemoglobin $\geq$ 12 g/dL, then 1.5 μg/kg per week; Group 2, 4.5 μg/kg per week for 4 weeks, then 2.25 μg/kg per week for 8 weeks; Group 3, 4.5 μg/kg per week for 4 weeks, then 3.0 μg/kg every 2 weeks until Week 12.
[b] These patients received rHuEPO 40,000 U/week.

darbepoetin α groups and the rHuEPO group (61% and 68%, respectively). The reasons for early discontinuation of study drug treatment were similar for all patients who received darbepoetin α, for patients in the various dose cohorts of darbepoetin α, and for patients in the rHuEPO group. Study drug was discontinued primarily because of withdrawal of consent, death, disease progression, or changes in chemotherapy unrelated to the study drug. Five randomized patients (Group 2, n = 2 patients; Group 3, n = 2; and Group 4, n = 1 patient) did not receive study drug. The remaining 122 patients constituted the intent-to-treat set upon which all efficacy analyses were calculated.

Study Drug Administration

The mean weekly dose of study drug received over the course of the study was 3.76 μg/kg for Group 1, 3.24 μg/kg for Group 2, and 3.14 μg/kg for Group 3. In the rHuEPO-treated group, 33% of patients required an increase in their dose after approximately 6 weeks (Study Day 42) because of inadequate initial response.

Efficacy Endpoints

With all efficacy endpoints, a clear trend was noted that suggested greater hematologic improvement for patients who received front-loaded doses of darbepoetin α compared with patients who received rHuEPO.

Mean Change in Hemoglobin Values after 4 Weeks and 12 Weeks of Treatment

After 4 weeks, the mean change (95%CI) in hemoglobin value was 0.53 g/dL (95%CI, 0.05–1.02 g/dL), 0.70 g/dL (95%CI, 0.11–1.29 g/dL), and 0.90 g/dL (95%CI, 0.47–1.33 g/dL) in darbepoetin α Groups 1, 2, and 3,

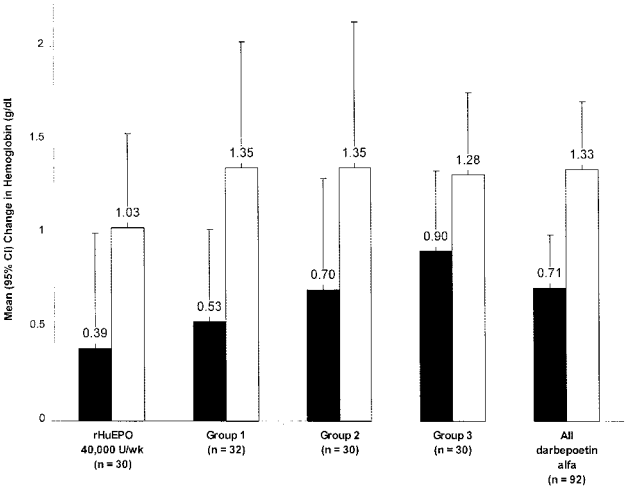

FIGURE 3. Mean change in hemoglobin levels after 4 weeks (solid bars) and 12 weeks (open bars). 95%CI: 95% confidence interval: rHuEPO: recombinant human erythropoietin.

respectively, and 0.39 g/dL (95%CI, 0.22–1.00 g/dL) in the rHuEPO group (Fig. 3). The proportion of patients with an available hemoglobin value after 4 weeks was 94%, 87%, and 87% in darbepoetin α Groups 1, 2, 3, respectively, and 90% in the rHuEPO group. The reasons for missing data were consistent among groups and mostly reflected withdrawals because of complications arising from chemotherapy or underlying malignancy. The mean change (95%CI) only for those patients with an available hemoglobin level after week 4 weeks was 0.58 g/dL (95%CI, 0.07–1.09 g/dL), 0.74 g/dL (95%CI, 0.06–1.41 g/dL), and 1.01 g/dL (95%CI, 0.54–1.48 g/dL) in darbepoetin α Groups 1, 2, and 3, respectively, and 0.26 g/dL (95%CI, − 0.40–0.91 g/dL) in the rHuEPO group.

By the end of 12-week treatment phase, the mean change (95%CI) in hemoglobin value was 1.35 g/dL (95%CI, 0.67–2.02 g/dL), 1.35 g/dL (95%CI, 0.57–2.12 g/dL), and 1.28 g/dL (95%CI, 0.84–1.73 g/dL) in darbepoetin α Groups 1, 2, and 3, respectively, and 1.03 g/dL (95%CI, 0.53–1.53 g/dL) in the rHuEPO group (Fig. 3). The proportion of patients who completed the 12-week treatment phase was 63%, 50%, and 80% in darbepoetin α Groups 1, 2, and 3, respectively, and 70% in the rHuEPO group. These proportions, although they were lower compared with proportions of patients with available hemoglobin levels after 4 weeks, primarily reflected attrition because of complications arising from chemotherapy or the underlying malignancy. The mean change (95%CI) only for those patients who completed 12 weeks of treatment was 1.79 g/dL (95%CI, 0.98–2.60 g/dL), 1.27 g/dL (95%CI, 0.11–2.42 g/dL), and 1.39 g/dL (95%CI, 0.99–1.79 g/dL) in darbepoetin α Groups 1, 2, and 3, respectively, and 0.97 g/dL (95%CI, 0.34–1.60 g/dL) in the rHuEPO group.

Proportion of Patients Achieving a Hemoglobin Response and Time to Response

The proportion (95%CI) of patients who achieved a hemoglobin response was 59% (95%CI, 38–80%), 58% (95%CI, 38–79%), and 65% (95%CI, 47–84%) in darbepoetin α Groups 1, 2, and 3, respectively, and 49% (95%CI, 29–69%) in the rHuEPO group (Table 2). Two of the three darbepoetin α groups had a median time to hemoglobin response at Day 50 (i.e., Study Week 8), whereas the median time to hemoglobin response could not be estimated for the rHuEPO group, because < 50% of the patients in that group achieved a response (Fig. 4).

Mean Change in FACT-Fatigue Scale Scores

The FACT-F Scale scores in the combined darbepoetin α-treated group showed positive improvement in fatigue at every time point during the course of the study (Table 2). This level of improvement in patient-reported fatigue was achieved by Week 6 and was maintained throughout the treatment period. In general, the rHuEPO group had small increases in these scores over time. However, because it has been shown that gender is a significant covariate for many quality-of-life measurements,[4,6] the larger proportion of men in the rHuEPO group (43% vs. 25% in the darbepoetin α groups), as well as its small sample size prevented any noteworthy comparison between the treatment groups. Table 2 shows that the proportion of patients with available data was high over time in the modified intent-to-treat analysis set (i.e., patients who completed the FACT-F assessment at baseline and at least once between Week 5 and the end of treatment). Therefore, results using the *last value carried forward* approach did not differ substantially from the results using only patients with no missing data. One exception was the mean change (95%CI) at Week 12 for the rHuEPO group, which was − 1.5 (95%CI, − 8.0–4.9) using the *last value carried forward* approach and 2.6 (95%CI, − 2.6–7.9) using the *no missing data* approach.

Safety

The most frequently reported adverse events (e.g., nausea, fatigue, diarrhea, anorexia, emesis, and dyspnea) were those expected in a population of patients with solid tumors who are receiving chemotherapy. No apparent correlation was noted between any adverse event and the dose of darbepoetin α over the range of doses tested. No patient experienced a sei-

TABLE 2
Mean Changes in the Functional Assessment of Cancer Therapy Fatigue Scale (FACT-F) Scores for Patients in the Intent-to-Treat Population who Completed the FACT-F at Baseline and at Least Once between Week 5 and the End of Treatment

	Darbepoetin α									
	Group 1		Group 2		Group 3		All		rHuEPO	
Study week	No.	Mean (95%CI)	No.	Mean (95%CI)	No.	Mean (95%CI)	No.	Mean (95%CI)	No.	Mean (95%CI)
Using the last value carried forward										
Week 4	26	3.1 (−0.8–7.0)	23	3.2 (−1.3–7.7)	25	5.6 (1.3–9.9)	74	4.0 (1.6–6.3)	25	1.8 (−0.7–4.3)
Week 6	26	2.8 (−1.4–7.1)	23	6.7 (2.4–11.0)	25	8.4 (3.6–13.3)	74	5.9 (3.4–8.5)	25	2.3 (−1.0–5.5)
Week 8	26	4.0 (0.8–7.1)	23	6.9 (2.7–11.0)	25	6.1 (0.8–11.5)	74	5.6 (3.2–8.0)	25	−2.7 (−7.9–2.5)
Week 10	26	5.8 (1.4–10.2)	23	7.8 (3.1–12.5)	25	8.2 (2.7–13.7)	74	7.2 (4.5–9.9)	25	1.2 (−4.8–7.2)
Week 12	26	4.6 (−0.7–9.9)	23	6.4 (2.1–10.8)	25	7.0 (1.9–12.1)	74	6.0 (3.2–8.7)	25	−1.5 (−8.0–4.9)
Using only nonmissing data										
Week 4	26	3.1 (−0.8–7.0)	23	3.2 (−1.3–7.7)	25	5.6 (1.3–9.9)	74	4.0 (1.6–6.3)	25	1.8 (−0.7–4.3)
Week 6	26	2.8 (−1.5–7.1)	23	6.7 (2.4–11.0)	25	8.4 (3.6–13.3)	74	5.9 (3.4–8.5)	24	2.6 (−0.8–5.9)
Week 8	25	4.0 (0.8–7.3)	22	6.7 (2.3–11.0)	24	6.7 (1.3–12.2)	71	5.8 (3.3–8.2)	24	−2.7 (−8.1–2.8)
Week 10	22	6.5 (1.6–11.4)	20	7.8 (2.7–12.8)	25	8.2 (2.7–13.7)	67	7.5 (4.7–10.4)	24	1.3 (−5.0–7.6)
Week 12	21	7.0 (1.8–12.3)	16	4.8 (−0.3–10.0)	23	7.6 (2.1–13.1)	60	6.9 (3.7–9.6)	21	2.6 (−2.6–7.9)

95%CI: 95% confidence interval; rHuEPO: recombinant human erythropoietin.

zure, and no neutralizing antibodies to darbepoetin α were identified.

When study drug was withheld for patients with hemoglobin concentrations that exceeded the protocol-specified thresholds (i.e., 15.0 g/dL for men and 14.0 g/dL for women), their hemoglobin concentrations decreased in a predictable and controlled manner. No apparent correlation between a rapid rise in hemoglobin concentrations and adverse events in general (and particularly cardiovascular and thromboembolic events) was observed. No antibodies, neutralizing or otherwise, were detected in any patient.

DISCUSSION

The recognition that fatigue is a frequent and severe symptom that limits the functional status and quality of life of patients who have malignant disease has led to an increased awareness of the importance of fatigue management to optimal therapy for these patients. Over the last 4 years, evidence has increased that one cause of the fatigue experienced by patients with malignant disease is mild-to-moderate degrees of anemia that previously were presumed asymptomatic.[3–6] It has been shown that functional status and quality of life improve when anemic patients with malignant disease who are receiving chemotherapy are treated with rHuEPO.[17] Despite an increase in the proportion of patients who receive rHuEPO, most patients in the United States who are receiving chemotherapy and who have a hemoglobin level < 10 g/dL still are not treated (Amgen; data on file).

Several factors may have a negative influence on the decision to use rHuEPO for the treatment of an anemic, fatigued patient with malignant disease. Three of these factors—a slow onset of response, a significant proportion of patients who do not respond, and the high acquisition costs relative to perceived benefit—may be addressed through innovative approaches to dosing and scheduling of erythropoietic protein administration. Indeed, the paradigm that has guided the use of rHuEPO in patients with malignant disease reflects the treatment practice for patients with renal failure, a pure erythropoietin-deficiency state. In this setting, rHuEPO therapy is started at a given dose, and the dose is adjusted upward for patients who do not respond until an appropriate maintenance dose is achieved. However, no studies have been reported that systematically investigated the optimal manner in which to use erythropoietic agents in patients with malignant disease, in whom therapy is of a shorter duration and the biology of the anemia is substantially more complex.

Our initial studies with darbepoetin α suggested that it may be possible to develop schedules that result in a more rapid benefit to a greater proportion of anemic patients who are receiving chemotherapy.[11,12] Moreover, if cost effectiveness is expressed in terms of the quality-of-life gain to the whole population of treated patients divided by the total cost of drug administered, front-loaded dosing may be both more efficacious and more cost effective. The study reported here explored the feasibility and safety of var-

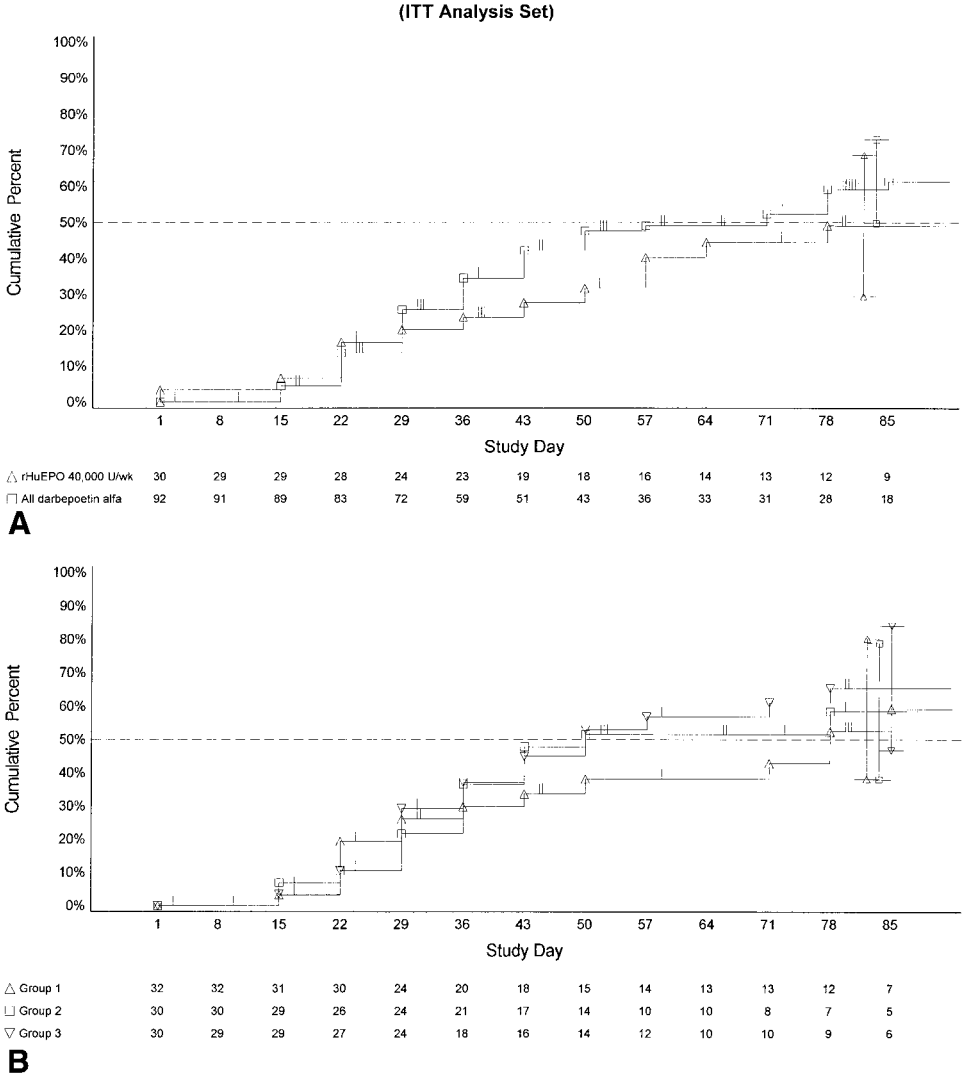

FIGURE 4. Time to hemoglobin response. (A) All darbepoetin α groups compared with the recombinant human erythropoietin (rHuEPO) group. (B) Individual darbepoetin α groups. The 95% confidence intervals are displayed for the cumulative percent of patients who responded by the end of 12 weeks (i.e., Day 85). A vertical bar represents a censored patient. Numbers next to the legend indicate the risk set at the start of each study week. ITT: intent to treat.

ious front-loaded dosing schemes for darbepoetin α with a pilot exploration of the effects on hematologic response and time to response compared with a control group of patients who received conventional erythropoietin therapy.

The current results indicate that darbepoetin α can be administered safely using front-loaded dosing regimens for patients with anemia who are receiving chemotherapy. The study has limited ability to formally compare treatment groups because of the small sample size; however, some comparisons can be made. A marked increase in the change in hemoglobin concentration early in the treatment period (i.e., Week 5) was observed for of all the front-loaded dosing regimens used in this study. The median time to a 2-g/dL increase in hemoglobin concentration from baseline values (i.e., the hemoglobin response) for two of the three darbepoetin α groups was 50 days. Fewer than 50% of the rHuEPO-treated patients reached this response criterion during the 85-day study period. These data suggest that a reduction in the time required to achieve a hemoglobin response may be possible if front-loaded dosing regimens of darbepoetin α are used instead of standard rHuEPO therapy. Furthermore, no detrimental impact on efficacy was observed when the dose and schedule were reduced in any of the darbepoetin α groups. Although the numbers of patients in this pilot study were small, the initial findings suggest that the early onset of action of darbepoetin α is associated with benefits in terms of relief of fatigue, which is maintained throughout the remainder of the therapy.

In summary, administering loading doses for 4 weeks followed by a lower dose and/or a less frequent administration schedule for darbepoetin α appears to decrease the time to response and increases the pro-

portion of patients who benefit from therapy compared with current approaches using rHuEPO. From the results available, it appears that no advantage is detected by continuing the high-dose phase beyond 4 weeks, after which, a relatively low-dose and less-frequent regimen (e.g., such as 3.0 μg/kg every 2 weeks) can be administered. We believe that an appropriately powered study of front-loaded versus traditional administration approaches to erythropoietic management in the oncology setting is feasible and is indicated, with outcomes that include an overall benefit to patients in terms of decreased number of transfusions and increased quality of life as well as decreased cost per unit of benefit.

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