Double-Blind, Placebo-Controlled, Randomized Phase III Trial of Darbepoetin Alfa in Lung Cancer Patients Receiving Chemotherapy

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For the Aranesp™ 980297 Study Group

Background: **Patients receiving chemotherapy often develop anemia. Darbepoetin alfa (Aranesp™) is an erythropoiesis-stimulating glycoprotein that has been shown, in dose-finding studies, to be safe and clinically active when administered to patients with cancer every 1, 2, or 3 weeks. This phase III study compared the safety and efficacy of darbepoetin alfa with placebo in patients with lung cancer receiving chemotherapy.** ***Methods:*** **In this multicenter, double-blind, placebo-controlled study, 320 anemic patients (hemoglobin ≤11.0 g/dL) were randomly assigned to receive darbepoetin alfa or placebo injections weekly for 12 weeks. The 297 patients who completed at least the first 28 days of study were assessed for red blood cell transfusions, the primary endpoint. Patients were also assessed for hemoglobin concentration (i.e., hematopoietic response), adverse events, antibody formation to darbepoetin alfa, hospitalizations, Functional Assessment of Cancer Therapy (FACT)–Fatigue score, and disease outcome. Efficacy endpoints were assessed using Kaplan–Meier analyses, Cox proportional hazards analyses, and chi-square tests where appropriate. All statistical tests were two-sided.** ***Results:*** **Patients receiving darbepoetin alfa required fewer transfusions (27% versus 52%; mean difference = 25%; 95% confidence interval [CI] = 14% to 36%; *P*<.001), required fewer units of blood (0.67 versus 1.92; mean difference = 1.25, 95% CI = 0.65 to 1.84; *P*<.001), had more hematopoietic responses (66% versus 24%; mean difference = 42%; 95% CI = 31% to 53%; *P*<.001), and had better improvement in FACT–Fatigue scores (56% versus 44% overall improvement; 32% versus 19% with ≥25% improvement; mean difference = 13%; 95% CI = 2% to 23%, *P* = .019) than patients receiving placebo. Patients receiving darbepoetin alfa did not appear to have any untoward effect in disease outcome and did not develop antibodies to the drug. Adverse events were similar between the groups.** ***Conclusions:*** **Patients with chemotherapy-associated anemia can safely and effectively be treated with weekly darbepoetin alfa therapy. Darbepoetin alfa decreased blood transfusion requirements, increased hemoglobin concentration, and decreased fatigue. Although no conclusions can be drawn about survival from this study, the potential salutary effect on disease outcome warrants further investigation in a prospectively designed study. [J Natl Cancer Inst 2002;94: 1211–20]**

Patients with cancer receiving multicycle chemotherapy are frequently anemic. The etiology of chemotherapy-related anemia is multifactorial, resulting from the myelosuppressive effects of chemotherapy and the direct effects on the renal tubules, particularly by platinum-based agents, which lead to a decrease in the production of the bone-marrow-stimulating hormone erythropoietin *(1).* Patients with cancer have been shown to have inappropriately low levels of circulating erythropoietin for their degree of anemia, reflecting a perturbation in this homeostatic mechanism *(2).* Anemia is associated with many symptoms, including shortness of breath (dyspnea) and fatigue. Fatigue is the most-often reported symptom in cancer patients receiving chemotherapy and has the most profound consequences on patients' reported quality of life *(3).* Although chemotherapy-induced fatigue often results from multiple factors, anemia has a common and treatable etiology. A study has shown a relationship among low hemoglobin values, fatigue, and poor quality of life in patients with cancer *(4).*

Until recently, treatment options for patients who develop severe or symptomatic anemia have been primarily limited to red blood cell transfusions. Risks associated with red blood cell transfusions include acute transfusion reactions, transmission of infectious agents, and the theoretical potential for decreased immunosurveillance of tumors by the recipient of allogeneic transfusions *(5,6).* However, another treatment option for the management of anemia is the administration of recombinant human erythropoietin (rHuEPO), which stimulates red blood cell formation. rHuEPO is effective for the treatment of anemia in patients receiving myelosuppressive chemotherapy *(7,8).* Early randomized trials demonstrated that rHuEPO therapy was asso-

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See "Appendix" section for the names and affiliations of the investigators in the Aranesp™ 980297 Study Group.

See "Notes" following "References."

ciated with up to a 50% reduction in the number of required red blood cell transfusions; however, there was a lag in the clinical effect, i.e., lag in increase in hemoglobin value, because the reduction in needed transfusions reached statistical significance only if transfusions during the first month of therapy were excluded from analysis *(9,10).* When administered three times per week, rHuEPO increases hemoglobin levels and decreases the number of required red blood cell transfusions, regardless of the tumor type or the type of chemotherapy *(7,11–15).*

Erythropoietin is a 46-kd glycoprotein that contains three N-glycosylation sites. A number of different erythropoietin isoforms exist that differ in their degree of glycosylation; some isoforms have as few as eight or as many as 14 sialic acid moieties *(16).* Sialic acid is a component of complex carbohydrates. Both endogenous erythropoietin and rHuEPO have varying degrees of glycosylation. The sialic acid content of these molecules is directly related to their *in vivo* half-life and inversely proportional to their affinity to bind the erythropoietin receptor. Although rHuEPO and erythropoietin can bind the erythropoietin receptor with similar affinity, preclinical research has demonstrated that the *in vivo* biologic activity of rHuEPO is dependent primarily on its half-life rather than on its receptor affinity *(16).*

One rHuEPO analogue, darbepoetin alfa, which has two additional N-glycosylation sites, has up to 22 sialic acid moieties. Preclinical studies have shown that darbepoetin alfa is a new erythropoiesis-stimulating protein that binds to the erythropoietin receptor and stimulates erythropoiesis by the same mechanism as rHuEPO *(16).* However, because of the additional sialic acid moieties, darbepoetin alfa has an approximately threefold (25.3 hours versus 8 hours, intravenous administration) longer serum half-life than rHuEPO in animal models and in patients with kidney disease. Darbepoetin alfa has been shown to maintain hemoglobin concentration as well as rHuEPO, despite being administered less frequently *(17).*

The prolonged half-life of darbepoetin alfa has been observed in patients with cancer undergoing multiple cycles of chemotherapy *(18,19).* Randomized phase I/II dose-finding studies have shown that darbepoetin alfa is safe and clinically effective in patients with cancer when administered every 1, 2, or 3 weeks *(20–22).* Moreover, when administered at a dose of 2.25 μg/kg/week (the dose used in this study), darbepoetin alfa has been shown in separate studies to be clinically effective in patients with solid tumors and lymphoproliferative malignancies who are receiving chemotherapy *(20,23).*

This double-blind, placebo-controlled, randomized phase III study compared weekly darbepoetin alfa with placebo as a treatment for anemia in patients with lung cancer receiving multicycle platinum-containing chemotherapy. The primary study endpoint was the proportion of patients who received a red blood cell transfusion during a specific time period—from week 5 until the end-of-treatment phase. Other endpoints were the proportion of patients who received transfusions during week 1 until the end-of-treatment period, the number of red blood cell transfusions, the hematopoietic response, the adverse event profile, the antibody formation to darbepoetin alfa, the Functional Assessment of Cancer Therapy–Fatigue (FACT–Fatigue) score, and the incidence and duration of hospitalization. Disease progression and survival were also assessed quarterly for a minimum of 1 year, if applicable.

Patients and Methods

Study Population

The independent ethics committee or central ethics committee for each of the 70 participating medical centers in Australia, Canada, and Europe approved the protocol, and all patients gave written informed consent before any study-specific procedures were done.

For entry into the study, patients were required to have lung cancer and were expected to receive at least 12 additional weeks of platinum-containing chemotherapy. Patients were eligible for the study if they were at least 18 years of age, had a life expectancy of at least 6 months, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. Patients were required to have anemia (i.e., hemoglobin level of $\leqslant$11.0 g/dL) primarily because of their cancer or chemotherapy; have adequate serum folate, vitamin B_{12}, ferritin, and saturated transferrin levels; and have adequate renal and hepatic functions. Patients were excluded if they were iron deficient; had primary or metastatic malignancy of the central nervous system; had received more than two red blood cell transfusions within 4 weeks of randomization or had received any red blood cell transfusion within 2 weeks of randomization; had received rHuEPO therapy within 8 weeks of randomization or any previous treatment with darbepoetin alfa; were pregnant, breastfeeding, or not using adequate birth control measures; or had a history of seizure disorders, active cardiac disease, uncontrolled hypertension, active infection or inflammation, or a primary hematologic disorder as the cause of their present anemia.

Randomization

This was a phase III, multicenter, randomized, double-blind, placebo-controlled study. After registration, patients were randomly assigned, by a central randomization service for all sites, in a 1 : 1 ratio to receive a blinded study drug, either darbepoetin alfa at a starting dose of 2.25 μg/kg/week or the volume equivalent of placebo (Fig. 1). All doses of study drug were administered weekly by subcutaneous injection. Randomization was stratified by tumor type (small-cell lung cancer or non-small-cell lung cancer) and geographic region (Australia, Canada, Western Europe, or Central and Eastern Europe) to ensure a balanced allocation of patients to darbepoetin alfa and placebo within each of the eight strata.

Treatment Schedule

The study consisted of a screening period of up to 7 days before randomization, followed by 12 weeks of blinded study treatment, a 4-week follow-up period after the last dose of study drug, and a long-term follow-up to determine tumor status and survival.

Darbepoetin alfa (Aranesp™; Amgen Inc., Thousand Oaks, CA) was formulated in a phosphate buffer (pH 6.2) with either human serum albumin or polysorbate. Once a week for 12 weeks, patients were to receive the study drugs from identical vials that contained either a starting dose of darbepoetin alfa (2.25 μg/kg) or the placebo. The delivered volume of either drug was identical. On the basis of preclinical data and data in patients with chronic kidney disease *(17),* the dose of darbepoetin alfa (2.25 μg/kg) was shown to have effects similar to those of rHuEPO 150 U/kg administered three times a week. If a patient's hemoglobin concentration measured at the beginning of

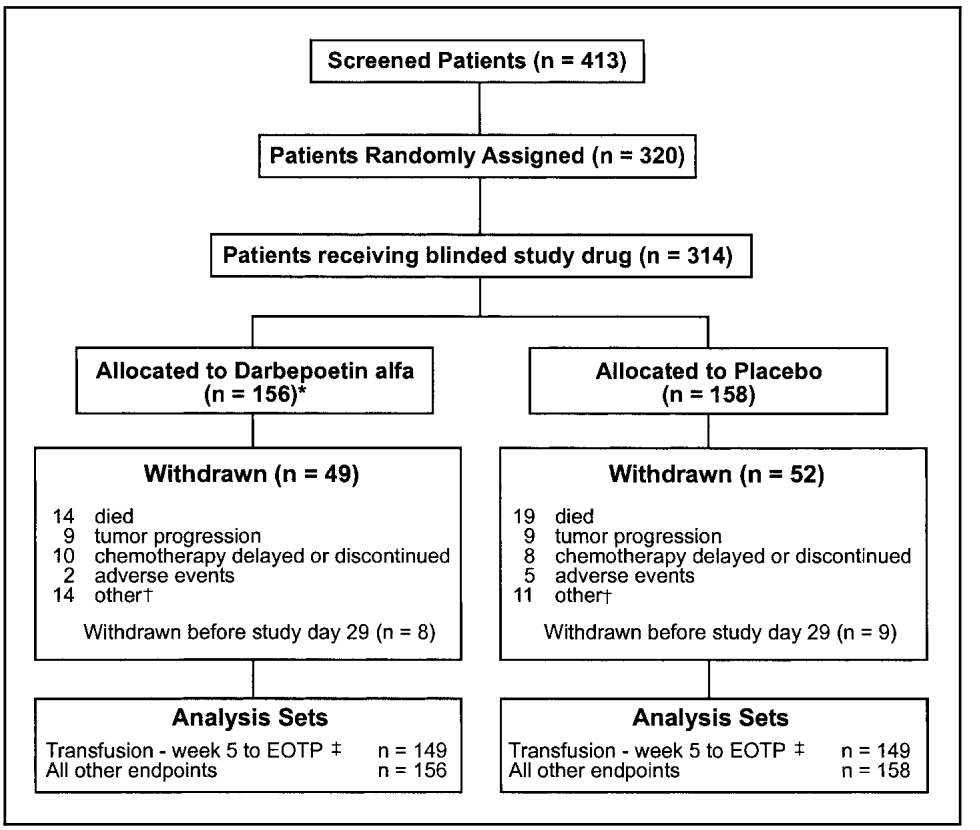

Fig. 1. CONSORT diagram for patients with lung cancer receiving chemotherapy who were screened and enrolled in the double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa. *One patient was randomly assigned to receive darbepoetin alfa but received placebo. This patient was evaluated for efficacy in the darbepoetin alfa group and for safety in the placebo group. †Other includes withdrawn consent, administrative decision, and loss to follow-up. ‡Primary endpoint. EOTP = end-of-treatment phase.

week 6 (approximately study day 35) had increased less than or equal to 1.0 g/dL over the baseline hemoglobin concentration, the dose of the study drug was doubled to 4.5 μg/kg/week, or the volume equivalent, beginning at week 7 (approximately study day 42) and continuing for the remainder of the study. At any time during the study, the dose of blinded study drug was withheld if a patient's hemoglobin concentration increased to greater than 15.0 g/dL (for men) or greater than 14.0 g/dL (for women). After the patient's hemoglobin concentration decreased to less than or equal to 13.0 g/dL, administration of the study drug was then reinstated at 50% of the previous dose.

Transfusion policies can vary widely from center to center and from country to country. In addition, many factors (e.g., age, comorbid conditions, tumor status, patient preference) are considered when deciding whether to administer a blood transfusion. Therefore, in this study, good medical practice necessitated that a transfusion recommendation (transfuse when hemoglobin concentration ⩽8.0 g/dL), rather than a mandated transfusion policy, be implemented to allow for the proper clinical judgment required in this treatment setting.

Efficacy Evaluation

The potential efficacy of darbepoetin alfa was determined primarily on the basis of the incidence of red blood cell transfusions. Information on the incidence and number of red blood cell transfusions was collected throughout the study. Data from studies of rHuEPO indicate that the effects on red blood cell transfusion requirements are not apparent until the second month of treatment *(7,24,25).* This result likely reflects the kinetics of rHuEPO-stimulated erythropoiesis and the time required to produce a quantity of red blood cells sufficient to avoid the need for transfusion; therefore, the proportion of patients receiving a transfusion from week 5 until the end-of-treatment phase was selected as the primary endpoint. In addition, three secondary transfusion-related endpoints were prospectively specified in the protocol: the incidence of red blood cell transfusion from week 1 until the end-of-treatment phase, the incidence of transfusion or hemoglobin concentrations less than or equal to 8.0 g/dL, and the number of units of blood transfused.

Effects on hemoglobin concentration were measured as an additional indication of efficacy. Samples to determine hemoglobin concentration were collected weekly before study drug administration throughout the study and were analyzed at a central laboratory. Sampling, shipping, and analyses were done according to a Food and Drug Administration (FDA)-approved protocol. A hematopoietic response was defined as an increase in hemoglobin concentration of greater than or equal to 2.0 g/dL or a hemoglobin concentration of greater than or equal to 12.0 g/dL in the absence of a red blood cell transfusion within the previous 28 days. This definition is consistent with studies of rHuEPO in patients with hemoglobin concentrations of less than or equal to 11.0 g/dL *(13,25,26).*

For this study, the primary health-related quality-of-life instrument was the FACT–Fatigue scale, which has been validated in the oncology setting *(27).* Patients completed a comprehensive, self-administered quality-of-life survey, which included the FACT–Fatigue scale, every 3–4 weeks on the first day of each cycle of chemotherapy, before any other study procedures.

Safety Evaluation

The safety profile of darbepoetin alfa was evaluated by examining the incidence of adverse events, changes from baseline in serum analyses and chemistries, changes in vital signs, and number of days hospitalized. The nature, frequency, severity,

relationship to treatment, and outcome of all adverse events were examined.

Serum was collected before study drug administration to provide a baseline for the anti-darbepoetin alfa antibody-screening assay and then at regular intervals throughout the study. The screening assay was a radioimmunoprecipitation-based assay used routinely in darbepoetin alfa studies in oncology and nephrology settings. Tumor status and survival information are being collected during an open-label, long-term follow-up period.

Statistical Analyses

This clinical study had a target sample size of 310 eligible patients (155 per treatment group). This sample size would have given the study 90% power to detect a 50% reduction (from 40% to 20%) in the proportion of patients with at least one transfusion during week 5 until the end-of-treatment phase (the primary endpoint of the study), if statistical testing was conducted using a two-sided significance level of $P = .05$. This sample size anticipated that 30% of patients would withdraw from the study before week 12. No prospectively specified interim analyses were planned or done.

Because of the anticipated withdrawal rate, the Kaplan–Meier method was used to calculate the proportion of patients who received at least one transfusion during week 5 until the end of the treatment phase; crude proportions were also calculated as part of the sensitivity analyses. The Kaplan–Meier method was also used to calculate the proportion of patients who achieved secondary endpoints of the study, including the proportion of patients with any transfusion during week 1 until the end of the treatment phase and the proportion of patients with hematopoietic response (a 2.0 g/dL increase in hemoglobin compared with baseline or a hemoglobin concentration of at least 12.0 g/dL in the absence of a red blood cell transfusion during the previous 28-day period). Using the Kaplan–Meier approach, we included all patients randomly assigned into the study who received at least one dose of study drug in the analyses with the following exception: In the analysis of transfusions during week 5 until the end-of-treatment phase, patients who withdrew (n = 17) before study day 29 were excluded. For transfusion-related endpoints, patients who withdrew from the study for reasons other than disease progression or death before the completion of the treatment period had the occurrence of a transfusion inputed at the time of withdrawal. The standard error (SE) of the Kaplan–Meier proportion was calculated using Greenwood's formula *(28).* The Kaplan–Meier approach was also used to estimate the median time to the first transfusion (with two-sided 95% confidence intervals [CIs]).

Efficacy endpoints were analyzed with and without adjusting for the two factors used to stratify the randomization: tumor type and geographic region. Results of both types of analyses were consistent, so only results of the unstratified analyses are presented. Cox proportional hazards and logistic regression were used to compare treatment groups after adjusting for tumor type, geographic region, and other potentially prognostic factors after determining that data complied with assumption for this method. No adjustments were made for multiple significance tests.

The percentage of change from baseline for the FACT–Fatigue score was analyzed as two dichotomous variables (any improvement and at least a 25% improvement) in patients who had the baseline and at least one post-treatment score. The statistical comparison was based on the uncorrected chi-square test. Safety was evaluated in all patients who received at least one dose of study drug. The frequency and percentage distributions of adverse events to study drug were summarized.

Long-term follow-up is in progress and is planned for at least 1 year. In this article, the results are provided of the initial assessment of progression-free and overall survival, which was done 6 months after the last patient completed the study. The Kaplan–Meier method was used to estimate the median duration of progression-free survival and overall survival. The statistical analyses were done using SAS (version 6.12; SAS Institute, Cary, NC).

RESULTS

Study Population

Of the 413 screened patients, 320 were randomly assigned between September 1999 and July 2000 to receive darbepoetin alfa (159) or to receive placebo (161) (Fig. 1). Six patients withdrew from the study before they received the first dose of study drug. One patient was randomly assigned to receive darbepoetin alfa but received placebo instead. One hundred one patients (32%) withdrew from the study. This rate is consistent with the study sample size assumptions in which a 30% withdrawal rate was anticipated in this population of cancer patients receiving chemotherapy. Three hundred fourteen patients (98%) received study drug and were included in the analysis for all endpoints. Two hundred ninety seven patients (93%) completed the first 28 days of the study and were included in the analysis of the primary endpoint (transfusions from week 5 until the end-of-treatment phase). Baseline demographics and clinical characteristics were similar between the two treatment groups (Table 1).

Efficacy Evaluations

Red blood cell transfusions. A lower percentage of patients receiving darbepoetin alfa were transfused (27%; 95% CI = 20% to 35%) during week 5 until the end-of-treatment phase than patients receiving the placebo (52%; 95% CI = 44% to 66%) (Fig. 2, A). The difference of 25% (95% CI = 14% to 36%) was statistically significant ($P<.001$). The robustness of this result was assessed by comparing the percentage of patients who reached the transfusion trigger of a hemoglobin value of less than or equal to 8.0 g/dL or who received a red blood cell transfusion during week 5 until the end-of-treatment phase in the two treatment groups. This alternative definition allowed the assessment of whether potentially different transfusion policies among study centers affected the percentages of patients in each group who received a transfusion.

The estimated percentages of patients who received a transfusion or had a hemoglobin value less than or equal to 8.0 g/dL were slightly higher than the percentages of patients transfused, with 62% (95% CI = 54% to 70%) of patients in the placebo group and 32% (95% CI = 24% to 39%) in the darbepoetin alfa group (Fig. 2, B). The difference was statistically significant ($P<.001$). This result suggests that differences in transfusion policies among the study centers did not differentially affect the proportion of patients in the darbepoetin alfa group who received a red blood cell transfusion.

We calculated the mean number of red blood cell units transfused per patient. The mean number of red blood cell units transfused was less in the darbepoetin alfa group (0.67 ± 1.70 standard blood units) (mean ± SD) than in the placebo group (1.92 ± 3.27 standard blood units) (mean ± SD), a statistically

Table 1. Baseline demographic and clinical characteristics of the two treatment groups*

	Placebo group	Darbepoetin alfa group	Total
Total no. of patients	158	156	314
Sex, No. (%)			
Men	116 (73)	111 (71)	227 (72)
Women	42 (27)	45 (29)	87 (28)
Age, y			
Mean (SD)	61.3 (8.8)	61.6 (9.2)	61.4 (8.9)
Median	61.0	62.5	62.0
Range	36 to 79	39 to 80	36 to 80
Type of tumor, No. (%)†			
Small-cell lung cancer	44 (28)	48 (31)	92 (29)
Limited disease	19 (12)	16 (10)	35 (11)
Extensive disease	25 (16)	32 (21)	57 (18)
Non-small-cell lung cancer	114 (72)	108 (69)	222 (71)
Stage I	2 (1)	2 (1)	4 (1)
Stage II	2 (1)	2 (1)	4 (1)
Stage III	48 (30)	29 (19)	77 (25)
Stage IV	62 (39)	75 (48)	137 (44)
ECOG performance status, No. (%)‡			
0	23 (15)	22 (14)	45 (14)
1	98 (62)	109 (70)	207 (66)
2	37 (23)	24 (15)	61 (19)
>2	0 (0)	1 (1)	1 (0)
Hemoglobin, g/dL			
Mean (SD)	9.93 (1.01)	10.28 (1.08)	10.11 (1.06)
Median	10.15	10.40	10.30
Range	6.6 to 12.3	7.4 to 13.6	6.6 to 13.6
Serum endogenous EPO, mU/mL			
N	151	145	296
Mean (SD)‡	53.17 (58.87)	51.10 (71.72)	52.16 (65.38)
Median	36.43	36.06	36.24
Range	12.0 to 599.4	12.0 to 739.8	12.0 to 739.8
Ferritin, μg/L			
Mean (SD)	534.50 (528.10)	552.22 (453.45)	543.33 (491.57)
Median	402.00	431.00	409.00
Range	14.0 to 4895.0	36.0 to 3046.0	14.0 to 4895.0
Transferrin saturation, %			
Mean (SD)	18.95 (12.26)	20.98 (13.25)	19.96 (12.78)
Median	16.00	18.00	17.00
Range	6.0 to 73.0	5.0 to 90.0	5.0 to 90.0

*ECOG = Eastern Cooperative Oncology Group; EPO = erythropoietin; SD = standard deviation.

†Tumors were staged according to the International System for Staging Lung Cancer.

‡One patient had a baseline serum endogenous EPO of 1998.57 mU/mL. Because this value was considered extreme, it was excluded from the analyses.

significant difference (mean difference = 1.25, 95% CI = 0.65 to 1.84; $P<.001$) (Fig. 2, C).

When the entire treatment phase (weeks 1–12) was considered, the percentages of patients receiving red blood cell transfusions, the percentage of those receiving red blood cell transfusions or having a hemoglobin level of less than or equal to 8.0 g/dL, and the number of units of red blood cells transfused were statistically significantly lower for patients in the darbepoetin alfa group than for patients in the placebo group ($P<.001$) (data not shown). The length of time before requiring a red blood cell transfusion was longer for patients in the darbepoetin alfa group than for patients in the placebo group (Fig. 3).

Hematopoietic response. A hematopoietic response, defined as an increase in hemoglobin level of 2.0 g/dL or a hemoglobin level of 12.0 g/dL in the absence of a red blood cell transfusion in the previous 28 days, was determined as an additional measure of efficacy. The percentage of patients with a hematopoietic response was statistically significantly higher in the darbepoetin alfa group (66%; 95% CI = 58% to 74%) than in the placebo group (24%; 95% CI = 16% to 31%) (mean difference = 42%; 95% CI = 31% to 53%; $P<.001$).

Patient self-reported assessment of fatigue. Overall, the patient compliance rates for the FACT–Fatigue scale were high, with 95.2% (95% CI = 92.1% to 97.3%) of patients completing the scale at baseline and 91.2% (95% CI = 87.4% to 94.2%) completing the scale at least once during their treatment phase. Fatigue was evaluated for 255 (127 darbepoetin alfa, 128 placebo) patients who received a study drug, who completed the FACT–Fatigue scale through study week 4, and who completed the scale at baseline and at least one time from week 5 until the end-of-treatment phase.

Fifty-six percent (95% CI = 47% to 65%) of the patients in the darbepoetin alfa group and 44% (95% CI = 35% to 52%) of patients in the placebo group had an improvement in the FACT–Fatigue scale score ($P = .052$). Although any improvement in the FACT–Fatigue scale score may be clinically meaningful, analyses to investigate the proportion of patients with at least a 25% improvement from baseline were done. Thirty-two percent (95% CI = 23% to 40%) of patients in the darbepoetin alfa group showed at least a 25% improvement, whereas only 19% (95% CI = 12% to 26%) of patients in the placebo group showed at least a 25% improvement (mean difference = 13%; 95% CI = 2% to 23%; $P = .019$).

Safety

The adverse events reported in both treatment groups and, in general, those reported as treatment-related, were consistent with adverse events associated with the toxic effects of chemotherapy reported by patients with malignant disease. Adverse events reported by at least 13% of patients across both treatment groups are summarized in Fig. 4. The most frequently reported adverse events were nausea, vomiting, fatigue, shortness of breath (dyspnea), and weakness (asthenia). Hypertension was reported as an adverse event in nine patients (6%) in the darbepoetin alfa group and in six patients (4%) in the placebo group. Thrombotic events occurred in seven patients (5%) in the darbepoetin alfa group and in five patients (3%) in the placebo group. Similar proportions of patients from both groups withdrew because of an adverse event (other than death) (Fig. 1).

The incidence of death was also similar between the two treatment groups: 22 patients (14%) in the darbepoetin alfa group and 19 patients (12%) in the placebo group. No deaths were considered by the investigators to be related to the study drug, and most of the deaths (61% in the darbepoetin alfa group and 58% in the placebo group) were attributed to progression of the disease.

Changes in laboratory test variables and patient vital signs from baseline were similar between the darbepoetin alfa group and the placebo group. In addition, the minimum absolute neutrophil count (ANC) values on study in both treatment groups were similar. No anti-darbepoetin alfa antibodies were detected in 1054 serum samples (531 serum samples from patients in the darbepoetin alfa group and 523 serum samples from patients in the placebo group) tested during the study and no clinical se-

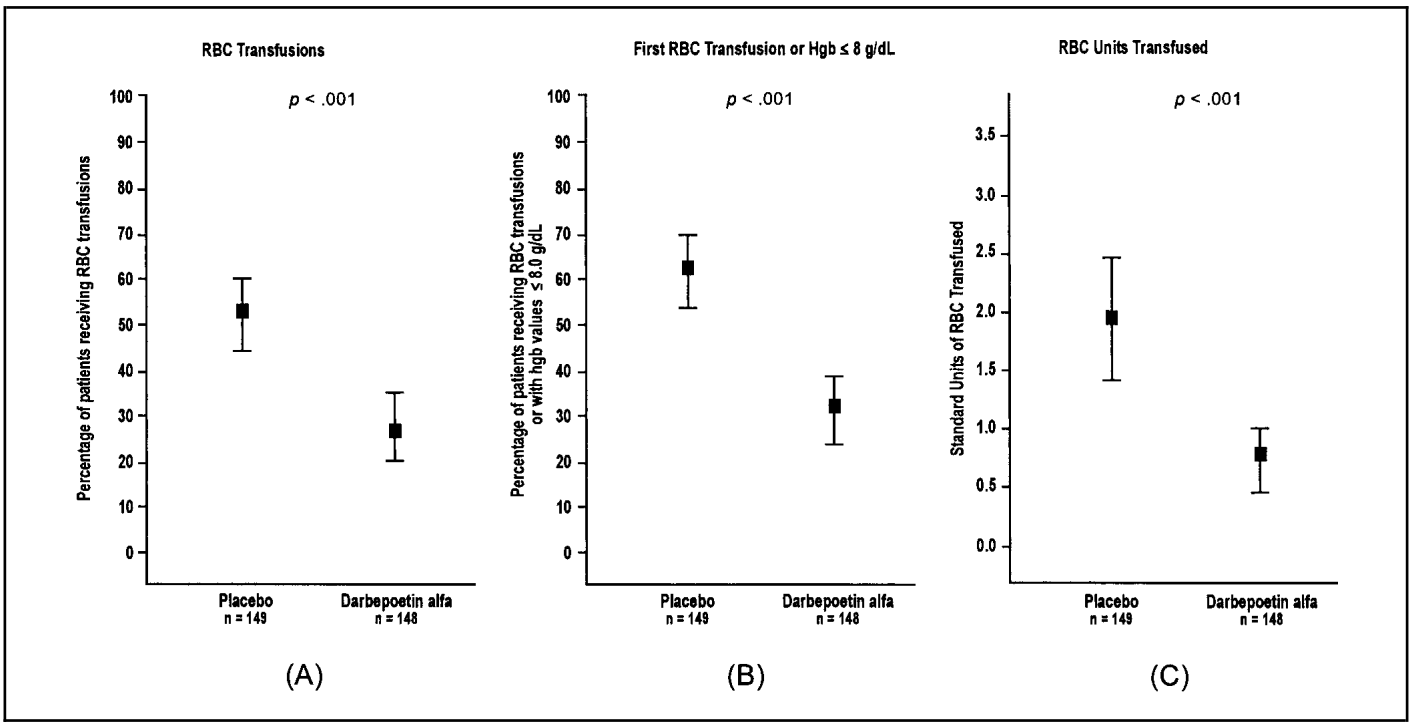

Fig. 2. Comparison of the Kaplan–Meier percentage of patients in the placebo or darbepoetin alfa groups that received a red blood cell (RBC) transfusion from week 5 until the end-of-treatment phase (**A**) and who received an RBC transfusion or who had a hemoglobin level that decreased to less than or equal to 8.0 g/dL (**B**). **C**) Comparison of the number of the standard units of RBCs transfused to patients receiving placebo or darbepoetin alfa.

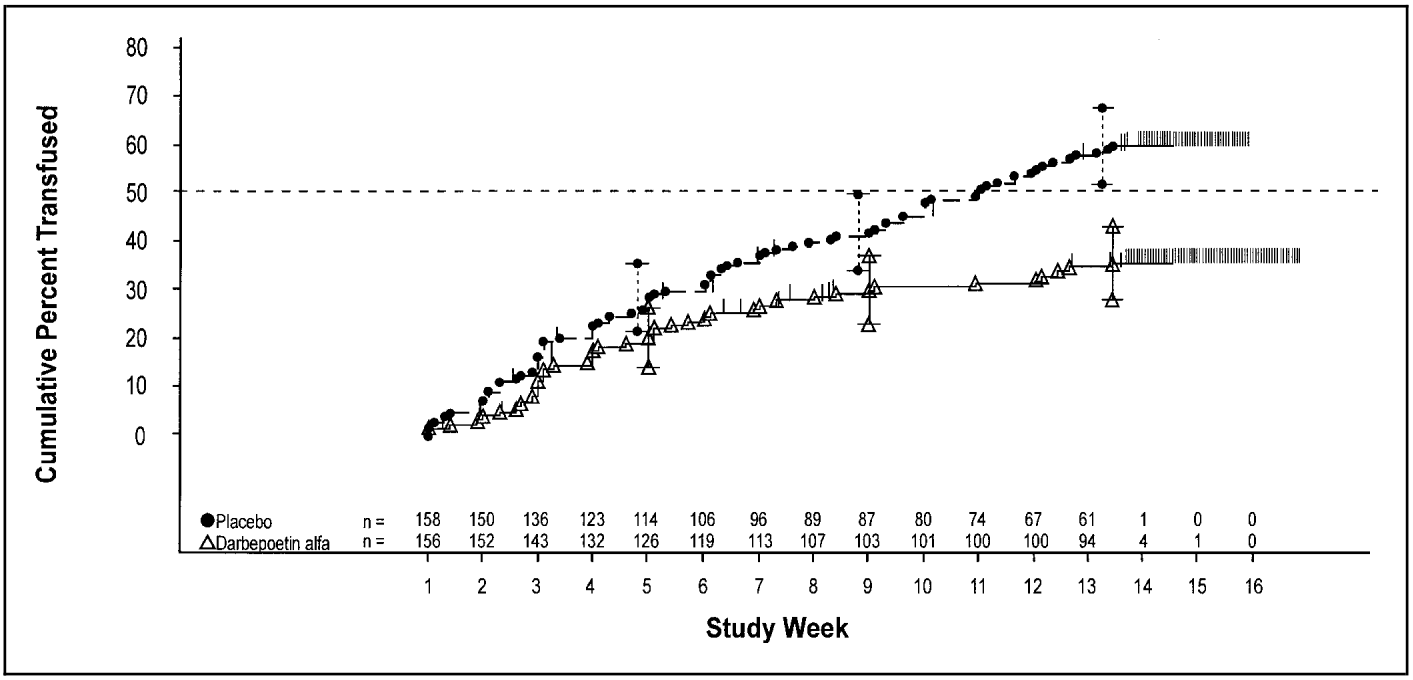

Fig. 3. Kaplan–Meier curve of the time to first red blood cell (RBC) transfusion during the entire treatment phase (from week 1 until the end-of-treatment phase) for patients receiving placebo (**closed circles**) or darbepoetin alfa (**open triangles**). Ninety-five percent confidence intervals are displayed for the cumulative percentage of patients transfused by study weeks 5, 9, and 13. Censored patients are represented by the **vertical lines.** The number of patients at risk at each week of the study is shown just above the *x*-axis.

quelae indicative of antibody formation have been observed during the follow-up period.

Additional Outcomes

Hospitalizations. The proportion of patients hospitalized for at least one overnight stay was similar between the treatment groups. We only considered hospitalizations for overnight stays, to eliminate hospitalizations for procedures such as transfusions and administration of chemotherapy that may reflect regional policy differences. Patients in the darbepoetin alfa group were hospitalized for 10.3 ± 13.7 (mean ± SD) days, and patients in the placebo group were hospitalized for 13.0 ± 17.7 days (mean

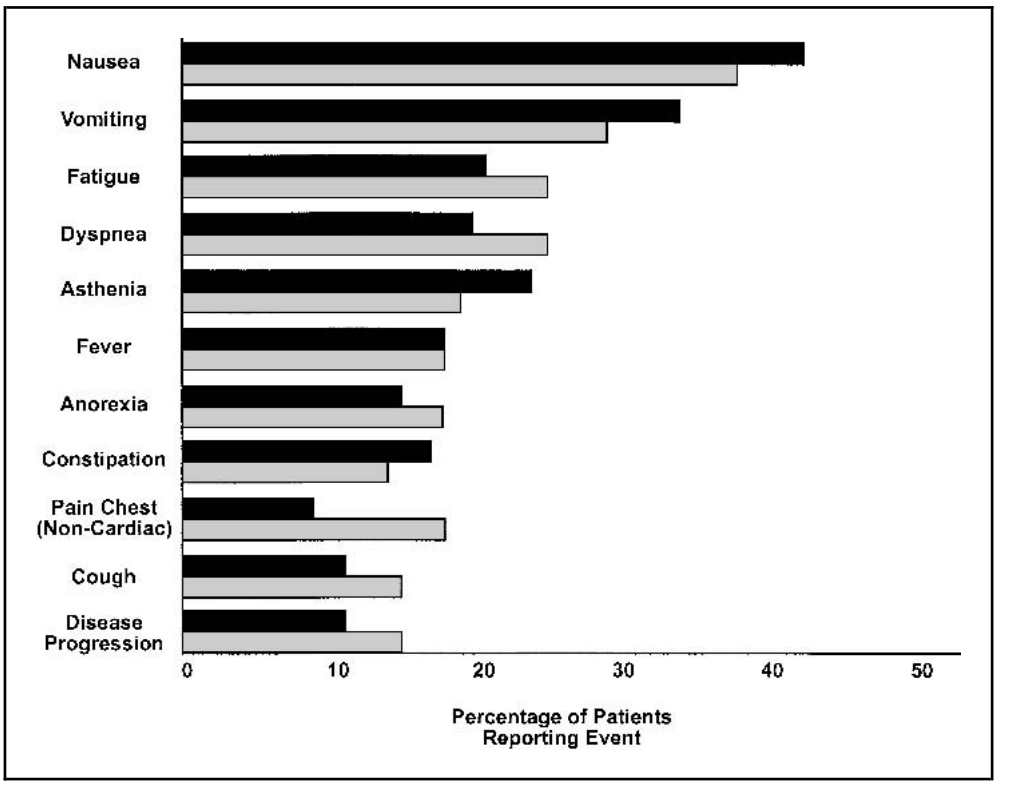

Fig. 4. The adverse events reported in at least 13% of patients across both treatment groups. **Black bars** = darbepoetin alfa (n = 155); **gray bars** = placebo (n = 159).

± SD) (nominal *P* value = .13). An analysis of the proportion of patients hospitalized was also done considering all hospitalizations (i.e., with or without an overnight stay), with similar results.

Progression-free and overall survival. For this article, data for study follow-up of disease progression and survival were current through August 2001. As of this date, patients had been followed an average of 1 year after their first dose of study drug and continue to be evaluated at specified time points. All 314 patients who received study drug were included in the analyses of progression-free survival and overall survival. One hundred twenty-nine patients (83%) in the darbepoetin alfa group and 141 patients (89%) in the placebo group had disease progression or died either during the study or during the follow-up period. The median duration of progression-free survival was 22 weeks (95% CI = 18 to 31 weeks) in the darbepoetin alfa group and 20 weeks (95% CI = 17 to 23 weeks) in the placebo group (Fig. 5).

Ninety-two patients (59%) in the darbepoetin alfa group and 109 patients (69%) in the placebo group died either on study or during the follow-up period. The median duration of survival

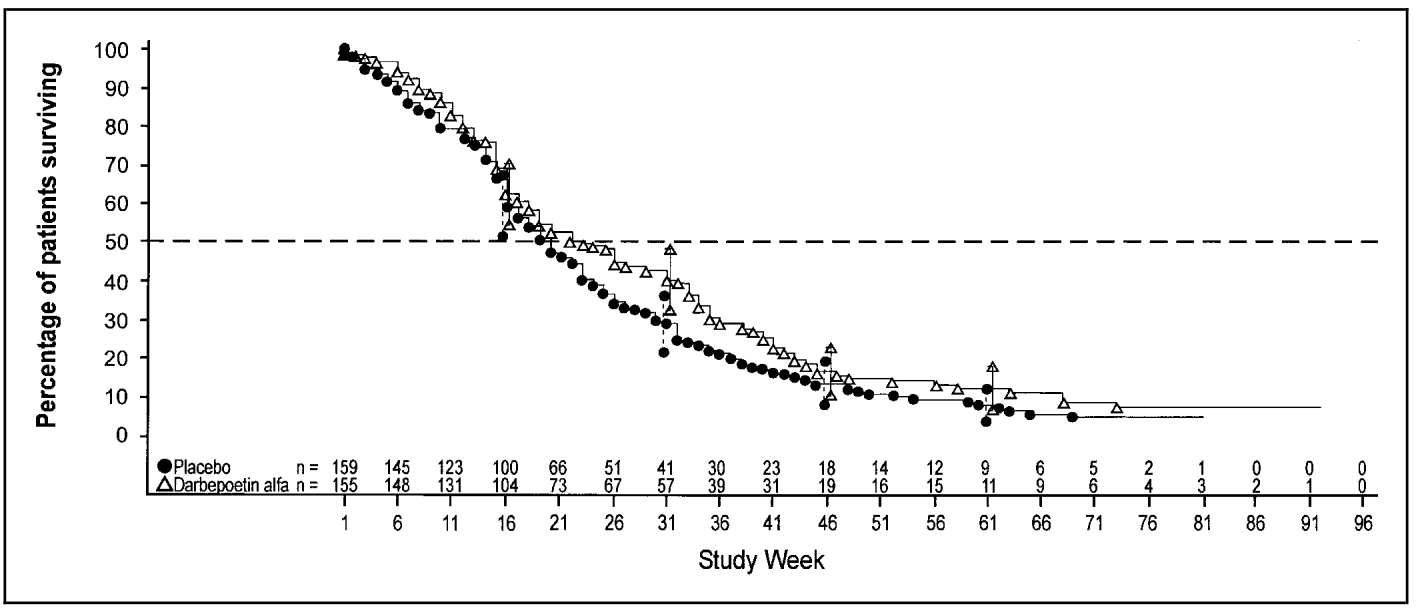

Fig. 5. Kaplan–Meier curve of the time to disease progression or death for patients receiving placebo (**closed circles**) or darbepoetin alfa (**open triangles**). The median survival time was 20 weeks for patients receiving the placebo and 22 weeks for patients receiving darbepoetin alfa. The number of patients at risk is shown above the *x*-axis. **Error bars** indicate the 95% confidence interval for different time points.

was 46 weeks (95% CI = 39 to 53 weeks) in the darbepoetin alfa group and 34 weeks (95% CI = 29 to 39 weeks) in the placebo group (Fig. 6).

DISCUSSION

Darbepoetin alfa is an erythropoietic agent with a longer serum half-life than rHuEPO *(16).* Darbepoetin alfa is approved in the United States and European Union for the treatment of anemia in patients with chronic kidney disease. This placebo-controlled, double-blind, randomized phase III study tested the safety and efficacy of darbepoetin alfa administered weekly for the treatment of anemia in patients with lung cancer receiving multicycle chemotherapy. A statistically significant and clinically meaningful reduction of greater than 50% was observed in both the incidence of transfusions and the number of units transfused for patients who received darbepoetin alfa compared with those who received placebo. A marked increase in the proportion of patients who achieved a hematopoietic response was also observed. In addition, a decrease in fatigue was shown for those patients who received darbepoetin alfa. Darbepoetin alfa appears to be safe because of the lack of a statistically significantly higher incidence of specific adverse events, such as thrombosis and hypertension, in the patients treated with darbepoetin alfa.

The results of this study are noteworthy for several reasons, including a reduction in the number of required blood transfusions, less frequent administration with concomitant increased patient compliance, and reduced cost of care. The effect on the reduction of the number of required red blood cell transfusions was apparent even when data from the first 4 weeks of therapy were included. Several studies have demonstrated a 1-month lag in the clinical effect of rHuEPO *(7,24,25),* and some were unable to demonstrate statistical significance compared with placebo when data from the first month of therapy were included in the analysis *(7).* This lag likely reflects the influence of pharmacologic doses of rHuEPO on the kinetics of erythropoiesis, the response of which is not rapid enough to affect the need for transfusions within the first month of treatment. The results from the current study suggest that this is not the case for this dose and schedule of darbepoetin alfa. Direct comparative data are needed before it can be concluded that the onset of action is faster for darbepoetin alfa than for rHuEPO.

Compared with rHuEPO, the prolonged half-life of darbepoetin alfa should allow less frequent administration of the drug to cancer patients, as has been demonstrated in the nephrology setting *(17,29).* The benefits of less frequent administration for patients are obvious in terms of a reduced number of injections. In addition, other benefits to patients and their caregivers include less time missed from work for physician visits and potentially better patient compliance. The weekly administration of darbepoetin alfa used in this study represents an improvement over the thrice weekly administration of rHuEPO, which is the approved schedule worldwide. It should be noted, however, that in the United States, the common clinical practice in oncology is to administer a single weekly injection of rHuEPO of 40 000 U. Although there are data suggesting the adequacy of this dosage from a single-arm, uncontrolled study *(25),* the ability to administer rHuEPO weekly seemingly requires a 33% increase in dose and cost compared with the thrice-weekly dose of 10 000 U. The increased cost for equivalent clinical effect is likely the reason for the lack of adoption of weekly administration of rHuEPO in Europe. Furthermore, data from controlled, phase II studies demonstrate the ability of darbepoetin alfa to be administered every 2 or 3 weeks *(20,22).* Further studies are warranted to confirm the ability of darbepoetin alfa to be administered at these reduced frequencies.

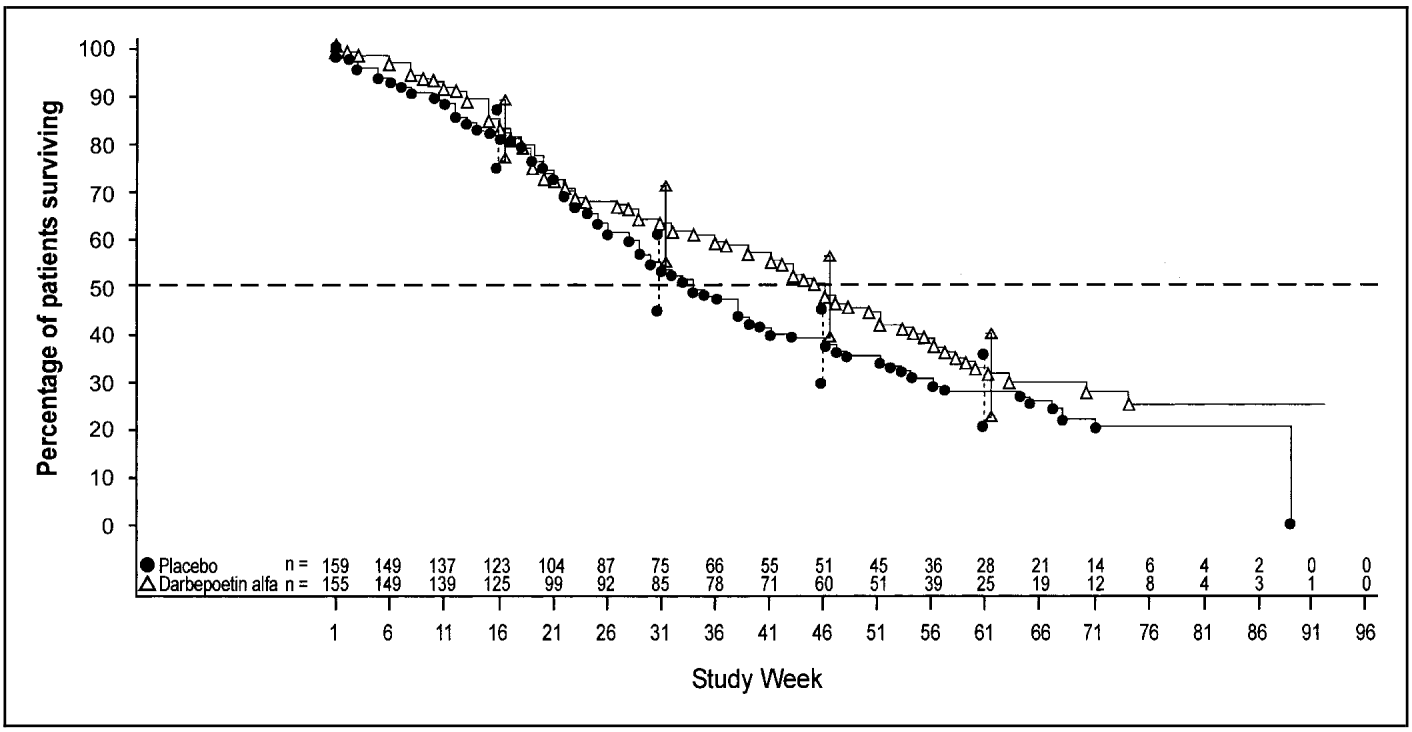

Fig. 6. Kaplan–Meier curve of the time to death for patients receiving placebo (**closed circles**) or darbepoetin alfa (**open triangles**). The median time to death was 34 weeks for patients receiving the placebo and 46 weeks for patients receiving darbepoetin alfa. The number of patients at risk is shown above the *x*-axis. **Error bars** indicate the 95% confidence interval for different time points.

This study has important implications for the total cost of care for cancer patients receiving chemotherapy, because patients receiving darbepoetin alfa required shorter hospitalization stays than did patients receiving placebo. Although this study was not designed to identify a causal relationship between hospitalization and the use of darbepoetin alfa, and the difference was not statistically significant, it is possible that patients with higher hemoglobin concentrations may benefit from an overall improvement in performance status that may allow for overall decreased resource utilization. The cost of erythropoiesis-stimulating agents could be offset by a potential reduction in the duration of hospitalization and demonstrated reductions in the total number of red blood cell units transfused. Further prospective work is warranted to account for all costs associated with the treatment of patients with anemia.

The observation of possible improvements in disease outcome in patients who received darbepoetin alfa could simply be an artifact of a lack of balance between prognostic factors and treatment characteristics for the two treatment groups. Although this study was not designed to definitively assess this possibility, because it did not include prospective stratification by important prognostic factors and there was no policy about specific doses and regimens of chemotherapy, there was good balance between the placebo and darbepoetin alfa groups with respect to most known important prognostic factors (e.g., ECOG status, age, percentage of patients receiving first-line therapy) (Table 1). In addition, the minimum ANC values on study in both treatment groups were very similar, suggesting that a higher dose intensity of the chemotherapy administered in the darbepoetin group is not responsible for the difference in survival. This finding mirrors that from a study of patients with nonmyeloid malignancies in which there was an observation of a trend toward a survival advantage for patients treated with rHuEPO compared with those treated with placebo *(24).* Clearly, neither of these studies [*(24)* and the current study] provides any evidence of causality, but they do suggest that there are few, if any, negative effects associated with darbepoetin alfa or rHuEPO that indicate that the drugs stimulate tumor growth. Further work is needed to confirm these findings in a study that is designed specifically to address the question of the impact of treatment with darbepoetin alfa on progression-free and overall survival in patients receiving chemotherapy.

In summary, the findings from this study indicate that darbepoetin alfa administered weekly is safe and effective for the treatment of anemia in patients with cancer receiving chemotherapy. Further studies are focusing on confirming the efficacy of this drug when administered every 2 or 3 weeks. In addition, interesting hypothesis-generating observations in this study with respect to the effects of darbepoetin alfa on disease outcome, as well as potential health economic benefits associated with a reduced length of stay in the hospital, should be confirmed in prospective randomized controlled studies.

APPENDIX

The names and affiliations of the additional members of the Aranesp™ 980297 Study Group are as follows:

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REFERENCES

(1) Koury MJ, Bondurant MC. Control of red cell production: the roles of programmed cell death (apoptosis) and erythropoietin. Transfusion 1990; 30:673–4.

(2) Miller CB, Jones RJ, Piantadosi S, Abeloff MD, Spivak JL. Decreased

erythropoietin response in patients with the anemia of cancer. N Engl J Med 1990;322:1689–92.
(3) Curt GA. Impact of fatigue on quality of life in oncology patients. Semin Hematol 2000;37:14–7.
(4) Cella D. Factors influencing quality of life in cancer patients: anemia and fatigue. Semin Oncol 1998;25:43–6.
(5) Walker RH. Special report: transfusion risks. Am J Clin Pathol 1987;88: 374–8.
(6) Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine. First of two parts—blood transfusion. N Engl J Med 1999;340: 438–47.
(7) Abels RI. Use of recombinant human erythropoietin in the treatment of anemia in patients who have cancer. Semin Oncol 1992;19:29–35.
(8) Maraveyas A, Pettengell R. What is the role of erythropoietin in patients with solid tumors? Ann Oncol 1998;9:239–41.
(9) Cascinu S, Fedeli A, Del Ferro E, Fedeli SL, Catalano G. Recombinant human erythropoietin treatment in cisplatin-associated anemia: a randomized, double-blind trial with placebo. J Clin Oncol 1994;12:1058–62.
(10) Henry DH, Abels RI. Recombinant human erythropoietin in the treatment of cancer and chemotherapy-induced anemia: results of double-blind and open-label follow-up studies. Semin Oncol 1994;21:21–8.
(11) Platanias LC, Miller CB, Mick R, Hart RD, Ozer H, McEvilly JM, et al. Treatment of chemotherapy-induced anemia with recombinant human erythropoietin in cancer patients. J Clin Oncol 1991;9:2021–6.
(12) Glaspy J, Bukowski R, Steinberg D, Taylor C, Tchekmedyian S, Vadhan RS. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. J Clin Oncol 1997;15:1218–34.
(13) Demetri GD, Kris M, Wade J, Degos L, Cella D. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. J Clin Oncol 1998;16:3412–25.
(14) Oberhoff C, Neri B, Amadori D, Petry KU, Gamucci T, Rebmann U, et al. Recombinant human erythropoietin in the treatment of chemotherapy-induced anemia and prevention of transfusion requirement associated with solid tumors: a randomized, controlled study. Ann Oncol 1998;9:255–60.
(15) Thatcher N, De Campos ES, Bell DR, Steward WP, Varhese G, Morant R, et al. Epoetin alpha prevents anaemia and reduces transfusion requirements in patients undergoing primarily platinum-based chemotherapy for small cell lung cancer. Br J Cancer 1999;80:396–402.
(16) Egrie J, Browne J. Development and characterization of novel erythropoiesis stimulating protein (NESP). Br J Cancer 2001;84:3–10.
(17) Macdougall I, Gray SJ, Elston O, Breen C, Jenkins B, Browne J, et al. Pharmacokinetics of novel erythropoiesis stimulating protein compared with epoetin alfa in dialysis patients. J Am Soc Nephrol 1999;10:2392–5.
(18) Glaspy J, Colowick AB, Heatherington A. Novel erythropoiesis stimulating protein (NESP) exhibits a prolonged serum half-life ($T_{1/2}$) in oncology patients (Pts.). Proc ASCO 2000;19:54a.
(19) Heatherington A, Schuller J, Mercer J. Pharmacokinetics of novel erythropoiesis stimulating protein (NESP) cancer patients: preliminary report. Br J Cancer 2001;84:11–6.
(20) Glaspy J, Jadeja JS, Justice G, Kessler J, Richards D, Schwartzberg L, et al. Darbepoetin alfa given every one or two weeks alleviates anaemia associated with cancer chemotherapy. Br J Cancer. In press 2002.
(21) Glaspy J, Singh Jadeja J, Justice G, Kessler J, Richards D, Schwartzberg L, et al. A dose-finding study of novel erythropoiesis stimulating protein (NESP) for the treatment of anaemia in patients receiving multicycle chemotherapy. Br J Cancer 2001;84:17–23.
(22) Kotasek D, Berg R, Poulsen E, Colowick A. Randomized, double-blind, placebo controlled, phase I/II dose-finding study of ARANESP™ administered once every three weeks in solid tumor patients [abstract]. Blood 2000;96:294a–5a.
(23) Hedenus M, Hansen S, Dewey C, Watson D, Colowick A, Osterberg O. A randomized, blinded, placebo-controlled, phase II, dose-finding study of ARANESP in patients with lymphoproliferative malignancies. Proc ASCO 2001;20:393a.
(24) Littlewood T, Bajetta E, Nortier J, Vercammen E, Rapoport B. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol 2001;19:2865–74.
(25) Gabrilove JL, Cleeland CS, Livingston RB, Sarokhan B, Winer E, Einhorn LH. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. J Clin Oncol 2001;19:2875–82.
(26) Dammacco F, Castoldi GL, Rodjer S. Efficacy of epoetin alfa in the treatment of anaemia of multiple myeloma. Br J Haematol 2001;113:172–9.
(27) Cella D. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. Semin Hematol 1997;34:13–9.
(28) Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York (NY): John Wiley & Sons; 1980.
(29) Locatelli F, Olivares J, Walker RH, Wilkie M, Jenkins B, Dewey C, et al. Novel erythropoiesis stimulating protein for treatment of anemia in chronic renal insufficiency. Kidney Int 2001;60:741–7.

NOTES

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