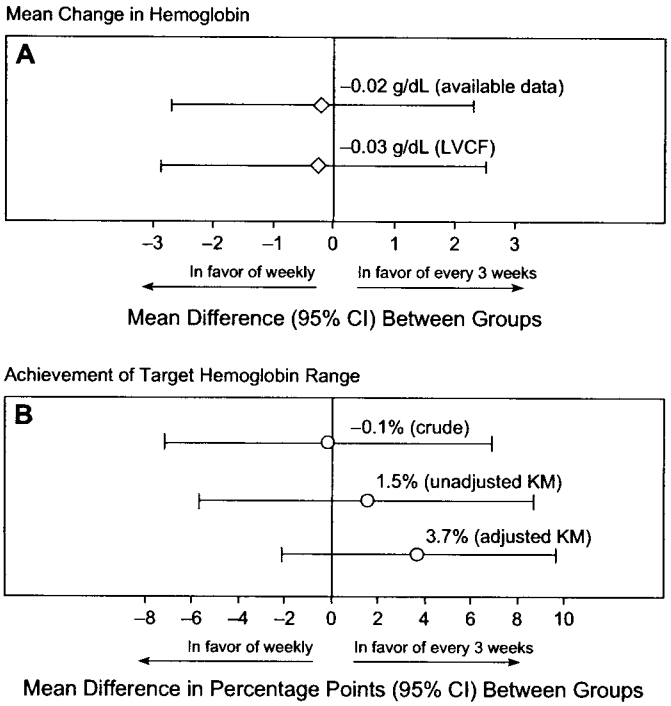

Fig. 5. Differences between study arms in mean hemoglobin concentrations and in achievement of target hemoglobin concentration between study arms. **A)** Differences in mean change in hemoglobin by the end of the treatment phase. Differences between the two treatment groups with respect to the mean hemoglobin concentration by the end of the treatment phase are shown with 95% confidence interval bars. These differences were based on the mean hemoglobin concentration estimated using the available data and last-value-carried-forward (LVCF) approaches, as indicated. These differences were based on the adjusted Kaplan–Meier estimates (adjusted for the baseline stratification factors of tumor type, screening hemoglobin concentration, and European region). Patients with no hemoglobin value after baseline were excluded from the analysis. **B)** Differences in proportions of patients achieving target hemoglobin concentration by the end of the treatment phase. Differences between the two treatment groups in the proportion of patients achieving a target hemoglobin concentration (11–13 g/dL) by the end of the treatment phase are shown with 95% confidence interval bars. These differences were based on the crude, unadjusted and adjusted Kaplan–Meier (KM) estimates, as indicated. Patients with no hemoglobin value after baseline were excluded from the analysis.

nausea, vomiting, fatigue, dyspnea, and weakness. No differences with respect to cardiovascular and thromboembolic events were observed between groups for patients who experienced a rise in hemoglobin concentration of 1 g/dL or greater in any 14-day period or hemoglobin values greater than 13 g/dL. Furthermore, there was no evidence of a delayed response to dose titration or dose withholding in the every-3-week arm compared with the weekly arm (data not shown).

A total of 28 patients (8%) in each treatment group experienced adverse events that were determined to be possibly, probably, or definitely related to the study drug by the treating investigator. Deep vein thrombosis occurred in four patients (1.1%) in the every-3-week group and in six patients (1.7%) in the weekly group. Pulmonary embolism occurred in three patients (0.8%) in the every–3-week-group and in no patients in the weekly group. Hypertension was reported in one patient (0.3%) in the every-3-week group and in four patients (1.1%) in the weekly group. Serious adverse events that were treatment related, as determined by the investigator, occurred in 11 patients (3%) in both treatment groups.

A total of 38 (11%) (every 3 weeks) and 52 (15%) (weekly) patients died during the study or within 30 days after the last

Table 4. Cardiovascular/thromboembolic and fatal adverse events

Adverse event	No. of patients with adverse event (%)	
	Darbepoetin alfa 500 μg every 3 weeks	Darbepoetin alfa 2.25 μg/kg weekly
Arrhythmia	15 (4)	19 (5)
Congestive heart failure	9 (3)	13 (4)
Cerebrovascular accident	0 (0)	3 (1)
Hypertension	8 (2)	12 (3)
Myocardial infarction, ischemic, coronary artery disease	5 (1)	3 (1)
Seizure	1 (0)	1 (0)
Embolism/thrombosis (arterial and venous)	28 (8)	27 (8)
Death (any reason)	38 (11)	52 (15)
Cancer-related (primary or metastasis)	25 (7)	32 (9)
Cardiac disorders	4 (1)	7 (2)
Cerebral infarction	0 (0)	1 (0)
Gastrointestinal disorders	1 (0)	1 (0)
Hepatic failure	1 (0)	2 (1)
Infections and infestations	2 (1)	2 (1)
Hemolytic anemia	0 (0)	1 (0)
Pyrexia	0 (0)	1 (0)
Renal insufficiency	0 (0)	1 (0)
Respiratory disorders	4 (1)	3 (1)
Sudden death	1 (0)	1 (0)

administered dose. Causes of death were ascribed to disease progression, such as infections, or to cardiac and respiratory complications (Table 4). Results of stratified analysis of safety data by weight and BMI categories did not reveal differences for lighter versus heavier patients in either treatment group nor for men or women (data not shown).

As with all recombinant protein therapies, potential immunogenicity is an important safety concern. No anti–darbepoetin alfa antibodies were detected in this population of patients receiving darbepoetin alfa.

Discussion

Darbepoetin alfa is an erythropoietic agent with a prolonged serum half-life that has been shown to be safe and effective for the treatment of chemotherapy-induced anemia when administered using weekly or every-3-week dosing schedules *(3,4,18–20)*. The primary objective of this randomized, double-blind, double-dummy, active-controlled, phase 3, noninferiority study was successfully achieved, demonstrating that a 500-μg darbepoetin alfa treatment every 3 weeks was at least as effective as a weekly treatment of 2.25 μg/kg.

This is the first clinical trial, to our knowledge, to formally compare the effectiveness of the extended every-3-week dosing schedule of darbepoetin alfa with standard weekly dosing with respect to clinically important endpoints such as reduction in RBC transfusion requirements, improvement of fatigue, and achievement of a relevant target hemoglobin concentration. The noninferiority design, previously used in the study of erythropoiesis-stimulating agents *(37–41)*, is endorsed by regulatory agencies to rigorously test whether a new therapeutic intervention is at least as effective as standard therapy *(42)*. In this study, the noninferiority margin of 12.5% was based on transfusion incidence data from week 5 to the end of the treatment phase of two previous, placebo-controlled darbepoetin alfa 2.25 μg/kg

weekly studies *(3,4)* and ensured that a substantial fraction of the treatment effect could be observed. The results of all analyses met the prespecified criterion for noninferiority. Moreover, because the upper limit of the 95% confidence interval for the difference in RBC transfusions between every-3-week and weekly treatment groups was 0.1, substantially less than 12.5%, the same conclusion would have been reached if, hypothetically, a lower, more conservative noninferiority margin were used.

A series of sensitivity analyses were performed to confirm the robustness of the noninferiority conclusion. The results of the primary analysis were consistent across analysis sets (primary transfusion versus per-protocol analysis sets), analysis methods (adjusted versus unadjusted, Kaplan–Meier proportions versus crude rates), and censoring mechanisms (primary versus secondary censoring), with a suggested decreased in incidence of transfusions in the every-3-week group compared with the weekly group. Analyses of transfusion endpoints and data analysis sets that were adjusted for stratification factors were statistically significantly in favor of the every-3-week dosing schedule (data not shown).

The results of this study were consistent with results from the two previous randomized, double-blind, phase 3 studies of darbepoetin alfa 2.25 μg/kg weekly for 12 weeks *(3,4)*, which showed statistically significant and clinically meaningful differences from placebo. If the treatment period is standardized to 12 weeks, the blood transfusion incidence from week 5 to the end of the treatment phase for the weekly arm of this study (unadjusted Kaplan–Meier estimate = 26% [95% CI = 21% to 31%]) corresponds to the transfusion rates associated with the active treatment arms of these two previous studies [27% (95% CI = 20% to 35%) *(3)* and 31% (95% CI = 24% to 38%) *(4)*] and to the rate observed in the 2.25 μg/kg control arm in another randomized, active-controlled, phase 3 trial *(41)*.

An important difference in the design of this study, as compared with previously published studies evaluating the efficacy and safety of erythropoietic agents in oncology, was the use of strict dose adjustment rules. These rules, described in the package inserts for erythropoiesis-stimulating agents *(16,43)*, stem from recommendations by the Oncology Drugs Advisory Committee of the Food and Drug Administration *(44)* in response to two placebo-controlled trials reporting adverse survival outcomes for the epoetin alfa (Eprex) and epoetin beta (NeoRecormon) groups *(45,46)*. Consequently, greater than two-thirds of patients in both groups in the current study required dose reductions or withholding. Although previously reported analyses have shown an increased risk of cardiovascular or thromboembolic events associated with a 2 g/dL rise in hemoglobin in 28 days *(47,48)*, data from this study did not indicate an increased risk among patients who exceeded a 1 g/dL increase in hemoglobin in 14 days (in the absence of an RBC transfusion). It is interesting to note, however, that similar rates of rise (i.e., increases in hemoglobin concentration of ≥1 g/dL in 14 days) have been observed in a substantial number of patients in the placebo groups of randomized, controlled trials of darbepoetin alfa for chemotherapy-induced anemia *(3,4)*, reflecting the inherent variability of hemoglobin levels in patients receiving chemotherapy. These data suggest that further work is needed to determine the most appropriate recommendations for dose titration to prevent inappropriately rapid rises in hemoglobin concentrations in cancer patients receiving chemotherapy.

The hemoglobin concentration profiles over time were similar for the two treatment groups and were characterized by an increase in hemoglobin concentration during the initial 7 weeks of therapy, followed by a slower rate of increase in hemoglobin levels that coincided with the median time to first dose reduction; incidentally, this occurred as the mean hemoglobin concentrations were greater than 11 g/dL. These hemoglobin profiles are consistent with the current National Comprehensive Cancer Network guidelines for cancer- and treatment-related anemia, which state that the goal of therapy should be to attain hemoglobin concentrations between 11 and 12 g/dL *(28)*. Despite the strict dose adjustment rules in this study, the comparability of the two darbepoetin alfa regimens was supported by the high proportion of patients who achieved target hemoglobin levels and subsequently maintained these levels for the remainder of their treatment period. The response to darbepoetin alfa therapy before dose reduction suggests that the initial doses of darbepoetin alfa (2.25 μg/kg weekly and 500 μg every 3 weeks) were highly effective in stimulating erythropoiesis and correcting anemia. These data support the use of a reduced dose, after initial alleviation of anemia, to maintain hemoglobin concentrations throughout the remainder of chemotherapy treatment.

A fixed dose was selected for the every-3-week treatment arm of this study because unit dosing has been shown to be safe, effective, convenient (simplifying drug administration), and consistent with the pattern of usage of erythropoiesis-stimulating agents in clinical practice *(7,22,24–26)*. Specifically, the 500-μg dose examined in this study approximates the approved every-3-week dose in Europe of 6.75 μg/kg *(17)* as well as an equivalent exposure to the standard weekly 2.25-μg/kg dose *(16)*, for an average-weight patient of 74 kg. In this trial, the efficacy of a fixed dose of 500 μg every 3 weeks was compared with the approved weight–based starting dose. In both transfusion- and hemoglobin-related endpoints, no evidence of decreasing effect was observed with increasing weight or BMI, nor was there any evidence of inferior effectiveness for the fixed-dose group relative to the weight-based comparator at higher weight categories.

Determining the safety of the infrequent fixed dose of darbepoetin alfa was a key objective of this trial. There was no evidence of trends indicating a differential adverse event profile or adverse hemoglobin profile between groups or across weight or BMI categories. Importantly, the every-3-week regimen was not associated with an increased incidence of cardiovascular or thromboembolic adverse events when compared with the currently approved weekly starting dose. Furthermore, there was no evidence of differences in the rate of rise in hemoglobin concentration or maximum hemoglobin threshold concentration of 13 g/dL, nor was there any apparent delay in response to dose titration or dose withholding, indicating that a level of control similar to the weekly schedule is possible.

Although the noninferiority design is appropriate for the hypothesis tested in this study, it does not allow for a direct assessment of the treatment effect because there is no placebo group. An indirect assessment of the treatment effect was possible by comparing results from this trial with the results of the weekly 2.25 μg/kg arms of previous phase 3 trials of darbepoetin alfa *(3,4)*. Analyses revealed results consistent with those obtained in the current study for the primary endpoint. Another limitation of the noninferiority design is the choice of population; in noninferiority studies, the intent-to-treat approach may not be conservative because protocol deviations tend to minimize differences between treatments. To assess the impact on our findings of analysis population, protocol deviations, and the pattern

of withdrawal, a series of prespecified sensitivity analyses were performed. These demonstrated the consistency of the findings regardless of the analysis set use, confirming the validity of the noninferiority conclusion. In addition, the strict dose adjustment rules applied in this study appeared to lessen the observed overall change in hemoglobin, as compared with historical data, thereby potentially limiting the conclusions to the use of darbepoetin alfa under these dose modification conditions. However, because these rules are consistent with the revised product labels for erythropoietic therapies in oncology *(16,43)*, these findings are relevant to current usage of this agent. Moreover, these rules appeared to have no obvious impact on the transfusion requirements in this population when compared with the historic data *(3,4)*. Finally, the primary endpoint selected in this study excluded the first 4 weeks of therapy because noninferiority studies inherently rely on historic data, and this has been the standard transfusion endpoint used in placebo-controlled trials for erythropoietic product registration in oncology. Transfusion incidence from week 5 to the end of treatment phase may be a conservative endpoint in placebo-controlled trials; however, in active-controlled trials, the exclusion of the first 4 weeks of therapy may introduce bias, particularly in relation to unequal distribution of early withdrawal. To address this potential bias, a prespecified secondary endpoint evaluated transfusion incidence over the entire treatment phase. This key secondary endpoint yielded results consistent with the analysis of the primary endpoint.

This study represents the progress of randomized, controlled trials in the study of erythropoiesis-stimulating agents from more frequent to less frequent administration and from weight-based to single, fixed doses. The results of this randomized, controlled trial conducted in Europe unequivocally demonstrate that darbepoetin alfa, administered every 3 weeks using a fixed 500-μg dose, achieves clinical outcomes comparable to those with the current labeled starting dose of darbepoetin alfa (2.25 μg/kg weekly). There was no decrease in effectiveness observed for heavier patients, nor were there increased safety concerns apparent in patients with lower weights. Therefore, patients receiving chemotherapy who develop anemia can safely and effectively be treated with darbepoetin alfa every 3 weeks. The fixed every-3-week dosing allows for a convenient, infrequent schedule that permits the synchronization of anemia treatment with the administration of many common chemotherapy regimens. The ability to administer erythropoietic therapy on a schedule that synchronizes with chemotherapy administration can enhance patient convenience and lessen resource utilization. Although differences in practice patterns may exist between Europe and North America with respect to the rates of erythropoietic therapy use in oncology *(49,50)*, there is no evidence to suggest that patients from these two regions would exhibit different anemia-related outcomes when given comparable regimens of darbepoetin alfa. The potential health economic benefit of reduced number of patient visits associated with anemia intervention administered on the same schedule as chemotherapy should be examined in prospective randomized, controlled trials.

Appendix

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Notes

The research of Drs. Canon and Vansteenkiste is funded by Amgen, and Drs. Ferreira, Rossi, and Amado work for Amgen and hold stock in the company. Amgen Limited, Cambridge, U.K. sponsored and funded the study (Amgen Study No. 20030231).

The authors thank the investigators, study coordinators, and participants at each of the institutions for their contributions to this study. We thank Sarah Carter and Elaine Harrop, MSc, for coordinating study conduct and data collection, and Alexander Liede, PhD, for assistance in writing this manuscript.

Funding to pay the Open Access publication charges for this article was provided by Amgen Inc.

Manuscript received July 26, 2005; revised December 2, 2005; accepted December 27, 2005.

ELSEVIER

European Journal of Cancer 41 (2005) 1140–1149

European Journal of Cancer

www.ejconline.com

Effects of chemotherapy on endogenous erythropoietin levels and the pharmacokinetics and erythropoietic response of darbepoetin alfa: A randomised clinical trial of synchronous *versus* asynchronous dosing of darbepoetin alfa

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Received 11 October 2004; received in revised form 5 January 2005; accepted 27 January 2005
Available online 8 April 2005

Abstract

The introduction of longer-acting erythropoietic agents into the practice of oncology has demanded an understanding of the interaction of chemotherapy with the pharmacokinetics and haematological effects of these erythropoietins. We report results of a randomised trial comparing the haematological effects of darbepoetin alfa, 6.75 μg/kg, administered once every 3 weeks to anaemic cancer chemotherapy patients on either an asynchronous (day 15) or synchronous (day 1) schedule relative to their every-3-week chemotherapy. A total of 81 patients were randomised and received the study drug (43 asynchronous; 38 synchronous). No difference was observed between groups in the primary endpoint of mean haemoglobin change after 6 weeks of therapy ($P = 0.45$) and change scores were similar to those observed with standard weekly darbepoetin alfa therapy. In a subset of patients evaluated with intensive pharmacokinetic sampling, an increase in endogenous erythropoietin concentration (up to 4-fold) lasting approximately 1 week following chemotherapy administration was observed in both groups. Synchronous administration of darbepoetin alfa was associated with a 1.3-fold increase in the area under the darbepoetin alfa concentration–time curve compared with asynchronous administration. Our data suggest that darbepoetin alfa is effective administered every 3 weeks regardless of timing of administration with respect to chemotherapy and that receptor-mediated uptake by the erythron may be an important clearance mechanism for erythropoietic proteins.

Keywords: Darbepoetin alfa; Pharmacokinetics; Chemotherapy; Erythropoietin synchronous; Asynchronous

1. Introduction

Anaemia due to chronic illness and chemotherapy is frequently observed in patients with cancer and may

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doi:10.1016/j.ejca.2005.01.021

be treated with erythropoietic agents, such as darbepoetin alfa (Aranesp®) and epoetin alfa [1]. Erythropoietic therapy increases haemoglobin concentrations, decreases the incidence of red blood cell (RBC) transfusions, and improves health-related quality of life in patients with chemotherapy-induced anaemia [2–12]. Darbepoetin alfa has the unique structure of increased sialic acid content compared with epoetin alfa. This structure appears to confer a longer serum half-life and may allow for less frequent dosing with similar efficacy as epoetin alfa [13].

The pharmacokinetics and pharmacodynamics of endogenous and recombinant human erythropoietin (eEPO and rHuEPO, respectively) are of clinical interest but are not well understood. A few studies have attempted to elucidate these characteristics, especially regarding the clearance mechanism of eEPO. One hypothesis supports a two-step clearance process [14] in which blood- or tissue-resident sialidases remove terminal sialic acids from eEPO. The asialoerythropoietin then interacts with an asialoglycoprotein receptor (ASGR) in the liver, which causes uptake and catabolism [15–17]. Some limitations, however, exist for this hypothesis, as no evidence of this asialyation for the recombinant human erythropoietin molecule in humans and no sialidase activity or specificity for glycoproteins (rather than gangliosides) have been demonstrated [18]. Furthermore, rHuEPO does not preferentially accumulate in the liver [14] and hepatectomy does not affect the rate of clearance in sheep [19]. These data suggest that the liver is not a route of clearance for erythropoietin. Another hypothesis is that EPO receptor-bearing target cells may be a route of clearance, through the mechanism of binding, internalisation, and degradation [20–26]. Evidence that serum eEPO levels increased transiently in humans after administration of high-dose chemotherapy suggested that the bone marrow may clear erythropoietic proteins [27]. For darbepoetin alfa, pharmacokinetic data [28] indicated that the terminal half-life increased with standard-dose chemotherapy (compared with the half-life calculated in dialysis patients), presumably through decreased clearance.

Since the bone marrow may be a key route of clearance of erythropoietic agents, the timing of administration of these agents relative to that of myelosuppressive chemotherapy may be critical to producing the maximum erythropoietic response. In a randomised, placebo-controlled clinical trial investigating the dose response relationship of darbepoetin alfa in patients with chemotherapy-induced anaemia, darbepoetin alfa was effective when administered every 3 weeks [29]. As many chemotherapy regimens are administered every 3 weeks, darbepoetin alfa administered every 3 weeks represents an opportunity to synchronise dosing with chemotherapy. However, while synchronous dosing of erythropoietic agents with chemotherapy is convenient, the efficacy of the agent may not be maximised, as the marrow may be too myelosuppressed by the cytotoxic chemotherapeutic agents to enable a maximum response to erythropoietin.

Pre-clinical data using a murine model of carboplatin chemotherapy/radiotherapy (CRT)-induced anaemia indicate that pre-treatment (7 d prior to administration of CRT) with darbepoetin alfa represented the most effective dosing approach compared with same day dosing or post-treatment (10 d post-CRT) dosing algorithms [30]. However, changes in the pharmacokinetic profiles were also observed; which included a reduction in clearance (CL/F) and an increase both in overall exposure ($AUC_{(0-\infty)}$) and in time to peak concentration (T_{max}) in animals in the same day dosing group compared with animals in the pre-treatment group. These findings indicated that clinical investigation into the effect of synchronisation of chemotherapy and erythropoietic therapy is warranted.

To evaluate the effect of the timing of administration of darbepoetin alfa with that of chemotherapy, we conducted a randomised clinical trial in anaemic patients with cancer receiving chemotherapy once every 3 weeks, who received darbepoetin alfa once every 3 weeks, either asynchronously (day 15) or synchronously (day 1) with chemotherapy. Our goals were to determine any differences in erythropoietic efficacy between schedules, to characterise the effects of chemotherapy on serum eEPO concentrations and on darbepoetin alfa pharmacokinetics, and to study the temporal effects of chemotherapy on haemoglobin concentrations.

2. Methods

2.1. Study population

Institutional review boards approved the protocol and patients gave written informed consent before entry. Eligible patients were $\geqslant 18$ years old, had non-myeloid malignancies, received cyclic chemotherapy once every 3 weeks, were anaemic (haemoglobin concentration $\geqslant 9.0$ and $\leqslant 11.0$ g/dl), had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and had adequate renal and hepatic function. Patients with histories of seizures, significant cardiac or inflammatory disease, primary haematological disorders that could cause anaemia, or received any rHuEPO or more than two RBC transfusions within 4 weeks of randomisation were excluded.

2.2. Study drug

Darbepoetin alfa (Aranesp®, Amgen Inc., Thousand Oaks, California, USA) was supplied in vials containing 1 mg/ml darbepoetin alfa.

2.3. Study design

This was a multi-centre, open-label, randomised trial conducted from January 2002 to October 2002. Patients receiving chemotherapy every 3 weeks were randomly assigned 1:1 to receive subcutaneous (s.c.) darbepoetin alfa 6.75 μg/kg once every 3 weeks asynchronously or synchronously with chemotherapy. Randomisation was stratified by baseline haemoglobin concentration (<10.0 *versus* ⩾10.0 g/dl), study centre (UCLA Medical Center *versus* all others), and optional participation in the intensive pharmacokinetic study.

The primary endpoint assessment was after 6 weeks of darbepoetin alfa therapy, to allow sufficient time to detect differences in haematological response while ensuring that most patients retained chemotherapy cycles of once every 3 weeks. Since chemotherapy cessation, delays and modifications of cycle length were likely to occur after 2 cycles, assessment of haemoglobin change beyond 6 weeks may have confounded results of synchronicity.

Darbepoetin alfa was withheld from patients if haemoglobin concentrations were >15.0 g/dl for men or >14.0 g/dl for women. When haemoglobin concentration decreased to ⩽13.0 g/dl, darbepoetin alfa was restarted at 66% of the previous dose. Patients receiving chemotherapy remained in the study for up to 16 weeks. After 6 weeks, darbepoetin alfa dose could be doubled for patients with <1-g/dl increase in haemoglobin concentration from baseline. Blood samples for eEPO, darbepoetin alfa pharmacokinetics, and safety and efficacy analyses were obtained at predefined time points throughout the study.

2.4. Pharmacokinetic assessments

All patients had baseline eEPO measured. A subset of patients from each treatment group signed an additional consent form and participated in the optional pharmacokinetic study. After the first dose of darbepoetin alfa, blood samples were collected over the 3-week dosing interval at frequent predefined points up to 504 h (21 d) after administration. Weekly samples were collected thereafter. Darbepoetin alfa and eEPO concentrations were determined in all of these samples by separate methods.

Darbepoetin alfa concentrations were measured using the Quantikine IVD human erythropoietin enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA) by MDS Pharma Services (Montreal, Canada). The standard curve concentrations range was 5.00–0.125 ng/ml and the lower limit of quantification was generally 0.14 ng/ml. The assay was validated [31] and demonstrated recovery of spike experiments, parallelism, accuracy, inter-assay precision (coefficient of variation for darbepoetin alfa was 1–4%) and stability. Endogenous EPO cross-reacted in this ELISA.

An additional EPO-specific assay was used to determine eEPO concentrations when darbepoetin alfa was present. This assay used a different erythropoietin-specific monoclonal antibody (F12) as the capture antibody [32,33]. This antibody does not bind to darbepoetin alfa at concentrations ⩽5000 ng/ml (maximum tested). The detection antibody was the same anti-rHuEPO rabbit polyclonal antibody used in R&D Systems rHuEPO ELISA kit. This assay used rHuEPO for standard and quality control samples. The standard curve range was 333.3–5.2 mU/ml and the lower limit of quantification was generally 6 mU/ml. This research assay was developed at Amgen Inc. and validated and performed by MDS Pharma Services.

2.5. Study endpoints

The primary efficacy endpoint was change in haemoglobin concentration after 6 weeks of therapy (study week 7). Secondary efficacy endpoints included the proportion of patients who had a ⩾1.0 g/dl increase in haemoglobin concentration by week 7, time to ⩾1.0 g/dl increase in haemoglobin concentration, change in haemoglobin concentration over treatment, haematopoietic response (increase in haemoglobin concentration of ⩾2.0 g/dl over baseline or haemoglobin concentration ⩾12.0 g/dl without RBC transfusions during the preceding 28 d), time to haematopoietic response, and transfusion requirements (week 5 through end of treatment phase (EOTP) and week 1 through EOTP).

Standard non-compartmental pharmacokinetic parameters were estimated for darbepoetin alfa in the pharmacokinetic subset, including peak serum concentration (C_{max}), time of peak serum concentration (T_{max}), area under the serum concentration–time curve from time 0 to infinity (area under the curve, AUC) ($AUC_{(0-\infty)}$), terminal half-life ($t_{1/2,z}$), mean residence time to infinity ($MRT_{(0-\infty)}$), and relative clearance (CL/F). Serum eEPO concentrations were summarised relative to baseline for the same subset of patients.

Safety was assessed by incidence and severity of adverse events by treatment group. Events were categorised and graded according to the World Health Organization system. Another safety endpoint was the proportion of patients in whom anti-darbepoetin alfa antibodies were detected.

2.6. Statistical analysis

The planned sample size was 80 patients randomised 1:1 to 1 of the 2 treatment groups. This sample size was chosen to achieve a minimum of 30 evaluable patients in each treatment group at week 7 of treatment. The standard deviation (SD) of change from baseline

haemoglobin measurement was assumed to be approximately 1.4 g/dl. The study had approximately 90% power using a one-sided t-test ($\alpha = 0.05$) to detect a difference between treatment groups, assuming the true difference was $\geqslant 1.0$ g/dl. Since this was the first clinical investigation that evaluated the superiority of one dosing schedule over another (i.e., asynchronous dosing over more standard synchronous dosing of darbepoetin alfa), a one-sided t-test was appropriate.

Analyses of all endpoints except transfusions from week 5 to EOTP were conducted on patients who received at least 1 dose of darbepoetin alfa (primary analysis data-set). To handle missing haemoglobin values, both the available data and the last value carried forward (LVCF) approaches were used. Available data analyses included only values at a specified period not within 28 d of an RBC transfusion; missing values were excluded. The LVCF approach imputed missing haemoglobin values or values within 28 d of a transfusion using the last available value (last value carried forward) that was not within 28 d of RBC transfusion. This LCVF approach accounted for all patients randomly assigned to treatment who received study drug and reduced chances of selection bias inherent in a methodology that often excludes more anaemic patients from mean haemoglobin calculation at any given point. Samples drawn outside a 10% window from protocol-specific sampling times were excluded from all summary statistics but not from individual analyses.

The incidence of transfusions was analysed for the subset of patients who received at least 1 dose of darbepoetin alfa and remained in the study after 4 weeks. Previous studies evaluating transfusion requirements have suggested that treatment effects are not expected until after 4 weeks of erythropoietic treatment [34]. The Kaplan–Meier estimate was calculated for the proportion of patients with a haematopoietic response and the proportion transfused from week 5 to EOTP. Approximate 95% confidence intervals (95% CI) for Kaplan–Meier estimates of proportions were calculated using Greenwood's estimate of the variance [35].

To determine the association of asynchronous/synchronous darbepoetin alfa administration and greater haemoglobin increase at week 7, a one-sided Wilcoxon procedure [36] was used stratified by baseline haemoglobin concentration (<10.0 *versus* $\geqslant 10.0$ g/dl) and by study centre. Point estimates (95% CI) of mean change for each schedule and point estimate (with a one-sided 95% CI) for difference in means were presented for both analyses.

Pharmacokinetic analyses of darbepoetin alfa were conducted on data generated by ELISA. Concentrations less than the limit of quantification were given a value of zero. To account for the baseline eEPO that cross-reacts in the assay, baseline-corrected values for each patient were calculated by subtracting the measured pre-study eEPO concentration on day 1, as assessed in the darbepoetin alfa assay, from all subsequent values for that patient. No correction was necessary when the pre-dose value was less than the limit of quantification of the assay. When baseline correction resulted in a negative value, it was converted to zero. This correction does not account for fluctuations in eEPO throughout the course of the study, but eliminates 1 confounding variable.

Pharmacokinetic parameters after a single subcutaneous dose of darbepoetin alfa were estimated by standard non-compartmental methods using WinNonlin Professional Version 1.5 (Pharsight Corp., Mountain View, CA, USA). Data points were included in the regression if they were the last 3 (or more) non-increasing concentrations, and if these concentrations were greater than twice the limit of quantification. This method was used to prevent over-interpretation of data in the region where relative contribution of eEPO was greatest. Actual sampling times and doses were used for estimation of all parameters. For eEPO data, measured concentrations were summarised.

3. Results

3.1. Patient demographics and baseline characteristics

Eighty-four patients were enrolled (Fig. 1). Three patients (all assigned to synchronous dosing) did not receive study drug; thus, 81 were included in the primary analysis set. A total of 74 patients (41 asynchronous, 33 synchronous) completed 6 weeks of study (time of the primary endpoint). The median duration of therapy was 10 weeks. Baseline demographics were well balanced between treatment groups, with slight differences in the proportion of patients with breast and gynaecologic malignancies observed (Table 1). Mean baseline haemoglobin concentration was slightly lower in the asynchronous (10.0 g/dl) than the synchronous group (10.5 g/dl); however, the baseline value of the asynchronous group was taken mid-cycle (7 d before the next chemotherapy administration) rather than immediately before the start of the next cycle as in the synchronous group. This difference may be the result of the impact of chemotherapy.

3.2. Efficacy

Mean increases in haemoglobin concentration after 6 weeks were similar between groups (1.0 g/dl (95% CI 0.6–1.3) asynchronous, 1.0 g/dl (95% CI 0.6–1.5) synchronous) with a P-value of 0.45 (Table 2). Over the treatment period, no major differences were observed in either the magnitude or rate of haemoglobin change (Fig. 2). However, an impact of each chemotherapy cycle on haemoglobin concentration was clearly seen in

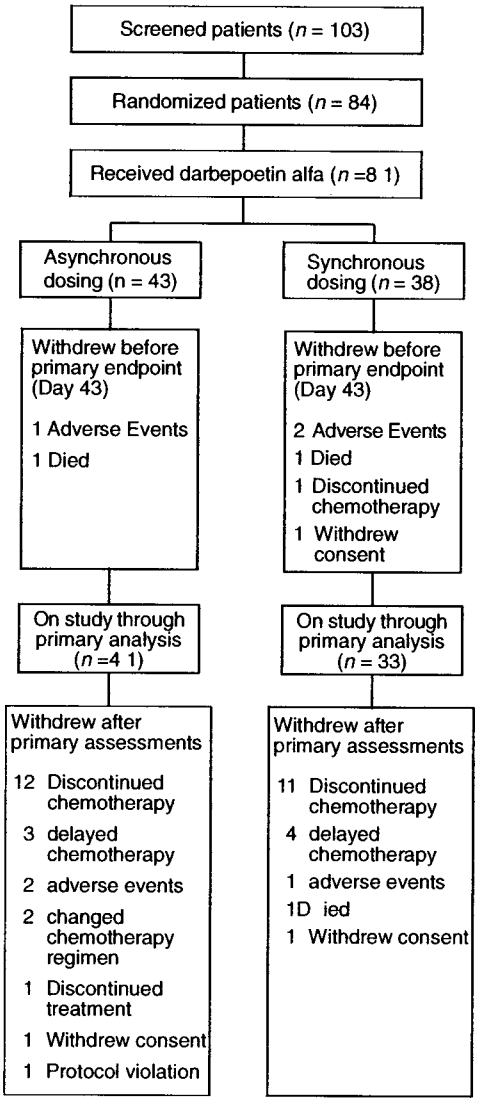

Fig. 1. Patient disposition. CONSORT diagram.

both groups throughout treatment, with a slight decline or stabilisation during the week immediately after chemotherapy administration followed by an increase over the remainder of the chemotherapy cycle length.

Table 1
Baseline demographic and clinical characteristics

Characteristics	All patients[a]	
	Asynchronous	Synchronous
Number of patients	43	38
Sex, *n* (%)		
Women	32 (74%)	28 (74%)
Men	11 (26%)	10 (26%)
Age (years)		
Mean (SD)	61.4 (13.9)	62.2 (13.8)
Primary tumour type, *n* (%)		
Breast	20 (47%)	12 (32%)
Gastrointestinal	2 (5%)	3 (8%)
Genitourinary	4 (9%)	4 (11%)
Gynaecological	4 (9%)	9 (24%)
Lung	3 (7%)	5 (13%)
Other	10 (23%)	5 (13%)
Chemotherapy		
Platinum-containing	12 (28%)	14 (37%)
ECOG performance status, *n* (%)		
0	16 (37%)	13 (34%)
1	24 (56%)	24 (63%)
2	3 (7%)	1 (3%)
Baseline haemoglobin (g/dl)		
Mean (SD)	10.03 (1.15)	10.47 (0.97)
Serum endogenous EPO (mU/ml)		
n	41	38
Median	33.58	25.38
Ferritin (μg/l)		
n	41	38
Median	242.60	202.85
Range (min, max)	19.6, 2976.0	25.4, 1659.0
Transferrin saturation (%)		
n	40	37
Median	23.00	23.00
Range (min, max)	8.0, 60.0	5.0, 57.0

ECOG, Eastern Cooperative Oncology Group.
[a] All patients who were administered at least 1 dose of darbepoetin alfa.

No significant between-group differences were observed in any secondary haematological and clinical efficacy endpoints (Table 2, Fig. 3). The haematological response rates for both groups (69% asynchronous, 81% synchronous) compare favourably to rates reported with standard, more frequently administered erythropoietic therapy [8,11,12].

Table 2
Summary haemoglobin results for each dose group and both groups combined (overall)

	Asynchronous	Synchronous	Overall
Mean (95% confidence (CI)) change in haemoglobin after 6 weeks of treatment (week 7) (g/dl)	1.0. (0.6–1.3)	1.0 (0.6–1.5)	1.0 (0.7–1.3)
[a]K–M proportion (95% CI) of patients with ⩾1 g/dl increase in haemoglobin after 6 weeks of treatment	68% (54–83)	64% (48–80)	66% (56–77)
K–M proportion (95% CI) of haematopoietic response	69% (52–86)	81% (61–100)	74% (61–87)
K–M median (95% CI) time to haematopoietic response (d)	50 (36–92)	43 (36–92)	49 (36–58)
K–M proportion (95% CI) of transfusions (week 5 to EOTP)	19% (6–33)	18% (5–31)	19% (9–28)
K–M proportion (95% CI) of transfusions (week 1 to EOTP)	33% (18–48)	22% (9–36)	28% (18–39)

[a] Kaplan–Meier proportion.

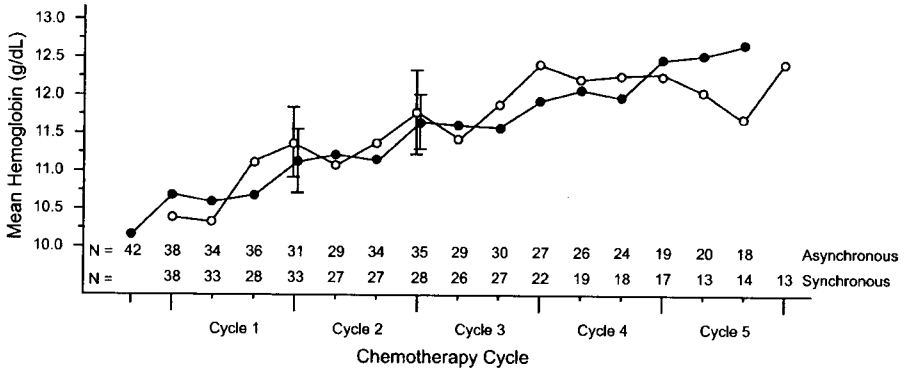

Fig. 2. Mean haemoglobin over time by chemotherapy cycle (available data analysis). Filled circles = asynchronous administration; empty circles = synchronous administration. Error bars represent 95% confidence intervals with point estimates shown for end of chemotherapy cycle 1 and 2 for each dose schedule (asynchronous and synchronous).

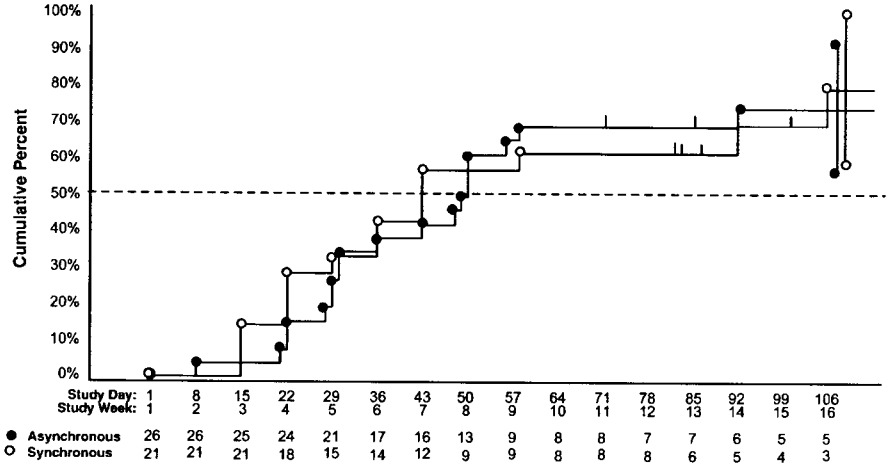

Fig. 3. Haematopoietic response from baseline through the end of study (Kaplan–Meier proportions). Filled circles = asynchronous administration; empty circles = synchronous administration.

3.3. Pharmacokinetic evaluations

Thirty-three patients were in the pharmacokinetic subset, of which 25 patients (12 asynchronous, 13 synchronous) had evaluable profiles after the first dose. Eight patients contributed only to the weekly sampling and 1 was excluded because of high baseline serum eEPO concentration. Demographic and baseline characteristics were generally balanced between groups, with a few exceptions. In the asynchronous group, there were more men than women (7 (44%) asynchronous; 5 (29%) synchronous). The median baseline eEPO levels were 25.2 mU/ml for the asynchronous group and 31.6 g/dl for the synchronous group.

Endogenous EPO concentrations before and during chemotherapy were estimated for the pharmacokinetic subset. The mean (SD) baseline eEPO concentration for asynchronous patients was 81.2 (235) and 34.0 (29.6) mU/ml for synchronous patients. One asynchronous patient, however, had a high baseline eEPO concentration of 1523 mU/ml. This patient also had a severely low baseline haemoglobin level (<6 g/dl), which may have influenced the baseline eEPO value. After exclusion of this patient from the analysis, mean (SD) baseline eEPO concentration for the asynchronous group was 45.2 (47.6) mU/ml.

Increase in eEPO concentrations was observed in the week after chemotherapy administration. Peak concentration was observed 48 h after chemotherapy administration in both groups. In the synchronous group, mean eEPO concentrations were elevated approximately 5-fold over baseline. The individual ratio of 48-h value to baseline ranged from 2 to 32, with mean and median ratios for the group of 8.6 and 6.4, respectively. The eEPO of most patients in the synchronous returned to near baseline values by the 168-h point (end of week 1). In the asynchronous group, eEPO concentrations over the week before chemotherapy administration were relatively constant. In the synchronous group, mean eEPO concentrations rose to a peak value 48 h after chemotherapy (i.e., day 9) with a 4-fold increase in mean eEPO concentration compared with the pre-chemotherapy value. The

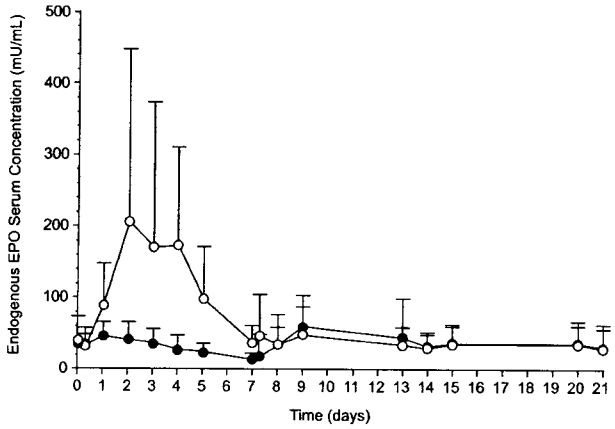

Fig. 4. Mean endogenous erythropoietin (eEPO) concentrations during the first 3 weeks of study for the asynchronous (7–17 patients) and synchronous groups (8–15 patients). Filled circles = asynchronous administration; empty circles = synchronous administration. Error bars represent standard deviations.

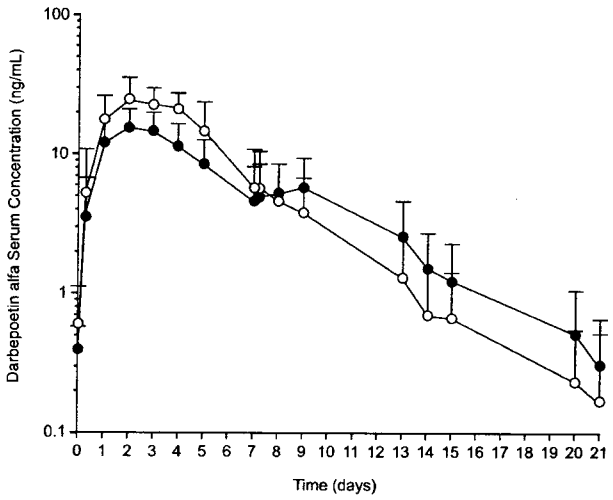

Fig. 5. Mean darbepoetin alfa concentrations after a subcutaneous dose of 6.75 μg/kg during the first 3 weeks of study for the asynchronous (10–13 patients) and synchronous (10–13 patients) groups. Filled circles = asynchronous administration; empty circles = synchronous administration. Error bars represent standard deviations.

individual ratio of 48-h post-chemotherapy to baseline value ranged from 1 to 4, with mean and median ratios for the asynchronous group of 2.6 and 2.8, respectively (see Fig. 4).

Same-day dosing of darbepoetin alfa and chemotherapy was associated with an increase in maximal concentration (1.7-fold increase in mean C_{max}), and area under the serum concentration–time curve (1.3-fold increase in mean $AUC_{(0-\infty)}$) compared with asynchronous dosing (Table 3, Fig. 5). After peak concentration, serum darbepoetin alfa concentrations declined in the expected monophasic manner for patients in the synchronous group. However, for the asynchronous group, the decline in mean serum concentration was interrupted after chemotherapy administration (i.e., 7 d after darbepoetin alfa administration) for 3 d, then declined at a rate similar to that observed in the synchronous group (Table 3).

3.4. Safety

The types of adverse events reported were consistent with those observed in clinical trials of darbepoetin alfa [7,29] and were generally associated with malignant disease and toxic effects of chemotherapy. The safety profile of darbepoetin alfa was similar between groups. Two patients (2%) had thrombotic adverse events: one had pulmonary embolism with disease progression, including spinal cord compression and the other had subclinical left-arm deep-vein thrombosis (DVT). The second patient also had an excess rate of rise in haemoglobin within ±14 d of the thrombotic event; however, this patient also received a transfusion within these 14 d (haemoglobin = 8.2 g/dl before receiving the transfusion). The DVT event occurred 9 d after the transfusion. The rapid rise in haemoglobin reached a maximum level of 10.9 g/dl during these 14 d. Despite the investigator's initial possible association of the rapid rate of haemoglobin rise with darbepoetin alfa, this haemoglobin rise was associated with the transfusion.

No evidence of anti-darbepoetin alfa antibodies was detected in any patient.

4. Discussion

In clinical practice, erythropoietic agents and chemotherapy have been administered synchronously when-

Table 3
Summary pharmacokinetic parameters after a single subcutaneous dose of darbepoetin alfa

Parameter	Asynchronous	Synchronous	Overall
	Mean (SD) (min, max)	Mean (SD) (min, max)	Mean (SD) (min, max)
C_{max} (ng/ml)	15.5 (5.25) (7.39, 26.1)	26.5 (9.67) (9.76, 47.3)	21.2 (9.52 (7.39, 47.3)
T_{max} (h)	59.8 (16.6) (27.5, 85)	70.5 (25.3) (47.1, 120)	65.4 (21.9) (27.5, 120)
$AUC_{(0-\infty)}$(ng h/ml)	2570 (1110) (955, 5070)	3280 (1280) (1090, 6080)	2940 (1230) (955, 6080)
$t_{1/2,z}$ (h)	87.7 (26.0) (58.3, 144)	60.9 (22.3) (23.5, 111)	73.7 (27.3) (23.5, 144)
$MRT_{(0-\infty)}$ (h)	159 (38.1) (118, 247)	111 (23.0) (81.1, 155)	134 (39.3) (81.1, 247)
CL/F (ml/h/kg)	3.18 (1.59) (1.34, 7.14)	2.45 (1.29) (1.11, 6.24)	2.80 (1.46) (1.11, 7.14)

AUC, area under the curve; MRT, mean residence time; CL/F, relative clearance.

ever possible, but without a clear understanding of the underlying biology or guidance from randomised trials addressing the issue. The assumption is that the practice is safe and as effective as asynchronous administration. As longer-acting erythropoietic agents are developed, moving treatment toward less-frequent administration, studies elucidating the potentially complex interaction of chemotherapy and erythropoiesis have become increasingly important. This randomised trial provided several important and relevant insights.

The results from this trial did not provide sufficient evidence to suggest that asynchronous dosing was superior to synchronous dosing when administering darbepoetin alfa every-3-weeks. The two schedules of darbepoetin alfa had similar haematological efficacy and safety profiles, despite some differences in the pharmacokinetic and pharmacodynamic profiles between the two schedules. In the synchronous group, either the increased drug exposure was of insufficient magnitude to produce a detectable difference in efficacy or the target organ, the marrow, did not remain fully responsive during the immediate post-chemotherapy period. Notably, after each dose of myelosuppressive chemotherapy, the rate of haemoglobin rise was consistently and repeatedly impacted in both groups for approximately 1 week, a time frame similar to that observed for the post-chemotherapy increases in eEPO levels.

The pharmacokinetic and pharmacodynamic (PK/PD) findings provide insight into the mechanism of clearance of eEPO and darbepoetin alfa. The increase in eEPO concentrations in both groups occurring as soon as 6 h after chemotherapy and lasting approximately 1 week afterwards suggest that the clearance of eEPO was impaired by chemotherapy rather than that the production of eEPO was increased. Previous studies have shown that eEPO serum concentrations associated with chemotherapy increased up to 7-fold [37–39]. Similarly, chemotherapy may be associated with interruption of clearance of darbepoetin alfa, as a larger AUC for this agent with synchronous administration relative to that of asynchronous administration was observed. One might predict that from this increased drug exposure, the pharmacodynamics (haematopoietic efficacy) of darbepoetin alfa may be enhanced by synchronous dosing, especially if the bone marrow remained responsive to this agent during the immediate post-chemotherapy period.

One possible explanation for our PK/PD findings is that chemotherapy alters the volume of distribution of all erythropoietins and/or the activity of ASGR- based, non-receptor-mediated clearance. However, we believe that the hypothesis that best fits the totality of our data is that the receptor-bearing cells in the bone marrow contribute to the clearance of both eEPO and darbepoetin alfa through binding, internalisation and catabolism of these hormones. This would explain the apparent temporal association of the elevated eEPO levels and relative marrow unresponsiveness observed in our patients, both lasting approximately 1 week. A study in sheep administered busulfan and rHuEPO verified that the clearance, and not the volume of distribution, was significantly decreased by chemotherapy [39]. *In vitro* work has supported the model that rHuEPO is internalised and degraded by target cells [21], and it has been postulated that saturable uptake by bone marrow is mediated by the EPO receptor [40,41]. Reduced clearance of rHuEPO has been reported in patients with myelodysplastic syndromes, who have reduced bone marrow activity [42]. Finally, this hypothesis is consistent with the observed inverse relationship between receptor affinity and serum half-life as well as *in vivo* potency of different erythropoietic proteins.

A few differences in baseline characteristics between the asynchronous and synchronous groups were noted, which based on recent clinical findings may suggest a better prognosis for response for one group over the other. A large study of approximately 1500 patients by Vadhan-Raj *et al.* [43] analysed potential covariates of response. Tumour type (breast and colorectal cancer), non-platinum-containing therapy, and lower baseline haemoglobin levels were identified as important independent variables that conferred better transfusion-based and haematological responses. In our study, baseline characteristics favoured the asynchronous group for better prognosis for response *versus* the synchronous group (breast cancer: 47% *versus* 32%, respectively; platinum-containing chemotherapy: 28% *versus* 37%, respectively; baseline haemoglobin levels: 10.0 *versus* 10.5 g/dl, respectively). However, despite a possible bias in favour of the asynchronous group, no clinically relevant difference in haematological response was observed between the groups. Thus, we feel that our data do not suggest a benefit of asynchronous dosing over synchronous dosing.

We note a few limitations to our study. First, we did not carry out formal drug disposition studies to confirm our suspicion that chemotherapy changes the clearance as opposed to the distribution of darbepoetin alfa, and we did not obtain repeated blood and/or marrow samples for progenitor cell studies to further explore our hypothesis that the responsiveness of the marrow is impaired in the immediate post-chemotherapy period. Therefore, the mechanisms by which chemotherapy impacts on serum eEPO concentrations, darbepoetin alfa pharmacokinetics and haematopoietic responsiveness have not been fully elucidated. Future studies to elucidate the exact role of the bone marrow in the mechanism of erythropoietin clearance need to be conducted using repeated blood and/or marrow samples. Also, the effects of different chemotherapeutic regimens that may influence the pharmacokinetic and pharmacodynamic properties of darbepoetin alfa were not studied and need to be addressed in future studies.

Another important limitation is that the measured drug concentrations were actually a composite of endogenous EPO and darbepoetin alfa because the assay recognises both proteins, albeit differentially. The reported darbepoetin alfa concentrations have been corrected individually for the baseline eEPO concentrations, as measured by cross-reactivity in the darbepoetin alfa assay; standard methodology for recombinant proteins [44]. Corrections were not made for the fluctuations in endogenous erythropoietin levels resulting from chemotherapy because direct subtraction of one from another is not feasible when different assays, with different affinities for the ligand, are used. However, as endogenous erythropoietin contributes no more than approximately 15% to the overall signal up to 216 h after administration of darbepoetin alfa, these fluctuations are insufficient to alter the overall pharmacokinetic conclusions of the study.

Our findings support the hypothesis that the bone marrow is an effector site and clearance site for erythropoietins. With synchronous administration of darbepoetin alfa, transient decreased marrow responsiveness is precisely offset by the observed increased concentration and AUC associated with synchronous administration. The net result is a nearly identical overall erythropoietic benefit between the two dosing schedules. This hypothesis provides a mechanism explaining the observed lack of decrease in efficacy with synchronous every-3-week darbepoetin alfa administration. Therefore, since no advantage appears to be gained with asynchronous dosing as initially expected, synchronous dosing with every-3-week darbepoetin alfa is preferable and offers greater convenience to the patients.

We conclude the following: myelosuppressive chemotherapy is associated with a rapid increase in the concentration of eEPO, probably due to decreased clearance by progenitor cells in the bone marrow. Maximal concentrations and AUC of darbepoetin alfa are increased by synchronous compared with asynchronous chemotherapy administration, again probably due to decreased clearance. Erythropoiesis is compromised during the days after chemotherapy, offsetting the pharmacokinetic advantages of synchronous dosing. Therefore, darbepoetin alfa administered every 3 weeks has similar effectiveness whether given synchronously or asynchronously with chemotherapy, and is highly effective in producing haematopoietic responses that are indistinguishable from those observed with more frequent dosing.

Conflict of interest statement

Russell Berg, Matt Austin and Greg Rossi are employees of Amgen Inc.

None declared for John Glaspy, David Henry, Ravi Patel, Simon Tchekmedyian, Steve Applebaum, Donald Berdeaux and Richard Lloyd.

Acknowledgements

Anne C. Heatherington, PhD, conducted the pharmacokinetic and pharmacodynamic studies. Sameer Doshi and Jose Rodriguez assisted with the analysis of the pharmacokinetics data. Catherine Allen, BS, assisted with managing the study. Christopher Davidson, BS; and MaryAnn Foote, PhD, assisted with the writing of the manuscript.

This study was supported financially by Amgen Inc. Thousand Oaks, CA, USA.

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VOLUME 24 · NUMBER 15 · MAY 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Comparison of Every-2-Week Darbepoetin Alfa and Weekly Epoetin Alfa for the Treatment of Chemotherapy-Induced Anemia: The 20030125 Study Group Trial

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Submitted August 29, 2005; accepted January 25, 2006.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/06/2415-2290/$20.00

DOI: 10.1200/JCO.2005.03.8570

ABSTRACT

Purpose
Chemotherapy-induced anemia is widely treated in the United States with darbepoetin alfa (DA) or epoetin alfa (EA). This noninferiority study systematically compares efficacy and safety of DA and EA using common doses and schedules used in clinical practice.

Methods
Patients had a diagnosis of nonmyeloid malignancy with ≥ 8 weeks of planned chemotherapy, age ≥ 18 years, and anemia (hemoglobin ≤ 11 g/dL). Patients were randomly assigned 1:1 to DA 200 μg every two weeks (Q2W) or EA 40,000 units every week (QW) for up to 16 weeks with identical dose adjustment rules. Efficacy was assessed by the incidence of RBC transfusion (Kaplan-Meier estimate). The definition of noninferiority was that the upper 95% CI limit of the observed difference in RBC transfusions between groups was less than 11.5%; this noninferiority margin was based on the treatment effect observed in placebo-controlled EA studies.

Results
Of 1,220 patients randomly assigned, 1,209 received ≥ one dose of the study drug. Common tumor types were lung (26%), breast (21%), and gastrointestinal (18%). Transfusion incidence from week 5 to the end of the treatment phase (the primary end point) was 21% in the DA group and 16% in the EA group; noninferiority was concluded because the upper 95% CI limit of the difference between groups (10.8%) was below the prespecified noninferiority margin. Sensitivity analyses using alternate statistical methods and analysis sets yielded similar results. Hemoglobin, quality of life, and safety end points further support equivalency of the erythropoietic therapies.

Conclusion
This large, phase III study demonstrates comparable efficacy of DA Q2W and EA QW. Less frequent dosing offers potential benefits for patients, caregivers and health care providers.

J Clin Oncol 24:2290-2297. © 2006 by American Society of Clinical Oncology

INTRODUCTION

Anemia is common in patients receiving multicycle chemotherapy and may adversely affect health-related quality of life (HRQOL).[1-3] Chemotherapy-induced anemia is commonly treated using the erythropoiesis-stimulating agents, darbepoetin alfa (DA; Aranesp; Amgen Inc, Thousand Oaks, CA) and epoetin alfa (EA; Procrit; Amgen, Inc), both proven to achieve significant reductions in RBC transfusion requirements and clinically relevant improvements in fatigue and other patient-reported outcomes.[4-12]

For the treatment of chemotherapy-induced anemia, the most common initial dosage is 200 μg every 2 weeks (Q2W) for DA and 40,000 units (U) every week (QW) for EA.[13,14] At these dosages, the two agents have similar clinical effectiveness based on results from randomized, controlled trials,[15-17] community-based studies,[8,18] and large observational studies of clinical practice.[13,14,19,20] Nonetheless, there was a clear demand for a formal, sufficiently powered, noninferiority study to allow for the rigorous comparison of these two therapies with respect to clinical outcomes. Questions regarding the comparability of clinical outcomes of these two agents and appropriate reimbursement have been raised by the US Centers for Medicare & Medicaid Services and the National Cancer Institute (Bethesda, MD), further emphasizing the importance of definitive data to define healthcare policy regarding

erythropoietic agents (OPPS [Outpatient Prospective Payment System] rule 2003; NCI RFQ 72743).

The large, phase III study reported here was designed to formally evaluate noninferiority of 200 μg Q2W DA with 40,000 U QW EA in cancer patients with anemia receiving multicycle chemotherapy. The primary hypothesis tested was that the incidence of RBC transfusion from week 5 to the end of treatment phase (EOTP) in patients receiving Q2W DA is comparable (defined as not inferior) with that of patients receiving QW EA. This is the standard transfusion end point used for the registration of erythropoietic therapies in oncology.[4,6,21-23] Secondary objectives included comparison of HRQOL and hemoglobin surrogate end points, as well as the evaluation of safety.

METHODS

Study Design

This was a randomized, open-label, active-controlled, multicenter study of DA at a starting dose of 200 μg Q2W administered over a 16-week period for the treatment of anemia in patients with nonmyeloid malignancies receiving multicycle chemotherapy. The active control arm received EA at a starting dose of 40,000 U QW. For both treatment arms, a 50% dose escalation was permitted at week 5 if the hemoglobin increase was < 1 g/dL. Study drug was withheld if a patient's hemoglobin concentration exceeded 13 g/dL at any time, and was reinstated at 75% of the previously administered dose after the hemoglobin concentration decreased to ≤ 12 g/dL. After the 16-week treatment period, patients were monitored for 2 weeks for adverse events, concomitant medications, and transfusions received.

The initial planned treatment period was 12 weeks. After the first 680 patients were randomly assigned, the study protocol was amended to be more representative of current clinical practice. The treatment period was extended from 12 weeks to 16 weeks, and the dose escalation rules were changed from a mandatory requirement to physician discretion. The sample size was increased to 1,200 patients, ensuring that the distribution of patients accrued under the original and amended protocols were similar. At the time of the amendment, patients who had already enrolled in the study reconsented and were treated under the amended protocol. Patients included in the amended protocol are referred to as the 16-week cohort and comprise a homogenous patient population with respect to dose escalation criteria and duration of therapy.

Random Assignment

Eligible patients were randomly assigned 1:1 to either DA or EA. Randomized treatment was assigned using a central interactive voice response system. Randomization was stratified by screening hemoglobin concentration (obtained within 24 hours before randomization from a local laboratory; < 10 *v* ≥ 10 g/dL) and planned chemotherapy (platinum-based *v* nonplatinum-based) based on studies showing that platinum-containing regimens[22] and baseline hemoglobin concentration[8] are important independent determinants of anemia development and RBC transfusion requirements.

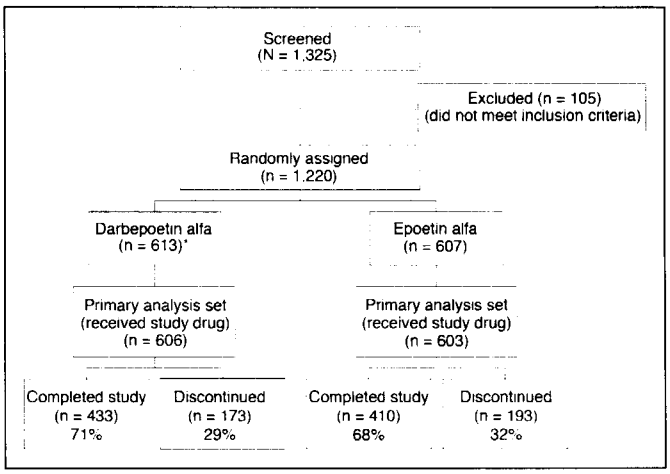

Fig 1. CONSORT diagram of patient disposition. The flow of patients screened and enrolled is shown in accordance to the CONSORT statement for reporting clinical trials.

Eligibility Criteria

Key eligibility criteria included: ≥ 18 years old; diagnosis of anemia (hemoglobin ≤ 11 g/dL) and a nonmyeloid malignancy with ≥ 8 additional weeks of planned chemotherapy; adequate renal and liver function; and the ability to provide written informed consent. Key reasons for exclusion included: history of primary hematologic disorders causing anemia other than nonmyeloid malignancy; unstable/uncontrolled cardiac conditions; clinically significant inflammatory disease; neutralizing antibodies to recombinant human erythropoietin; and EA or DA therapy within 4 weeks before randomization.

Efficacy Evaluations

The primary end point was the incidence of RBC transfusion from week 5 to the EOTP. The primary end point was analyzed for all randomly assigned patients who remained on study through day 29 (defined as the primary transfusion analysis set). A key secondary end point was transfusion requirements over the entire treatment period (week 1 to EOTP). Transfusion was recommended if a patient's hemoglobin concentration decreased to ≤ 8 g/dL. Transfusions with hemoglobin greater than 8 g/dL were allowed provided there were signs or symptoms of anemia.

Efficacy was assessed using secondary hemoglobin-based end points, including the proportion of patients achieving a hemoglobin ≥ 11 g/dL, and those who subsequently maintained hemoglobin concentration in the target range (11 g/dL to 13 g/dL) consistent with three well-recognized, evidence-based, practice guidelines.[24-26] Mean hemoglobin change from baseline was compared between groups at study midpoint (week 9) and EOTP.

HRQOL changes were compared using standard instruments (Functional Assessment of Cancer Therapy-Fatigue [FACT-Fatigue],

Table 1. Data Sets Used in This Study From All Randomly Assigned Patients

Data Set	No. of Patients	
	Darbepoetin Alfa	Epoetin Alfa
Primary analysis set (patients randomly assigned and treated)	606	603
16-week cohort	396	402
Per-protocol analysis set	441	441
Primary transfusion analysis set (patients randomly assigned, treated, and on-study as of study day 29)	582	571
16-week cohort	380	385
Per-protocol analysis set	422	422
Safety analysis set	611	598

FACT-Anemia, Energy, Daily Activity, Overall Health, and Patient Satisfaction Questionnaire for Anemia Treatment questionnaires)[27] administered to patients at baseline, weeks 5, 9, and 17.

Safety Evaluation

Safety end points included incidence, frequency, severity, relationship to treatment, and outcome of all reported adverse events and incidence of neutralizing antibody formation to erythropoietic agents. A central laboratory provided antibody testing and measurement of endogenous erythropoietin. Because this was a trial comparing two active therapies, long-term survival and tumor progression data were not collected.

Statistical Considerations

This study was designed to test the hypothesis that DA 200 μg Q2W is comparable (ie, noninferior) to EA 40,000 U QW as starting doses. This design requires that a noninferiority margin is prespecified to assess the primary end point. The noninferiority margin in this study was 11.5% based on the combined estimate of treatment effect as reported in large, placebo-controlled EA trials.[4,21,22,28] The difference in transfusion rates between EA and placebo was 20% with a lower 95% CI limit of 11.54%. This estimate was adjusted for studies where only platinum-based chemotherapy was administered,[22] using a weight of 40% that corresponds to the percentage of patients who received platinum-based chemotherapy in large, community-based studies of EA.[5,9,10] If the upper 95% CI limit of the difference in transfusion rates between groups is less than the noninferiority margin, then DA is considered noninferior to EA (ie, the null hypothesis that the difference is ≥ 11.5% is rejected in favor of the alternative hypothesis that DA is noninferior to EA).

The sample size specified in the original protocol had approximately 90% power to conclude noninferiority. Power calculations were based on unstratified analysis and confirmed using a Bayesian two-stage resampling technique applied to data from previous studies; with 1,200 patients, there is approximately 99% power to conclude noninferiority.

It is critical that results from noninferiority studies are shown to be robust with respect to the method of analysis used or analysis set (population effect). Accordingly, preplanned sensitivity analyses were performed with respect to transfusion end points. The population effect was examined using different patient cohorts; the 16-week cohort and a predefined per-protocol analysis set. The per-protocol subset comprised randomly assigned patients who received ≥ 75% and < 125% of planned dose during treatment period and received ≤ 30 Gy radiotherapy to the pelvis during treatment. The impact of analytic methods was examined using unadjusted and adjusted estimates from the Kaplan-Meier approach employed for the primary analysis, as well as crude proportions. Adjusted Kaplan-Meier estimates represent the weighted averages of the Kaplan-Meier estimate obtained for each randomization strata. The Cochran-Mantel-Haenszel approach was used to calculate differences in these weighted (adjusted) Kaplan-Meier estimates. Sensitivity analyses were carried out with adjustment based on actual type of chemotherapy received.

Statistical analyses were performed by the sponsor using SAS statistical software version 8.2 (SAS Institute, Cary, NC); study investigators reviewed these results. Descriptive statistics included frequencies and means (with 95% CIs or standard deviation [SD]) for categoric and continuous variables, respectively. Changes in hemoglobin levels, total number of RBC units, total number of days transfused, and patient-reported outcomes for each patient were analyzed using the analysis of covariance (ANCOVA) model, which included the stratification factors. Analysis of patient-reported outcomes was also adjusted for the baseline score (as a continuous or dichotomous variable). Two analytic approaches were used to account for missing hemoglobin data: imputation (last-value-carried forward) and available data. Hemoglobin values within 28 days after a transfusion were considered to be missing; using the last-value-carried forward method, the pretransfusion hemoglobin value was used to impute all weekly hemoglobin values during the 28 days following a transfusion. Change in hemoglobin was evaluated using both methods; achieving target hemoglobin was calculated only using the last-value-carried forward method. Hemoglobin end points were adjusted by the same stratification factors as the transfusion end points.

Adverse events were defined using the Medical Dictionary for Regulatory Activities (MedDRA MSSO, Reston, VA) terms. The number and percentage of patients reporting adverse events (all, serious, related, and serious related) were tabulated by the actual treatment received (safety analysis set).

Table 2. Patient Demographics and Baseline Disease Characteristics

Characteristic	Darbepoetin Alfa (n = 606) No.	%	Epoetin Alfa (n = 603) No.	%
Sex				
Female	415	68	381	63
Race				
White	506	83	502	83
Black	59	10	64	11
Other*	41	7	37	6
Age, years				
Mean	63.2		63.7	
SD	12.4		11.6	
Geriatric age group, years				
≥ 65	305	50	290	48
≥ 75	129	21	118	20
Primary tumor type				
Breast	131	22	126	21
Gastrointestinal	104	17	108	18
Gynecologic	60	10	41	7
Lung	156	26	164	27
Lymphoproliferative	45	7	46	8
Other	110	18	118	20
Disease stage				
I/II	86	14	94	16
III	131	22	123	20
IV	334	55	325	54
Other†	32	5	46	8
Unknown	23	4	15	2
ECOG				
0 to 1	518	85	509	84
> 1	83	14	84	14
Unknown	5	1	10	2
Baseline hemoglobin, g/dL				
Mean	10.2		10.2	
SD	0.9		0.9	
Hemoglobin categories				
< 10 g/dL	222	37	209	35
≥ 10 g/dL	384	63	394	65
Transferrin saturation, percent	564		560	
Mean	31.6		31.1	
SD	22.8		22.6	
Ferritin, μg/L	583		583	
Mean	473.0		488.5	
SD	430.0		445.5	

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Other racial categories included (darbepoetin alfa *v* epoetin alfa): Hispanic (5% *v* 3%), Asian (1% *v* 2%), Native American (0% *v* < 1%), Japanese (< 1% both groups), Pacific Islander (< 1% both groups), and unspecified other (< 1% both groups).
†Other disease stage classification refers to tumor types that did not routinely utilize TMN classification for disease staging (eg, small-cell lung cancer).

RESULTS

Patient Characteristics

A total of 177 US centers enrolled 1,220 patients (Table 1). All patients were randomly assigned and 1,209 received ≥ one dose of

study drug (primary analysis set; Fig 1). During the final analysis, one patient was identified who was randomly assigned to receive DA but who received only EA (eight doses). Efficacy analyses were performed as planned using an intent-to-treat approach, for example, analyzing this patient as randomized (ie, in the DA group), rather than as treated. Patient demographic and baseline disease characteristics are summarized in Table 2.

Efficacy Evaluations

RBC transfusions. The adjusted Kaplan-Meier percentages of patients who received an RBC transfusion between week 5 and EOTP were 21% (95% CI, 17% to 24%) for the DA 200 μg Q2W group and 16% (95% CI, 12% to 19%) for the EA 40,000 U QW group. These are KM estimates adjusted for stratification factors; crude rates are suboptimal in the study of erythropoietic agents because they cannot account for response to therapy and time at risk when patients discontinue early. Noninferiority was demonstrated because the upper limit of the 95% CI of the difference between groups (10.8%) was below the prespecified noninferiority margin of 11.5%. When the first 4 weeks were included in the analysis, the proportions of patients receiving ≥ one transfusion were 27% (95% CI, 24% to 31%) for the DA group and 22% (95% CI, 19% to 26%) for the EA group. Comparison of transfusion results with the expected rates observed in placebo-controlled trials provides a good measure of external validity (Fig 2A).

The robustness of the noninferiority conclusion was evaluated in a series of sensitivity analyses of the primary (week 5 to EOTP) and secondary (week 1 to EOTP) transfusion end points (Fig 2B). Results were consistent with the primary analysis; the upper 95% CI limit of the difference between the two treatment groups excluded 11.5%. Additionally, inclusion of the patient randomly assigned to DA but who received EA only as treated (rather than as randomly assigned) in the analysis of the primary end point did not alter the noninferiority conclusion.

The average hemoglobin at the time of transfusion was 9.05 g/dL for the DA group and 9.06 g/dL for the EA group, indicating that there was no suggestion of bias in the decision to transfuse. Exploratory analyses were also performed to evaluate transfusion intensity among patients who received ≥ one transfusion. From week 5 to EOTP, the time frame corresponding to the evaluation of the primary end point, the mean number of RBC units transfused (3.2 units; 95% CI, 2.8 to 3.6 units for DA; 3.0 units; 95% CI, 2.6 to 3.3 units for EA) and the mean number of days on which a patient received a transfusion (1.6 days; 95% CI, 1.4 days to 1.8 days for DA; 1.5 days; 95% CI, 1.3 days to 1.7 days for EA) did not differ between treatment groups. For the

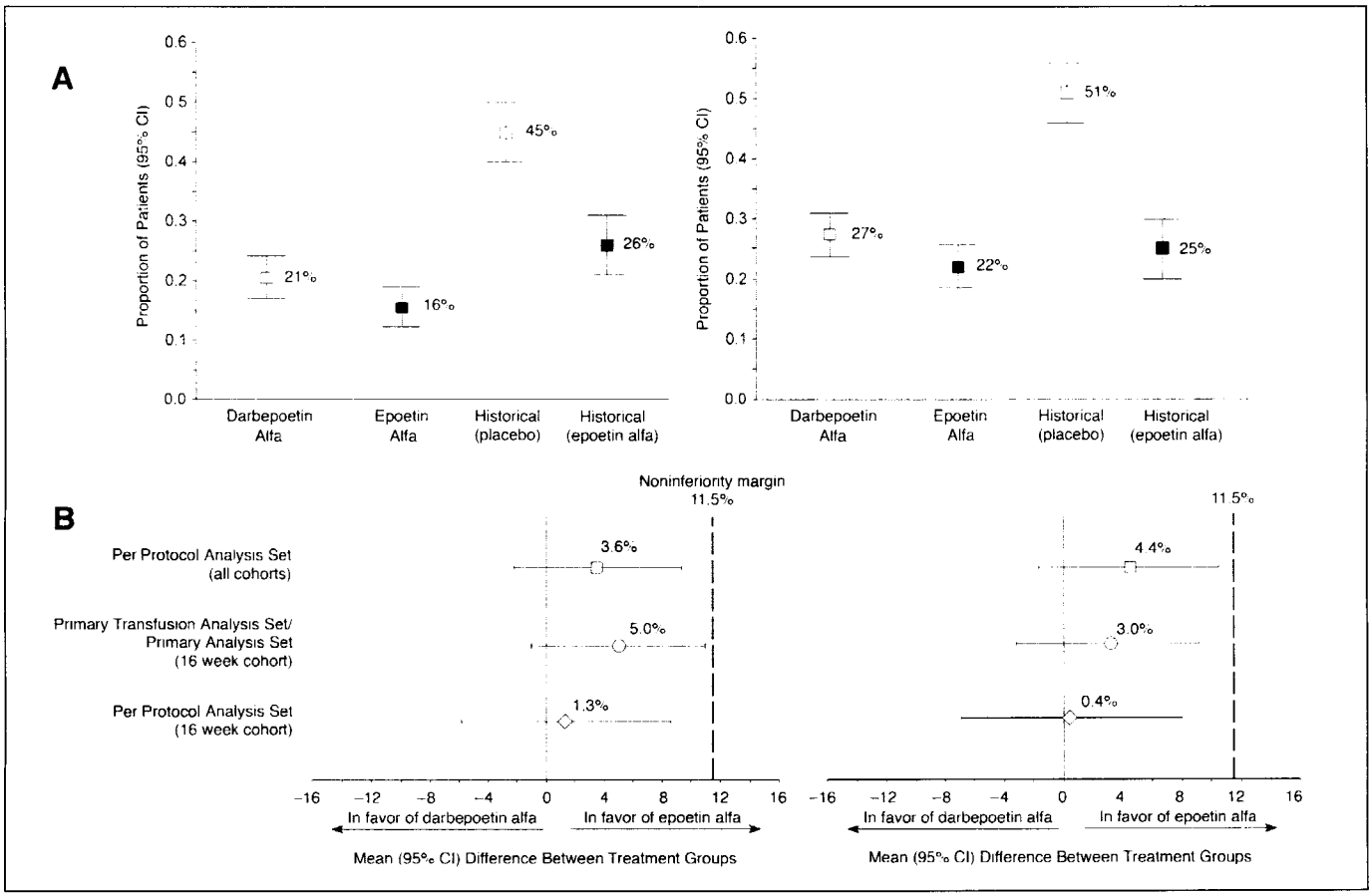

Fig 2. Incidence of RBC transfusions and sensitivity analyses. (A) Percentages of patients receiving ≥ one transfusion are shown with 95% CIs. Historical transfusion incidences are shown from placebo-controlled epoetin alfa trials.[4,12,21-23,28] (B) Sensitivity analyses—adjusted by screening hemoglobin category (< 10 g/dL *v* ≥10 g/dL) and type of chemotherapy administered (platinum-based *v* nonplatinum-based)—were performed using the 16-week cohort and the per-protocol subset of the 16-week cohort. Differences in Kaplan-Meier percentages were calculated using the Cochran-Mantel-Haenszel approach and may therefore not equal the arithmetic difference between groups.

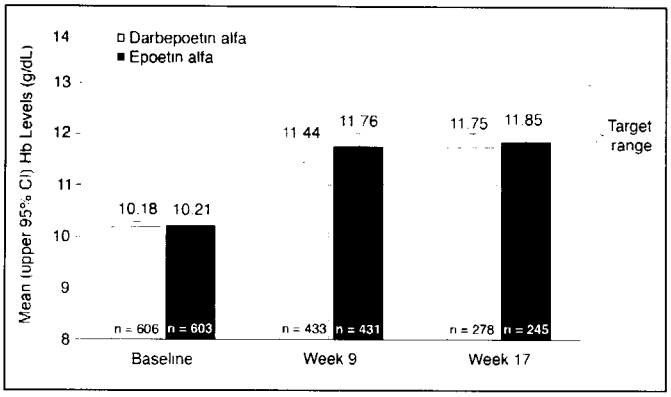

Fig 3. Hemoglobin (Hb) concentration over treatment period. The hemoglobin concentrations for the two treatment groups are shown at baseline, week 9, and week 17, with upper 95% CI bars (available data approach). Patients with no hemoglobin value after baseline were excluded from the analysis. The total number of patients with hemoglobin values is shown by study week.

subset of patients who were transfused in the first month (weeks 1 to 4), no differences were observed; the mean number of units transfused was 2.3 units (95% CI, 2.1 to 2.5 units) for DA and 2.5 units (95% CI, 2.2 to 2.7 units) for EA, and the mean number of days on which a patient received a transfusion was 1.2 (95% CI, 1.1 days to 1.3 days) for DA and 1.3 (95% CI, 1.2 days to 1.4 days) for EA.

Hemoglobin end points. In both groups, the mean hemoglobin concentrations improved from approximately 10.2 g/dL at baseline to 11.8 g/dL by the EOTP, with no meaningful differences in mean hemoglobin change observed at week 9 or EOTP (Fig 3). Using the last-value-carried forward approach, mean hemoglobin levels at EOTP were 11.6 g/dL for DA and 11.8 g/dL for EA.

More than three quarters of patients in each group achieved the target hemoglobin range of 11 g/dL to 13 g/dL. The median time to achieve target hemoglobin was 6 weeks for the DA group and 5 weeks for the EA group (Fig 4). The majority of these patients maintained hemoglobin levels in this range for the remainder of the treatment period (Table 3). Due to the dose titration rules employed in the study, the mean hemoglobin after achievement of the target stabilized at approximately 12 g/dL in both groups.

Patient-reported outcomes. The improvements in FACT-Fatigue subscale scores from baseline between the two treatment groups were similar and no differences were observed between the two groups for any of the other HRQOL assessment (Figs 5 and 6).

Safety

In order to minimize hyporesponse or hyper-response to therapy, rules regarding dose titration were included in this trial. Dose was modified at least once for more than 80% of patients in both groups, with a mean actual dose per patient delivered for DA of 229 μg Q2W compared with 42,714 U QW for EA (Table 4).

The safety profiles of DA and EA were consistent with existing clinical experience for adverse events in anemic cancer patients receiving cytotoxic chemotherapy with no differences observed between groups. Safety was evaluated for patients who received one or more study drug; patients who were randomly assigned to the EA treatment group who received one or more dose of DA were analyzed as EA for safety. Six percent of DA patients and 7% of EA patients reported cardiovascular/thromboembolic events. No antibodies to erythropoietic compounds were detected, and no clinical sequelae suggestive of neutralizing antibody formation were observed. The rates of death on study were 11% for DA and 14% for EA (safety analysis set).

DISCUSSION

In this noninferiority study, DA 200 μg Q2W was shown to be as effective as EA 40,000 U QW with respect to transfusion requirements, with multiple sensitivity analyses providing internal validity and supporting the noninferiority conclusion. Despite the open-label design, no differences were observed between groups in the decision to transfuse patients. The validity of this outcome was further supported by results of the secondary end points in the trial (eg, improvement in HRQOL, increase in hemoglobin concentration, and safety); these findings are consistent with previously reported observational studies[13,14,19,20] and phase II trials.[15,17] Transfusion rates observed in the control group of this trial were comparable with pooled rates from large, phase III, placebo-controlled EA trials,[4,21,22,28] and provided confirmation of external validity.

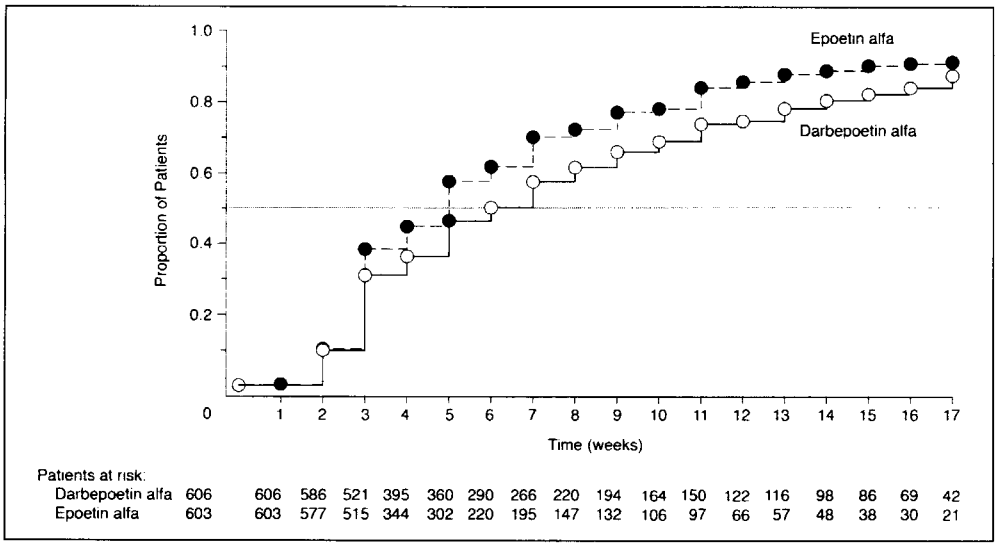

Fig 4. Achievement of target hemoglobin range (11 g/dL to 13 g/dL) by study week. The Kaplan-Meier plot displays the (unadjusted) proportion of patients achieving a target hemoglobin concentration (11 g/dL to 13 g/dL) consistent with evidence-based practice guidelines for anemia management in cancer patients.[24-26,31] Patients with no hemoglobin value after baseline were excluded from the analysis. The number of patients remaining after censoring is shown by study week (available data approach).

Table 3. Patients Achieving and Maintaining Target Hemoglobin Concentration (11 g/dL to 13 g/dL)

Hemoglobin Concentration Information	Darbepoetin Alfa (n = 606) No.	Darbepoetin Alfa (n = 606) %	Epoetin Alfa (n = 603) No.	Epoetin Alfa (n = 603) %
Achievement of target hemoglobin				
No. of patients	463	80	487	86
Median time to target hemoglobin, weeks	6.0		5.0	
Maintenance of target hemoglobin range*				
Hemoglobin concentration after target, g/dL				
Mean	12.0		12.1	
SD	0.9		0.8	
< 10	7	2	3	1
10 to < 11	58	13	38	8
11 to 13	341	74	389	80
> 13	57	12	57	12

Abbreviation: SD, standard deviation.
*Among patients who achieved target hemoglobin concentration.

The intent-to-treat approach, commonly used in conventional clinical trials where the objective is to demonstrate that one treatment is superior to another (ie, a null hypothesis that treatments are equivalent), represents a conservative approach and minimizes any observed differences from sources other than true differences related to the treatment effect. However, in noninferiority trials where the aim is to demonstrate equivalence (ie, a null hypothesis that one treatment is superior), the intent-to-treat approach may be anticonservative for the reason that it minimizes differences between groups. To assess this potential for bias towards equivalency, preplanned sensitivity analyses of the transfusion end points used two alternate cohorts: per-protocol analysis set, which examined the impact of patient attrition and protocol deviations, and 16-week cohort, which examined the impact of the extended treatment period resulting from the study amendment. The results of these analyses did not demonstrate differences between groups and confirmed the conclusion of noninferiority. Indeed, point estimates of the difference between treatments trended further toward 0 for patients who were compliant with the protocol.

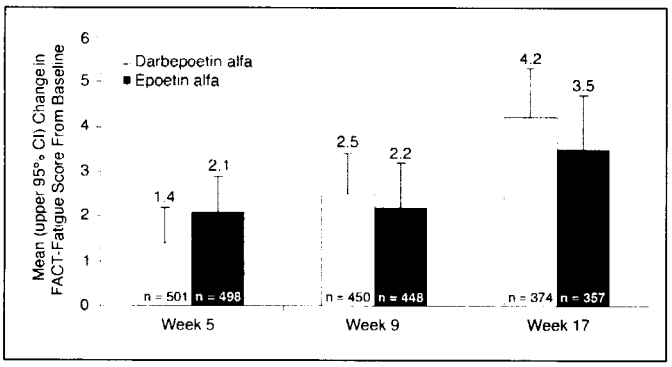

Fig 5. Change in FACT-Fatigue subscale scores over treatment period. Mean change in FACT-Fatigue scores from baseline are shown for weeks 9 and 17, with upper 95% CI bars. Estimates were obtained from an analysis of covariance (ANCOVA) model, which included treatment group, the two stratification variables (baseline hemoglobin and planned chemotherapy type), and baseline FACT-Fatigue score.

A number of questions have been raised regarding relative rapidity of response for DA 200 μg Q2W compared with EA 40,000 U QW.[29] Given these concerns, a potential criticism of this study may be the choice of primary end point, which excludes the first month of therapy. Selection of this end point was necessary, as most placebo-controlled trials of erythropoiesis-stimulating agents have reported transfusion incidence from week 5 to EOTP, and thus the evidence base on which to derive a noninferiority margin was limited to this timeframe. To address this limitation, an analysis of the transfusion requirements over the entire treatment period was prespecified as a key secondary end point. Results from these analyses confirm that the exclusion of the first month of therapy did not bias in favor of DA. Secondary HRQOL and hemoglobin surrogate end points also addressed the rapidity of response to therapy and evidence of differences between treatment groups. To further evaluate time to therapeutic effect, analysis of the proportion of patients who achieved a clinically relevant target hemoglobin concentration was performed. The difference between groups in mean time to this target hemoglobin range was 1 week (6 weeks for the DA group compared with 5 weeks for EA group), suggesting little difference in the ability to reach a therapeutic range. Moreover, as the intent of erythropoietic therapy is to decrease transfusion requirements and improve fatigue, any differences in hemoglobin change between treatment groups must be coupled with

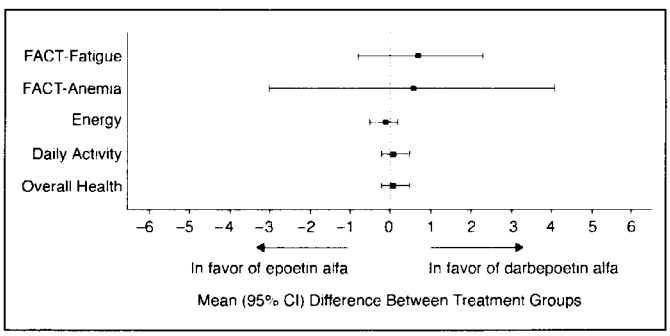

Fig 6. Summary of patient-reported outcomes. The differences between the two treatment groups in health-related quality of life assessment scores at the end of treatment phase are shown with 95% CI bars.

Table 4. Drug Usage

Dose Information	Darbepoetin Alfa (n = 611)*		Epoetin Alfa (n = 598)*	
	No.	%	No.	%
No. of patients with a dose change	509	83	508	85
No. of weeks of dosing				
Mean	12.1		12.3	
SD	4.0		4.5	
Dose delivered				
Mean	229 μg Q2W		42,714 U QW	
SD	43		8,645	
No. of doses delivered				
Mean	6.5		11.5	
SD	2.0		4.2	

Abbreviations: SD, standard deviation; Q2W, every 2 weeks; U, units; QW, every week.
*Safety analysis set differed slightly from the primary analysis set. Nine patients randomly assigned to darbepoetin alfa received one dose of epoetin alfa during the study; however, this did not impact the treatment group assignment.

demonstrable differences in these outcomes. Our data show no significant differences between the two treatment groups regarding these clinical outcomes.

Much of the debate regarding comparable efficacy of these two agents has been centered on relative cost and appropriate payment policy. Therefore, the dose requirements as well as the clinical efficacy were both important data to be derived from this trial. Given that this study demonstrated the noninferiority of DA with respect to clinical outcomes, no adjustment of effectiveness is required in the comparison of these agents (ie, a cost analysis rather than an incremental cost-effectiveness analysis suffices). For purposes of cost/benefit analysis, the costs for the mean weekly doses of the two agents can be compared without adjusting for significant differences in effectiveness.

This head-to-head study demonstrated that DA 200 μg Q2W is as effective and safe as EA 40,000 U QW. Special considerations in design and statistical analysis were implemented to definitively evaluate the comparability of two commonly used erythropoietic agents. The ability to extend dosing intervals represents an important potential benefit for patients and their caregivers. [30]

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Acknowledgment

We thank study investigators, coordinators, and participants from each institution, Alexander Liede for assistance in the writing of this report, Russell Berg for coordinating this study, and Yuriy Shamanov, Steven Pearce, and Matt Ness for statistical programming support. The sponsor of this study was Amgen Inc, Thousand Oaks, CA (NESP 20030125).

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Dollar Amount Codes (A) < $10,000 (B) $10,000-99,999 (C) ≥ $100,000 (N/R) Not Required

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ORIGINAL RESEARCH ARTICLE

Pharmacoeconomics 2006; 24 (5): 479-494
1170-7690/06/0005-0479/$39.95/0

Economic Evaluation of Weekly Epoetin Alfa versus Biweekly Darbepoetin Alfa for Chemotherapy-Induced Anaemia

Evidence from a 16-Week Randomised Trial

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Abstract

Introduction: A 16-week, open-label, multicentre, randomised trial of weekly epoetin alfa 40 000 units versus biweekly darbepoetin alfa 200μg among 358 patients with solid-tumour cancers and chemotherapy-induced anaemia demonstrated superior haematological outcomes with epoetin alfa. We sought to compare resource use, costs and clinical outcomes between treatment groups and report the results using a cost-consequences framework.

Methods: Pre-specified methods were used to assign costs ($US, year 2004–5 values) to medical resources and patient time using a societal perspective. Costs for inpatient care, outpatient care and physician services were based on US Medicare reimbursement rates. Indirect costs assigned to patient time spent receiving study medication were based on the mean hourly wage in the US. In the base-case analysis, the average wholesale price was used to assign costs to medications. Clinical outcomes included all haemoglobin levels and transfusions recorded throughout the trial. Sensitivity analyses were performed to evaluate the impact of different costing methods, cost sources, perspectives and methods to assign haemoglobin values following a blood transfusion.

Results: Over a mean follow-up duration of 11.8 weeks, the average cost of study medications and their administration was the single largest component of total costs and was similar between groups (epoetin alfa $US5979 and darbepoetin alfa $US5935, difference $US44; 95% CI −590, 692). There were no significant differences in the proportions of patients hospitalised (epoetin alfa 24.6%, darbepoetin alfa 22.0%; $p = 0.57$). Patients randomised to epoetin alfa experienced more inpatient days, on average, than patients randomised to darbepoetin alfa (2.6 vs 1.6, 95% CI for the difference, 0.07, 2.27). However, with regard to transfusions, patients in the epoetin alfa arm required fewer units of blood than patients in the darbepoetin alfa arm (0.46 vs 0.88, 95% CI for the difference −0.77, −0.08).

Mean total costs, comprising costs for study medications and their administration, inpatient care, transfusions, unplanned radiation therapy, haematology and laboratory services, chemotherapy and non-chemotherapy drugs and indirect costs were $US14 976 in the epoetin alfa arm compared with $US14 101 in the darbepoetin alfa arm, a difference of $US875 (95% CI for difference −849, 2607), of which 98% of the difference was attributable to higher inpatient costs in the epoetin alfa arm ($US2374 vs $US1520; 95% CI for difference −33, 1955). Assessments of multiple clinical measures demonstrated improved outcomes with epoetin alfa relative to darbepoetin alfa.

Conclusion: Most clinical outcome measures suggested greater improvement with epoetin alfa relative to darbepoetin alfa, but most costs for both agents appeared similar. Decision makers must evaluate the differences in costs and efficacy measures that are most relevant from their perspectives.

Between 30% and 90% of cancer patients receiving chemotherapy develop anaemia, which typically results in reduced functional capacity and decreased health-related quality of life (QOL).[1,2] Patients are considered anaemic when blood haemoglobin drops below a certain level, usually <10 g/dL or 12 g/dL.[1] Before the 1980s, chemotherapy-induced anaemia was primarily treated with red blood cell transfusions.[3] With the development of recombinant DNA technologies, therapy with erythropoietic agents has become the standard treatment for most patients with chemotherapy-induced anaemia.[4,5] The two erythropoietic agents approved by the US FDA for the treatment of chemotherapy-induced anaemia in patients with nonmyeloid malignancies are epoetin alfa (Procrit®[1], Ortho Biotech Products, LP, Raritan, NJ, USA) and darbepoetin alfa (Aranesp®, Amgen Inc., Thousand Oaks, CA, USA).

Several randomised clinical trials have demonstrated the efficacy and safety of epoetin alfa or darbepoetin alfa relative to placebo for the treatment of chemotherapy-induced anaemia.[6-15] With the recent completion of randomised trials of epoetin alfa versus darbepoetin alfa,[16,17] the oncology community stands to gain important information on comparative benefits and costs associated with these treatments. The objective of this study was to compare medical resource use, costs and haematological outcomes incurred among patients randomised into a clinical trial that compared treatment with epoetin alfa versus darbepoetin alfa and to report the results using a cost-consequences framework.

Methods

Overview of the Clinical Trial

A randomised, open-label, 16-week trial compared the efficacy of epoetin alfa administered once weekly at a starting dose of 40 000 units versus darbepoetin alfa administered biweekly at a starting dose of 200μg in 358 patients with chemotherapy-induced anaemia.[17] Eligible patients were at least 18 years of age with a histologically confirmed solid tumour malignancy and a haemoglobin level ≤11 g/dL, and were scheduled to receive cyclic chemotherapy for at least 12 weeks during the study period. For patients receiving epoetin alfa, the dose of the study drug was increased to 60 000 units if the patient did not experience a ≥1 g/dL rise in haemoglobin by 4 weeks (week 5).[4,5] For patients receiving darbepoetin alfa, the dose was increased to 300μg if the patient did not experience a ≥1 g/dL rise in haemoglobin by 6 weeks (week 7). The primary endpoint of the trial was the proportion of patients experiencing a ≥1 g/dL rise in haemoglobin by 4 weeks of follow-up (week 5). The objective was to compare the efficacies of epoetin alfa and

1 The use of trade names is for product identification purposes only and does not imply endorsement.

darbepoetin alfa in providing an early response to therapy. Additional details regarding the trial protocol are available elsewhere.[17]

A prospectively planned economic evaluation from a societal perspective was incorporated as part of this trial. This included a plan to evaluate resource use as a secondary trial endpoint, as well as the collection of within-trial resource use data using the trial's case report form for all patients enrolled in the trial from baseline through to the patient's last study visit.

Resource Use Data

Data on medical resource use included information about hospitalisations, chemotherapy, radiation therapy, transfusions, laboratory tests, concomitant medications and study medications. Additional details regarding each resource-use category are provided in the sections describing cost assignment.

Data on the amount of time patients spent travelling to clinic and receiving study medications were not recorded during the trial. Therefore, we relied on estimates reported in a study by Beveridge et al.,[18] in which the majority of patients received weekly epoetin alfa or biweekly darbepoetin alfa. Although patients receiving darbepoetin alfa with this administration interval would require half the number of drug administrations as patients receiving epoetin alfa, patients with cancer concurrently receive other treatments and tests that may negate this potential advantage. In the Beveridge et al.[18] study, patients receiving epoetin alfa had 4 clinic visits over a 4-week period compared with 3.8 clinic visits for patients receiving darbepoetin alfa. For our analysis, we computed the expected number of clinic visits for patients in each treatment group based on their period of follow-up in the trial. For each visit, we relied on the estimate of 125 minutes reported by Beveridge et al.[18] as the average time patients spent in the clinic visit plus the time they spent preparing and travelling to and from clinic. The inclusion of indirect costs that are limited to time spent seeking therapy is consistent with the recommendations of the Panel on Cost-Effectiveness in Health and Medicine.[19] Data on days lost from work and other productivity measures were not collected in the clinical trial.

Cost Assignment

Cost assignment methods were pre-specified in an economic analysis plan. Furthermore, cost assignment was carried out for all medical resources, with the exception of study medications, before treatment assignment was revealed. In the base-case analysis, all costs were valued from the societal perspective. All costs were reported in $US, year 2004 values, with the exception of costs for study medications and administration, which were based on estimates from March 2005. Because the maximum period of follow-up was 16 weeks, costs were not discounted.

Hospitalisations

Using the primary and secondary discharge diagnoses reported by study investigators in the trial, an oncologist who was blinded to treatment group assigned an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code to each hospitalisation. We then mapped ICD-9-CM codes to diagnosis-related group (DRG) codes, giving preference to DRG codes representing complicated cases, because patients participating in the study had an underlying cancer diagnosis. Using these DRG codes, we assigned costs to each hospitalisation using the reimbursement rates reported in the 2004 DRG Expert.[20] Because these estimates do not account for differences in length of stay for each hospitalisation, we use the term 'unit cost method' to refer to this costing method.

However, in the base-case analysis, we adjusted DRG-specific costs to account for differences in the length of stay for each hospitalisation.[21] To do this, we divided the DRG-specific costs by the arithmetic mean of the length of stay for each DRG as reported by the Centers for Medicare and Medicaid Services to calculate the average daily reimbursement for each DRG.[22] Then, to calculate the total cost for each hospitalisation, we multiplied the number of inpatient days for each hospitalisation by the estimated daily reimbursement amount for the corresponding DRG. This methodology provided a more

valid representation of the variation in hospital costs between patients than the unit cost method.

Inpatient Physician Fees

To account for inpatient physician fees (not reflected in DRG payments), we assigned physician fees for the initial workup on the day of admission and fees for discharge responsibilities on the day of discharge. For all days in between, we assigned a daily rounding fee. Physician fees for inpatient services were estimated from the 2004 Medicare Physician Fee Schedule.[23]

Study Medications and Administration

The cost of study medications was calculated using the detailed administration information available from the clinical trial. In the base-case analysis, we assigned costs to epoetin alfa and darbepoetin alfa using 95% of the average wholesale price reported in the March 2005 update of the *Red Book*.[24] To assign costs for drug administration, we used a weighted average of published 2005 Medicare reimbursement rates for drug administration in a hospital outpatient setting[25] and a physician office (with transition adjustments).[26] The weights were based on market research data showing that 35% of patients are treated in a hospital outpatient setting and 65% of patients are treated in a community setting.[27]

Concomitant Medications

To assign costs to concomitant medications recorded throughout the trial, we reviewed listings of all medications by drug class and retained those with at least 10 records. Also, while blinded to treatment assignment, we manually added medications that were costly but less frequently recorded. Altogether, the selected medications represented 92.5% of all prescription medications recorded in the study. We assigned costs to medications using the recommended daily dose and the daily cost based on 95% of the 2004 average wholesale price for the representative medication in the drug class. The duration of treatment was based on start and stop dates recorded on the clinical trial's case report form. When the stop date was not available, we assumed that patients received the drug through to the end of the trial.

Chemotherapy and Administration

Upon examination of the chemotherapy data, it appeared that administration information was not recorded consistently in the case report form. In some cases, it appeared that the total dose per cycle for each drug administered was recorded, whereas in others it appeared that the doses given during each administration were recorded. Thus, for chemotherapy drugs recorded, we applied consistent assumptions to both treatment groups regarding the cycle length and frequency of administration. Using these modified data, we assigned costs to chemotherapy drugs using 95% of the 2004 average wholesale price. For drugs administered via injection or intravenous push/infusion, we assigned administration costs using the 2004 Medicare Part B physician fees with transition payments for drug administration in an outpatient physician's office.[26]

Radiation Therapy

Although radiation therapy was not planned for patients enrolled in the trial, unplanned radiation therapy was documented in the case report form. For these relatively few cases, we assigned costs to radiation therapy using the 2004 Medicare Part B Physician Fee Schedule.[23]

Blood Transfusions

To assign costs to blood transfusions recorded throughout the follow-up period, we used published estimates of the direct material and variable direct labour costs per unit of red blood cells transfused for patients with solid-tumour cancers (adjusted to $US, year 2004 values, using the Consumer Price Index for Medical Care).[28,29]

Laboratory Tests

Laboratory costs were assigned using the midpoint of 2004 base fee amounts reported in the Clinical Laboratory Fee Schedule available from the Centers for Medicare and Medicaid Services.[30] We included the costs of laboratory tests that were documented in the clinical trial case report forms. These included tests associated with the diagnosis and monitoring of anaemia, such as iron studies (serum iron, serum ferritin, total iron binding capacity, transferring saturation, serum folate and serum cya-

nocobalamin [vitamin B_{12}]), a comprehensive metabolic panel and a complete blood cell count performed at screening. We also assigned costs to all complete blood cell counts performed throughout the trial.

Patient Time

We assigned costs to patient time associated with the study drug administration using the mean hourly wage in the US in 2003 provided by the National Compensation Survey (adjusted to $US, year 2004 values, using the average annual growth rate in the hourly wage reported from 1997 to 2003).[31]

Efficacy Measures

We evaluated the following clinical outcomes: the proportion of patients experiencing a haemoglobin response, defined as a ≥1 g/dL rise in haemoglobin by week 5 (i.e. within 4 weeks of treatment); the proportion of patients experiencing a haematological response, defined as a ≥2 g/dL rise in haemoglobin by week 9; the area under the curve (AUC) for change in haemoglobin; the mean haemoglobin value at weeks 5, 9, 13 and 17; the proportion of patients experiencing a haemoglobin level of at least 11 g/dL by weeks 5 and 9; and the percentage of follow-up days on which a patient had a haemoglobin value within the therapeutic range of 11–13 g/dL.

The methods we used to derive measures of treatment efficacy for the economic evaluation differed from the methods commonly used for deriving clinical efficacy endpoints in trials of erythropoietic therapy, including those used in the clinical evaluation for this trial.[17] We relied on all observed haemoglobin values recorded in the trial, whereas clinical assessments often impute haemoglobin values for a 28-day period following a blood transfusion using a last-value-carried-forward approach. We reasoned that if the costs of red blood cell transfusions were included in the cost calculations, then their impact on haemoglobin should also be included. Another difference was that we did not impute missing values, nor did we extrapolate data beyond a patient's last study visit, whereas assessments used in the clinical trial reports often apply the last value carried forward to impute missing and censored haemoglobin values.[6,7,17,32] Finally, when we calculated the AUC for change in haemoglobin, we used patient-level haemoglobin readings and the actual time intervals that occurred between readings, whereas clinical assessments used in the clinical trial reports often rely on group-level mean haemoglobin levels calculated at different time points.

Cost-Consequences Analysis

Because there is no single clinical efficacy measure that is widely accepted to capture the clinical effects of erythropoietic agents, and based on our assessment that there was not sufficient evidence upon which to model QALYs (see the Discussion section for further explanation), we applied a cost-consequences framework in this analysis. Thus, we reported an array of costs and efficacy metrics for each treatment group.[33]

Sensitivity Analyses

To evaluate the consistency of the results, we conducted three pre-planned sets of sensitivity analyses. In the first set of sensitivity analyses, we varied the costs assigned to study medications and administration (table I). We first substituted the average wholesale price with the wholesale acquisition cost,[34] then with cost estimates from the Federal Supply Schedule.[35] We then evaluated medication and administration costs using 2005 Medicare reimbursement rates for both hospital-based clinics (Medicare Part A)[25,36] and outpatient physician offices (Medicare Part B).[26,37] In the second set of sensitivity analyses, we evaluated the impact of the assumptions used to estimate patient time costs. We assumed that patients receiving darbepoetin alfa could reduce the frequency of office visits to one visit every 2 weeks. Then, we evaluated the impact of assigning patient time costs only for time spent in the clinic rather than the total time for preparation, travel and the clinic visit. In the third set of sensitivity analyses, we evaluated the impact of using the last value carried forward to impute haemoglobin values within 28 days after a blood transfusion.

Table I. 2005 unit costs ($US) applied to study medications and administration

Study medications and administration	Cost/reimbursement
Medication	
Average wholesale price[24]	
Epoetin alfa	14.32 per 1000 units
Darbepoetin alfa	5.13 per μg
Medicare Part A reimbursement rate[36]	
Epoetin alfa	11.09 per 1000 units
Darbepoetin alfa	3.66 per μg
Medicare Part B reimbursement rate[37]	
Epoetin alfa (average sales price plus 6%)	9.81 × 1.06 = 10.39 per 1000 units
Darbepoetin alfa (average sales price plus 6%)	3.22 × 1.06 = 3.42 per μg
Wholesale acquisition cost[34]	
Epoetin alfa	11.93 per 1000 units
Darbepoetin alfa	4.27 per μg
Federal Supply Schedule[35]	
Epoetin alfa	5.48 per 1000 units
Darbepoetin alfa	2.36 per μg
Administration	
National average Medicare Part A reimbursement rate[25]	22.68
National average Medicare Part B reimbursement rate[26]	19.13

We also conducted three *post hoc* sensitivity analyses related to the estimation of inpatient costs. First, we applied the unit cost method to assign hospital costs, whereby we did not make adjustments for differences in length of stay. Then, we evaluated the impact of outliers by removing the top 5% and 10% of longest hospitalisations. Finally, we evaluated the impact of various methods to handle the recording of chemotherapy doses on costs attributed to chemotherapy drugs and their administration.

Statistical Methods

We included all patients with at least one post-baseline haemoglobin measure or transfusion. For consistency with the clinical reports of the trial, in comparisons of the proportion of patients experiencing a haemoglobin or haematological response, we applied a logistic regression model that included study treatment and whether patients received platinum- or nonplatinum-based chemotherapy as independent variables. Because absolute differences are the most meaningful for use in a cost-consequences analysis, we also evaluated differences on counts of resource use, costs and clinical efficacy metrics using the nonparametric bootstrap method (bias-corrected percentile method with 1000 bootstrap replications) to calculate 95% CIs for differences between treatment groups.[38]

Results

The clinical trial enrolled 358 patients at 50 sites in the US between April 2003 and June 2004.[17] Patients were randomised to epoetin alfa (n = 178) or darbepoetin alfa (n = 180). Table II reports demographic, disease- and treatment-related characteristics of the 352 patients enrolled in the trial who had either a post-baseline haemoglobin measure or blood transfusion. The mean duration of follow-up was approximately 11.8 weeks in both treatment groups (82.9 days for epoetin alfa, 82.2 days for darbepoetin alfa; p = 0.84). Approximately 40% of patients in both groups discontinued participation in the clinical trial prior to the 16 weeks of planned follow-up (week 17) [41.1% and 39.5% in the epoetin alfa and darbepoetin alfa groups, respectively; p = 0.76].

Table II. Characteristics of patients enrolled in the clinical trial with either a post-baseline haemoglobin measure or blood transfusion[17]

Characteristic	Epoetin alfa (n = 175)	Darbepoetin alfa (n = 177)
Female [n (%)]	107 (61.1)	118 (66.7)
Age (y) [mean (SD)]	62.0 (11.7)	63.3 (11.8)
Type of cancer [n (%)]		
breast	38 (21.7)	50 (28.2)
lung	45 (25.7)	46 (26.0)
other	92 (52.6)	81 (45.8)
Baseline haemoglobin level (g/dL) [mean (SD)]	10.1 (0.76)	10.0 (0.82)
Baseline ECOG status [n (%)]		
fully active	57 (32.6)	61 (34.5)
strenuous activity limited	92 (52.6)	87 (49.2)
self-care but no work	26 (14.9)	29 (16.4)
platinum chemotherapy [n (%)]	68 (38.9)	75 (42.4)

ECOG = Eastern Cooperative Oncology Group.

Within-Trial Resource Use

When counting each administration of epoetin alfa as 1 week of exposure and each administration of darbepoetin alfa as 2 weeks of exposure, the mean number of weeks of exposure to the study drug was lower among patients receiving epoetin alfa than among those receiving darbepoetin alfa (7.1 weeks vs 8.4 weeks; $p = 0.002$). This difference may have resulted from the greater proportion of patients receiving epoetin alfa having the study drug withheld as per the study protocol (40.6% vs 24.3% of patients receiving darbepoetin alfa; $p = 0.001$). Approximately the same proportions of patients required dose increases (34.3% of patients receiving epoetin alfa in week 5 vs 36.7% of patients receiving darbepoetin alfa in week 7; $p = 0.63$).

Although there were no significant differences between treatment groups in the proportion of patients hospitalised during the follow-up period or the distribution of counts of hospitalisations per patient between treatment groups (table III), on average, patients in the epoetin alfa group experienced significantly more inpatient days than patients in the darbepoetin alfa group. Among patients who were hospitalised, the mean number of inpatient days was

Table III. Within-trial resource use

Resource use[a]	Epoetin alfa (n = 175)	Darbepoetin alfa (n = 177)	95% CI[b]	p-Value[c]
Patients hospitalised [n (%)]	43 (24.6)	39 (22.0)		0.57
Hospitalisations [n (%)]				0.72
0	132 (75.4)	138 (78.0)		
1	31 (17.7)	32 (18.1)		
2	9 (5.1)	6 (3.4)		
≥3	3 (1.7)	1 (0.6)		
Hospitalisations	0.34 (0.72)	0.27 (0.55)	0.08 (−0.05, 0.22)	
Inpatient days	2.61 (6.00)	1.58 (4.10)	1.03 (0.074, 2.27)	
Blood transfusions	0.26 (0.65)	0.45 (1.08)	−0.19 (−0.37, −0.009)	
Units of blood transfused[d]	0.46 (1.19)	0.88 (2.11)	−0.42 (−0.77, −0.08)	
Days of unplanned radiation therapy	0.31 (2.97)	0.71 (4.38)	−0.40 (−1.24, 0.29)	

a Mean (SD) unless otherwise indicated.

b Confidence intervals for differences are provided for counts.

c p-Values based on the Pearson chi-square test are provided for categorical measures.

d Indicates units of blood transfused from day 0 to the end of the study.

10.6 in the epoetin alfa group and 7.2 in the darbepoetin alfa group (difference 3.5; 95% CI 0.35, 6.36).

Fewer patients in the epoetin alfa group required blood transfusions than patients in the darbepoetin alfa group (17.7% vs 23.7%; p = 0.16). When accounting for the units of blood required for each transfusion, patients receiving epoetin alfa required significantly fewer units of blood during the follow-up period (0.46 units vs 0.88 units for patients receiving darbepoetin alfa; 95% CI for the difference, −0.77, −0.08).

Within-Trial Costs

Total costs, comprising costs for inpatient care, blood transfusions, unplanned radiation therapy, haematology and laboratory services, chemotherapy and nonchemotherapy drugs, patient time and study medications and their administration averaged $US14 976 in the epoetin alfa group compared with $US14 101 in the darbepoetin alfa group, resulting in an incremental cost of $US875 per patient receiving epoetin alfa over 11.8 weeks of follow-up (table IV). This difference was almost entirely attributable to the $US855 higher average cost of inpatient care among patients receiving epoetin alfa ($US2374 vs $US1520). Study medication and its administration represented the largest single cost in both treatment groups. In the base-case analysis, when 95% of the average wholesale price was used to assign costs to study medications, average medication and administration costs among patients in the epoetin alfa group were $US5979, compared with $US5935 in the darbepoetin alfa group, a difference of $US44 (95% CI −590, 692). Costs attributed to patient time were similar between treatment groups ($US451 for epoetin alfa vs $US425 for darbepoetin alfa).

Clinical Outcomes

In the clinical analysis completed for the trial, where missing haemoglobin values and haemoglobin values within 28 days after a blood transfusion were imputed using the last value carried forward, the proportion of patients experiencing a ≥1 g/dL rise in haemoglobin within the first 4 weeks of treatment for the first 305 randomised patients indicated that the haemoglobin response rate was significantly higher for patients receiving epoetin alfa than for patients receiving darbepoetin alfa (47.0% vs 32.5%; p = 0.008, 1-sided as reported by Waltzman et al.[17]). Our assessment of haemoglobin response, using the analytic methods for this economic analysis described in the Methods section (i.e. using observed haemoglobin values that included blood transfusions), revealed that a greater proportion of patients receiving epoetin alfa experienced a haemoglobin response of ≥1 g/dL rise in haemoglobin by week 5 (50.3% vs 43.0%; p = 0.20), and a haematological response of ≥2 g/dL rise in haemoglobin by week 9 (47.4% vs 35.0%; p = 0.02) than darbepoetin alfa recipients. The direction of these findings was consistent across response metrics, including the AUC for change in haemoglobin, mean haemoglobin levels across time and the proportions of patients experiencing a haemoglobin level of at least 11 g/dL (table IV). We also found that patients receiving epoetin alfa experienced a greater proportion of days with haemoglobin levels within the therapeutic range of 11–13 g/dL during the study (table IV) than darbepoetin alfa recipients.

Cost-Consequences Analysis

The findings presented above regarding incremental costs and outcomes can be considered jointly and from different perspectives. For example, if one were interested primarily in the costs of study medications and administration from the perspective of an outpatient physician's office, the incremental costs of $US39 for epoetin alfa ($US81–42) could be divided by the increase in the proportion of patients experiencing a haematological response with epoetin alfa (0.124) to obtain an incremental cost-effectiveness ratio (ICER) of approximately $US314 per additional patient experiencing a haematological response.

From the perspective of the patient who is contemplating the use of an erythropoietic agent, the incremental cost per haematological response with each product may be most relevant. For patients who are required to pay a 20% co-payment for medica-