

Phase III Study of Two Different Dosing Schedules of Erythropoietin in Anemic Patients With Cancer

David P. Steensma, Roy Molina, Jeff A. Sloan, Daniel A. Nikcevich, Paul L. Schaefer, Kendrith M. Rowland Jr, Todor Dentchev, Paul J. Novotny, Loren K. Tschetter, Steven R. Alberts, Thomas F. Hogan, Amy Law, and Charles L. Loprinzi

A B S T R A C T

Purpose

To compare maintenance epoetin alfa administered once every 3 weeks with continued weekly epoetin alfa for patients with cancer-associated anemia.

Patients and Methods

Eligible patients were randomly assigned at enrollment to receive three weekly doses of epoetin alfa 40,000 U subcutaneously (SC), followed by either standard weekly epoetin alfa (40K arm) or 120,000 U of epoetin alfa (120K arm) SC every 3 weeks for 18 additional weeks.

Results

Three hundred sixty-five patients were enrolled. One hundred eighty-three patients were assigned to the 40K arm, and 182 were assigned to the 120K arm. There was no difference in the proportion of patients requiring transfusions during the study (23% in 40K arm and 18% in 120K arm, $P = .22$) or specifically during the maintenance phase (13% in 40K arm v 15% in 120K arm, $P = .58$). Patients randomly assigned to the 40K arm were more likely to have a ≥ 2 or ≥ 3 g/dL hemoglobin (Hb) increment, were more likely to have a drug dose held because of high Hb, and had higher mean end-of-study Hb levels. Toxicities, including thromboembolism, and overall survival were similar. Patients in the 40K arm had a higher global quality of life (QOL) at baseline for unclear reasons, whereas patients in the 120K arm had a greater global QOL improvement during the study, so end-of-study QOL was equivalent.

Conclusion

After three weekly doses of epoetin alfa 40,000 U, a dose of 120,000 U can be administered safely once every 3 weeks without increasing transfusion needs or sacrificing QOL. The Hb increment is somewhat greater with continued weekly epoetin alfa. Lack of blinding as a result of different treatment schedules may have confounded results.

J Clin Oncol 24:1079-1089. © 2006 by American Society of Clinical Oncology

INTRODUCTION

Anemia is a common complication of cancer and antineoplastic therapy, and anemia-associated symptoms can seriously impair patients' quality of life (QOL).¹⁻⁴ RBC transfusions reliably increase hemoglobin (Hb) levels and ameliorate symptoms of anemia, but transfusions are associated with adverse reactions, processing and administration costs, inconvenience, patient fears, and a small risk of infection.⁵ Renally secreted erythropoietin is the major endogenous hormonal regulator of marrow erythrocyte production. Recombinant human erythropoietin (epoetin alfa) has been used for more than a decade for treatment of renal failure-associated and cancer-associated anemia,^{1,6-8} which is a clinical practice supported by evidence-based guidelines published jointly by the American Society of Hema-

tology and the American Society of Clinical Oncology,⁹ by the National Comprehensive Cancer Network,¹⁰ and by other groups.

Although the initial epoetin alfa administration schedule approved by the US Food and Drug Administration for chemotherapy-associated anemia was 150 U/kg (approximately 10,000 U) three times per week, several studies have supported the utility of a more convenient weekly epoetin administration, and the drug is now approved by the US Food and Drug Administration for use at an initial fixed dose of 40,000 U on a once-weekly schedule.¹¹ Most anemic cancer patients receiving epoetin alfa are currently treated with a weekly fixed dose. The North Central Cancer Treatment Group (NCCTG) recently reported the results from a multicenter, randomized, double-blind, placebo-controlled trial of weekly epoetin alfa (40,000 U administered

From the Mayo Clinic and Mayo Foundation, Rochester; Duluth Community Clinical Oncology Program (CCOP), Duluth, MN; Iowa Oncology Research Association CCOP, Des Moines, IA; Toledo Community Hospital Oncology Program CCOP, Toledo, OH; Carle Cancer Center CCOP, Urbana, IL; Altru Health System, Grand Forks, ND; Sioux Community Cancer Consortium, Sioux Falls, SD; Scottsdale CCOP, Scottsdale AZ; and Geisinger Clinic and Medical Center CCOP, Danville, PA.

Submitted May 17, 2005; accepted November 18, 2005.

Supported in part by Public Health Service Grant Nos. CA-25224, CA-37404, CA-35103, CA-63849, CA-63848, CA-35195, CA-35272, CA-35269, CA-35101, CA-60276, CA-52352, CA-37417, CA-35448, and CA-35415. D.P.S. is supported by the Paul Calabresi Award for Clinical Oncology No. K12 CA-90628-04G from the National Cancer Institute.

This was an investigator-initiated study. Ortho Biotech provided study drug and unrestricted administrative funds to the North Central Cancer Treatment Group. National Cancer Institute Cooperative Group-Industry Relationship Guidelines were strictly observed. In accordance with these guidelines, the industry collaborator was provided with the manuscript from the trial for advisory review and comment before initial submission for publication. The study collaborator otherwise had no role in the analysis or reporting of the study data or in revising the manuscript.

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

Address reprint requests to David P. Steensma, MD, Mayo Clinic, 200 First St. SW, Rochester, MN 55905; e-mail: steensma.david@mayo.edu.

© 2006 by American Society of Clinical Oncology

0732-183X/06/2407-1079/\$20.00

DOI: 10.1200/JCO.2005.02.7276

subcutaneously [SC]) in patients with chemotherapy-associated anemia.¹² Compared with placebo, the active agent significantly improved Hb and reduced transfusion needs, but an overall QOL improvement was not demonstrated.

A weekly epoetin schedule is more convenient for patients than a thrice-weekly schedule, but it is still imperfect.¹³ Many common can-

cer treatments (eg, cyclophosphamide, doxorubicin, vincristine, and prednisone for lymphoma and the standard doublet regimens for lung cancer) are administered once every 3 weeks, and some patients receiving epoetin do not receive concurrent antineoplastic therapy.¹⁴ For these patients, as well as for Medicare beneficiaries who cannot be reimbursed for self-administered medications, epoetin

Table 1. Baseline Characteristics by Treatment Arm

Characteristic	Epoetin Alfa Dose						P
	40,000 U (n = 179)		120,000 U (n = 181)		Total (N = 360)		
	No.	%	No.	%	No.	%	
Age, years							.66
Mean	66.0		65.5		65.7		
Standard deviation	11.98		11.40		11.67		
Median	68.0		68.0		68.0		
Range	34.0-93.0		24.0-93.0		24.0-93.0		
Age group							.94
≤ 60 years	55	31	55	30	110	31	
> 60 years	124	69	126	70	250	69	
Actively receiving chemotherapy							.76
Yes	161	90	161	89	322	89	
No	18	10	20	11	38	11	
Actively receiving platinum chemotherapy							.64
Yes	61	34	66	36	127	35	
No	118	66	115	64	233	65	
Anemia degree							.88
Mild, ≥ 9 g/dL	164	92	165	91	329	91	
Severe, < 9 g/dL	15	8	16	9	31	9	
Neoplasm type							.38
Hematologic neoplasm	22	12	17	9	39	11	
Other neoplasm	157	88	164	91	321	89	
Sex							.35
Female	98	55	108	60	206	57	
Male	81	45	73	40	154	43	
Height, cm							.26
No. of patients	173		177		350		
Mean	168.5		167.4		167.9		
Standard deviation	9.97		9.22		9.60		
Median	169.0		166.0		168.0		
Weight, kg							.29
No. of patients	175		177		352		
Mean	75.8		77.8		76.8		
Standard deviation	18.01		16.55		17.29		
Median	73.5		75.8		74.9		
Range	37.1-137.0		42.5-122.3		37.1-137.0		
MCV > 100 fL*							.45
Missing	4	2	3	2	7	2	
Yes	6	3	11	6	17	5	
No	169	94	167	92	336	93	
No. of previous systemic therapies							.70
Missing	4	2	3	2	7	2	
1	67	37	75	41	142	39	
2	108	60	103	57	211	59	
Zubrod performance status at baseline							.68
0	55	31	52	29	107	30	
1	96	54	105	58	201	56	
2	28	16	24	13	52	14	

NOTE. Tables include only patients assessable for efficacy and toxicity.

Abbreviation: MCV, mean corpuscular volume.

*Vitamin B₁₂ and folate deficiency were ruled out.

treatment can require weekly physician's office visits that might not otherwise be required.

One potential solution to this problem is to alter the glycosylation pattern of recombinant erythropoietin to slow the hormone's metabolism and prolong its active half-life. Darbepoetin alfa, a newer erythropoietic agent with increased sialic acid content compared with epoetin alfa, has a longer terminal half-life than epoetin alfa and is currently approved by the US Food and Drug Administration for once-weekly dosing in chemotherapy-related anemia. Experience with this compound in less frequent dosing schedules is increasing; it is now commonly used once every 2 weeks in clinical practice. However, at present, neither epoetin alfa nor darbepoetin alfa are approved by the US Food and Drug Administration for longer interval dosing, and it is also unclear whether erythropoietic agents' tissue half-life or cycles of erythropoietin receptor activation are more critical in determining efficacy. Further study is needed for both agents to determine what the most effective doses and schedules might be.¹⁵⁻¹⁷

Administering weekly epoetin alfa for a few doses to induce an initial Hb increment (induction) and then switching to a more infrequent maintenance dosing schedule is another attractive approach. The potential efficacy of this strategy is supported by preclinical data¹⁸ and by a preliminary human trial.¹⁹ The goal of the present study was to compare 120,000 U of epoetin alfa administered every 3 weeks with standard weekly maintenance epoetin alfa treatment (40,000 U) in patients with cancer-associated anemia who had all received a short (three-dose) weekly epoetin induction regimen. Efficacy was measured in terms of RBC transfusion needs, QOL, and various Hb end points. These end points were studied in the context of a randomized, unblinded, cooperative group trial.

PATIENTS AND METHODS

Patient Eligibility

The NCCTG conducted this trial. All participants provided written informed consent. The NCCTG, the National Cancer Institute, and an institutional review board at each participating site approved the study. Eligible patients were at least 18 years old and had anemia (males: Hb < 12.0 g/dL; females: Hb < 11.0 g/dL) believed to be related to a nonmyeloid cancer or antineoplastic therapy, a life expectancy of more than 6 months, a Zubrod performance status of 0 to 2, and a normal or elevated serum ferritin (≥ 20 ng/mL). Patients did not have to be receiving antineoplastic therapy to enroll. Patients with anemia secondary to vitamin deficiency, bleeding, or hemolysis were excluded, as were pregnant or nursing women and patients undergoing stem-cell transplantation. Additional exclusions included uncontrolled hypertension or cardiac arrhythmia, recent thromboembolism (unless receiving anticoagulation), untreated brain metastases or seizures, and previous treatment with an erythropoietic agent within 6 months. Patients who had undergone surgery or erythrocyte transfusion were required to wait at least 14 days before enrollment. All patients had a CBC less than 7 days before study registration (baseline). Endogenous erythropoietin level, creatinine, and ferritin were measured less than 30 days before enrollment.

Study Treatment

All patients were centrally randomly assigned immediately upon enrollment and were scheduled to receive epoetin alfa 40,000 U SC for 3 weeks (weeks 0, 1, and 2) and then assigned either to continue epoetin alfa 40,000 U weekly (40K arm) or to receive epoetin alfa 120,000 U every 3 weeks (120K arm), both SC, starting on week 3 and continuing for 18 additional weeks. Because of the differing treatment schedules and their potential effect on QOL, patients and clinicians were not blinded to allocation. The dose of 120,000 U (drug concentration, 40,000 U/mL) required two or three simultaneous injec-

tions. The drug was administered by a health care provider; self-injection was not permitted, and dose escalation was not used for nonresponse.

If the Hb exceeded 13.0 g/dL during the study, epoetin alfa was held, and Hb was monitored weekly until Hb was ≤ 12.0 g/dL; then epoetin was restarted at a reduced dose (30,000 U weekly or 80,000 U every 3 weeks, depending on random assignment). No further dose adjustments were permitted. All patients were administered ferrous sulfate 324 mg orally daily but were permitted to discontinue this if GI adverse effects became intolerable.

Assessment of End Points

The primary study end point was the proportion of patients receiving RBC transfusions in each arm. Transfusions were administered only for Hb ≤ 8.0 g/dL, unless patients were judged by the treating clinician to have intolerable or dangerous ischemic symptoms at a higher level of Hb. Secondary end points included changes in Hb or QOL from baseline measurements. Hb was assessed weekly during induction and at least every 3 weeks thereafter, with additional measurements before transfusions and at clinician discretion.

QOL instruments included the anemia subscale of the Functional Assessment of Cancer Therapy (13 items),²⁰ the Symptom Distress Scale (13 items),²¹ the Brief Fatigue Inventory (BFI; nine items),²² and 12 linear analog self-assessment (LASA) items.²³ These instruments were incorporated into a booklet designed to be completed by patients in 10 to 15 minutes. Patients completed QOL assessments every 3 to 4 weeks at office visits before they were told their current Hb level or the status of their cancer to avoid confounding. All QOL scores were transformed to a 100-point scale (100 being optimal) to simplify comparisons.²⁴

Statistical Methods

The intent-to-treat patient population was defined as all registered patients. Eligible patients receiving at least one dose of study drug were considered assessable for safety and efficacy. The QOL-assessable population included patients who had a baseline QOL assessment and at least one subsequent QOL measurement.

There were five stratification variables, as follows: (1) actively receiving chemotherapy or radiotherapy or both versus not; (2) actively receiving platinum-based therapy (ie, carboplatin or cisplatin, which are agents that are especially toxic to renal cells) versus not; (3) degree of anemia (baseline Hb ≥ 9.0 v < 9.0 g/dL); (4) age (≤ 60 v > 60 years); and (5) type of neoplasm (hematologic neoplasm v all other neoplasms).

Fisher's exact test was used for comparing binary events across treatments, including efficacy and toxicity rates and categoric QOL variables. Independent sample *t* test procedures assessed QOL changes over time. Further analysis was carried out using repeated-measures analysis of

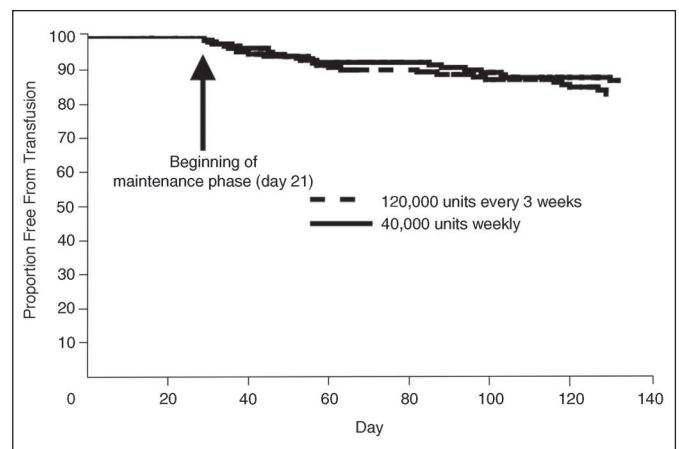


Fig 1. Kaplan-Meier curve of freedom from RBC transfusion during the maintenance phase of this study (ie, after 3 weeks of once-weekly induction therapy with epoetin alfa) for patients continuing to receive 40,000 U of epoetin alfa weekly (solid line) versus patients receiving 120,000 U of epoetin alfa every 3 weeks (dashed line).

Table 2. Changes in Hb During the Study

Measure	Epoetin Alfa Dose		Total (N = 360)	P
	40,000 U (n = 179)	120,000 U (n = 181)		
Baseline Hb, g/dL				.29
No. of patients	179	181	360	
Mean	10.2	10.1	10.2	
SD	0.73	0.80	0.77	
Range	8.1-11.5	7.6-11.8	7.6-11.8	
Last Hb, g/dL				.0006
No. of patients	179	181	360	
Mean	12.0	11.5	11.7	
SD	1.46	1.50	1.50	
Range	7.7-15.3	6.1-15.0	6.1-15.3	
Hb change during study, g/dL				.0097
No. of patients	179	181	360	
Mean	1.8	1.4	1.6	
SD	1.55	1.60	1.59	
Range	-2.5-5.3	-5.4-4.9	-5.4-5.3	
Maximum Hb, g/dL				.0002
No. of patients	179	181	360	
Mean	13.1	12.6	12.9	
SD	1.28	1.37	1.35	
Median	13.4	12.7	13.1	
≥ 2-point Hb increase from baseline				.05
No				
No. of patients	42	59	101	
%	23	33	28	
Yes				
No. of patients	137	122	259	
%	77	67	72	
≥ 2-point Hb increase from baseline after week 4				.02
No				
No. of patients	45	66	111	
%	25	36	31	
Yes				
No. of patients	134	115	249	
%	75	64	69	
≥ 3-point Hb increase from baseline				.0062
No				
No. of patients	81	108	189	
%	45	60	53	
Yes				
No. of patients	98	73	171	
%	55	40	48	
≥ 3-point Hb increase from baseline after week 4				.0031
No				
No. of patients	85	114	199	
%	47	63	55	
Yes				
No. of patients	94	67	161	
%	53	37	45	
Any Hb ≥ 13 g/dL				< .0001
No				
No. of patients	63	103	166	
%	35	57	46	
Yes				
No. of patients	116	78	194	
%	65	43	54	

(continued on following page)

Table 2. Changes in Hb During the Study (continued)

Measure	Epoetin Alfa Dose		Total (N = 360)	P
	40,000 U (n = 179)	120,000 U (n = 181)		
Any Hb \geq 13 g/dL after week 4				< .0001
No				
No. of patients	67	111	178	
%	37	61	49	
Yes				
No. of patients	112	70	182	
%	63	39	51	
Any Hb \geq 15				.30
No				
No. of patients	169	175	344	
%	94	97	96	
Yes				
No. of patients	10	6	16	
%	6	3	4	
Any Hb \geq 15 g/dL after week 4				.18
No				
No. of patients	169	176	345	
%	94	97	96	
Yes				
No. of patients	10	5	15	
%	6	3	4	

Abbreviations: Hb, hemoglobin; SD, standard deviation.

variance/generalized estimating equation modeling to assess the relative contributions of variables such as baseline demographics, Hb, ferritin, and endogenous erythropoietin.

With 150 patients planned per arm, there was \geq 80% power to detect a 13% difference (through Fisher's exact test) in the true percentage of patients who needed RBC transfusion (primary end point) if the proportion requiring transfusions in the inferior arm was less than 25%, using a 5% type I error rate and two-sided alternative. Secondary end points included Hb increment from baseline, toxicity, and QOL. With respect to QOL, the study had \geq 80% power to detect an 8% difference (through the *t* test) in QOL scores across the two groups. Although overall survival was monitored, the study was not powered to detect a difference.

RESULTS

Patient Characteristics

Three hundred sixty-five patients at 16 NCCTG sites were registered between study activation in June 2003 and closure in March 2004. There were three early cancellations (before an epoetin alfa dose was administered) and two ineligible patients (one had myelodysplasia and the other received epoetin within 6 months of random assignment). Therefore, 360 patients were assessable for efficacy and toxicity. During the 3-week induction phase, 16 patients (4%) died or dropped out and did not reach the maintenance phase. These patients (six in the 40K arm and 10 in the 120K arm) were included with their assignment arm in the intent-to-treat analysis. Results of the analysis were unchanged when data were reanalyzed with these patients excluded. Overall, 67% of the patients randomly assigned to the 40K arm and 69% of the patients assigned to the 120K arm completed at least 18 of the 21 weeks of the study. The majority of patients (63%) completed

all protocol therapy. Baseline characteristics were comparable (Table 1); 89% of patients were receiving chemotherapy.

Efficacy of Epoetin Alfa on Transfusion Requirements and Hb End Points

In terms of the primary end point, which was the proportion of patients in each arm requiring transfusions, the treatment groups were similar; overall, 41 patients (23%) in the 40K arm received transfusion compared with 32 patients (18%) in the 120K arm (+5% difference; 95% CI for the difference, -4% to +13%; *P* = .22). The total number of RBC units transfused during the study was 135 in the 40K arm and 109 in the 120K arm. Dividing these figures by the total number of days that patients in each arm were alive and on study yielded a transfusion units per patient per day alive on study measure of 0.0063 on the 40K arm and 0.0053 for the 120K arm (*P* < .0001 favoring 120K). The proportion of patients who received transfusion during or after week 4 (ie, during the maintenance phase) was 13% (*n* = 24) in the 40K arm and 15% (*n* = 28) in the 120K arm (*P* = .58; Fig 1).

Hb data are listed in Table 2 and shown in Figure 2. Patients enrolled onto the 40K arm had a slightly higher mean end-of-study Hb than patients enrolled onto the 120K arm (12.0 v 11.5 g/dL, respectively; *P* = .0006; 95% CI for the difference in means, 0.2 to 0.8 g/dL) and a greater mean increase in Hb from baseline to last measured value (1.8 v 1.4 g/dL, respectively; *P* = .01; 95% CI for the difference in means, 0.1 to 0.8 g/dL). In addition, patients on the 40K arm, compared with patients on the 120K arm, were more likely to have a \geq 2 g/dL or \geq 3 g/dL increase in Hb from baseline to last value (77% v 67%, respectively, for 2 g/dL; *P* = .05; 95% CI for the difference in proportions, 0% to 18%; and 55% v 40%, respectively, for 3 g/dL; *P* = .006; 95% CI for the difference in proportions, 4% to 25%) and

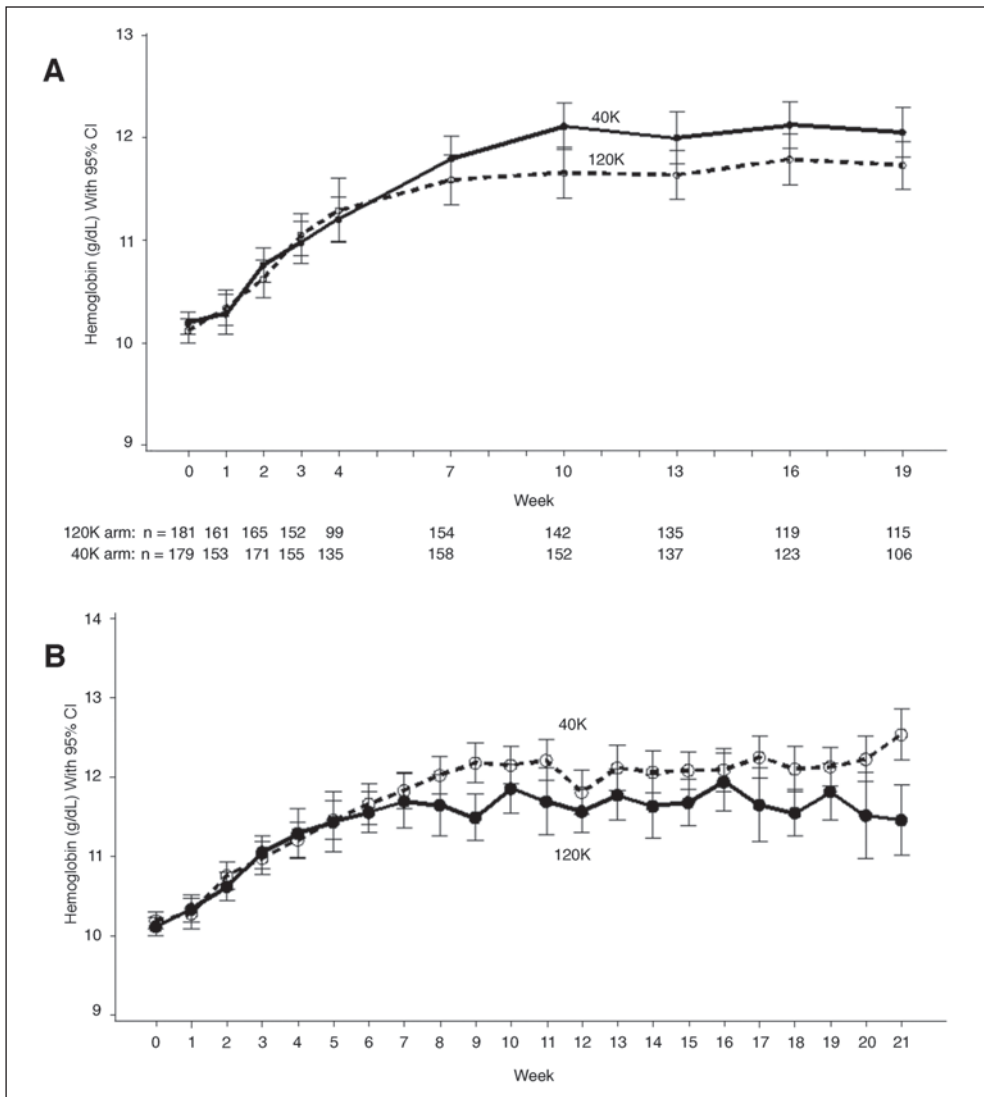


Fig 2. Mean hemoglobin (Hb) levels for each study group during induction and maintenance therapy with epoetin alfa. N denotes the number of patients with Hb assessments at each time point. Week 0 data indicate Hb value at the time of study registration and first dose. 40K, 40,000 U of epoetin alfa weekly; 120K, 120,000 U of epoetin alfa every 3 weeks.

were more likely to have an Hb value of ≥ 13 g/dL at some point (65% v 43%, respectively; $P < .0001$; 95% CI for the difference in proportions, 12% to 32%).

Because patients on the 40K schedule were seen more frequently for epoetin injections, they potentially had a chance to be assessed more frequently by a treating physician and have a CBC drawn, because although CBCs were mandated at least every 3 weeks for both treatment groups, they could be performed at any time at physician discretion. The mean number of Hb measurements per patient during the course of the study was 13.3 in the 40K arm and 9.8 in the 120K arm ($P < .0001$). However, if the comparison points are restricted to every-3-week intervals during the maintenance period (when patients on both arms had a CBC, except for the small group of patients who got off schedule as the result of the need to delay a dose of epoetin for high Hb), the Hb is still greater at each assessment in the 40K arm (Fig 2).

Changes in QOL

Three hundred three patients (84%) were assessable for QOL, and for these patients, only 8% of data were missing. Of the 360

efficacy-assessable patients, one had no QOL data, 24 had only baseline data, and 32 had follow-up data but no baseline QOL data. QOL data (Table 3) were analyzed using various approaches to missing data involving simple and multiple imputation.²⁵ Although the overall QOL profile changed depending on the imputation method, comparisons across treatment arms did not. In Table 3, the aggregate scores for the Symptom Distress Score items are listed; in addition to lack of difference in the aggregate score, no individual item showed a statistically significant difference between arms. Like Fatigue Now, shown in Table 3, the other BFI items (eg, Usual Level of Fatigue and Fatigue Interference With Work) also showed no statistically significant differences between arms. The baseline global QOL measurement (LASA) was lower in the 120K arm than in the 40K arm (mean score, 62 v 67, respectively; $P = .03$) for unclear reasons. However, the improvement in LASA score during the study was greater in the 120K arm (mean change, +5.9 in 120K arm v -0.3 in the 40K arm [+6.2]; $P = .02$; 95% CI for the difference, +0.9 to +11.4), so end-of-study scores for global QOL (LASA) were comparable. Other QOL scores (Symptom Distress Scale, BFI, and Functional Assessment of Cancer

Epoetin Maintenance Dosing Schedule in Anemia

Table 3. QOL Results

Measure	Epoetin Alfa Dose		Total (N = 360)	P
	40,000 U (n = 179)	120,000 U (n = 181)		
Baseline LASA score				.03
No. of patients	161	164	325	
Mean	66.9	62.0	64.4	
SD	21.80	21.22	21.62	
LASA score change during study				.02
No. of patients	161	164	325	
Mean	-0.3	+5.9	+2.8	
SD	22.43	25.57	24.23	
≥ 10% improvement in LASA				.09
No				
No. of patients	122	108	230	
%	68	60	64	
Yes				
No. of patients	57	73	130	
%	32	40	36	
Baseline SDS score				.29
No. of patients	161	164	325	
Mean	72.7	71.1	71.9	
SD	12.98	14.50	13.77	
SDS score change during study				.53
No. of patients	161	164	325	
Mean	+3.2	+4.9	+4.0	
SD	13.18	14.32	13.77	
≥ 10% improvement in SDS score				.88
No				
No. of patients	120	120	240	
%	67	66	67	
Yes				
No. of patients	59	61	120	
%	33	34	33	
Baseline BFI Fatigue Now score				.24
No. of patients	160	163	323	
Mean	43.4	39.8	41.6	
SD	25.13	23.66	24.42	
BFI Fatigue Now score change during study				.88
No. of patients	160	163	323	
Mean	+9.1	+10.7	+9.9	
SD	30.67	31.09	30.85	
≥ 10% improvement in BFI Fatigue Now score				.84
No				
No. of patients	100	103	203	
%	56	57	56	
Yes				
No. of patients	79	78	157	
%	44	43	44	
Baseline FACT-An score				.062
No. of patients	160	165	325	
Mean	55.7	51.8	53.7	
SD	20.13	17.10	18.73	
FACT-An score change during study				.51
No. of patients	160	165	325	
Mean	+5.7	+7.6	+6.6	
SD	17.21	19.17	18.23	
≥ 10% Improvement in FACT-An score?				.74
No				
No. of patients	102	100	202	
%	57	55	56	
Yes				
No. of patients	77	81	158	
%	43	45	44	

Abbreviations: QOL, quality of life; SD, standard deviation; LASA, Linear Analog Self-Assessment; SDS, Symptom Distress Score; BFI, Brief Fatigue Inventory; FACT-An, Functional Assessment of Cancer Therapy–Anemia.

Therapy–Anemia) were equivalent between groups at baseline, and changes during the study were not different between study arms. Table 4 lists the Uniscale data with various imputation methods for missing data. There were no statistically significant differences in changes in the Zubrod score between treatment arms during the study ($P = .62$).

Adverse Events

Adverse events were monitored and graded using the National Cancer Institute Common Toxicity Criteria version 2.0. The incidence of adverse effects was similar between the two arms. An epoetin alfa dose was held as a result of high Hb (> 13.0 g/dL) more frequently in the 40K arm than in the 120K arm (61% ν 36%, respectively; $P < .0001$). The incidence of ischemic and thrombotic events of any type (eight patients in 40K arm ν nine patients in 120K arm; $P = .80$) was low and comparable between arms. The rate of Hb increase at every time point was lower for patients who had thrombotic events than for the whole study population (eg, week 4, $P = .0001$).

Survival

Twenty-seven patients (8%; 14 on the 40K arm and 13 on the 120K arm) died during the treatment phase (21 weeks) of the study. The median survival time in the 40K arm (79 deaths) was 377 days,

whereas the median survival time in the 120K arm (73 deaths) was 403 days ($P = .24$; Fig 3). Enrolled patients had diverse tumor types and stages; these and other tumor site–specific prognostic data were not systematically collected.

DISCUSSION

Despite the potential benefits of erythropoietic agents in cancer-associated anemia, less than one half of eligible persons currently receive therapy with these drugs.²⁶ Many factors may contribute to this putative underuse, including inconvenience of the administration route (injection) and of US Food and Drug Administration–approved schedules (once weekly or three times per week). The results of this study suggest that, after three weekly doses of epoetin alfa, patients can safely receive 120,000 U (three times the fixed weekly dose) once every 3 weeks to consolidate and maintain erythropoietic gains, with similar efficacy in terms of transfusion end points and QOL compared with continuing weekly epoetin. Toxicity is also comparable between these two approaches. However, although the every-3-week epoetin alfa

Table 4. Summary of Imputed Uniscale AUC

Measure	Epoetin Alfa Dose		Total (N = 360)	P
	40,000 U (n = 179)	120,000 U (n = 181)		
Uniscale AUC				.53
No. of patients	155	147	302	
Mean	1,110.0	1,075.2	1,093.0	
SD	524.09	440.33	484.64	
Median	1,130.0	1,155.0	1,142.5	
Q1	745.0	875.0	795.0	
Q3	1,540.0	1,380.0	1,445.0	
Range	90.0-2,100.0	135.0-1,980.0	90.0-2,100.0	
Uniscale AVCF AUC				.54
No. of patients	179	181	360	
Mean	1,414.4	1,386.8	1,400.5	
SD	383.32	365.71	374.30	
Median	1,445.0	1,409.2	1,417.9	
Q1	1,147.1	1,171.3	1,152.5	
Q3	1,695.0	1,645.0	1,679.6	
Range	292.5-2,100.0	420.0-2,100.0	292.5-2,100.0	
Uniscale MVCF AUC				.40
No. of patients	179	181	360	
Mean	1,360.2	1,323.5	1,341.8	
SD	406.89	379.87	393.41	
Median	1,380.0	1,360.0	1,365.0	
Q1	1,070.0	1,110.0	1,097.5	
Q3	1,680.0	1,575.0	1,625.0	
Range	165.0-2,100.0	370.0-2,100.0	165.0-2,100.0	
Uniscale LVCF AUC				.86
No. of patients	179	181	360	
Mean	1,404.2	1,393.8	1,399.0	
SD	399.72	383.61	391.19	
Median	1,430.0	1,420.0	1,425.0	
Q1	1,130.0	1,200.0	1,145.0	
Q3	1,705.0	1,680.0	1,685.0	
Range	250.0-2,100.0	420.0-2,100.0	250.0-2,100.0	

Abbreviations: AUC, area under the curve; SD, standard deviation; Q, quartile; AVCF, average value carried forward (imputation method); MVCF, minimum value carried forward; LVCF, last value carried forward.

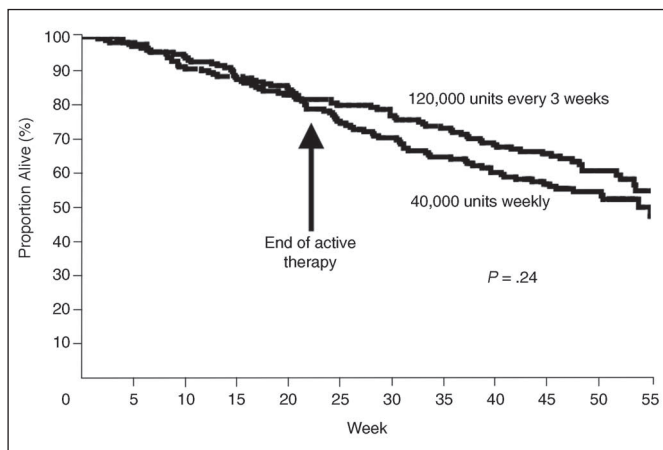


Fig 3. Kaplan-Meier curve of overall survival for patients receiving 40,000 U of epoetin alpha weekly versus patients receiving 120,000 U of epoetin alpha every 3 weeks. The minimum P [r] value achieved with week-by-week comparisons was $P = .09$ at week 35.

regimen may be more convenient than weekly dosing, there may be a trade-off; Hb end points were not equivalent between the two schedules, even when we accounted for the more frequent discretionary blood count measurements in the weekly therapy group.

The greater frequency with which blood counts were obtained in the 40K arm must be considered when analyzing this study's results. Because a health care provider assessed such patients more frequently (ie, while patients received the weekly injection), there were more opportunities for obtaining blood counts, considering transfusion, or documentation of potential drug toxicity. When this trial was being designed, blinding with placebo controls and mandating weekly Hb and toxicity assessments in both arms was considered. These ideas were ultimately rejected because doing so might have altered QOL assessment in the 120K group if the convenience of less frequent travel and office visits contributed to QOL. Indeed, global QOL improvement during the study was greater in the 120K group, although it is not possible to assign causation. Lack of blinding and assessment bias may also have confounded assessments of some transfusion and Hb end points. However, the mean Hb increase from baseline to end of study was superior in the 40K group, and this difference is unlikely to be a result of bias. Additionally, at each point during the maintenance phase when scheduled measurements were taken from patients in both groups, the mean Hb value favored the 40K arm (Fig 2).

There is growing concern about a possible increased risk of thrombosis in patients treated with erythropoietic agents to a goal Hb level of more than 12 g/dL.² Several erythropoietin treatment trials in which Hb normalization was attempted were stopped prematurely because of excess adverse events in the treatment arm, and other studies raised the specter of inferior overall or progression-free survival, although all published trials have had methodologic limitations.²⁷⁻³² When this study opened in 2003, maintenance epoetin alpha doses were to be withheld only for an Hb level of more than 15.0 g/dL, but new adverse event data prompted revision to an Hb level of more than 13.0 g/dL (at that time, only a few patients had been enrolled, and none had reached Hb > 15.0 g/dL). The epoetin alpha product labels were voluntarily changed in 2004 by the manufacturers to recommend holding epoetin alpha treatment if the Hb is more than 13.0 g/dL and reinitiating with a 25% dose reduction when Hb decreases to less

than 12.0 g/dL. Therefore, although the Hb increment in the weekly 40K arm was greater in this study, this is not necessarily salutary; the 40K arm also had epoetin alpha doses held more often for Hb levels of more than 13.0 g/dL. We do not know whether 120K therapy is associated with a similar time with Hb more than 13.0 g/dL because we did not mandate weekly Hb assessment between doses, but no immediate dosing decision could have been made if that information were available.

Although there was no difference between treatment groups in the proportion of patients receiving transfusions during the maintenance phase, the overall number of transfusion events in both arms was relatively low. This may be because this study enrolled patients with a higher mean Hb (10.1 g/dL) than some other trials of erythropoietic agents and because a transfusion rule was specified. Many patients were enrolled and started on epoetin therapy at Hb levels where transfusion would not ordinarily be contemplated. This reflects typical clinical practice, but specification of transfusions as the primary end point (chosen because of predicted Hb ascertainment bias) must be considered a study limitation. Differences in Hb assessment frequency could also affect transfusion frequency, resulting in more transfusions in the 40K arm, potentially equalizing the primary end point when the 120K arm would otherwise be inferior.

The total planned dose of epoetin alpha administered in this study was equivalent between arms to evaluate the specific effect of treatment schedule. It may actually be possible to administer epoetin alpha doses of less than 120K on an every-3-week schedule with similar efficacy, which would have an overall cost benefit. It might also be possible to administer epoetin alpha less frequently right from the start of therapy (ie, no induction phase), although a nonhuman primate model suggested that doing this might result in slower Hb improvement.¹⁸ Such questions could be addressed in a future study, perhaps also comparing darbepoetin alpha and including formal economic analysis.

This study was a comparative trial. Demonstrating strict equivalence between two therapies can require a much larger treatment group than what was enrolled onto this study.³³

Several previously published studies described improvement in various measurements of QOL in anemic cancer patients treated with epoetin alpha.³⁴⁻³⁶ However, the most recent placebo-controlled NCCTG epoetin study by Witzig et al,¹² although demonstrating Hb improvement and transfusion reduction with active therapy, showed no QOL difference despite apparently adequate power to detect a difference. In this study, we compared QOL changes between two active therapy arms, so the power to detect relevant differences is less than in a placebo-controlled trial. There was an increased QOL improvement in the 120K arm relative to the standard 40K arm, but patients started treatment at different QOL levels. The reasons for baseline differences in QOL between study groups are unknown and were observed only with the global QOL measurement tool.

In conclusion, a more convenient every-3-week epoetin alpha maintenance regimen is comparable to standard weekly epoetin alpha in terms of QOL and transfusion needs in patients with cancer-associated anemia. Clinicians must decide whether the possibly slightly inferior Hb measurements outweigh the added convenience of this dosing schedule and whether these inferior Hb measurements are clinically meaningful.

REFERENCES

1. Spivak JL: Cancer-related anemia: Its causes and characteristics. *Semin Oncol* 21:3-8, 1994
2. Steensma DP: Management of anemia in patients with cancer. *Curr Oncol Rep* 6:297-304, 2004
3. Cella D: Factors influencing quality of life in cancer patients: Anemia and fatigue. *Semin Oncol* 25:43-46, 1998
4. Ludwig H, Strasser K: Symptomatology of anemia. *Semin Oncol* 28:7-14, 2001
5. Goodnough LT: Erythropoietin therapy versus red cell transfusion. *Curr Opin Hematol* 8:405-410, 2001
6. Oster W, Herrmann F, Gamm H, et al: Erythropoietin for the treatment of anemia of malignancy associated with neoplastic bone marrow infiltration. *J Clin Oncol* 8:956-962, 1990
7. Eschbach JW, Egrie JC, Downing MR, et al: Correction of the anemia of end-stage renal disease with recombinant human erythropoietin: Results of a combined phase I and II clinical trial. *N Engl J Med* 316:73-78, 1987
8. Ludwig H, Fritz E, Kotzmann H, et al: Erythropoietin treatment of anemia associated with multiple myeloma. *N Engl J Med* 322:1693-1699, 1990
9. Rizzo JD, Lichtin AE, Woolf SH, et al: Use of epoetin in patients with cancer: Evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *Blood* 100:2303-2320, 2002
10. National Comprehensive Cancer Network: Cancer and treatment-related anemia, in *Clinical Practice Guidelines in Oncology* (version 2.2004), 2004. http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf
11. Gabrilove JL, Cleeland CS, Livingston RB, et al: Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: Improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. *J Clin Oncol* 19:2875-2882, 2001
12. Witzig TE, Silberstein PT, Loprinzi CL, et al: Phase III, randomized, double-blind study of epoetin alfa compared with placebo in anemic patients receiving chemotherapy. *J Clin Oncol* 23:2606-2617, 2005
13. Meehan K, Tchekmedyian S, Ciesla G, et al: The burden of weekly epoetin alfa injections to patients and their caregivers. *Proc Am Soc Clin Oncol* 22:543, 2003 (abstr 2186)
14. Abels RI: Use of recombinant human erythropoietin in the treatment of anemia in patients who have cancer. *Semin Oncol* 19:29-35, 1992
15. Vansteenkiste J, Pirker R, Massuti B, et al: Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. *J Natl Cancer Inst* 94:1211-1220, 2002
16. Smith RE Jr, Tchekmedyian NS, Chan D, et al: A dose- and schedule-finding study of darbepoetin alfa for the treatment of chronic anaemia of cancer. *Br J Cancer* 88:1851-1858, 2003
17. Kotasek D, Steger G, Faught W, et al: Darbepoetin alfa administered every 3 weeks alleviates anaemia in patients with solid tumours receiving chemotherapy: Results of a double-blind, placebo-controlled, randomised study. *Eur J Cancer* 39:2026-2034, 2003
18. Farrell FX, Jolliffe LK: Administration of epoetin alfa every two weeks is able to sustain target hemoglobin in a nonhuman primate alternate dosing model. *Blood* 98:297a, 2001 (abstr 1253)
19. Patton J, Kuzur M, Liggett W, et al: Epoetin alfa 60,000 U once weekly followed by 120,000 U every 3 weeks increases and maintains hemoglobin levels in anemic cancer patients undergoing chemotherapy. *Oncologist* 9:90-96, 2004
20. Cella D: The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: A new tool for the assessment of outcomes in cancer anemia and fatigue. *Semin Hematol* 34:13-19, 1997
21. McCorkle R, Young K: Development of a symptom distress scale. *Cancer Nurs* 1:373-378, 1978
22. Mendoza TR, Wang XS, Cleeland CS, et al: The rapid assessment of fatigue severity in cancer patients: Use of the Brief Fatigue Inventory. *Cancer* 85:1186-1196, 1999
23. Bretscher M, Rummans T, Sloan J, et al: Quality of life in hospice patients: A pilot study. *Psychosomatics* 40:309-313, 1999
24. Sloan JA, Dueck A: Issues for statisticians in conducting analyses and translating results for quality of life end points in clinical trials. *J Biopharm Stat* 14:73-96, 2004
25. Fairclough DL, Cella DF: Functional Assessment of Cancer Therapy (FACT-G): Non-response to individual questions. *Qual Life Res* 5:321-329, 1996
26. Demetri GD: Anaemia and its functional consequences in cancer patients: Current challenges in management and prospects for improving therapy. *Br J Cancer* 84:31-37, 2001 (suppl 1)
27. Rosenzweig MQ, Bender CM, Lucke JP, et al: The decision to prematurely terminate a trial of R-HuEPO due to thrombotic events. *J Pain Symptom Manage* 27:185-190, 2004
28. Leyland-Jones B: Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncol* 4:459-460, 2003
29. Henke M, Laszig R, Rube C, et al: Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: Randomised, double-blind, placebo-controlled trial. *Lancet* 362:1255-1260, 2003
30. Glaspy J, Dunst J: Can erythropoietin therapy improve survival? *Oncology* 67:5-11, 2004 (suppl 1)
31. Leyland-Jones B, Mahmud S: Erythropoietin to treat anaemia in patients with head and neck cancer. *Lancet* 363:80, 2004
32. Steensma DP, Loprinzi CL: Erythropoietin use in cancer patients: A matter of life and death? *J Clin Oncol* 23:5865-5868, 2005
33. Julious SA: Sample sizes for clinical trials with normal data. *Stat Med* 23:1921-1986, 2004
34. Patrick DL, Gagnon DD, Zagari MJ, et al: Assessing the clinical significance of health-related quality of life (HrQOL) improvements in anemic cancer patients receiving epoetin alfa. *Eur J Cancer* 39:335-345, 2003
35. Littlewood TJ, Bajetta E, Nortier JW, et al: Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving non-platinum chemotherapy: Results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 19:2865-2874, 2001
36. Crawford J, Cella D, Cleeland CS, et al: Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. *Cancer* 95:888-895, 2002

Appendix

The following institutions and investigators also participated in this study: Iowa Oncology Research Association Community Clinical Oncology Program (CCOP), Des Moines, IA (Roscoe F. Morton, MD); Rapid City Regional Oncology Group, Rapid City, SD (Larry P. Ebbert, MD); Mayo Clinic Scottsdale CCOP, Scottsdale, AZ (Robert F. Marschke Jr, MD); CentraCare Clinic, St Cloud, MN (Harold E. Windschitl, MD); Geisinger Clinical Oncology Program, Danville, PA (Suresh Nair, MD); Grand Forks Clinic, Ltd, Grand Forks, ND (John A. Laurie, MD); Metro-Minnesota CCOP, St Louis Park, MN (Patrick J. Flynn, MD); Quain and Ramstad Clinic, Bismarck, ND (Ferdinand Addo, MD); Meritcare Hospital CCOP, Fargo, ND (Ralph Levitt, MD); and Saskatchewan Cancer Foundation, Saskatoon, Saskatchewan, Canada (Maria Tria Tirona, MD).

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Author Contributions

Conception and design: David P. Steensma, Charles L. Loprinzi, Jeff A. Sloan

Administrative support: David P. Steensma, Jeff A. Sloan, Charles L. Loprinzi

Provision of study materials or patients: David P. Steensma, Roy Molina, Daniel A. Nikcevich, Paul L. Schaefer, Kendrith M. Rowland Jr, Todor Dentchev, Paul J. Novotny, Loren K. Tschetter, Steven R. Alberts, Thomas F. Hogan, Amy Law, Charles L. Loprinzi

Collection and assembly of data: David P. Steensma, Jeff A. Sloan, Charles L. Loprinzi, Paul J. Novotny

Data analysis and interpretation: David P. Steensma, Jeff A. Sloan, Charles L. Loprinzi, Paul J. Novotny

Manuscript writing: David P. Steensma, Charles L. Loprinzi, Jeff A. Sloan

Final approval of manuscript: David P. Steensma, Roy Molina, Jeff A. Sloan, Daniel A. Nikcevich, Paul L. Schaefer, Kendrith M. Rowland Jr, Todor Dentchev, Paul J. Novotny, Loren K. Tschetter, Steven R. Alberts, Thomas F. Hogan, Amy Law, Charles L. Loprinzi