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ORIGINAL REPORT

Randomized, Multicenter, Controlled Trial Comparing the Efficacy and Safety of Darbepoetin Alfa Administered Every 3 Weeks With or Without Intravenous Iron in Patients With Chemotherapy-Induced Anemia

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

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ABSTRACT

Purpose
The concomitant use of intravenous (IV) iron as a supplement to erythropoiesis-stimulating agents in patients with chemotherapy-induced anemia is controversial. This study was designed to evaluate the efficacy and safety of darbepoetin alfa given with IV iron versus with local standard practice (oral iron or no iron).

Patients and Methods
In this multicenter, randomized, open-label, phase III study, 396 patients with nonmyeloid malignancies and hemoglobin (Hb) less than 11 g/dL received darbepoetin alfa 500 μg with (n = 200) or without (n = 196) IV iron once every 3 weeks (Q3W) for 16 weeks.

Results
The hematopoietic response rate (proportion of patients achieving Hb ≥ 12 g/dL or Hb increase of ≥ 2 g/dL from baseline) was significantly higher in the IV iron group: 86% versus 73% in the standard practice group (difference of 13% [95% CI, 3% to 23%]; $P = .011$). Fewer RBC transfusions (week 5 to the end of the treatment period) occurred in the IV iron group: 9% versus 20% in the standard practice group (difference of −11% [95% CI, −18% to −3%]; $P = .005$). Both treatments were well tolerated with no notable differences in adverse events. Serious adverse events related to iron occurred in 3% of patients in the IV iron group and were mostly gastrointestinal in nature.

Conclusion
Addition of IV iron to darbepoetin alfa Q3W in patients with chemotherapy-induced anemia was well tolerated, resulting in an improved hematopoietic response rate and lower incidence of transfusions compared with darbepoetin alfa alone.

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INTRODUCTION

Chemotherapy-induced anemia (CIA) is a significant problem for patients with cancer, causing fatigue and reducing quality of life (QOL).[1,2] Mild-to-moderate anemia (hemoglobin [Hb] level of 9 to 11 g/dL) has been reported in up to 75% of patients with cancer who are undergoing chemotherapy and/or radiotherapy in clinical trials[1,3] and can be effectively managed with erythropoiesis-stimulating agents (ESAs).[4-8] Approximately 50% to 70% of patients treated with ESAs in clinical trials respond to treatment as measured by hematopoietic response rates.[4-8]

The significance of iron in the response to ESAs is increasingly recognized.[9-16] American Society of Hematology/American Society of Clinical Oncology guidelines do not address intravenous (IV) iron use[17]; National Comprehensive Cancer Network guidelines recommend iron supplementation, especially IV iron, if ferritin is less than 100 ng/mL and transferrin saturation is less than 20%.[18] European Organisation for Research and Treatment of Cancer guidelines cite improved response to ESAs with IV iron but indicate the need to define optimal dose and schedule.[19]

Although IV iron supplementation has been relatively well studied in the renal anemia setting,[12-14] little data in patients with CIA exist. One peer-reviewed, randomized, controlled trial with 157 patients with CIA receiving recombinant human erythropoietin (rHuEPO) reported significantly higher hematopoietic response rates with IV iron (68% in both weekly 100-mg bolus or total-dose

infusion groups) than with oral (36%) or no iron (25%).[16] A study with 129 assessable patients[20] showed enhanced response rates to rHuEPO with IV iron versus oral or no iron, whereas another[21] reported significantly increased responses when IV iron was administered with epoetin beta treatment in anemic patients with lymphoproliferative malignancies not receiving chemotherapy.

The present study investigates whether response to darbepoetin alfa in patients with CIA is improved with concomitant IV iron use compared with local standard practice (oral iron or no iron).

PATIENTS AND METHODS

Study Design and Population

This multicenter, randomized, open-label study compared hematopoietic response in patients with CIA receiving darbepoetin alfa 500 μg every 3 weeks (Q3W) subcutaneously (SC) with or without IV iron.

Men and women aged $\geq$ 18 years of age with anemia (Hb $<$11 g/dL within 24 hours before randomization) and nonmyeloid malignancy were enrolled. Patients were required to have an Eastern Cooperative Oncology Group performance status score of 0 to 2, adequate renal and liver function, and $\geq$ 8 weeks of cytotoxic chemotherapy planned. Patients with chronic myeloid leukemia, acute myeloid or lymphocytic leukemia, hairy cell leukemia, Burkitt's lymphoma, or lymphoblastic lymphoma were excluded, as were those with a history of thromboembolism or primary hematologic disorder (other than malignancy) that could cause anemia. Patients with iron deficiency (transferrin saturation $<$ 15% and serum ferritin $<$ 10 ng/mL), serum ferritin more than 800 ng/mL, or those who had received an RBC transfusion within 14 days or any ESA within the 4 weeks preceding randomization were excluded.

The study protocol was approved by the appropriate independent ethics committee at each participating center and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before study commencement.

Study End Points

The end points evaluated here are described more completely elsewhere.[7] The primary efficacy end point was the Kaplan-Meier proportion of patients achieving a hematopoietic response (Hb $\geq$ 12 g/dL or a $\geq$ 2-g/dL increase in Hb during the 16-week treatment period, in the absence of RBC transfusions within the previous 28 days). Secondary end points included time to hematopoietic response, proportion of patients requiring one or more RBC transfusion between week 5 and the end of the treatment period (EOTP) and between week 1 and EOTP, proportion of patients achieving Hb levels $\geq$ 11 g/dL (a level associated with symptom improvement[24]), QOL as measured by Functional Assessment of Cancer Therapy-Fatigue (FACT-F) questionnaires, and safety (primarily assessed by adverse event reporting).

Treatment Schedule and Assessments

Study visits occurred at weeks 1 (baseline), 4, 7, 10, 13, and 16. After a 14-day screening period, patients were randomly assigned 1:1 to receive darbepoetin alfa 500 μg Q3W SC plus 200 mg of IV iron delivered Q3W (IV iron arm); or darbepoetin alfa 500 μg Q3W SC plus oral or no iron (standard practice arm) at study visits, except for week 16. Randomization, assigned using an interactive voice response system, was stratified by tumor type (lung/gynecologic v other types) and baseline Hb category ($<$ 10 $v \geq$ 10 g/dL).

Darbepoetin alfa was administered using the Aranesp SureClick autoinjector (Aranesp; Amgen Inc., Thousand Oaks, CA). Patients whose Hb exceeded 14 g/dL had darbepoetin alfa withheld until Hb $\leq$ 13 g/dL. After a protocol amendment, dose adjustments were made to achieve an Hb concentration of 12 g/dL. Darbepoetin alfa doses were withheld if a patient's Hb level exceeded 13 g/dL and were reinstated with a 40% dose reduction (300 μg) after Hb $\leq$ 12 g/dL. Patients with more than a 2-g/dL Hb increase in a 4-week period received darbepoetin alfa 300 μg.

IV iron (either as sodium ferric gluconate complex in sucrose or as iron sucrose injection) was administered in a single Q3W dose of 200 mg on the same day and frequency as darbepoetin alfa or in two 100-mg doses during the 3-week interval if determined to be preferable by the investigator. If a patient's serum ferritin exceeded 1,000 ng/mL, IV iron was withheld and reinstated once ferritin decreased to $\leq$ 1,000 ng/mL.

Transfusions were performed at investigator discretion and were recommended, but not required, for patients with Hb $\leq$ 8.0 g/dL or patients with Hb more than 8 g/dL if they exhibited anemia symptoms.

CBC counts and iron status were evaluated. Hb was assessed before each darbepoetin alfa dose and within 7 to 14 days after study visits through week 10. Baseline endogenous erythropoietin levels were measured, and blood samples were analyzed for the presence of antidarbepoetin alfa antibodies at baseline and at week 16. FACT-F questionnaires were administered at weeks 1, 7, 10, and 16. Relatedness of adverse events to treatment was determined by the investigator.

Statistical Analysis

Primary efficacy data were analyzed for the full analysis set (all patients who were randomly assigned and received one or more darbepoetin alfa dose), with patients analyzed according to randomized treatment. The patient-reported outcome analysis set comprised patients in the full analysis set with both baseline and one or more postbaseline FACT-F score. The safety population comprised all patients who received one or more dose of darbepoetin alfa, with patients analyzed according to treatment received. With a sample size of 200 patients per treatment group, a χ^2 test with a 5% two-sided significance level would have $\geq$ 85% power to detect a difference in hematopoietic response of $\geq$ 15% between the two treatment groups.

Kaplan-Meier methods, adjusting for randomization strata and treatment group, were used to calculate the proportion of patients achieving an end point. A 95% CI was calculated for the overall difference between the treatment groups using Greenwood's formula[22] and tested for statistical significance based on a Z test. Time to hematopoietic response was summarized using Kaplan-Meier methodology and associated 95% CIs. All patients who ended treatment early were considered responders if they met the response criteria at any time before they stopped darbepoetin alfa treatment or were censored at time of withdrawal.

A post hoc sensitivity analysis was performed on the transfusion end point to determine whether there was any imbalance between treatment arms with respect to transfusion administration when Hb was less than 8.0 g/dL. A log-rank test was used to compare treatment groups.

Change in FACT-F subscale score from baseline to EOTP was summarized by an analysis of covariance model that included randomization strata, treatment group, and baseline score. After adjusting for these covariates, model-adjusted means for each treatment group were calculated and a contrast constructed for the difference in mean changes between the treatment groups. The Kaplan-Meier proportion of patients achieving a $\geq$ three-point increase in FACT-F scores, considered a clinically meaningful improvement,[23] was calculated, along with time to reach that change.

RESULTS

Patient Demographics and Baseline Characteristics

Patient disposition is presented in Fig 1. Most patients (67% in the IV iron group, 76% in the standard practice group) completed the study (Fig 1). Reasons for withdrawal were similar across arms (Fig 1).

Three patients in the standard practice arm received IV iron: they were analyzed as treated for safety analyses and as randomly assigned for efficacy analyses. Of the 203 patients who received IV iron, 25 patients (12%) did not receive all iron doses on the same day as darbepoetin alfa; 12 patients (6% of total) received IV iron in divided doses. In the standard practice arm, 51 patients (26%) received oral iron, with an apparent disproportionate administration to patients with lower baseline iron parameters (data not shown).

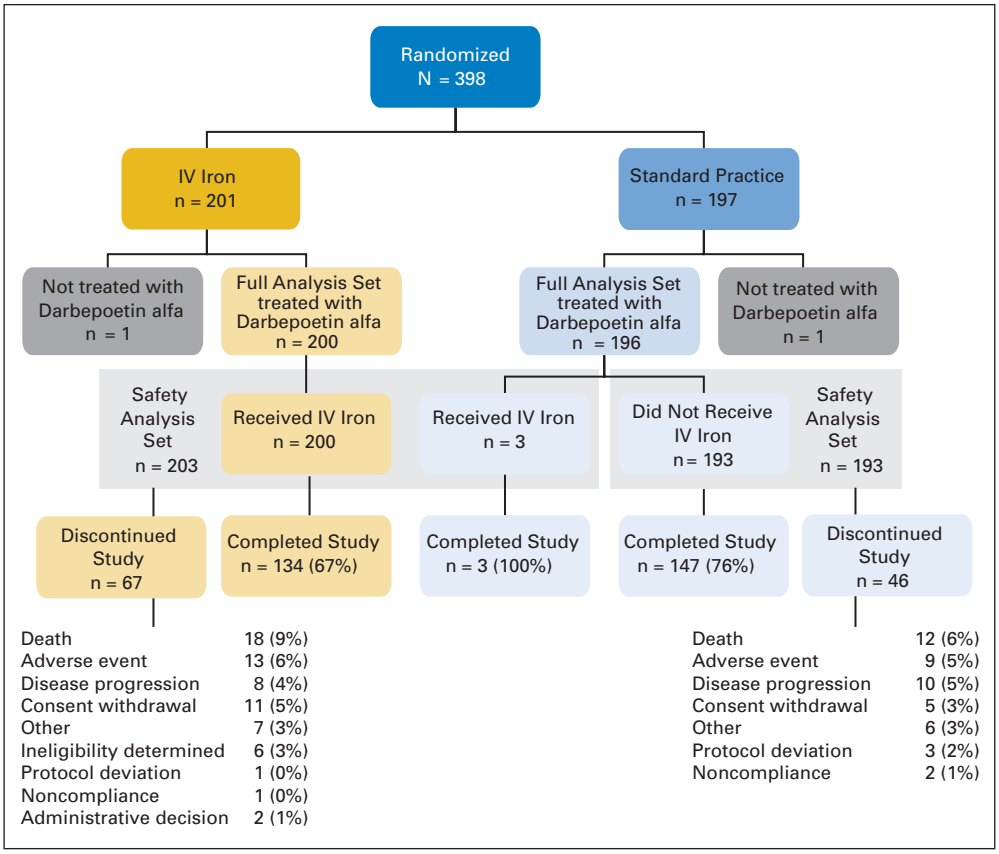

Fig 1. Patient disposition. IV, intravenous.

Baseline demographic, chemotherapy class, and disease characteristics were similar between study arms (Tables 1 and 2). No clinically relevant differences between treatment groups in baseline laboratory parameters were noted, with the exception of a slightly lower mean baseline endogenous erythropoietin level in patients receiving IV iron compared with standard practice (69.09 IU/L [standard deviation (SD) = 73.32] *v* 85.76 U/L [SD = 113.99]). At baseline, few patients (1%) had true iron deficiency,[11] and similar numbers of patients in each treatment group had functional iron deficiency[11] (Table 1).

Efficacy

Primary end point: hematopoietic response. Kaplan-Meier hematopoietic response rates were higher in the IV iron group (86%; 95% CI, 79% to 92%) than in the standard practice group (73%; 95% CI, 66% to 80%; Fig 2A). The difference (adjusted for randomization strata) of 13% (95% CI, 3% to 23%) was statistically significant ($P = .011$). Patients who received IV iron responded more rapidly to darbepoetin alfa than did patients receiving standard care, with a median time to hematopoietic response of the following: 50 days (95% CI, 43 to 63 days) versus 64 days (95% CI, 50 to 71 days) when evaluating all patients and 40 days (95% CI, 34 to 43 days) versus 43 days (95% CI, 36 to 48 days) when evaluating only those patients who exhibited a hematopoietic response. For the secondary end point, the proportion of patients achieving an Hb concentration ≥ 11 g/dL, the IV iron group was also statistically significantly superior to the standard practice group (94%; [95% CI, 90% to 98%] *v* 85% [95% CI, 80% to 91%]; $P = .029$; Fig 2B).

RBC transfusions. The Kaplan-Meier proportion of patients receiving one or more RBC transfusion (week 5 to EOTP) was significantly lower in the IV iron arm (9%; 95% CI, 5% to 14%) than in the standard practice arm (20%; 95% CI, 14% to 26%; $P = .005$; Fig 3A). Similar results were seen for transfusions in week 1 to EOTP (Fig 3B). In a sensitivity analysis of transfusion incidence, the IV iron and standard practice arms exhibited similar patient incidences of hemoglobin less than 8 g/dL (20 patients [10%] and 28 patients [14.3%], respectively), with these patients having similar transfusion incidence (Kaplan-Meier proportions of transfusions week 5 to EOTP, 58% [95% CI, 27% to 88%] and 65% [95% CI, 44% to 86%], respectively; $P = .864$).

QOL. Mean baseline FACT-F scores were 30.85 (SD = 11.16) in the IV iron arm and 32.98 (SD = 11.24) in the standard practice arm. Mean adjusted change in FACT-F score from baseline to EOTP was 2.40 (95% CI, 0.84 to 3.95) for IV iron versus 2.17 (95% CI, 0.65 to 3.69) for standard practice (not statistically significant). More patients in the IV iron group experienced a clinically meaningful decrease in fatigue (≥ three-point increase in FACT-F score) than in the standard practice arm (Kaplan-Meier proportions: 76% [95% CI, 67% to 84%] *v* 67% [95% CI, 56% to 78%]), although the difference was not statistically significant. Patients receiving IV iron achieved this meaningful improvement in QOL 1 month faster: Kaplan-Meier median time of 63 days (95% CI, 46 to 65 days) in the IV iron arm versus 96 days (95% CI, 65 to 110 days) in the standard practice arm.

Table 1. Baseline Demographic and Disease Characteristics

Characteristic	Darbepoetin Alfa: IV Iron (n = 200) No. of Patients	%	Darbepoetin Alfa: Standard Practice (n = 196) No. of Patients	%
Female sex	124	62	116	59
Race/ethnicity				
White	199	100	191	97
Black	0	0	2	1
Asian	1	1	1	1
Other	0	0	2	1
Age, years				
Mean	61.7		60.3	
SD	11.6		11.4	
≥ 65	89	45	78	40
Baseline Hb, g/dL				
Mean	9.94		9.96	
SD	0.83		0.89	
Baseline Hb ≥ 10 g/dL*	104	52	104	53
Baseline ferritin, μg/L†				
Mean	279.9		278.9	
SD	248.0		269.7	
Baseline transferrin saturation, %‡				
Mean	28.3		29.9	
SD	21.2		23.7	
Patients with iron deficiency at baseline				
True iron deficiency§	3	1	1	1
Functional iron deficiency‖	71	35	70	36
Primary tumor type at randomization*,¶				
Lung/gynecologic*	56	28	55	28
Other tumors*	144	72	141	72
Primary tumor type at screening¶				
Lung/gynecologic*	57	29	55	28
Non–small-cell lung	30	15	25	13
Ovarian	16	8	23	12
Other, each < 5% of either arm	11	6	7	3
Other tumors*	143	72	141	72
Breast	36	18	27	14
Large intestine	27	14	29	15
Non-Hodgkin's lymphoma	14	7	13	7
Stomach	10	5	6	3
Bladder	5	3	9	5
Pancreas	4	2	9	5
Other, each < 5% of either arm	47	23	48	24

Abbreviations: IV, intravenous; SD, standard deviation; Hb, hemoglobin.
*At randomization.
†For the IV iron arm, n = 199; for the standard practice arm, n = 195.
‡For the IV iron arm, n = 199; for the standard practice arm, n = 191.
§Per Ludwig et al,[11] true iron deficiency was defined as serum iron < 20 μg/dL and serum ferritin < 15 μg/L and transferrin saturation < 20%.
‖Per Ludwig et al,[11] functional iron deficiency was defined as serum iron < 60 μg/dL and serum ferritin > 20 μg/L and transferrin saturation < 20%.
¶Tumor types reported for two patients in the standard practice arm and one patient in the IV iron arm differed when reported for interactive voice response system randomization and when reported on the medical history case report form (CRF). For the patient in the IV iron arm, the reported tumor type was "other solid tumor" at randomization and "endometrial" on the CRF. For patients in the standard practice arm, the reported tumor types at randomization and on the CRF were "esophagus" and "non–small-cell lung" for the first patient, respectively, and "uterus" and "other solid tumor" for the second patient. Patients were analyzed for efficacy as randomly assigned.

Safety

Overall, 78% of patients (n = 159) in the IV iron arm and 83% of patients (n = 160) in the standard practice arm reported one or more adverse event, with nausea being most common (19% in both groups). Adverse event incidence was similar between treatment groups, except for fatigue (11% for IV iron; 19% for standard practice) and diarrhea (7% for IV iron; 17% for standard practice).

Serious adverse events related to darbepoetin alfa were reported by 2% of patients in both the IV iron (n = 4) and standard practice (n = 3) arms. There were no major differences between the groups in the types of serious adverse events. The incidence of iron-related serious adverse events was 3% (n = 6) in the IV iron arm; these included hypotension (n = 3), abdominal pain (n = 3), nausea (n = 3), vomiting (n = 3), deep vein thrombosis (n = 1), paresthesia (n = 1), syncope (n = 1),

Table 2. Chemotherapy and Darbepoetin Alfa Received Based on the Safety Analysis Set

Parameter	Darbepoetin Alfa			
	IV Iron (n = 203)		Standard Practice (n = 193)	
	No. of Patients	%	No. of Patients	%
Duration of darbepoetin alfa exposure, days				
Median	15.0		15	
Minimum	3		3	
Maximum	17.4		18.1	
No. of patients	203		193	
Duration of iron treatment exposure, days				
Mean	11.7*		11.8†	
Minimum	1.5		1.6	
Maximum	17.4		17.9	
No. of patients	203		49	
Duration of chemotherapy exposure, days				
Median	80.0		79.0	
Minimum	1		1	
Maximum	3,481		780	
No. of patients	197		190	
Type of chemotherapy received				
Antimetabolites	95	47	96	50
Platinum containing	92	45	76	39
Taxane	52	26	52	27
Alkylating agents	37	18	40	21
Anthracyclines	28	14	37	19
Biologics	18	9	25	13
Hormonal agents	4	2	1	1
Other	65	32	55	28

Abbreviation: IV, intravenous.
*IV iron exposure.
†Oral iron exposure.

tachyarrhythmia (n = 1), peripheral edema (n = 1), pain in extremity (n = 1), and blister (n = 1).

Incidence of cardiovascular and thromboembolic adverse events were similar (10% for IV iron; 13% for standard practice) (Table 3), with the specific event of embolism/thrombosis being most frequently reported among these (6% in each group). There was a slightly higher incidence of Hb excursions (levels exceeding 14 g/dL) in patients receiving IV iron (18%, n = 37) versus standard practice (12%, n = 23); however, no trend was observed with respect to the incidence of cardiovascular and thromboembolic adverse events by maximum Hb concentration (≤ 14 or > 14 g/dL) or by maximum increase in Hb (≤ 2 or > 2 g/dL in 28 days; data not shown).

The number of deaths during the study was 21 (10%) in the IV iron group and 15 (8%) in the standard practice group. No patient tested had a positive result for the presence of neutralizing antibodies to darbepoetin alfa.

DISCUSSION

In this randomized, controlled study, adding IV iron to Q3W darbepoetin alfa significantly increased the rate of response, decreased the lag time to response, and reduced the transfusion rate. Only 9% of patients receiving the combination of IV iron and darbepoetin alfa required RBC transfusions, whereas transfusion rates are 20% to 28%[5,7] in patients only treated with darbepoetin alfa and 50%[2,5] in the absence of both ESA and iron treatment. Here, we have shown that the transfusion rate was halved again with the addition of IV iron. As a major goal of ESA therapy is reducing the need for RBC transfusions, these results suggest that progress toward this goal can be achieved by adding IV iron therapy. Lower transfusion rates mean lower risks of infection with blood-borne pathogens and immune-related transfusion reactions, fewer hospital visits, potentially improved compliance with chemotherapy, and lower treatment costs.[25,26]

In this study, we did not observe statistically significant between-group differences in the change in QOL scores. A statistically significant difference in QOL scores was observed in the Auerbach study[16] with a much smaller sample size (approximately 40 per group versus approximately 200 per group in this study). This difference may have several contributing factors. First, Auerbach et al reported low response rates in the control arms (25% and 36%), leading to wider between-group differences and hence greater likelihood of detecting a QOL difference; second, the patient population in the study of Auerbach et al had lower baseline iron parameters than in the present study; and third, Auerbach et al used a the Linear Analog Scale Assessment, which may offer greater sensitivity than FACT-F. The present study was not powered to detect a difference in FACT-F results; further, FACT-F may not be an appropriate measure for the detection of between-group QOL

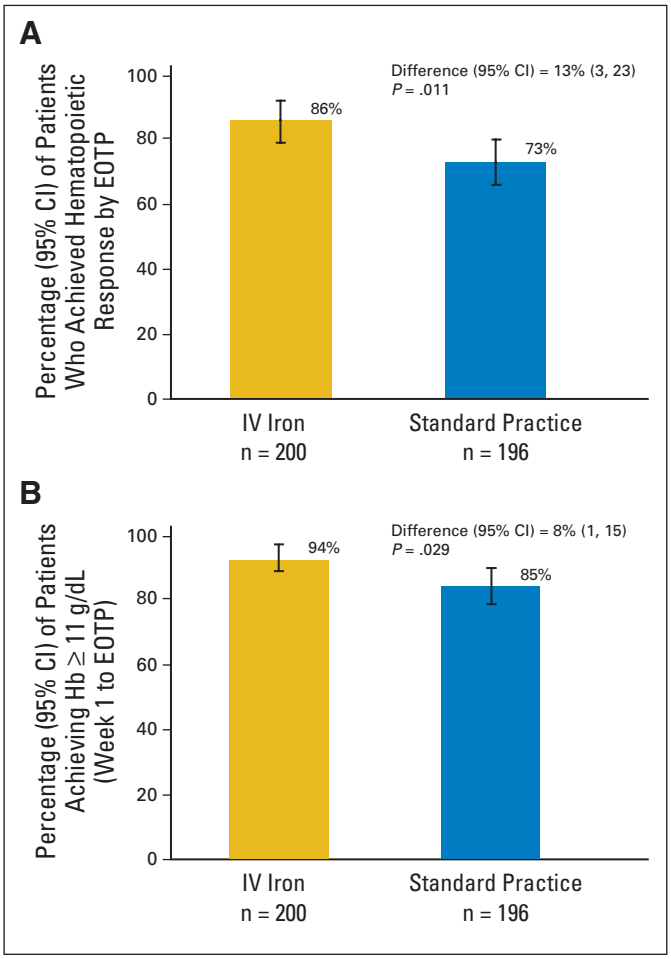

Fig 2. (A) Kaplan-Meier proportion of patients achieving hematopoietic response (hemoglobin [Hb] ≥ 12 g/dL or an increase from baseline of ≥ 2 g/dL). (B). Kaplan-Meier proportion of patients achieving Hb ≥ 11 g/dL. EOTP, end of treatment phase; IV, intravenous.

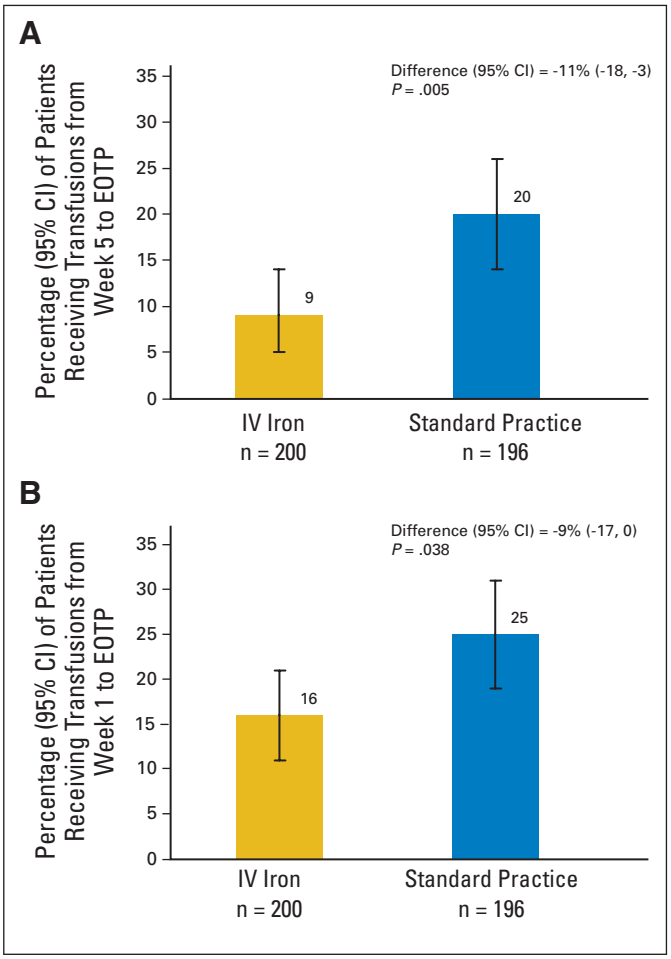

Fig 3. (A) Kaplan-Meier proportion of patients receiving a RBC transfusion between week 5 to the end of treatment phase (EOTP). (B). Kaplan-Meier proportion of patients receiving an RBC transfusion between week 1 to the EOTP. IV, intravenous.

differences in this setting. Of note, clinically meaningful improvements in fatigue were observed 1 month earlier in those treated with IV iron versus standard practice, suggesting that IV iron supplementation may hasten symptom relief.

In our patients, the benefit-to-risk ratio of IV iron supplementation during darbepoetin alfa therapy was favorable, with no substantial changes in the safety profile relative to standard practice. Despite the theoretical concern that administration of IV iron might stimulate tumor growth,[27] no supporting evidence has been found.

This is the largest reported randomized controlled trial of concomitant IV iron and ESAs in patients with CIA. In addition to strengthening the case for the use of IV iron with ESAs, the study provides a novel option for iron dosing and schedule. A limitation of this study is that it provides no information as to whether all patients with CIA or only a subset should receive IV iron with ESAs. Plus, the study lacks a standardized transfusion policy, similar to previous trials of ESAs, although a sensitivity analysis suggests there is no resultant treatment group difference, because transfusion rates in patients with hemoglobin levels less than 8 g/dL were similar. Another study limitation was the use of a control arm with a mixed patient population: in other words, some received oral iron and others did not. Although it was intended to be a standard-of-care comparison, the number of patients (26%) receiving oral iron in the control arm represents a potential confounding factor, especially because these patients who received oral iron apparently differed in terms of baseline iron status. Further, the study was not stratified according to gastrointestinal malignancy, a disease state that may make patients more susceptible to iron deficiency; however, the two arms in this study were reasonably balanced in incidence of gastrointestinal tumors (22.5% in the IV iron group and 17.9% in the standard arm).

The results of this study add to previous findings with rHuEPO,[16,21,22] suggesting a class effect for the benefit of IV iron supplementation with ESAs. Improved response to IV iron and darbepoetin alfa may be explained by functional iron deficiency (FID), a state in which available iron is insufficient to support increased iron demand created by ESA treatment, despite adequate iron stores.[10-13] Chronic inflammation, which increases cytokines and hepcidin, a negative regulator of iron uptake, may contribute to FID.[28,29] FID is marked by transferrin saturation less than 20%, serum ferritin more than 20 μg/L, and serum iron less than 60 μg/dL.[11] The present study excluded patients with absolute iron deficiency (transferrin saturation $<$ 15% and serum ferritin $<$ 10 ng/mL). Therefore, patients who had FID at baseline (approximately 35% in both groups), as well as

Table 3. Patient Incidence of Cardiovascular and Thromboembolic Adverse Events

	Darbepoetin Alfa			
	Intravenous Iron (n = 203)		Standard Practice (n = 193)	
Parameter	No. of Patients	%	No. of Patients	%
No. of patients reporting specific adverse events	21	10	26	13
Embolism/thrombosis, arterial and venous	12	6	12	6
Arrhythmia	3	1	8	4
Myocardial infarction, ischemic and coronary artery disease	3	1	1	1
Hypertension	2	1	5	3
Congestive heart failure	1	0	3	2
Seizure	0	0	1	1
Cerebrovascular accident	0	0	0	0

those in which the state was induced by ESA treatment, may have benefited from IV iron supplementation.

In conclusion, IV iron supplementation can be used to enhance the efficacy of darbepoetin alfa Q3W in patients with CIA. Concomitant use of ESAs and IV iron is an important advance in anemia management, allowing more patients to experience the benefit of anemia treatment, with a shorter lag time to response and fewer transfusions.

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.

Employment: Tamas S. Suto, Amgen; Tony W. Mossman, Amgen; Kay E. Smith, Amgen **Leadership:** N/A **Consultant:** N/A **Stock:** Kay E. Smith, Amgen **Honoraria:** Johan F. Vansteenkiste, Amgen **Research Funds:** Johan F. Vansteenkiste, Funds, Educational Amgen Chair in Supportive Cancer Care at the Leuven University **Testimony:** N/A **Other:** N/A

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REFERENCES

1. Groopman JE, Itri LM: Chemotherapy-induced anemia in adults: Incidence and treatment. J Natl Cancer Inst 91:1616-1634, 1999

2. 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

3. Ludwig H, Van Belle S, Barrett-Lee P, et al: The European Cancer Anaemia Survey (ECAS): A large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. Eur J Cancer 40:2293-2306, 2004

4. Chang J, Couture F, Young S, et al: Weekly epoetin alfa maintains hemoglobin, improves quality of life, and reduces transfusion in breast cancer patients receiving chemotherapy. J Clin Oncol 23: 2597-2605, 2005

5. 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

6. Osterborg A, Brandberg Y, Molostova V, et al: Randomized, double-blind, placebo-controlled trial of recombinant human erythropoietin, epoetin beta, in hematologic malignancies. J Clin Oncol 20:2486-2494, 2002

7. Canon JL, Vansteenkiste J, Bodoky G, et al: Randomized, double-blind, active-controlled trial of every-3-week darbepoetin alfa for the treatment of chemotherapy-induced anemia. J Natl Cancer Inst 98:273-284, 2006

8. Cazzola M, Beguin Y, Kloczko J, et al: Once-weekly epoetin beta is highly effective in treating anaemic patients with lymphoproliferative malignancy and defective endogenous erythropoietin production. Br J Haematol 122:386-393, 2003

9. Cazzola M, Mercuriali F, Brugnara C: Use of recombinant human erythropoietin outside the setting of uremia. Blood 89:4248-4267, 1997

10. Henry DH: Supplemental iron: A key to optimizing the response of cancer-related anemia to rHuEPO? Oncologist 3:275-278, 1998

11. Ludwig H: Iron metabolism and iron supplementation in anemia of cancer. Semin Hematol 43:S13–S17, 2006 (suppl 6)

12. Goodnough LT: The relevance of iron in erythropoietin-stimulated erythropoiesis. Semin Hematol 43:S3–S8, 2006 (suppl 6)

13. Macdougall IC: Experience with intravenous iron in nephrology. Semin Hematol 43:S9–S12, 2006 (suppl 6)

14. Macdougall IC, Tucker B, Thompson J, et al: A randomized controlled study of iron supplementation in patients treated with erythropoietin. Kidney Int 50:1694-1699, 1996

15. Sepandj F, Jindal K, West M, et al: Economic appraisal of maintenance parenteral iron administration in treatment of anaemia in chronic haemodialysis patients. Nephrol Dial Transplant 11:319-322, 1996

16. Auerbach M, Ballard H, Trout JR, et al: Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-induced anemia: A multicenter, open-label, randomized trial. J Clin Oncol 22:1301-1307, 2004

17. 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. J Clin Oncol 20:4083-4107, 2002

18. Rodgers GM: NCCN Clinical Practice Guidelines in Oncology: Cancer- and Treatment-Related Anemia, version 3.2007. http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf

19. Bokemeyer C, Aapro MS, Courdi A, et al: EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update. Eur J Cancer 43:258-270, 2007

20. Henry DH, Dahl NV, Auerbach M, et al: Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. Oncologist 12:231-242, 2007

21. Hedenus M, Birgegård G, Näsman P, et al: Adjuvant intravenous iron therapy potentiates epoetin beta treatment in anemic, non iron-depleted patients with lymphoproliferative disorders: Results of the NIFe study. Haematologica 91:365, 2006 (suppl 1, abstr 0996)

22. Kalbfleisch JD, Prentice RL: The statistical analysis of failure time data. New York, NY, John Wiley & Sons, 1980

23. Cella D, Eton DT, Lai JS, et al: Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. J Pain Symptom Manage 24:547-561, 2002

24. 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

25. Madjdpour C, Spahn DR: Allogeneic red blood cell transfusions: Efficacy, risks, alternatives and indications. Br J Anaesth 95:33-42, 2005

26. Davies L, Brown TJ, Haynes S, et al: Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: A systematic review and economic model. Health Technol Assess 10:1-228, 2006

27. Cavill I, Auerbach M, Bailie GR, et al: Iron and the anaemia of chronic disease: A review and strategic recommendations. Curr Med Res Opin 22:731-737, 2006

28. Henke M, Guttenberger R, Barke A, et al: Erythropoietin for patients undergoing radiotherapy: A pilot study. Radiother Oncol 50:185-190, 1999

29. Ganz T: Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. Blood 102:783-788, 2003

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