VOLUME 26 · NUMBER 10 · APRIL 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Trial of Intravenous Iron Supplementation in Patients With Chemotherapy-Related Anemia Without Iron Deficiency Treated With Darbepoetin Alfa

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Submitted April 23, 2007; accepted December 11, 2007.

Supported by Dompé Biotec. S.S. is recipient of a research contract supported in part by Oncologia Ca' Granda ONLUS Fondazione.

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

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0732-183X/08/2610-1619/$20.00

DOI: 10.1200/JCO.2007.12.2051

ABSTRACT

Purpose

Unresponsiveness to erythropoiesis-stimulating agents, occurring in 30% to 50% of patients, is a major limitation to the treatment of chemotherapy-related anemia. We have prospectively evaluated whether intravenous iron can increase the proportion of patients with chemotherapy-related anemia who respond to darbepoetin.

Patients and Methods

Between December 2004 and February 2006, 149 patients with lung, gynecologic, breast, and colorectal cancers and ≥ 12 weeks of planned chemotherapy were enrolled from 33 institutions. Patients were required to have hemoglobin ≤ 11 g/L and no absolute or functional iron deficiency. All patients received darbepoetin 150 μg subcutaneously once weekly for 12 weeks and were randomly assigned to sodium ferric gluconate 125 mg intravenously (IV) weekly for the first 6 weeks (n = 73) or no iron (n = 76). Primary end point of the study was the percentage of patients achieving hematopoietic response (hemoglobin ≥ 12 g/dL or ≥ 2 g/dL increase).

Results

Hematopoietic response by intention-to-treat analysis was 76.7% (95%CI, 65.4% to 85.8%) in the darbepoetin/iron group and 61.8% (95%CI, 50.0% to 72.7%) in the darbepoetin group (P = .0495). Among patients fulfilling eligibility criteria and having received at least four darbepoetin administrations, hematopoietic responses in the darbepoetin/iron group (n = 53) and in the darbepoetin-only group (n = 50) were 92.5% (95% CI, 81.8% to 97.9%) and 70% (95% CI, 55.4% to 82.1%), respectively (P = .0033). Increase of hemoglobin during treatment period showed a time profile favoring darbepoetin/iron with statistically significant effect from week 5 on. The safety profile was comparable in the two arms.

Conclusion

In patients with chemotherapy-related anemia and no iron deficiency, IV iron supplementation significantly reduces treatment failures to darbepoetin without additional toxicity.

J Clin Oncol 26:1619-1625. © 2008 by American Society of Clinical Oncology

INTRODUCTION

Anemia is common in cancer patients, and is an important contributor to the morbidity of malignancy.[1] The etiology of cancer-related anemia is multifactorial, but in most cases it is a consequence of the chronic disease process associated with malignancy, anemia of chronic disease (ACD).[2,3] Key contributors to the pathogenesis of ACD are a shortened RBC life span and the failure of the bone marrow to increase RBC production. This occurs also through the inadequate production of erythropoietin for the grade of anemia.[3,4] Anemia in cancer patients is exacerbated by chemotherapy, which further impairs erythropoietin production.[5]

The ability of recombinant erythropoiesis-stimulating agents (ESA)—epoetin alfa and beta and darbepoetin alfa (DA)—to correct chemotherapy-related anemia (CRA) and to reduce the need of blood transfusion in patients receiving chemotherapy has been well defined by several large clinical trials.[6] When given according to evidence-based clinical practice guidelines,[7,8] ESA can provide clinically meaningful improvements in overall health including physical, functional, and emotional well-being[9,10] independent of tumor

response.[11] DA possesses comparable activity to epoeitins in CRA[12] but, due to differences in the pharmacokinetic properties, it can be administered less frequently without changes in efficacy and safety.[13]

While epoetins and DA represent a remarkable advance in the treatment of CRA, approximately 30% to 50% of patients do not achieve a meaningful response to ESA.[9,11,14] The reasons are mainly unknown, but some patients who fail to respond may have, or develop during treatment with ESA, functional iron deficiency (FID).[2] The efficacy of intravenous (IV), not oral, iron to correct FID and improve anemia has been well documented in chronic kidney disease (CKD) during epoetin therapy.[15] Despite these findings, clinicians have been reluctant to prescribe IV iron routinely for patients with CRA, probably because of the false perception that cancer patients do not have decreased iron stores (as measured by serum ferritin); the lack of clinical trials of ESA energetically pursuing iron usage in cancer patients and the risk of anaphylaxis associated with IV iron. However, the latter is an uncommon occurrence as the severe reactions rate with lower molecular weight iron dextran, iron sucrose, and ferric gluconate occurs in less than one in 200,000 patients.[16]

The effects of iron during epoetin therapy have been initially studied by Auerbach et al[17] in anemic patients with cancer and iron deficiency. This study demonstrated that correcting functional, as well as absolute iron deficiency with iron supplementation will improve response to ESA. It also confirmed that iron supplement should be given IV rather then orally. However, a major point that remains to be elucidated in the field of ESA therapy for CRA is whether iron supplementation is capable to increase the fraction of patients who respond to epoetin and DA even in the absence of iron deficiency. This issue is clinically relevant because appropriate iron supplementation, apart from allowing more patients to benefit from ESA therapy, may represent a strategy to improve the cost-effectiveness of ESA in oncology as it has in nephrology.

PATIENTS AND METHODS

Study Population

Participants were recruited from 33 medical oncology institutions in Italy between December 2004 and February 2006. The independent ethics committee or central ethics committee for each of the institutions approved the protocol. All patients provided written informed consent before study participation. Randomization was conducted centrally to avoid selection bias.

For entry into the study, patients were required to have a diagnosis of breast, colorectal, lung, or gynecologic cancer and at least 12 additional weeks of planned cancer chemotherapy. Patients were eligible for the study if they were at least 18 years of age, had an Eastern Cooperative Oncology Group performance status ≤ 2, a life expectancy of at least 6 months and had adequate renal and hepatic function. Patients were required to have anemia (ie, hemoglobin (Hb) level of $\leq$ 11 g/dL) within 24 hours of random assignment, secondary to malignancy and chemotherapy treatment and not to harbor absolute or functional iron deficiency (ie, having serum ferritin level $\geq$ 100 ng/mL and transferrin saturation (TSAT) $\geq$ 20%).[18] Patients with anemia attributable to factors other than cancer or chemotherapy (ie, B_{12}, or folate deficiency; hemolysis; gastrointestinal bleeding; or myelodysplastic syndromes) were not eligible to participate in the study. Patients were excluded if they had iron overload (defined as serum ferritin $>$ 800 μg/L and TSAT $>$ 40%); had received more than two RBC transfusions within 4 weeks of random assignment or any RBC transfusions within 14 days of the first dose of DA; had received therapy with ESA within 4 weeks of random assignment; or were pregnant, breastfeeding, or not using adequate birth control measures. Patients were also excluded if they had a history of seizure disorders, active cardiac disease, thromboembolic disease, or uncontrolled hypertension, or active infection.

Protocol

This was a randomized, open-label, multicenter study. All eligible patients underwent an initial screen within 7 days of enrollment. Baseline information included patient characteristics and current chemotherapy regimen. Baseline laboratory tests included complete blood count, chemical profile, iron profile, serum ferritin, B_{12} and folate levels. After rechecking Hb levels within 24 hours from treatment start, patients were randomized to receive subcutaneous DA 150 μg/wk for 12 weeks plus sodium ferric gluconate 125 mg/wk IV for the first 6 weeks or DA only for 12 weeks. Where no response was seen after 4 weeks (Hb increase $\leq$ 1.0 g/dL), the dose of DA was doubled to 300 μg/wk until the end of the study. At any time during the study, DA was withheld if the subject's Hb increased to more than 13.0 g/dL. Administration of the drug was restarted at 150 μg every two weeks if the Hb decreased to $\leq$ 12.0 g/dL. Patients were followed for additional 4 weeks after completion of DA therapy. The protocol recommended, but did not mandate, transfusions for patients with Hb concentrations of $\leq$ 8 g/dL. Transfusions were allowed for Hb more than 8 g/dL in symptomatic patients or as recommended by the physician.

Efficacy Assessment

The primary objective of the study was to assess the proportion of subjects achieving hematopoietic response (eg, the primary end point) at any time point during the study. Hematopoietic response was defined as either an increase in Hb $\geq$ 2.0 g/dL or the achievement of Hb $\geq$ 12.0 g/dL in the absence of a RBC transfusion within the previous 28 days. This definition is consistent with studies of ESA in patients with Hb concentrations of $\leq$ 11.0 g/dL.[14,19] Hemoglobin levels were measured at the start of and weekly throughout the treatment period. The secondary efficacy variables included time to reach hematopoietic response, transfusion requirement, Hb profiles over time, and time-adjusted area under the Hb-time curve between weeks 5 and 12 (Hb area under the curve $[AUC]_{5-12}$)[20] in the two study groups. Hemoglobin AUC has been considered recently as a clinically meaningful alternative measure to assess the overall efficacy of ESA.[21,22]

Safety

The safety profile of DA and IV iron was evaluated by examining the incidence of adverse events (AEs), changes from starting levels in serum analyses and chemistry, changes in vital signs, and number of days hospitalized. The nature, frequency, severity, relationship to treatment, and outcome of all AEs were examined.

Data Analysis and Statistical Methods

Four hundred twenty patients were planned to be enrolled within 10 months from 61 Institutions. One hundred eighty-five patients per treatment arm had 80% power (α = .05, two sided) to identify a 20% improvement in hematopoietic response rate in favor of the DA/iron group (Δ = 0.13), with 0.66 as the reference proportion for patients treated with DA only.[14] The sample size was increased to 210 patients per arm because of a planned dropout rate of more than 10%.

Statistical analyses were performed using SAS statistical software version 8.2 (SAS Institute, Cary, NC). Descriptive statistics included frequencies and means (with standard deviation (SD) and 95% CI) for categoric and continuous variables, respectively. All analyses were performed on both intention to treat (ITT) and per protocol (PP) populations. ITT population was defined as all patients who were randomly assigned and received at least one administration of DA. PP population included patients meeting eligibility criteria and completing at least 4 weeks of treatment with DA.

The hypothesis of no difference in response rate between treatment groups was tested using the Pearson χ^2 statistics. Data on Hb profile over time were analyzed by means of repeated measure analysis of variance. The time-adjusted Hb AUC from week 5 and week 12 ($AUC_{5\text{-}12}$/time adjustment $(T)_{5\text{-}T12}$) was calculated using the linear trapezoidal rule and the resultant AUC value was corrected in accordance with the estimated time interval from

the first Hb measurement and the last Hb measurement for the week considered ($AUC_{\text{time corrected}} = AUC/T_{\text{first}}\text{-}T_{\text{last}}$). $AUC_{5\text{-}12}/T_{5\text{-}T12}$ was calculated and treatment groups were compared by means of student's t test. Time to achievement of target Hb was estimated by Kaplan-Meier method. The estimated difference in event probability between treatments was tested by means of log-rank test.

The safety analysis was performed on all patients who received at least one administration of study drug. Treatment-related AEs, according to NCI Common Terminology for Adverse Events Version 3.0, were tabulated according to seriousness and relation to the actual treatment received. Comparison between treatment groups was performed by means of Fisher's exact test.

RESULTS

Study Population

Due to lower than expected accrual, 104 patients from nearly half of planned nstitutions were randomly assigned in 10 months. The steering committee and the sponsor decided, also based on favorable results from previous studies with a limited number of patients,[13,17] to prolong the accrual for additional 4 months. No interim analysis was performed.

A total of 149 patients were eventually enrolled and underwent random assignment to receive DA and IV iron (n = 73) or DA only (n = 76). Patients were well balanced in the two groups as for age, sex, tumor type, and disease stage. Relevant patients' characteristics are presented in Table 1. Of the 149 patients randomized, 33 were subsequently excluded due to eligible criteria violations (evidence of baseline iron deficiency or no/incomplete data on iron profile in most cases). Among 116 patients strictly fulfilling inclusion criteria, 103 had completed at least 4 weeks of treatment with DA. The study profile is shown in Figure 1.

Efficacy Evaluations

Hematopoietic response. Among randomly assigned subjects that had received at least one administration of DA (ITT population, n = 149), 56 of 73 (76.7%; 95% CI, 65.4% to 85.8%) in the DA/iron group and 47 of 76 (61.8%; 95% CI, 50.0% to 72.7%) in the DA-only group achieved hematopoietic response ($P = .0495$, Fig 2). In the PP population, response occurred in 49 of 53 patients (92.5%; 95% CI, 81.8% to 97.9%) in the DA/iron group and in 35 of 50 patients (70%; 95% CI, 55.4% to 82.1%) in the DA-only group ($P = .0033$, Fig 2).

The Hb profiles over time also favor DA/iron group in both ITT and PP populations (Fig 3). The time-adjusted Hb $AUC_{5\text{-}12}$ confirms previous result with a significant increase ($P = .025$ and $P = .023$ in the ITT and PP populations, respectively) in AUC in the DA/iron group: ITT saw a 0.2 Hb increase in g · day/dL (95% CI, 0.095 to 0.305 Hb) and PP saw a 0.2 Hb increase in g · day/dL (95% CI, 0.08 to 0.32 Hb).

Median times to achievement of target Hb in the DA/iron and DA-only groups were 36 days(95% CI, 29 to 42 days) and 46 days(95% CI, 33 to 55 days), respectively (log-rank test, $P = .0778$) in the ITT population; and 35 days (95% CI, 28-42 days) and 42 days (95% CI, 29 to 56 days), respectively (log-rank test, $P = .0305$) in the PP population. RBC transfusions were required in two and five patients in the DA/iron and DA-only groups, respectively.

The dose of DA was doubled for no response in 34.2% of patients the DA/iron group and in 31.5% of patients in the DA-only group. Exploratory analysis performed in this subset of patients showed that hematopoietic response occurred in 68.2% in the DA/iron group and in 32% in the DA-only group ($P = .0199$). This finding is expected if considering that avoidance of the development of FID is the mechanisms involved in hematopoietic response to iron supplementation in

Table 1. Baseline Demographic and Disease Characteristics

Characteristic	Darbepoetin Plus Intravenous Iron (n = 73)		Darbepoetin Only (n = 76)		All Patients (N = 149)	
	No.	%	No.	%	No.	%
Sex						
Female	52	71.2	52	68.4	104	70
Male	21	28.8	24	31.6	45	30
Primary tumor type						
Gynecologic	17	23.3	14	18.4	31	20.8
Breast	23	31.5	26	34.2	49	32.9
Lung	13	17.8	18	23.7	31	20.8
Colorectal	19	26.0	18	23.7	37	24.8
Other	1	1.4	0	0	1	0.7
Disease stage						
I/II/III	30	41.1	27	35.5	57	38.3
IV	41	56.2	47	61.8	88	59.1
Unknown	2	2.7	2	2.6	4	2.6
Hemoglobin (g/dL), baseline						
Mean	9.9		9.9		9.9	
Standard deviation	0.78		0.82		0.83	
Ferritin (ng/mL), baseline						
Mean	350.7		333		341.8	
Standard deviation	238.3		232		235	
Transferin saturation, baseline						
Mean	30.6		27.6		29	
Standard deviation	14.6		11.3		13	

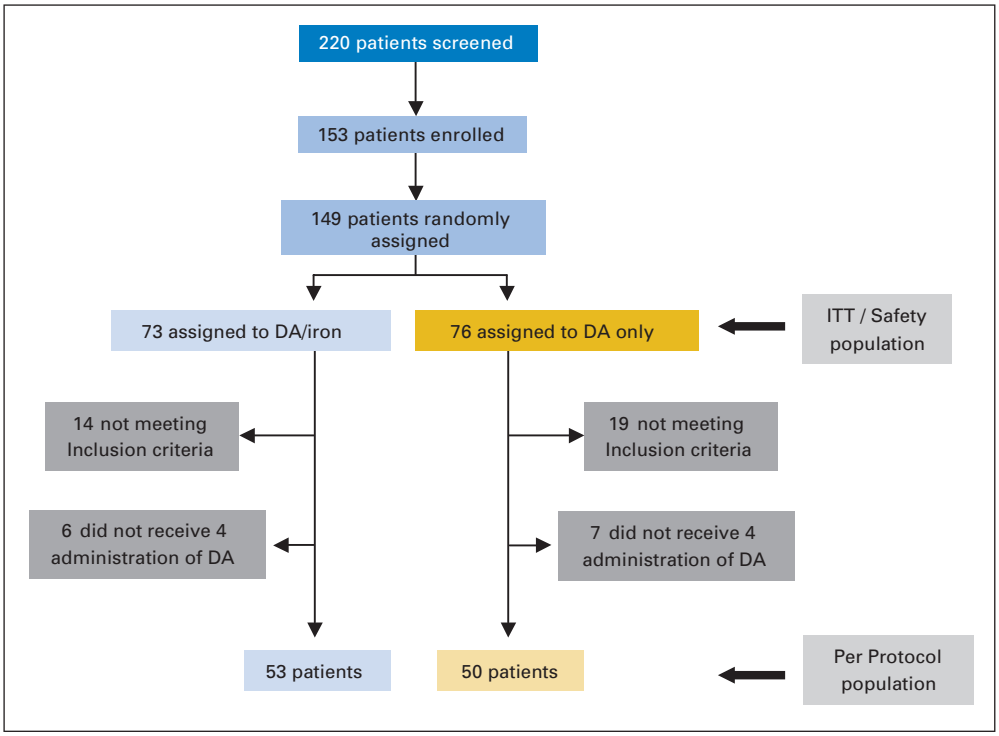

Fig 1. Trial flow-chart. DA, darbepoetin alfa; ITT, intention to treat.

iron-replete patients receiving ESA. Any effect of IV iron in such patients is not likely to occur during the first weeks of ESA treatment (when the patient has enough iron to meet the increased iron needs of an expanding erythroid marrow) and therefore does not influence significantly early response to ESA. In fact, in our study DA dose was doubled at 4 weeks in the almost same percentage of patients in the two groups, but subsequently hematopoietic response occurred more frequently in the DA/iron group. Time to hematopietic response was shorter in the DA/iron group but it largely exceeded 4 weeks.

Safety Results

Table 2 summarizes the AEs in the study population. Most AEs were deemed by investigators to be unrelated to DA or iron and were attributable to chemotherapy or underlying malignancy. The most frequently reported AEs were nausea/vomiting, asthenia, dyspnea, diarrhea, and leukopenia. Infection rates were similar among groups and no infectious event was considered to be related to study treatment. A total of seven patients on DA/iron and six patients in the DA-only group experienced AEs that were determined to be possibly, probably, or definitely related to the study drugs by the treating investigator; one in the DA/iron group was defined as severe (thrombophlebitis). No significant differences with respect to cardiovascular and thromboembolic events were observed between the two groups. No side effects related to iron infusion were reported. Seven patients, four on DA/iron and three on DA only, died during the study or within 4 weeks after the last administered dose of DA. Deaths were ascribed to disease progression, two cases in each group, and respiratory complications, one in the DA-only group (infection), two in the DA/iron group (bleeding in one, ARDS in one) not related to study drugs administration.

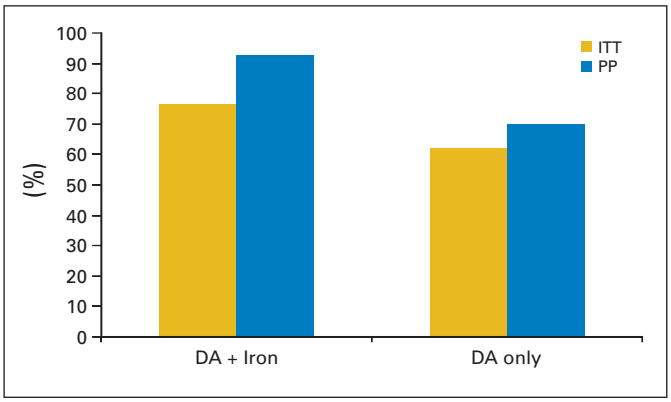

Fig 2. Percentage of responders in the study groups. Responders were patients who achieved a maximal hemoglobin levels ≥12 g/dL or an increase in hemoglobin of ≥ 2 g/dL during the study. Intention-to-treat population (ITT; n = 149; $P = .0495$); per protocol population (PP; n = 103; $P = .0033$). DA, darbepoetin alfa.

DISCUSSION

When patients with CRA are treated with ESA, an important response-limiting factor is represented by FID, an imbalance between iron needs in the erythropoietic marrow and iron supply.[2] FID is well recognized in anemia of CKD where systematic IV iron supplementation is routinely utilized in course of ESA therapy[24,25] resulting in improved efficacy of ESA and substantial cost savings.[15] Surprisingly, oncologists have so far mostly ignored the issue of iron requirements during ESA therapy in despite this issue has been being raised by ASCO/ASH guidelines published in 2002.[7] The use of iron supplementation has been investigated by Auerbach et al[17] and, more recently, by Henry et al[26] in patients with nonmyeloid malignancies

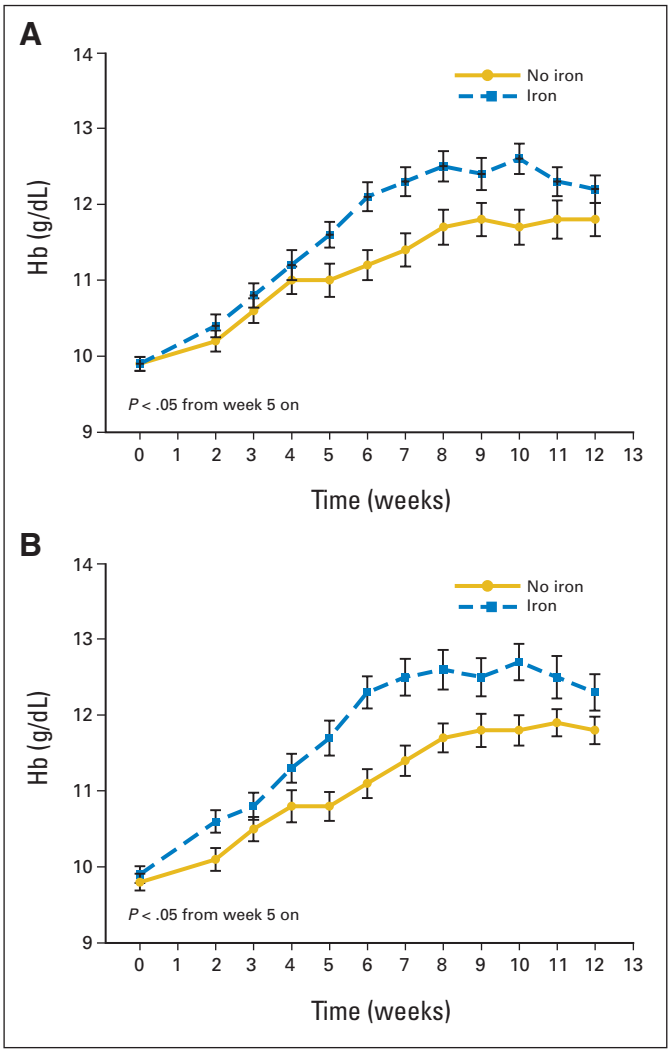

Fig 3. Time course of mean hemoglobin (Hb) level in the two study groups. (A) intention-to-treat population (n = 149); (B) per protocol population (n = 103).

receiving epoetin alfa for CRA, showing that IV iron improves hematopoietic response. However, the Auerbach study included only patients harboring iron deficiency (functional in most cases), while the Henry study had an unexpected low response rate (41%) in the epoetin-only arm, which might be related to having selected also patients not iron-replete (TSAT < 15% or ferritin < 100 ng/mL).[26] The efficacy of IV iron in improving hematopoietic response to epoetin beta has been demonstrated by Hedenus et al[27] in a limited series of 60 patients with lymphoproliferative malignancies. This study included moderately anemic patients not receiving chemotherapy who were considered iron-replete if having stainable iron in bone marrow aspirates. This method is not routinely applicable in patients with solid tumors where iron status is commonly assessed using serum ferritin and TSAT values.

In our study, IV iron supplementation during therapy with DA significantly improved by 14.9% the proportion of patients in the ITT population achieving hematopoietic response, the primary efficacy parameter. The percentage of responders in the control group (62%) was comparable to rates reported in previous studies using DA.[14,28] Most importantly, when looking at patients strictly fulfilling the eligibility criteria and having received at least four administrations of DA (PP population), the response rate in the IV iron group was greater than 90%, a magnitude never reached in previously published studies of ESA in CRA. Additional parameters of efficacy, including time to reach hematopoietic response, Hb profile over time and Hb $AUC_{5\text{-}12}$ were also significantly better in the DA/iron arm.

The favorable results obtained might be due to IV iron preventing the development of FID which otherwise could occur when the increased iron needs of an expanding erythroid marrow, stimulated by ESA, cannot be matched by sufficient mobilization, even in the presence of adequate iron stores.[18,29]

Darbepoetin and IV iron were well tolerated, with no safety concerns in either arms, in accordance with previous reports.[6,16] No allergic reactions related to IV iron administration occurred, thus supporting the safety profile of both DA and iron gluconate.[30] Concerns about the potential effect of iron on tumor stimulation, based on laboratory studies, have never been demonstrated in vivo in humans.[31] In our study the amount of iron per patient administered (750 mg) was lower than that employed by others (up to 3000 mg in the study by Auerbach et al[17]). It also has to be considered that the transfusion of one RBC unit provides about 200 mg of iron. Multiple units of RBC are often given in unresponsive patients, thereby delivering similar amounts of iron, albeit more slowly available. Recent concerns that ESA may negatively alter patient survival[32] are largely based on clinical trials in patients who were either nonanemic or not receiving chemotherapy. In contrast, a meta-analysis of ESA therapy

Table 2. Summary of Adverse Events

Parameter	Darbepoetin Plus Intravenous Iron (n = 73)		Darbepoetin Only (n = 76)		All Patients (N = 149)	
	No.	%	No.	%	No.	%
Patients with adverse events	55	75.3	49	64.5	104	70
Patients with serious adverse events	8	11	10	13.2	18	12
Patients with treatment-related adverse events	7	9.6	6	7.9	13	8.7
Vascular/thromboembolic events	3	4.1	2	2.6	5	3.3
Fatal averse events						
All	4	5.5	3	3.9	7	4.7
Treatment related	0	0	0	0	0	0

in patients with the same clinical characteristics as those enrolled in the present study failed to show the same detrimental effect.[6]

In conclusion, we have demonstrated that IV iron supplementation significantly reduces treatment failures to DA in patients with CRA and normal iron status without additional toxicity. This is the only trial published so far which is based on iron-replete patients only with solid tumors and represents a major step forward in the optimization of ESA therapy in CRA. Based on our study, and the two other published papers,[26,27] IV iron supplementation should become an integral and routine component of ESA therapy, and should be incorporated in clinical guidelines. Furthermore, the use of DA every three weeks and total dose infusion of iron, which are as effective as the dose and schedule utilized in our study,[13,17] may well provide additional benefits for patients and health care providers. The potential health economic impact of IV iron supplementation in this setting for example, by decreasing the required doses of ESA, should be further examined in prospective trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. 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 or Leadership Position: Enrico Crucitta, Dompé Biotec (C); Federica Apolloni, Dompé Biotec (C); Antonio Del Santo, Dompé Biotec (C) **Consultant or Advisory Role:** Paolo Pedrazzoli, Dompé Biotec (C); Teresa Gamucci, Dompé Biotec (C) **Stock Ownership:** None **Honoraria:** Giuseppe Colucci, Dompé Biotec; Roberto Labianca, Dompé Biotec; Francesco Di Costanzo, Dompé Biotec; Salvatore Siena, Dompé Biotec **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

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Acknowledgment

We thank all patients who had the strength to fight their disease and help others to find better treatment options; all doctors and nurses and all investigators contributing to this trial; Guido Fedele and Giovanni Pappagallo for assistance in data analysis and statistical plan design; and Mario Cazzola for valuable suggestions.

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).