Received: 10 February 2017 | Revised: 17 May 2017 | Accepted: 18 June 2017

DOI: 10.1111/ajco.12762

ORIGINAL ARTICLE

WILEY

Phase III randomized trial comparing intravenous to oral iron in patients with cancer-related iron deficiency anemia not on erythropoiesis stimulating agents

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Funding Information
Tata Memorial Center Research Administration Council (Tata Memorial Center, Mumbai, Maharashtra, India)

Abstract

Aim: We aimed to find the optimal route of iron supplementation in patients with malignancy and iron deficiency (true or functional) anemia not receiving erythropoiesis stimulating agents (ESA).

Methods: Adult patients with malignancy requiring chemotherapy, hemoglobin (Hb) <12 g/dL and serum ferritin <100 mcg/mL, transferrin saturation <20% or hypochromic red blood cells >10% were randomized to intravenous (IV) iron sucrose or oral ferrous sulfate. The primary endpoint was change in Hb from baseline to 6 weeks. Secondary endpoints included blood transfusion, quality of life (QoL), toxicity, response and overall survival.

Results: A total of 192 patients were enrolled over 5 years: 98 on IV arm and 94 on oral arm. Median age was 51 years; over 95% patients had solid tumors. The mean absolute increase in Hb at 6 weeks was 0.11 g/dL (standard deviation [SD]: 1.48) in IV arm and −0.16 g/dL (SD: 1.36) in oral arm, $P = 0.23$. Twenty-three percent patients on IV iron and 18% patients on oral iron had a rise in Hb of ≥1 g/dL at 6 weeks, $P = 0.45$. Thirteen patients (13.3%) on the IV iron arm and 14 patients (14.9%) on the oral arm required blood transfusion, $P = 1.0$. Gastrointestinal toxicity (any grade) developed in 41% patients on IV iron and 44% patients on oral iron, $P = 1.0$. 5 patients on IV iron and none on oral iron had hypersensitivity, $P = 0.06$. QoL was not significantly different between the two arms.

Conclusion: IV iron was not superior to oral iron in patients with malignancy on chemotherapy and iron deficiency anemia.

KEYWORDS
anemia, blood transfusion, ferric compounds, iron, iron-deficiency

1 | INTRODUCTION

Anemia is common in patients with malignancy. Ludwig *et al.* performed a prospective survey in 15,367 European cancer patients, and found that at enrolment, the overall prevalence of anemia was 39.3% and patients who received chemotherapy had the highest incidence of anemia at 62.7%.[1] Anemia in cancer patients is multifactorial; nutritional deficiencies (iron, vitamin B_{12} and folate) are important etiologies.[2]

Iron deficiency anemia is one of the commonest forms of nutritional anemia, characterized by inadequate iron stores. Iron deficiency can be a true or functional deficiency. The standard therapy for iron deficiency anemia is iron supplementation, most commonly by oral iron supplements. The established indications for parenteral, that is intravenous (IV) iron supplementation include failure of oral iron, intolerance to oral iron, a condition that confers refractoriness to oral iron (e.g., post-gastrectomy, celiac disease, atrophic gastritis, *H. pylori* infection, etc.), need for rapid anemia reversal (e.g., late in pregnancy, chronic

bleeding), with erythropoietin stimulating agents (ESA) in chronic renal failure patients and as a substitute for blood transfusions in persons who refuse blood products on religious grounds. In patients on cytotoxic chemotherapy, receiving ESA, who have concomitant iron deficiency or inadequate ESA response, iron supplementation is recommended. Several studies have shown that these patients respond better to parenteral iron supplementation compared to oral iron.[3–7] Gafter-Gvili *et al.* conducted a meta-analysis comparing IV iron to no iron or to oral iron in patients with chemotherapy-induced anemia. They included 1681 patients from 11 trials, majority of which tested the addition of IV iron to ESA (1562 patients, 92.9%). They found that IV iron added to ESA improved the hematopoietic response by 28% and decreased RBC transfusion requirement by 26% in patients with chemotherapy induced anemia. Only two of the trials (119 patients) included patients not on ESA; there were no data on the hematopoietic response in these patients, however there was a 48% reduction in transfusion requirement. Only nine trials reported patients' baseline iron levels and only two of these permitted inclusion of patients with iron deficiency. Thus, the meta-analysis did not help to make any conclusions on the efficacy of oral iron supplementation, especially as compared to IV iron in iron deficiency anemia in cancer.[8]

Currently the use of ESA is falling out of favor due to concerns of shortened survival and increase in thromboembolic events. Updated National Comprehensive Cancer Network (NCCN) guidelines do not recommend the use of ESA in patients receiving chemotherapy with curative intent.[9] At present, patients are arbitrarily treated with either oral or IV iron. We therefore planned to find out whether there is any difference in hematopoietic response in patients treated with oral versus IV iron. We hypothesized that IV iron would be superior to oral iron supplementation in patients with cancer-related iron deficiency anemia on chemotherapy who were not receiving ESA.

2 | MATERIALS AND METHODS

2.1 | Participants

Patients were recruited from the outpatient medical oncology department at Tata Memorial Hospital (TMH) in Mumbai, Maharashtra, India. We included patients over 18 years old with malignancy requiring chemotherapy, who had hemoglobin (Hb) level <12 g/dL with at least one feature indicating iron deficiency: serum ferritin <100 mcg/mL, transferrin saturation <20% or hypochromic red blood cells >10%. Vitamin B_{12} and folate levels had to be adequate. Patients with a history of hypersensitivity to iron or uncontrolled medical illness were excluded. Patients who had taken iron supplements or received a blood transfusion within the preceding month, had a prior history of anemia or a history of significant bleeding were also excluded.

2.2 | Protocol

This was a prospective single-center open label randomized controlled phase III trial. The protocol and informed consent form were approved by the institutional review board, consisting of the scientific review committee and the human ethics committee of TMH. The trial was registered with Clinical Trials Registry India, number CTRI/2016/01/006520. Written informed consent was obtained from all study participants. The trial was conducted in accordance with the principles laid down by the 18th World Medical Assembly in Helsinki (1964) and subsequent amendments. The trial was funded by an intramural grant from the Tata Memorial Center Research Administration Council.

Patients underwent an initial screening process which consisted of a detailed history and physical, determination of the tumor type and site, the therapy intent and plan and baseline blood testing, including a complete blood count (CBC), hypochromic red blood cells assessment, serum iron, total iron binding capacity, ferritin, vitamin B_{12} and folate levels. Patients were stratified according to the type of malignancy (solid tumor *vs* hematolymphoid) and the level of Hb (≤10 g/dL *vs* >10 g/dL). Randomization was by a computer generated schedule with block randomization, using a block size of 10. The patients were randomly assigned to two arms: IV or oral iron.

2.3 | Treatment

Patients randomized to the IV iron arm received injectable iron sucrose in two divided doses, each diluted in 250 mL of 5% dextrose administered intravenously over 120 min with cycle 1 and cycle 2 of chemotherapy (three weeks apart). The dose of iron sucrose was calculated from the formula for total iron deficit: dose of iron in mg = weight in kg × Hb deficit (13-actual Hb in g/dL) × 2.4 + 500. Patients randomized to the oral iron arm were given ferrous sulfate capsules (100 mg) three times a day, started with cycle one of chemotherapy and continued until the end of cycle 2 (i.e., for 42 days). Oral iron could be continued beyond trial completion, if desired by the patient or the treating physician.

Patients were evaluated, underwent blood tests (CBC) and were asked to complete the quality of life (QoL) questionnaire [Functional Assessment of Cancer Therapy-Anemia (FACT-An)] on day 1 of weeks 1, 3 and 6. Adverse events were recorded at every study visit and graded according to Common Terminology Criteria for Adverse Events (CTCAE) v 4.03. Compliance to oral iron was tracked at every study visit, that is every 3 weeks by patient interview.

The primary efficacy endpoint was the change in Hb from baseline to that at 6 weeks. A change in Hb of 1 g/dL was chosen as a significant hematopoietic response. Patients who received blood transfusion during the 6-week study period were taken off study and their subsequent Hb values were not recorded or analyzed. For patients who defaulted or died prior to completing the study and for whom the 6-week Hb value was not available were excluded from the analysis of the primary endpoint. Secondary endpoints included the requirement for blood transfusions in each study arm, QoL, response rate to therapy, overall survival (OS) in each study arm and the safety profile of the two iron formulations. OS was defined as the time between date of randomization and date of last follow-up or death. Patients who were lost to follow-up were censored at the last date they were known to be alive

and were coded as dead on that date for the sake of survival analysis. QoL was measured at baseline and every 3 weeks using the FACT-An scale.

2.4 | Statistical analysis

The sample size was calculated based on the results of the 2004 study by Auerbach *et al.* in which the investigators reported that patients with chemotherapy-related anemia on ESO treated with IV iron dextran had a hematopoietic response of 68% compared to 36% in patients on oral iron.[4] We hypothesized that IV iron administered to patients with cancer-related iron-deficiency anemia would lead to a 20% difference in hematopoietic response compared to oral iron. To prove this hypothesis with a type 1 error of 5% and a power of 80%, we needed 178 patients, assuming a binomial distribution. Accounting for an 8% rate of lost-to-follow, the final sample size was 192 patients.

The data were entered into the Statistical Package for the Social Sciences (SPSS), version 17. For analysis of the primary endpoint, the mean of the change in Hb between the two treatment arms was compared using independent samples *t*-test. The number of patients who had an increase in Hb of 1 g/dL in the two treatment arms was compared using Fisher's exact test, two-sided. Similarly, the number of patients who had an increase in Hb of 1.5 g/dL in the two treatment arms was compared using Fisher's exact test, two-sided. As an exploratory analysis, the change in Hb from baseline to 3 weeks was also compared.

All patients randomized to each arm were included for analysis of the efficacy variables (except patients who received blood transfusions during the study period and patients who defaulted or died prior to study completion) as per the modified intention-to-treat principle. All patients were included in the toxicity analysis, except patients who defaulted and for whom no side-effect information was available. Survival was estimated by the Kaplan–Meier method and follow-up was estimated by the reverse Kaplan–Meier technique.

3 | RESULTS

3.1 | Patient characteristics

A total of 192 patients were enrolled between March 2010 and March 2015; 98 were randomized to IV iron and 94 to the oral iron. A total of 71 patients on IV iron and 77 patients on oral iron completed the entire planned therapy. Prior to competing the study, 13 patients on IV iron and 14 patients on oral iron required a blood transfusion (Figure 1).

The demographics and clinical details are provided in Table 1. Median age was 51 years; male-to-female ratio was 0.68. Over 95% patients had solid tumors, most commonly gynecologic, lung, head and neck and breast cancer. Intent of therapy was curative in 66%. The majority of patients (82%) were treated with platinum based two-drug combination chemotherapy regimen.

In the patients randomized to the IV iron arm, the mean planned dose of IV iron was 869.35 mg (standard deviation [SD]: 203.1) and the mean dose received was 760.17 mg (SD: 241.78).

3.2 | Primary efficacy outcome: Hb response (Table 2)

The mean absolute increase in Hb at 6 weeks was 0.11 g/dL (SD: 1.48) in the IV arm and −0.16 g/dL (SD: 1.36) in the oral arm, $P = 0.23$ (Figure 2). The number of patients who had a rise in Hb of ≥1 g/dL at 6 weeks was 23% (20 out of 94) in the IV iron arm and 18% (16 out of 98) in the oral iron arm, $P = 0.45$. 19% (14 out of 74; 95% confidence interval [CI], 11.5–29.5%) of patients on IV iron and 12% (9 out of 75; 95% CI, 6.3–21.6%) of patients on oral iron had a rise in Hb of 1.5 g/dL at 6 weeks, $P = 0.27$.

The mean absolute increase in Hb at 3 weeks was 0.01 g/dL (SD: 1.08) in the IV arm and −0.11 g/dL (SD: 1.15) in the oral arm, $P = 0.49$. A total of 13.8% (13 out of 94) patients on IV iron and 14.3% patients (14 out of 98) on oral iron had an increase in Hb of ≥1 g/dL, $P = 1.0$. The number of patients who had a rise in Hb of ≥1.5 g/dL at 3 weeks was 8.5% (8 out of 94) in the IV iron arm and 9.2% (9 out of 98) in the oral iron arm, $P = 1.0$.

Multivariate analysis done by Cox Regression revealed that mode of administration of iron, age, gender, intent of therapy and baseline Hb did not significantly impact response to iron therapy (Appendix A).

3.3 | Secondary outcomes

Prior to completing the trial, 13 patients in the IV iron arm and 14 in the oral arm required a blood transfusion, $P = 1.0$. There was no delay in chemotherapy due to anemia in any patient. A total of 69 patients underwent restaging scans following chemotherapy in the IV iron arm and 64 in the oral arm, excluding the patients who received adjuvant chemotherapy, did not have measurable disease, defaulted or did not perform repeat scans. The response rate to chemotherapy was 53.6% in the IV iron arm [complete response: 3 (4.3%), partial remission: 34 (49.3%)] and 45.3% in oral iron arm [complete response: 4 (6.3%) and partial remission: 25 (39.1%)], $P = 0.17$. At a median estimated follow-up of 24 months (95% CI, 19.5–28.5), 78 patients (40.6%) have died, 37 in the IV iron arm and 41 in the oral iron arm. Estimated median OS for all patients was 17 months (95% CI, 10.9–23.1). Estimated median OS for patients on IV iron was 16 months (95% CI, 7.3–24.7) and that of patients on oral iron was 20 months (95% CI: 11.7–28.4 months; SE: 4.3 months), $P = 0.73$ by log-rank test.

3.4 | Toxicity

Toxicity to iron supplementation was minimal and easily manageable. Grade 3 diarrhea occurred in 3% patients on IV iron and 7% patients on oral iron. Two percent patients on oral iron experienced grade 3 vomiting. Overall, gastrointestinal toxicity (any grade) developed in 41% patients on IV iron and 44% patients on oral iron, $P = 1.0$. Hypersensitivity reactions (any grade) developed in five patients on IV iron, and none on oral iron, $P = 0.059$. Three of the hypersensitivity reactions (3%) were ≥grade 3, although none were fatal. A 56-year-old man with

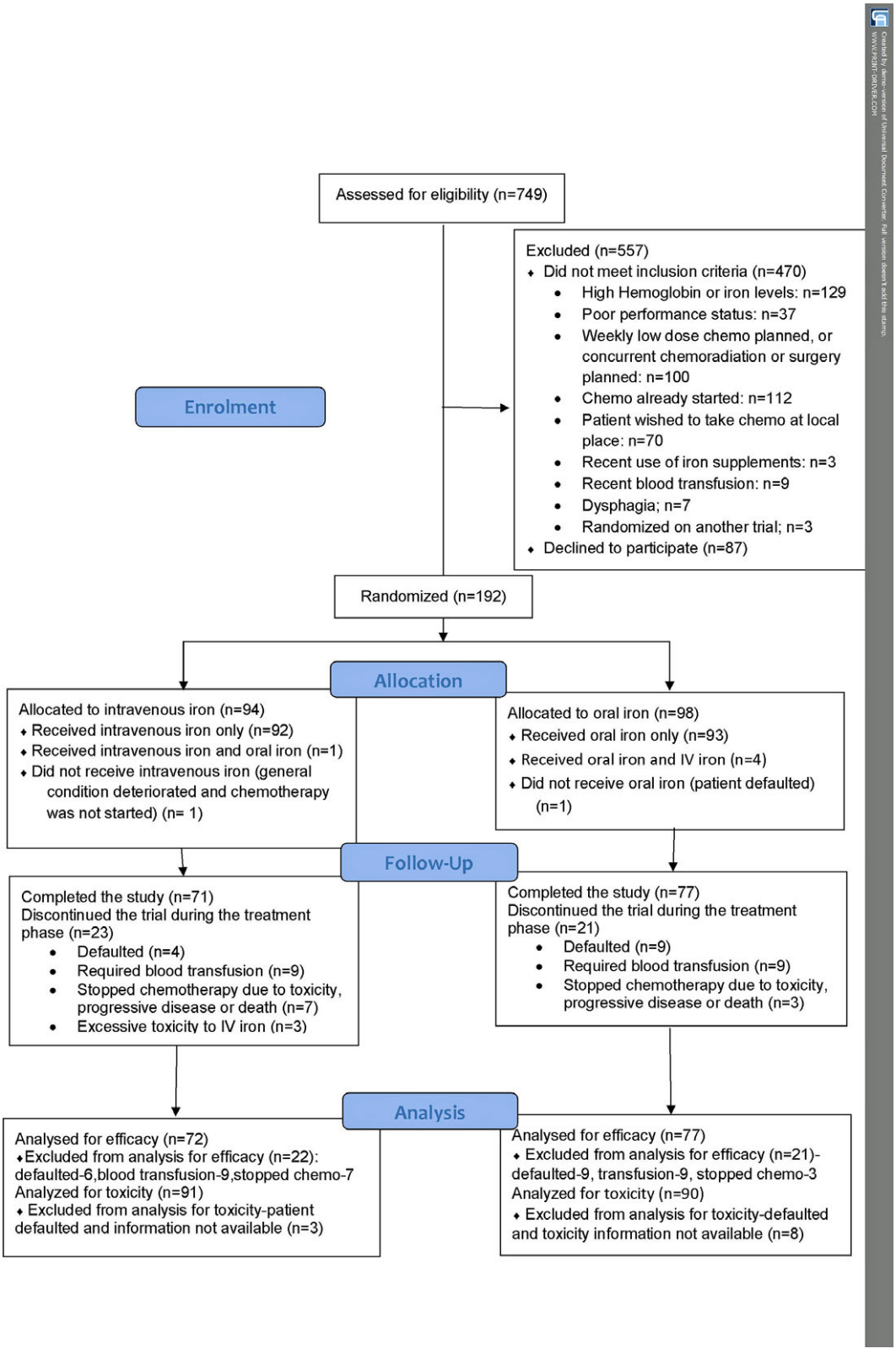

FIGURE 1 Flowchart of iron study. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Demographic details of patients randomized to IV *vs* oral iron supplementation

	IV iron (*N* = 94)	Oral iron (*N* = 98)	Total (*N* = 192)
Age (years)			
Median	55.5	50	51
Range	29-73	18-73	18-73
Gender, no. (%)			
Male	44 (46.8)	34 (34.7)	78 (40.6)
Female	50 (53.2)	64 (65.3)	114 (59.4)
Primary site of disease, no. (%)			
Solid tumor	90 (95.7)	93 (94.9)	183 (95.3)
Head and neck	23 (24.5)	16 (16.3)	39 (20.3)
Lung	23 (24.5)	21 (21.4)	44 (22.9)
Gynecologic	18 (19.1)	30 (30.6)	48 (25)
Breast	11 (11.7)	15 (15.3)	26 (13.5)
Esophagogastric	11 (11.7)	5 (5.1)	16 (8.3)
Other	4 (4.3)	6 (6.1)	10 (5.2)
Hematolymphoid	4 (4.3)	5 (5.1)	9 (4.7)
Diffuse large B-cell lymphoma	4 (4.3)	3 (3.1)	7 (3.6)
Burkitt's lymphoma	0	1 (1)	1 (0.5)
Mantle cell lymphoma	0	1 (1)	1 (0.5)
Stage, no. (%)			
I	2 (2.1)	4 (4.1)	6 (3.1)
II	14 (14.9)	15 (15.3)	29 (15.1)
III	33 (35.1)	26 (26.5)	59 (30.7)
IV	45 (47.9)	52 (53.1)	97 (50.5)
Unknown	0	1 (1)	1 (0.5)
Intent of therapy, no. (%)			
Curative	67 (71.3)	60 (61.2)	127 (66.1)
Palliative	27 (28.7)	38 (38.8)	65 (33.9)
Comorbidities[a], no. (%)			
None	85 (90.4)	79 (80.6)	164 (85.4)
Diabetes mellitus	6 (6.4)	12 (12.2)	18 (9.4)
Chronic hepatitis	2 (2.1)	4 (4.1)	6 (3.1)
Hypothyroidism	1 (1.1)	3 (3.1)	4 (2.1)
ECOG performance status[b], no. (%)			
0	3 (3.2)	4 (4.1)	7 (3.6)
1	77 (81.9)	84 (85.7)	161 (83.9)
2	12 (12.8)	7 (7.1)	19 (9.9)
3	1 (1.1)	3 (3.1)	4 (2.1)
Information not available	1 (1.1)	0	1 (0.5)
Chemotherapy regimen, no. (%)			
CHOP[c]	4 (4.3)	5 (5.1)	9 (4.7)
Platinum based 3-drug regimen[d]	6 (6.4)	14 (14.3)	20 (10.4)
Platinum based 2-drug regimen	82 (87.2)	76 (77.6)	158 (82.3)
Single agent chemotherapy	2 (2.1)	3 (3.1)	5 (2.6)

(Continues)

TABLE 1 (Continued)

	IV iron (*N* = 94)	Oral iron (*N* = 98)	Total (*N* = 192)
Baseline Hb (g/dL)			
Mean	10.2	10.1	10.1
Range	7.2–11.9	7.2–12.5	7.2–12.5

[a]Only comorbidities like diabetes mellitus and chronic renal dysfunction that could affect the hemoglobin level have been considered. Comorbidities like controlled hypertension and coronary artery disease which usually have no effect on anemia have not been considered.
[b]The European Oncology Cooperative Group (ECOG) performance status is a measure of the patient's functional status. It is scored on a five-point scale, with 0 indicating a patient with maximum functional ability, whereas higher numbers indicate increasing disabilities.
[c]A regimen that includes cyclophosphamide, doxorubicin, vincristine and prednisolone.
[d]The platinum-based 3-drug regimens included DCF (docetaxel, cisplatin and 5-flurouracil), ECF (epirubicin, cisplatin and 5-fluorouracil), TIP (paclitaxel, ifosfamide, cisplatin) and BEP (bleomycin, etoposide, cisplatin).
The platinum-based 2-drug regimens included various regimens in which platinum was combined with a taxane, pemetrexed, etoposide, doxorubicin, gemcitabine or 5-fluorouracil.

TABLE 2 Efficacy of IV *vs* oral iron

	IV iron (*N* = 94)	Oral iron (*N* = 98)
Baseline Hb (g/dL)		
Mean	10.2	10.1
Range	7.2–11.9	7.2–12.5
Hb at 3 weeks (g/dL)		
Mean	10.3	10.2
Range	7.4–13.7	7.1–13.2
Hb at 6 weeks (g/dL)		
Mean	10.0	9.7
Range	6.3–15.2	6.0–12.8
Absolute change in Hb at 6 weeks (g/dL)	(*n* = 87)	(*n* = 90)
Mean	0.11	−0.16
Standard Deviation (SD)	1.48	1.36
Increase in Hb ≥1 g/dl at 6 weeks, no. of patients (%)	(*n* = 87)	(*n* = 90)
No	67 (77)	74 (82.2)
Yes	20 (23)	16 (17.8)
Increase of Hb ≥ 1.5 g/dL at 6 weeks, no. of patients (%)	(*n* = 87)	(*n* = 90)
No	73 (83.9)	81 (90)
Yes	14 (16.1)	9 (10)
Absolute change in Hb at 3 weeks (g/dL)		
Mean	0.01	−0.11
Standard deviation (SD)	1.08	1.15
Requirement for blood transfusion during the study, no. (%)	(*N* = 94)	(*N* = 98)
No	79 (84.1)	79 → (80.6)
Yes	13 → (9.6)	14 (9.2)
Patient defaulted, details not available	2 (2.1)	5 (5.1)

[a]Hb, hemoglobin.

locally advanced adenocarcinoma of the lower third esophagus, who was planned for paclitaxel and carboplatin induction chemotherapy, was randomized to the IV iron arm. His performance status was 2 and baseline Hb was 9.4 g/dL. Following the IV iron infusion, he developed giddiness, nausea, difficulty breathing and hypotension (blood pressure: 70/60 mm Hg). He was managed in the intensive care unit, with vasopressor support. He was subsequently stabilized and taken off trial due to grade 4 hypersensitivity reaction. Two additional patients developed grade 3 hypersensitivity reactions. Toxicity details are provided in Table 3.

3.5 | Compliance to therapy

Compliance to therapy was comparable in the two arms: 76% patients on the IV iron arm and 79% on the oral iron arm were compliant. Of the 94 patients who were randomized to IV iron, 71 received both IV iron

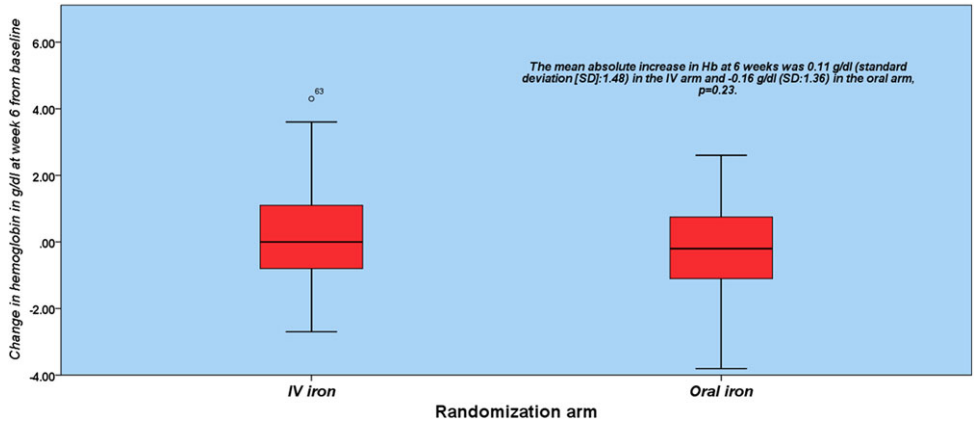

FIGURE 2 The mean absolute increase in hemoglobin at 6 weeks for patients treated with IV iron as compared to the oral iron. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Toxicity of IV and oral iron

	IV iron ($n = 91$)					Oral iron ($n = 90$)				
	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Nausea	77 (85)	8 (9)	6 (7)	0	0	79 (88)	5 (6)	6 (7)	0	0
Vomiting	78 (86)	11 (12)	2 (2)	0	0	71 (79)	12 (13)	5 (6)	2 (2)	0
Diarrhea	79 (87)	2 (2)	7 (8)	3 (3)	0	71 (79)	5 (6)	8 (9)	6 (7)	0
Constipation	84 (92)	5 (6)	2 (2)	0	0	82 (91)	5 (6)	3 (3)	0	0
Fever	87 (96)	3 (3)	1 (1)	0	0	87 (97)	3 (3)	0	0	0
Pain	83 (91)	5 (6)	3 (3)	0	0	83 (92)	4 (4)	7 (8)	0	0
Pruritus	88 (97)	2 (2)	1 (1)	0	0	87 (97)	2 (2)	1 (1)	0	0
Skin rash	90 (99)	0	1 (1)	0	0	89 (99)	1 (1)	0	0	0
Headache	87 (96)	4 (4)	0	0	0	87 (97)	1 (1)	2 (2)	0	0
Giddiness	90 (99)	0	1 (1)	0	0	88 (98)	2 (2)	0	0	0
Hypersensitivity	86 (95)	0	2 (2)	2 (2)	1 (1)	90 (100)	0	0	0	0

doses as per the protocol, 22 received only one dose and one patient did not receive any IV iron. Seven patients discontinued chemotherapy due to toxicity, progressive disease or death, nine required a blood transfusion, three were taken off study due to excessive toxicity (≥ grade 3 hypersensitivity) and three patients defaulted. Of the 98 patients who were randomized to oral iron, 77 patients were compliant with the entire course of oral iron therapy, whereas 21 discontinued their oral iron prior to completion of trial. Three patients discontinued chemotherapy due to toxicity, progressive disease or death, nine required a blood transfusion and nine patients defaulted.

3.6 | Quality of life

There was no significant difference between the 2 treatment arms in the various subscales like physical well-being domain (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB) and the anemia sub-scale (AnS). There was also no significant difference between the 2 treatment arms in the trial outcome index (TOI), FACT-G total score and FACT-An total score. The mean health related (HRQoL) scores did not change from visit 1 to visit 3 in either treatment arm. Overall, there was no significant difference between the IV and oral arm scores, indicating no change in HRQoL between the IV iron treated patients and the oral iron treated patients (Appendix B).

4 | DISCUSSION

In our study, IV iron did not lead to a significantly greater increase in Hb at 6 weeks, did not decrease the requirement for blood transfusion, did not have a favorable side-effect profile and did not improve the patients' QoL. Prior studies and a meta-analysis have shown that IV iron added to ESA significantly improves the hematopoietic response and that IV iron leads to a better hematopoietic response than oral iron.[3–8] However, there are also some trials that have opposite results, that is they have shown that IV iron added to ESA did not have any additional benefit as compared to oral iron.[10,11] As a result of these conflicting data, the American Society of Hematology (ASH) and the

American Society of Clinical Oncology (ASCO) guidelines recommend the use of supplemental iron to enhance the effect of ESA, however they state that since there is a lack of sufficient evidence, parenteral iron cannot be recommended as the standard of care.[12] Data from our trial suggest that in the absence of ESA administration, IV iron is not significantly better at inducing a hematopoietic response than oral iron.

Regardless of the route of iron supplementation, the response to iron therapy in patients in our study was low. Overall only 18.8% patients responded to iron supplementation. This low response to iron is puzzling, given the fact that all patients included in the trial were iron deficient, based on measurement of baseline iron levels. We defined iron deficiency as ferritin <100 mcg/mL, transferrin saturation <20% or hypochromic red blood cells >10%. True iron deficiency is defined as ferritin <15–30 mcg/mL, however in the setting of chronic inflammation and in disorders like malignancy, using a ferritin cut-off of 100 mcg/mL and a transferrin saturation <20% is widely accepted.[13,14] Kanuri *et al.* reported that rather than the ferritin level alone, the ratio of the soluble transferrin receptors to ferritin index was a more reliable method of detecting iron-deficiency anemia.[15] The physiologic response to iron supplementation in an iron-deficient individual should consist of a brisk reticulocytosis within a few days leading to a rise in Hb of 1–2 g/dL per week.[13] In patients on cytotoxic chemotherapy, this response is likely to be blunted due to the myelosuppressive effects of chemotherapy. In the trial by Auerbach *et al*., the number of patients who achieved a hematopoietic response was 68% in the IV iron group, 36% in the oral iron group and 25% in the no-iron group.[4] However, the key difference between the trial by Auerbach *et al* and our trial was that all patients in the Auerbach trial received erythropoietin. This probably abrogated the suppressive effect of chemotherapy on erythropoiesis, permitting the iron supplementation to lead to an appropriate rise in Hb. In the meta-analysis by Gafter-Gvili *et al*., there were no data on the hematopoietic response to iron supplementation in patients who were not on ESA.[8]

Other possible explanations for the low observed efficacy of iron supplementation include a possibly short time to assessment of response, an inadequate dose of iron added to the myelosuppressive effects of chemotherapy and the type of malignancy. We selected the timeframe of 6 weeks as the appropriate time for assessment of the hematopoietic response based on several prior studies.[4,7] However, all these studies were in patients who received ESA in addition to iron. Perhaps, iron supplementation in patients on cytotoxic chemotherapy and not on ESA takes a longer time to manifest an increase in Hb. We did not follow patients' Hb levels after completion of the trial, which is one of the shortcomings of our trial. We calculated the dose of IV iron from the Ganzoni formula for iron deficit,[16] and the mean dose of IV iron received by our patients was lower than the flat dose of 1000 mg of IV iron that is now commonly used. The optimal dose of iron replacement is controversial, and various investigators have used differing formulae to calculate the dose of parenteral iron supplementation, with absolute doses ranging as high as 3000 mg in divided doses.[14] Koch *et al.* reported that a higher cumulative dose of parenteral iron, i.e. 1500 mg led to a more rapid and effective rise in Hb as compared to a lower dose of 1000 mg.[16] However, concerns exist with higher doses of iron regarding adverse interaction with chemotherapy drugs and increased risk of tumor progression.[14]

At our center, ESA are rarely prescribed. How then should we treat our iron deficiency anemia patients who are on cytotoxic chemotherapy? We believe that iron supplementation continues to be the therapy of choice for these patients. However, the optimal route, dose and duration of iron supplementation have yet to be determined, and possibly administering iron at a higher dose or for a longer duration than was administered in our trial may have led to a better hematopoietic response. Both routes of administration were well tolerated and did not differ significantly in terms of toxicity profile, patient compliance or QoL. This has been observed in other trials as well.[8] Other factors would then play a role in the decision regarding the optimal route of iron. These factors would include patient and physician preference, convenience of administration (need to visit the hospital for an IV infusion versus the requirement to continue taking oral supplements three times a day for several months) and cost. Given the lower than expected hematopoetic response to iron therapy, our trial was underpowered to assess a difference between IV iron and oral iron.

5 | CONCLUSION

Our study suggests that IV iron is not superior to oral iron in cancer patients on chemotherapy with iron deficiency anemia. It will be important to investigate further as to the cause for limited response to iron supplementation in such patients.

ACKNOWLEDGEMENTS

The trial was funded by an intramural grant from the Tata Memorial Center Research Administration Council (Tata Memorial Center, Mumbai, Maharashtra, India).

CONFLICT OF INTEREST

There are no conflicts of interest.

COMPLIANCE WITH ETHICAL STANDARDS

All procedures performed in our study were in accordance with the ethical standards of our institutional research committee (Tata Memorial Center, Mumbai, Maharashtra, India) and of the Indian council of medical research (ICMR guidelines), good clinical practice guidelines and with the 1964 Helsinki Declaration and its later amendments.

Written informed consent was obtained from all individual participants included in the study.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Noronha V, Joshi A, Patil VM, et al. Phase III randomized trial comparing intravenous to oral iron in patients with cancer-related iron deficiency anemia not on erythropoiesis stimulating agents. *Asia-Pac J Clin Oncol*. 2017;1-9. https://doi.org/10.1111/ajco.12762