RESEARCH ARTICLE

Efficacy and safety of ferric carboxymaltose infusion in reducing anemia in patients receiving chemotherapy for nonmyeloid malignancies: A randomized, placebo-controlled study (IRON-CLAD)

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Abstract

Erythropoiesis-stimulating agents (ESA) are effective for chemotherapy-induced anemia (CIA) but associated with serious adverse events. Safer alternatives would be beneficial in this population. The efficacy and safety of ferric carboxymaltose (FCM) as monotherapy for CIA was evaluated. This Phase 3, 18-week, double-blind, placebo-controlled study randomized adults with ≥ 4 weeks of chemotherapy remaining for treatment of nonmyeloid malignancies with CIA to FCM (two 15 mg/kg infusions 7 days apart; maximum dose, 750 mg single/1500 mg total) or placebo. The primary efficacy endpoint was percentage of patients with decreases in hemoglobin (Hb) ≥ 0.5 g/dL from weeks 3 to 18; the key secondary efficacy endpoint was change in Hb from baseline to week 18. Inclusion criteria included: (Hb) 8–11 g/dL, ferritin 100–800 ng/mL, and transferrin saturation (TSAT) ≤35%. In 244 patients ($n = 122$, both groups), the percent of patients who maintained Hb within 0.5 g/dL of baseline from weeks 3 to 18 was significantly higher with FCM versus placebo (50.8% vs. 35.3%; $p = 0.01$). Mean change in Hb from baseline to week 18 was similar between FCM and placebo (1.04 vs. 0.87 g/dL) but significantly greater with FCM with baseline Hb ≤ 9.9 g/dL (1.08 vs. 0.42 g/dL; $p = 0.01$). The percent with ≥ 1 g/dL increase from baseline was significantly higher with FCM versus placebo (71% vs. 54%; $p = 0.01$), occurring in a median 43 versus 85 days ($p = 0.001$). Common adverse events in the FCM arm included neutropenia (17%), hypophosphatemia (16%), and fatigue (15%). FCM monotherapy effectively maintained Hb and was well tolerated in CIA.

1 | INTRODUCTION

Chemotherapy-induced anemia (CIA) is common among solid tumor and hematologic malignancies and is often exacerbated by myelosuppressive chemotherapy or other antineoplastic therapies.[1–6] These patients often develop inflammation, especially in advanced disease.[6] Additionally, CIA can impair quality of life, well-being, and performance status[5,7,8] and has been identified as an independent predictor of shorter survival time, highlighting the need for prompt diagnosis and treatment.[9]

While CIA is primarily believed to result from decreased erythropoiesis due to the myelosuppressive effects of treatment,[10] numerous contributing factors related to the underlying disease exist, and may include inflammation, blood loss, erythropoietin

deficiency due to renal disease, iron deficiency, and marrow involvement, among others.[1] Standard treatment for moderate to severe CIA includes packed red blood cell (pRBC) transfusion and erythropoiesis-stimulating agents (ESAs); in contrast, intravenous (IV) iron may be used to treat any grade of CIA when iron deficiency exists.[10–12] Blood transfusion provides rapid increase in hemoglobin (Hb) concentrations yet must be balanced against associated risks of serious transfusion reactions inclusive of circulatory overload, lung injury, and alloimmunization.[10,13–15]

Importantly, underreporting of transfusion reactions is widespread, with only 5% of the episodes of circulatory overload and 25% of the episodes of lung injury cases being reported to transfusion services despite clinical notes citing adverse events (AEs).[15] While ESAs can decrease transfusion requirements, they work optimally in the iron sufficiency setting. Regarding ESA risks, according to Food and Drug Administration, ESAs are not indicated in patients with cancer when the anticipated outcome is a cure, and importantly, increase the relative risk of thromboembolism by 48–69%.[10,16–22] Anemia due to myelosuppressive chemotherapy is inadequately managed by transfusion, and many patients may not qualify for or respond to treatment with an ESA, highlighting the need for alternative treatments.[23] Although some studies suggest that there may be no increase in mortality when receiving ESAs, the risk of thromboembolism and cancer type must be considered.

Adding IV iron to ESA therapy provides sufficient iron to support ESA-driven erythropoiesis.[24] Studies have shown that concomitant IV iron improves Hb response, shortens the time to achieve target Hb concentrations, reduces the need for transfusion, improves quality of life, and facilitates ESA dose reduction, with no additional risk of thromboembolism beyond that associated with ESAs alone.[4,23,25–29] Although few studies have evaluated IV iron as monotherapy in CIA, data in this population have demonstrated increased Hb concentrations and/or reductions in transfusion rates.[23,30–32] These data suggest that IV iron is a feasible treatment option for CIA when ESA therapy is not appropriate.[23] Currently, however, no IV iron formulations are approved specifically in patients with cancer for CIA.[23]

Ferric carboxymaltose (FCM) is an IV iron replacement therapy approved as monotherapy for patients with iron deficiency anemia (IDA) and intolerance or an unsatisfactory response to oral iron[33,34] or nondialysis-dependent chronic kidney disease (NDD-CKD).[35–37] In two Phase 3 pivotal studies conducted in patients with IDA with and without impaired renal function, FCM monotherapy was well tolerated and demonstrated substantial clinical benefits in patients with IDA, including rapid, clinically meaningful increases in Hb and reductions in transfusion requirement. In the 2 pivotal trials, a decrease in blood phosphorus levels was reported as an adverse event by the study investigators in 2.1% of the patients.[33,34] FCM has also shown benefit in IDA associated with CKD,[35,36] congestive heart failure,[38] postpartum anemia,[39] heavy uterine bleeding,[40] inflammatory bowel disease,[41] and CIA.[42,43] The current study compared the efficacy and safety of IV FCM monotherapy and placebo for maintaining Hb concentrations in patients with CIA.

2 | MATERIAL AND METHODS

2.1 | Patients and study design

The 18-week IRON-CLAD study was a randomized, double-blind, parallel-group, placebo-controlled, Phase 3 trial conducted at 58 sites in the United States, Bulgaria, Georgia, Hungary, and Poland (NCT02453334). Eligible patients were ≥ 18 years of age receiving chemotherapy for a nonmyeloid malignancy, with ≥ 4 weeks of treatment remaining and life expectancy ≥ 6 months. Other key eligibility criteria were screening Hb 8–11 g/dL, ferritin 100–800 ng/mL, transferrin saturation (TSAT) ≤ 35%, and an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–2. Patients were excluded if they had received oral or IV iron, RBC transfusion, or an ESA within 4 weeks of screening or were currently taking an ESA. Iron-containing multivitamins were permitted.

Patients were randomized 1:1 to receive FCM injection (Injectafer®, American Regent Inc., Shirley, NY)[37] or placebo via the Interactive Response Technology system. FCM was diluted in ≤ 250 mL saline and administered in two 15-min infusions 7 days apart, each at a dose of 15 mg/kg (maximum permitted single and total doses of 750 mg and ≤1500 mg, respectively). The placebo was ≤ 250 mL of normal saline administered in two 15-min infusions. All patients, investigators, and study personnel were blinded to the content of the study drug, with the exception of the unblinded study personnel who used the Interactive Response Technology system to retrieve the randomized study arm assignments and prepared, concealed, and administered the drug. Patients were blinded to treatment using a sleeping mask before receiving study drug. Investigator(s) who performed efficacy and safety evaluations were not present during study drug administration.

2.2 | Ethics and compliance

All study documents, including the trial protocol and informed consent forms, were approved by a central institutional review board (IRB) and local IRBs/ethical committees before study initiation. The study was conducted in compliance with the principles of the Declaration of Helsinki, using Good Clinical Practice according to International Council for Harmonization Tripartite Guidelines, and in accordance with standard operating procedures provided by the sponsor and contract research organization (KCR S.A., Warsaw, Poland). All enrolled patients provided written informed consent before study enrollment.

2.3 | Endpoints and assessments

The primary efficacy endpoint was the percentage of patients with a decrease in Hb of ≥ 0.5 g/dL from weeks 3 to 18. The primary endpoint was considered to have been met if Hb was (1) 0.5–1.0 g/dL lower than baseline on two consecutive visits between weeks 3 and 18, OR (2) ≥ 1.0 g/dL lower at a single visit OR (3) if the patient discontinued the study before week 18 owing to lack of efficacy or AEs.

Receipt of a nonstudy intervention (initiation of an ESA, a blood transfusion, or additional IV or oral iron) before week 18 was also considered to have met the primary endpoint. Failure to meet criteria was considered to not meet the primary endpoint and to have maintained Hb levels.

The key secondary efficacy endpoint was change in Hb from baseline to week 18 or to nonstudy intervention (i.e., end of study treatment). Other secondary efficacy endpoints were an increase in Hb ≥ 1 g/dL from baseline and the time taken to reach this endpoint from baseline to week 18; with a decrease in Hb ≥ 0.5 g/dL from baseline at each study visit and the time taken to reach this endpoint; who received a nonstudy intervention and required a blood transfusion; and who reached Hb > 12 g/dL from baseline to each study visit; correlation of change in Hb with baseline hepcidin level; and the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale total score.

Safety was assessed by vital signs, physical examination, AEs, and laboratory assessments which comprised hematology, chemistry, iron indices (serum iron [normal range: 60–170 μg/dL], serum ferritin [normal ranges: 12–300 ng/mL in men and 12–150 ng/mL in women], total iron-binding capacity [TIBC; normal range: 240–450 μg/dL], TSAT [normal range: 20–50%], and serum hepcidin [normal range: 1–55 ng/mL]).[44] Nonserious anemia and iron deficiency (Hb or hematocrit and iron indices, respectively, which fell below the normal range or worsened from baseline) were not considered AEs. The severity of AEs was quantified using the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4) (CTCAE), with terms defined based on the Preferred Term listings in the Medical Dictionary for Regulatory Activities (MedDRA; version 17.0).

2.4 | Statistical methods

Based on the expectation that 65% of patients in the placebo group would not maintain baseline Hb concentrations,[5] 212 patients (106 per treatment group) would provide 90% power at a two-sided p value of 0.05 to detect a clinically relevant proportional reduction of 35% between the two treatment groups.

Safety was assessed for all patients who were randomized and received at least one dose of study drug. Efficacy was assessed for a modified intent-to-treat (mITT) population, defined as patients who were randomized, received at least one dose of study drug, and had a baseline and postbaseline Hb measurements.

The primary efficacy endpoint was analyzed using the Cochran–Mantel–Haenszel (CMH) Chi-squared test, adjusting for country. Other binary endpoints were analyzed analogous to the primary endpoint. Time-to-event endpoints were assessed using a log-rank test stratified by country. Continuous endpoints were analyzed using a mixed effects model for repeated measures (MMRM). Assessments of correlations were based on Spearman rank and Pearson product–
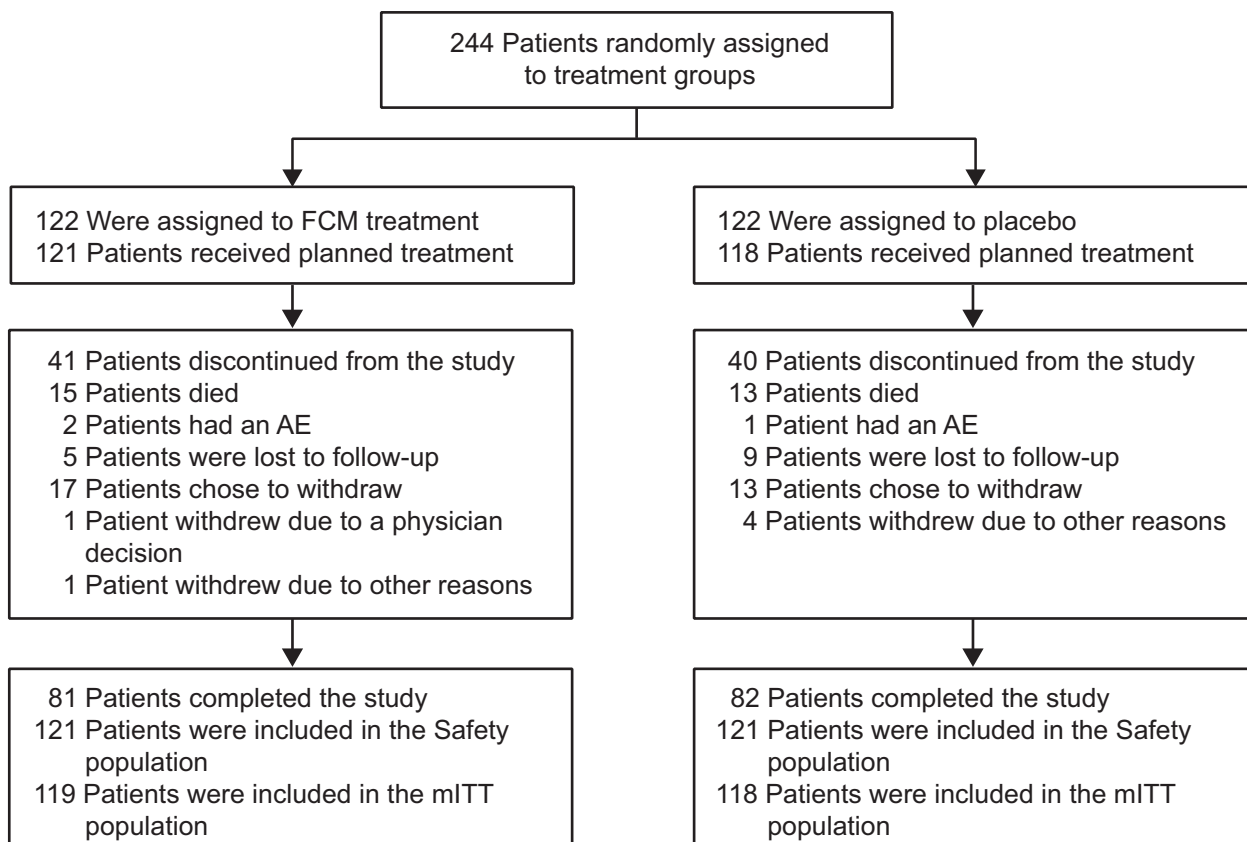

FIGURE 1 Patient disposition. AE, adverse event; FCM, ferric carboxymaltose; ITT, intent-to-treat; mITT, modified ITT

moment correlation coefficients. For all efficacy analyses, data were censored at the time of nonstudy intervention. Hypothesis testing was carried out at the 2-sided $\alpha = 0.05$ level. No adjustments were made for multiplicity.

3 | RESULTS

3.1 | Patients

A total of 244 patients were randomized, 122 each in the FCM and placebo group, of whom 163 (66.8%; 81 in the FCM group, 82 in the placebo group) completed the study (Figure 1). Demographics and baseline disease characteristics were similar between groups; most were white (93.9%) and had an ECOG PS score of 0 or 1 (93.0%) (Table 1). The FCM group included a higher percentage of stage 4 cancer at baseline compared with the placebo group (66.4% vs. 56.6%, respectively). All had at least one medical condition in their history, with a similar incidence in both groups, most commonly anemia (225 [94.1%]), hypertension (93 [38.9%]), and fatigue (56 [23.4%]). Ten percent had a history of neutropenia and, at baseline, most were taking antinausea/antiemetic medications (72.8%) and corticosteroids (67.8%). Patients in the FCM and placebo groups had mean baseline leukocyte counts of 6.7 and 6.2 $\times 10^3$ cells/μL, respectively, with slightly higher values for mean serum ferritin (362 vs. 337 ng/mL) and mean TSAT (24.6% vs. 20.8%), respectively. A total of 81 (33.2%) discontinued the study, most commonly attributed to patient decision (30 [37.0%]), death (28 [34.6%]), or loss to follow-up (14 [17.3%]) (Figure 1).

3.2 | Efficacy

For the primary endpoint of decreased Hb of $\geq$ 0.5 g/dL from baseline at weeks 3 to 18, a significantly higher percentage in the FCM group maintained Hb within 0.5 g/dL of baseline (50.8%) compared with the placebo group (35.3%; between-treatment difference: -15.6% [95% CI: -28.0%, -3.1%]; $p = 0.01$). The FCM/placebo odds ratio was 0.51 (95% CI: 0.30, 0.87; $p = 0.01$). The median time to a decrease in Hb of $\geq$ 0.5 g/dL was three times longer in the FCM group compared with the placebo group (127 vs. 43 days; $p = 0.006$) (Figure 2).

Increases from baseline Hb were observed as early as day 7 in patients receiving FCM, whereas Hb levels remained almost unchanged in the first 6 weeks with placebo (Figure S3). There was no significant difference in Hb between-treatment groups at week 18. However, in the subgroup with baseline Hb levels < 10 g/dL, the least-squares (LS) mean (standard error) change from baseline significantly favored the FCM group over the placebo group (1.08 [0.18] vs. 0.42 [0.19] g/dL, respectively; between-group difference: 0.67 [0.26] g/dL; $p = 0.01$).

The percent with an increase from baseline Hb of $\geq$ 1 g/dL at week 18 was significantly greater in the FCM group compared with the placebo group (70.6% vs. 54.2%, respectively; $p = 0.0097$), with a significantly shorter median time to achieve a $\geq$ 1 g/dL increase in Hb in the

FCM group (43 vs. 85 days; $p = 0.001$). The percent with Hb levels > 12 g/dL at any time without receiving nonstudy intervention were similar with FCM or placebo (26.1% [$n = 31$] vs. 20.3% [$n = 24$], respectively).

No differences were identified between the FCM and placebo groups in the percentages of those who received nonstudy

TABLE 1 Patient demographics and baseline characteristics

	FCM ($n = 122$)	Placebo ($n = 122$)
Age (year)		
Mean (SD)	63.0 (10.0)	63.1 (9.3)
Median (range)	63.0 (39–88)	63.0 (34–83)
Female sex, n (%)	67 (54.9)	69 (56.6)
Race, n (%)		
White	117 (95.9)	112 (91.8)
Black/African American	5 (4.1)	8 (6.6)
Multiple	0	2 (1.6)
Other	0	0
Leukocyte count (cells/L[a])		
Mean (SD)	6.7 (6.9)	6.2 (4.5)
Median (range)	5.0 (0.7–48.4)	5.1 (1.7–31.3)
History of Iron intolerance,[b] n (%)		
No	119 (97.5)	119 (97.5)
Yes	3 (2.5)	3 (2.5)
Iron parameters[a]		
Ferritin (ng/mL)		
Mean (SD)	361.7 (291.0)	337.2 (270.2)
Median (range)	281.8 (57.6–1948.5)	263.0 (25.9–1899.5)
TSAT (%)		
Mean (SD)	24.6 (16.8)	20.8 (13.4)
Median (range)	20.0 (6–87)	18.0 (5–79)
ECOG performance status, n (%)		
0	39 (32.0)	30 (24.6)
1	75 (61.5)	83 (68.0)
2	8 (6.6)	9 (7.4)
$\geq$3	0	0
Cancer stage, n (%)		
0	2 (1.6)	0
1	0	0
2	2 (1.6)	7 (5.7)
3	9 (7.4)	12 (9.8)
4	81 (66.4)	69 (56.6)
Unknown	28 (23.0)	34 (27.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FCM, ferric carboxymaltose; SD, standard deviation; TSAT, transferrin saturation; WBC, white blood cell count.
[a]FCM $n = 121$, placebo $n = 118$.
[b]Oral iron supplements, which are usually in the form of ferrous (Fe^{2+}) salts, are toxic to the gastrointestinal mucosa. As a result, intolerance is common and results in poor compliance and treatment failure.

FIGURE 2 Kaplan–Meier curve: Time to decrease in baseline hemoglobin of ≥0.5 g/dL. Hb, hemoglobin; wk, week [Color figure can be viewed at wileyonlinelibrary.com]
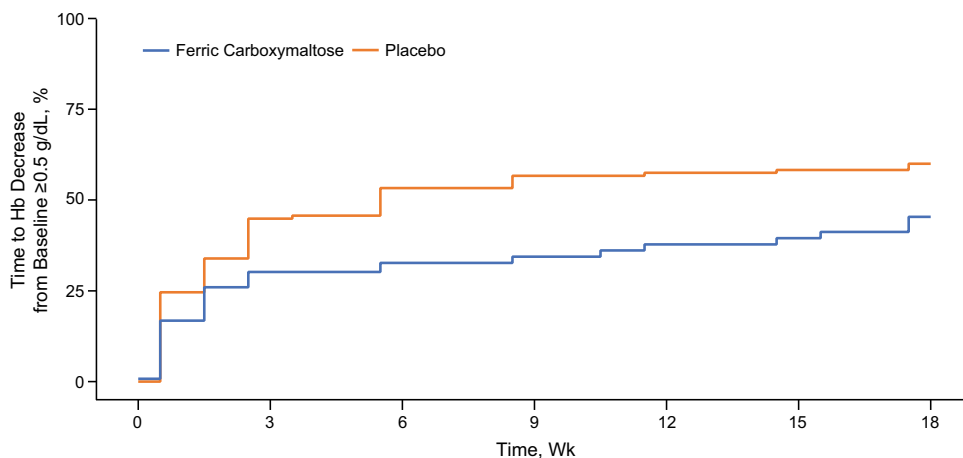
TABLE 2 Percentage of patients with hemoglobin decrease from baseline of ≥0.5 g/dL from weeks 3 to 18 by baseline hepcidin (mITT population)

	Baseline Hepcidin					
	1st tertile (0–42 ng/mL)	2nd tertile (43–102 ng/mL)		3rd tertile (106–755 ng/mL)		
Category	FCM (n = 33)	Placebo (n = 38)	FCM (n = 32)	Placebo (n = 40)	FCM (n = 41)	Placebo (n = 31)
Hb decrease from baseline ≥ 0.5 g/dL from Weeks 3 to 18, n (%)	10 (30.3)	15 (39.5)	6 (18.8)	22 (55.0)	19 (46.3)	17 (54.8)
Percentage difference (95% CI)	−9.2 (−31.25, 12.91)		−36.3 (−56.76, 15.74)		−8.5 (−31.73, 14.74)	
Odds ratio (95% CI)	0.74 (0.28, 1.96)		0.21 (0.07, 0.65)		0.63 (0.24, 1.65)	
p value	0.5435		0.0041		0.3466	

Abbreviations: CI, confidence interval; FCM, ferric carboxymaltose; Hb, hemoglobin; mITT, modified intent-to-treat.

interventions (18.5% [$n = 22$] vs. 21.2% [$n = 25$], respectively) or required a blood transfusion (12.6% [$n = 15$] vs. 11.9% [$n = 14$]), and no differences were identified between the FCM and placebo groups in the mean (standard deviation [SD]) changes from baseline to week 18 in the FACIT-Fatigue Scale scores (−1.5 [8.8] vs. 0 [8.9]).

3.3 | Relationship between hepcidin concentrations and changes in Hb

Spearman rank correlations demonstrated a weak negative association between baseline hepcidin and change from baseline Hb concentrations over time in the placebo group (−0.278; $p = 0.004$) and no association in the FCM group (−0.085; $p = 0.39$). Pearson correlation analysis showed similar results.

In a post hoc analysis, the percent of patients who maintained Hb within 0.5 g/dL of baseline was significantly higher with FCM than with placebo only in the hepcidin tertile 2 (43–102 ng/mL; 55.0% vs. 18.8%; $p = 0.004$) (Table 2). Adjusting for baseline hepcidin levels, LS mean changes from baseline to week 18 in Hb were significantly higher in the FCM group versus the placebo group (0.65 [95% CI: 0.35, 0.95] vs. 0.21 [−0.08, 0.51], respectively; $p = 0.04$). Information

on underlying absolute iron deficiency or functional iron deficiency (FID) for this analysis was not available.

3.4 | Safety

A total of 118 patients in the placebo group and 121 in the FCM group received at least one dose of study drug. Investigator-identified treatment-emergent AEs (TEAEs) were reported in approximately 80% of patients overall (FCM, 79.3%; placebo, 80.5%), including neutropenia (FCM, 17.4%; placebo, 11.9%), hypophosphatemia (FCM, 15.7%; placebo, 2.5%), and fatigue (FCM, 14.9%; placebo, 14.4%) (Table S3). No events of venous thromboembolism were reported. There were no differences between groups in the number of serious AEs or discontinuations. Serious AEs, none of which were treatment related, were reported in 28 (23.1%) and 22 (18.6%) patients in the FCM and placebo group, respectively. Based on CTCAE (version 4) grading, hypophosphatemia was the only severe AE that was more common after FCM than placebo (13 [10.7%] vs. 2 [1.7%], respectively) (Table S3). Analysis of shifts in serum phosphate levels during the study revealed a marked decrease from baseline to day 7 and from baseline to week 2, corresponding to FCM infusions at baseline and

day 7. After week 2, phosphate concentrations increased, returning to baseline levels by week 6 in most patients. Based on the laboratory findings, 70 patients in the FCM group with normal serum phosphate concentrations at baseline were observed to progress to phosphate CTCAE grade 2 ($n = 25$ [35.7%]), grade 3 ($n = 42$ [60%]), and grade 4 ($n = 3$ [4.3%]) during the study, returning to normal in a mean of 20.4, 29.4, and 61.0 days, respectively. The percentage of patients in the FCM group shifting from phosphate CTCAE grade 0 to 3 (36%) or grade 0 to 4 (2.5%) was higher than in the placebo group (4% and 0%, respectively). Although 70 of 121 (58%) FCM-treated patients developed low phosphate values, only 19 of 121 (15.7%) experienced hypophosphatemia as a TEAE requiring intervention (for example, dietary modification or prescription for phosphate supplementation), per investigator discretion and institutional guidelines. Hypophosphatemia did not lead to any serious AEs or study discontinuations, and associated AEs were reported of similar proportion in both groups.

Twenty-one (17%) patients who received FCM and 8 (7%) who received placebo had ≥ 1 treatment-related TEAE. The only treatment-related TEAE occurring in ≥ 5% of patients in either group was hypophosphatemia, occurring in 10 (8%) patients in the FCM group and 2 (2%) in the placebo group. In all, 17 (14%) patients in the FCM group and 14 (12%) in the placebo group discontinued the study because of AEs, most commonly for malignant neoplasm progression (the progression of pre-existing cancer and/or aggravation of a malignant neoplasm; 6 [5.0%] vs. 1 [0.8%], respectively), disease progression (any cancer that continued to grow or spread; 3 [2.5%] vs. 4 [3.4%]), dyspnea (2 [1.7%] vs. 0), or death (1 [0.8%] vs. 2 [1.7%]; cause could not be confirmed in all cases). Malignant neoplasm progression was similar among treatment and placebo groups and was considered unrelated to study drug among the patients who discontinued because of this AE. AEs leading to death were reported in 15 (12%) patients in the FCM group and 13 (11%) in the placebo group; just over half (8 and 7, respectively) were due to cancer progression. No deaths were considered treatment related.

At week 3, patients receiving FCM had higher mean (SD) serum ferritin levels (1228.7 [603.9] vs. 406.5 [604.2] ng/mL; Figure S4) and higher mean TSAT (31.8% [15.9] vs. 22.8% [15.9]) than those receiving placebo. Mean serum ferritin levels decreased to below 1000 ng/mL by week 9.

4 | DISCUSSION

The major finding of this study was that the FCM treatment group, relative to the placebo group, maintained baseline Hb levels in patients receiving chemotherapy for nonmyeloid malignancies. The odds of a decrease from baseline Hb of ≥ 0.5 g/dL after FCM receipt was approximately half that of patients receiving placebo (median lag time three times longer, 127 vs. 43 days) and the odds of an increase in Hb of ≥ 1 g/dL after FCM receipt were double that of a patient in the placebo group (achieved in 43 vs. 85 days, respectively). There were no significant between-group differences observed in nonstudy interventions or transfusion requirements during the study, change in

FACIT-Fatigue Scale score, or Hb levels from baseline to week 18. Treatment with FCM led to a more rapid increase from baseline in Hb compared with placebo; however, the difference between groups was not sustained at 18 weeks.

Currently, National Comprehensive Cancer Network (NCCN) guidelines on treating CIA recommend blood transfusion in symptomatic patients with anemia and advise that transfusion be considered in high-risk patients and asymptomatic patients with certain cardiovascular or pulmonary comorbidities.[10] Multiple guidelines recommend considering IV iron supplementation in conjunction with ESA therapy in patients with CIA[10,45,46]; however, there is no consensus on which specific populations should receive it. The NCCN and European Organization for Research and Treatment of Cancer guidelines recommend considering IV iron in patients receiving ESAs who meet the criteria for FID,[10,46] while guidelines from the American Society of Clinical Oncology/American Society of Hematology recommend iron replacement therapy (IV or oral) in conjunction with ESAs in patients with CIA, independent of iron status (assuming periodic monitoring of iron indices).[45] Current NCCN guidelines note that data are insufficient to recommend IV iron monotherapy in patients with FID.[10] Findings from the present study support the benefits of IV FCM monotherapy in patients with CIA, particularly in the subgroup of patients who are eligible for ESA therapy (i.e., those with Hb < 10 g/dL). In addition, based on the rapid increase in Hb and prolonged delay in the time to Hb decrement with IV iron monotherapy, this treatment could also benefit patients who do not qualify for an ESA and/or those receiving chemotherapy whose religious beliefs prohibit receipt of blood transfusion.

Ferric carboxymaltose raised no new safety signals and was well tolerated, with no notable difference between groups in the incidence of AEs other than hypophosphatemia, which occurred in 16% of FCM patients and 3% of placebo patients (treatment related in 8% vs. 2%) but was transient and asymptomatic. Short-term iron-induced hypophosphatemia has been reported previously.[47,48] In a study of a single 1000 mg infusion of FCM in patients with NDD-CKD, a significant reduction in serum phosphate was reported at week 3 and remained lower than baseline for up to 3 months after FCM infusion.[47] Neutropenia was a TEAE in 17.4% of FCM patients and 11.9% of placebo patients, but is not a common AE in clinical trials (i.e., reported in > 1% of patients) or in post-marketing experience, per the FCM product labeling. Key confounding factors that may decrease neutrophil count—chemotherapy (a key eligibility criterion), concomitant medications, history of neutropenia at baseline (10% of patients), other comorbidities, and underlying morbidities—were present in the study population and should be considered when ascribing causality of neutropenia. Although patients with cancer are at an increased risk of thrombosis,[49] there were no reports of venous thromboembolism during the study. Growing evidence suggests that iron-deficient erythropoiesis increases thrombotic tendency and that IV iron may reduce the risk of thromboembolic events.[50,51]

Overall, 54.2% of patients in the placebo group experienced an increase from baseline in Hb of ≥ 1 g/dL during the study. A differing level of aggressiveness of myelosuppressive chemotherapies received

or shorter duration of treatment compared to the FCM arm may have contributed to this result. Additional studies with more stringent enrollment criteria using iron parameters may help understand this response.

Evidence suggests that low serum hepcidin levels may aid in identifying iron-deficient patients who are more likely to benefit from IV iron. This relationship was suggested by an analysis of data from patients receiving ESA for CIA, in which improved Hb in response to IV iron supplementation was observed only in the subgroup of patients whose hepcidin levels were ≤ 64.3 ng/mL.[52] However, in the present study, no clear correlation was found between baseline hepcidin level and change in Hb in the FCM group, although post hoc analysis revealed that a significantly lower percentage of patients in hepcidin tertile 2 receiving FCM had a decrease in Hb ≥ 0.5 g/dL.

In conclusion, this study demonstrated that IV iron supplementation in the form of FCM monotherapy allowed the majority of patients receiving myelosuppressive chemotherapy to maintain Hb levels within 0.5 g/dL of baseline and was significantly more effective in doing so when compared to placebo. FCM was well tolerated in patients with CIA, with transient, asymptomatic serum hypophosphatemia being the most common AE. These data support a role for FCM monotherapy in anemic patients receiving myelosuppressive chemotherapy for nonmyeloid neoplasms who are unsuitable candidates for, or cannot tolerate, ESAs and/or blood transfusion. Further study aimed at defining the predictive serum hepcidin response threshold for IV iron is needed.

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