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Intravenous Ferric Gluconate Significantly Improves Response to Epoetin Alfa Versus Oral Iron or No Iron in Anemic Patients with Cancer Receiving Chemotherapy

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Key Words. Epoetin alfa • Anemia • Chemotherapy • Iron • Cancer

ABSTRACT
Purpose. To evaluate the safety and efficacy of intravenous (IV) sodium ferric gluconate complex (FG), oral ferrous sulfate, or no iron to increase hemoglobin (Hb) in anemic cancer patients receiving chemotherapy and epoetin alfa.

Patients and Methods. In this open-label, multicenter trial, 187 patients with chemotherapy-related anemia (Hb < 11 g/dl; serum ferritin ≥100 ng/ml or transferrin saturation > 15%) scheduled to receive chemotherapy and epoetin alfa were randomized to 8 weeks of 125 mg of IV FG weekly, 325 mg of oral ferrous sulfate three times daily, or no iron. The primary outcome was a change in Hb from baseline to endpoint, first whole-blood or red blood cell transfusion, or study withdrawal.

Results. One hundred twenty-nine patients were evaluable for efficacy (FG, n = 41; oral iron, n = 44; no iron, n = 44). Mean increase in Hb was 2.4 g/dl (95% confidence interval [CI], 2.1–2.7) for FG (p = .0092 vs. oral iron; p = .0044 vs. no iron), 1.6 g/dl (95% CI, 1.1–2.1) for oral iron (p = .7695 vs. no iron), and 1.5 g/dl (95% CI, 1.1–1.9) for no iron. Hb response (increase > 2 g/dl) was 73% for FG (p = .0099 vs. oral iron; p = .0029 vs. no iron), 46% for oral iron (p = .6687 vs. no iron), and 41% for no iron. FG was well tolerated.

Conclusion. For cancer patients with chemotherapy-related anemia receiving epoetin alfa, FG produces a significantly greater increase in Hb and Hb response compared with oral iron or no iron, supporting more aggressive treatment with IV iron supplementation for these patients. The Oncologist 2007;12:231–242

INTRODUCTION
Anemia is a common complication of cancer and its treatment. The prevalence of anemia (hemoglobin [Hb] < 12 g/dl) approaches 50% in patients with cancer and may increase to more than 90% in patients with certain types of cancer and in those undergoing chemotherapy or radiation therapy [1]. Recombinant human erythropoietin (epoetin alfa) is an effective treatment for chemotherapy-related anemia. In multicenter, randomized clinical trials and community-based studies in patients with chemotherapy-related anemia, epoetin alfa produced significant increases in Hb levels, significant decreases in transfusion requirements, and significant improvements in quality of life [2–5]. However, approximately 30%–50% of patients re-
receiving epoetin alfa therapy for chemotherapy-related anemia do not achieve a clinically meaningful hematologic response [2–5]. The lack of response to erythropoietic therapy is poorly understood but has been attributed to a functional iron deficiency in that the high rate of erythropoietic agent-induced erythropoiesis exceeds the delivery of usable iron, despite adequate iron stores [6]. Absolute iron deficiency, in contrast, occurs when iron delivery is impaired because iron stores are depleted (in healthy subjects, serum ferritin <100 ng/ml and transferrin saturation [TSAT] <20%) [7]. Patients with functional iron deficiency require supplementation of usable iron to optimize response to erythropoietic therapy, which might not be accomplished with oral iron [8].

Sodium ferric gluconate complex (FG) (Ferrlecit; Watson Pharma, Inc., Morristown, NJ, http://www.watsonpharm.com) is safe and effective in optimizing response to erythropoietic therapy in patients undergoing hemodialysis [9–11]. However, its efficacy in patients with chemotherapy-related anemia receiving erythropoietic therapy has not been well characterized. This 12-week, multicenter, randomized trial compared the efficacy of FG, oral iron, and no iron in increasing Hb levels in iron-replete patients with chemotherapy-related anemia receiving epoetin alfa.

**PATIENTS AND METHODS**

**Study Design and Patients**

This was an open-label, randomized, controlled, multicenter, prospective trial. Randomization was conducted centrally to avoid selection bias. Patients received study treatment for 8 weeks followed by a 4-week follow-up period. Eligible patients were at least 18 years old, were about to start a cycle of chemotherapy, and had a nonmyeloid malignancy, Hb <11 g/dl, a life expectancy ≥24 weeks, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients were also required to have a serum ferritin level ≥100 ng/ml or TSAT ≥15% and to have received no epoetin alfa or IV iron therapy within 30 days and no oral iron therapy (>27 mg/day) within 7 days before enrollment.

Patients were excluded for hemolysis, gastrointestinal bleeding, folate or vitamin B12 deficiency, elevated serum ferritin (>900 ng/ml) or TSAT (>35%), pregnancy or lactation, liver dysfunction (grade ≥2 based on National Cancer Institute Common Toxicity Criteria), renal dysfunction (serum creatinine >2.0 mg/dl), active infection requiring systemic antibiotics, personal or family history of hemochromatosis, comorbidities precluding study participation, hypersensitivity to FG or its components, contraindication to epoetin alfa therapy, red blood cell (RBC) transfusion within the past 2 weeks, or any investigational agent within 30 days before enrollment.

Patients were not allowed to take any vitamin, mineral, or herbal supplements containing >27 mg/day of iron or >100 mg/day of vitamin C during the study or follow-up. Blood transfusions were permitted at the investigator’s discretion if Hb decreased to <8 g/dl. Changes to the chemotherapy plan were permitted.

Written informed consent was provided by all patients before study participation, and the protocol and supporting documents were approved by the institutional review board at each participating institution. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice as contained in the U.S. Code of Federal Regulations that governs the protection of human subjects and the obligations of clinical investigators.

**Treatment**

Eligible patients were randomized in a 1:1:1 ratio to 8 weeks of treatment with 125 mg of FG intravenously once weekly (q.w.), 325 mg of ferrous sulfate (tablets or liquid if clinically indicated) orally three times daily (t.i.d.), or no iron treatment (Fig. 1). FG was either diluted in 100 ml of normal saline and infused over 1 hour or administered undiluted as an IV push over 10 minutes at the discretion of the investigator. During the first clinic visit (±4 days from the initiation of the chemotherapy cycle), patients randomized to FG received their first 125-mg dose, and patients randomized to oral iron received—and were instructed to immediately begin taking—their medication. Oral iron was dispensed weekly, with adherence monitored via tablet count. If TSAT increased to ≥50%, FG was withheld until TSAT decreased to <50% and then restarted at the original dose.

Epoetin alfa treatment was initiated at the first clinic visit and was continued for 12 weeks. The initial dose was 40,000 U administered subcutaneously q.w. If after 4 weeks Hb did not increase by ≥1 g/dl, the dose was increased to 60,000 U q.w. If Hb increased >1.3 g/dl in any 2-week period, the dose was reduced by 25%. If Hb increased to >13 g/dl, epoetin alfa was discontinued until Hb decreased to ≤12 g/dl and then resumed at 75% of the previous dose.

**Assessments**

Within 7 days before the start of a chemotherapy cycle, eligible patients underwent a comprehensive assessment, in-
including medical and oncologic history, physical examination, vital signs, laboratory assessment, fecal occult blood test, and ECOG performance status assessment. Laboratory assessments included Hb, serum ferritin, reticulocyte Hb content (CHr), reticulocyte count, transferrin, TSAT, serum iron, total iron binding capacity, percentage of hypochromic RBCs (%HYPO), red cell indices, white blood cell count with differential, platelet indices, and serum chemistries.

At the first clinic visit (week 1; baseline), a blood sample was obtained for laboratory assessments, vital signs and concomitant medications were recorded, and study treatment commenced. Patients attended weekly clinic visits for treatment and assessment and returned for follow-up visits at weeks 10 and 12, which included a complete physical examination. Adverse events were assessed at each clinic visit until study completion or withdrawal and during the 30 days following the last study-related procedure.

Statistical Analysis

Results from previous clinical investigations were used to determine the sample size, based on using two-tailed t tests to detect a significant difference in change in Hb from baseline between treatment groups while using a Bonferroni correction to control the maximum experiment-wise type I error rate (α = .05). Using this adjustment for two comparisons (i.e., FG to no iron and FG to oral iron), the significance level for each comparison is α = .025. On the basis of previous clinical investigations in hemodialysis patients, it was anticipated that FG would have a 1.00-g/dl greater mean change in Hb from baseline than would the no-iron comparator and that the expected standard deviation would be 1.50. Using these calculations, a sample size of 45 patients per group was needed to detect a significant difference in Hb levels between treatment groups of 1.0 g/dl with 80% power for this pilot study, assuming an SD of 1.5 g/dl [11], so a target enrollment of 60 patients per group was planned to allow for a 30% dropout rate.

The safety population comprised all patients who received study drug (oral iron and FG groups) or who completed the baseline clinic visit (no-iron group). The evaluable population included all patients with no major protocol deviations who had at least one postbaseline Hb assessment before first transfusion, received treatment for ≥7 weeks, and received at least four doses (or 120,000 U) of epoetin alfa. In addition, patients randomized to FG must have received ≥0.875 g of the drug, and patients randomized to oral iron were required to be at least 66.7% adherent.

The evaluable population was used for analysis of primary and secondary efficacy endpoints, except for the number of transfusions and patients receiving transfusions, which were analyzed using the safety population. The evaluable population, rather than the intent-to-treat (ITT) population, was chosen to determine the effect of anemia treatment that was administered as the protocol intended. All efficacy evaluations were conducted on pretransfusion values. Missing data were handled using the conservative last observation carried forward method, in which the last observed data recorded for each parameter before receiving a transfusion were carried forward through the endpoint.

The primary efficacy analysis was the mean change in Hb from baseline to last value (endpoint, first whole-blood or RBC transfusion, or study withdrawal, whichever came first). Secondary efficacy analyses included comparisons among groups of Hb response (Hb increase ≥2 g/dl from baseline to last value) and change from baseline in other laboratory parameters. The primary endpoint and secondary efficacy analyses were performed using an analysis of covariance (ANCOVA) model, with the baseline parameter value as the covariate. To identify between-group differences in continuous variables, three pairwise comparisons were performed using Student’s t test (FG vs. oral iron, FG vs. no iron, and oral iron vs. no iron). Differences were considered significant if the p value was <.0167 because of multiple-comparison adjustment using the Bonferroni correction.

To determine whether the change in Hb response profile over time was different among the treatment groups, a repeated-measures ANCOVA using mixed-analysis methodology, with adjustment of baseline Hb, was used to compare FG to the oral iron and no-iron groups at each visit. Differences were considered significant if the p value was ≤.025 because of multiple-comparison adjustment using the Bonferroni correction.

Additional analyses included (a) evaluation of the relationship between TSAT, ferritin, CHr, and change in Hb from baseline (analyzed using ANCOVA, including the effects of treatment and baseline TSAT, ferritin, or CHr as the covariate); and (b) evaluation of the consistency of treatment effect across chemotherapy types (i.e., platinum- vs. nonplatinum-containing; analyzed by ANCOVA with the
effects of treatment, chemotherapy type, and baseline Hb). All analyses were conducted with SAS version 8.2 (SAS Institute, Inc., Cary, NC, http://www.sas.com) or higher using procedures appropriate for the particular analysis.

RESULTS

Patient Disposition
Of the 187 patients in the safety population, 154 (82.4%) completed the study. Reasons for study discontinuation in the FG, oral iron, and no-iron groups, respectively, were adverse events (n = 4, 5, 3), death (n = 3, 2, 1), protocol violation (n = 0, 1, 4), progressive disease (n = 1, 1, 2), withdrawn consent (n = 1, 1, 1), or another reason (n = 0, 3, 0). No patients were excluded for hypersensitivity to FG. Of the 189 patients randomized, 187 patients were included in the safety population (FG, n = 63; oral iron, n = 61; no iron, n = 63) and 129 patients were included in the evaluable efficacy population (FG, n = 41; oral iron, n = 44; no iron, n = 44; Fig. 2). The difference between the number of patients completing the study (n = 154) and number of patients included in the evaluable population (n = 129) was mainly a result of early transusions or discontinuations, thus excluding them from the evaluable population.

Demographics and Patient Characteristics
The mean age of the evaluable population was 65.3 years, and most patients were female (69%) and white (70%; Table 1). The most common diagnoses were lung (26%) and breast (17%) cancer, and most patients had stage III (24%) or IV (45%) disease. Overall, 85% of patients received a previous chemotherapy regimen for their disease. There were no significant differences among groups in the percentage of patients receiving platinum-containing chemotherapy. Mean baseline iron and RBC indices were generally comparable among groups (Table 2). Nearly all (94%) of the 50 patients with baseline TSAT <20% also had baseline serum ferritin >100 ng/ml.

Drug Administration
The mean total FG dose was 990.9 mg (7.9 doses). Adherence with oral iron was 93.3% of tablets dispensed. There were no significant differences among treatment groups in the overall average weekly epoetin alfa dose; however, the dose of epoetin alfa was fixed at 40,000 U q.w. for the first 4 weeks. No patients had FG dose withheld for TSAT ≥50%.

Hb Parameters
Hb increased by a mean of 2.4 g/dl (95% confidence interval [CI], 2.1–2.7) from baseline to endpoint for evaluable patients receiving FG (p = .0092 vs. oral iron; p = .0044 vs. no iron), by 1.6 g/dl (95% CI, 1.1–2.1) for patients receiving oral iron (p = .7695 vs. no iron), and by 1.5 g/dl (95% CI, 1.1–1.9) for patients receiving no iron (Fig. 3A, 3B; Table 3). The Hb response rate was 73% for patients receiving FG (p = .0099 vs. oral iron; p = .0029 vs. no iron), 45% for patients receiving oral iron (p = .6687 vs. no iron), and 41% for patients receiving no iron (Fig. 4). Among the subgroup of 50 patients with a baseline TSAT <20%, those in the FG group had an 81% response rate, whereas those in the oral iron group had a 37% response rate (p = .0091) and those in the no-iron group had a 27% response rate (p = .0027). Among the subgroup of 79 patients with a baseline TSAT ≥20%, those in the FG group had a 68% response rate, whereas those in the oral iron group had a 52% response rate (p = .2530 between groups) and those in the no-iron group had a 48% response rate (p = .1476 between groups).

In the ITT population, which included all patients with at least one postbaseline Hb assessment before first transfusion, regardless of protocol violations, study treatments actually received, or length of participation in study, baseline Hb levels were 10.1 g/dl, 10.4 g/dl, and 10.4 g/dl, respectively, for the FG, oral iron, and no-iron groups. Hb increased by a mean of 1.6 g/dl from baseline to endpoint in the FG group (n = 60), by 1.2 g/dl in the oral iron group (n = 61), and by 1.1 g/dl in the no-iron group (n = 59). The Hb response rate was 53% for patients receiving FG (n = 60), 36% for patients receiving oral iron (n = 61), and 36% for patients receiving no iron (n = 59).

Overall, in the evaluable population, there was no linear relationship between baseline TSAT and mean Hb change from baseline (p = .2224) or between baseline CHr and mean Hb change from baseline (p = .4346). Similarly, baseline ferritin was not a significant predictor for response. Treatment effects were consistent across patient groups regardless of the type of chemotherapy received (i.e., platinum- vs. nonplatinum-containing). No significant interaction was identified between treatment and chemotherapy type (p = .4469). All treatment groups experienced the same degree of myelosuppression; the adjusted area under neutrophil curve did not vary by treatment group (9.8 ± 13.1, 9.7 ± 6.4, and 9.6 ± 10.3 cells/mm3 · weeks for the FG, oral iron, and no-iron, respectively).

Iron Indices
Patients receiving FG experienced a mean increase from baseline to endpoint in serum ferritin of 343.7 ng/ml compared with a mean decrease of 13.9 ng/ml in patients receiving oral iron (p < .0001 vs. FG) and a mean decrease of 95.8 ng/ml in patients receiving no iron (p < .0001 vs. FG) (Table 3). TSAT decreased and CHr and %HYPO increased in
all treatment groups from baseline to endpoint (Figs. 5–7, respectively). Other indices varied over the course of the study, depending on treatment group (Table 3). No patients had FG withheld as a result of TSAT increasing to \(\geq 50\%\).

Transfusion Requirements
There were no differences in the number of patients requiring transfusions according to iron treatment; however, the study was not powered to detect a difference in transfusion requirements. Of 187 enrolled patients, transfusions were given to 11 FG patients (18%), 6 oral iron patients (10%), and 14 no-iron patients (22%). Transfusions were more likely to be given after the first 4 weeks in the oral iron (five of six, 83%) and no-iron groups (7 of 14; 50%) compared with the FG group (2 of 11, 18%; Fisher’s exact test \(p = .039\)).

Safety
Survival and infection rates were similar among all iron treatment groups. Infection rates were 14.3%, 23.3%, and 14.5% for the FG, oral iron, and no-iron groups, respectively, and no infectious event was considered to be related to study treatment. FG and oral iron were well tolerated, and most adverse events were mild or moderate in severity. The most common adverse events occurring in \(\geq 20\%\) overall of FG, oral iron, and no-iron patients, respectively, were asthenia (41.3%, 42.6%, 33.3%), nausea (38.1%, 26.2%, 30.2%), constipation (19.0%, 39.3%, 15.9%), pain (23.8%, 26.2%, 15.9%), vomiting (27.0%, 19.7%, 15.9%), diarrhea (22.2%, 21.3%, 17.5%), and leukopenia (25.4%, 16.4%, 19.0%). Fifteen FG patients (23.8%), 18 oral iron patients (29.5%), and 16 no-iron patients (25.4%) experienced serious adverse events (SAEs). Of these, one SAE in each of the FG and oral iron groups was considered possibly related to study drug (angina and dehydration, respectively). Eight patients in the FG group reported 12 drug-related adverse events, compared with 38 drug-related adverse events reported in 19 patients receiving oral iron (Table 4). Six patients discontinued the study due to drug-related adverse events (FG, \(n = 2\) [one angina, one nausea]; oral iron, \(n = 4\) [all gastrointestinal]).

DISCUSSION
This multicenter, randomized trial demonstrated that FG significantly improves the response to epoetin alfa in this population of cancer patients with chemotherapy-related anemia. Patients in all treatment groups responded to epoetin alfa therapy, but responses were significantly better in patients treated with FG compared with those treated with oral iron or no iron. The relatively low overall response to epoetin alfa observed in patients treated with oral iron or no iron is likely a function of the duration of the study (9 weeks), which is shorter than that of most published epoetin alfa studies (12 weeks or more) [2–5]. Treatment with FG produced significantly greater increases in Hb and serum ferritin from baseline to endpoint compared with oral iron or no iron. Although baseline values of serum ferritin, CHr, and TSAT overall were not significant predictors of Hb response in this trial, the difference in response between the FG and other groups seemed to be more pronounced among
patients with baseline TSAT <20% than among those with baseline TSAT ≥20%. Nearly all transfusions in FG patients occurred during the first 4 weeks of therapy, before the effect of epoetin alfa therapy could be achieved, whereas many more of the oral iron and no-iron patients required transfusions after 4 weeks of treatment.

There was a randomization imbalance in this study, with more patients with breast cancer in the FG group and more patients with colorectal cancer in the no-iron and oral iron groups. Patients with colorectal cancer would be more likely to have iron deficiency than would patients with breast cancer, but this factor was controlled in the iron eli-
gibility criteria at study entry, so the iron status of these two populations was likely similar at the start of the study. The prevalence of anemia is greater in patients with colorectal cancer than in patients with breast cancer (39% vs. 31%) [12], but the reverse is true after these patients have received chemotherapy, with 70.8% of patients with breast cancer being anemic at least once after starting chemotherapy compared with 62.4% of patients with colorectal cancer [12].

Large amounts of iron are needed to fulfill the requirements for epoetin alfa-stimulated erythropoiesis. Functional iron deficiency occurs when storage iron cannot be mobilized [13]. This is in contrast to absolute iron deficiency, in which patients have inadequate iron stores (TSAT <20% and serum ferritin <100 ng/ml) and require iron supplementation to replete iron stores even before the addition of epoetin alfa-enhanced erythropoiesis [1]. Functional iron deficiency in patients receiving epoetin alfa is consistent with the theory that iron supply to the erythron is the rate-limiting step in the erythropoietic process. Thus, iron supplementation may be required even in the presence of adequate iron stores to achieve or maintain the most optimal response to epoetin alfa therapy in anemic cancer patients receiving chemotherapy. In addition, serum ferritin is an acute-phase reactant and is elevated in inflammatory conditions [14, 15], thus making it an unreliable measure of iron stores in patients with cancer. This limitation of serum ferritin as a measure of iron availability was evident in the current study, as 94% of patients with baseline TSAT <20% had baseline serum ferritin >100 ng/ml.

The route of iron administration is a major factor influencing response to epoetin alfa therapy. Clinical trials eval-

### Table 2. Baseline values of iron status and red blood cell indices

<table>
<thead>
<tr>
<th>Value (mean ± SD)</th>
<th>FG (n = 41)</th>
<th>Oral iron (n = 44)</th>
<th>No iron (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb, g/dl</td>
<td>10.1 ± 0.9</td>
<td>10.3 ± 0.7</td>
<td>10.5 ± 0.8</td>
</tr>
<tr>
<td>CHR, pg</td>
<td>33.8 ± 3.2</td>
<td>34.7 ± 3.6</td>
<td>34.4 ± 3.1</td>
</tr>
<tr>
<td>Transferrin, mg/dl</td>
<td>214.6 ± 32.9</td>
<td>230.9 ± 48.3</td>
<td>224.6 ± 41.3</td>
</tr>
<tr>
<td>Ferritin, ng/ml</td>
<td>321.5 ± 209.6</td>
<td>373.9 ± 270.1</td>
<td>388.2 ± 266.1</td>
</tr>
<tr>
<td>Iron, mcg/dl</td>
<td>79.8 ± 73.2</td>
<td>80.8 ± 53.7</td>
<td>111.6 ± 86.2</td>
</tr>
<tr>
<td>TIBC, mg/dl</td>
<td>262.9 ± 40.1</td>
<td>276.2 ± 60.5</td>
<td>268.8 ± 48.6</td>
</tr>
<tr>
<td>TSAT, %</td>
<td>29.4 ± 26.5</td>
<td>29.1 ± 21.0</td>
<td>36.3 ± 26.6</td>
</tr>
<tr>
<td>Hypochromic RBCs, %</td>
<td>8.6 ± 9.5</td>
<td>7.2 ± 8.1</td>
<td>8.8 ± 7.2</td>
</tr>
</tbody>
</table>

Absolute values for the percentage of hypochromic RBCs (%HYPO) should be interpreted with caution because there are limitations of this marker related to its sensitivity to temperature and storage (red blood cells increase in size over time causing an increase in %HYPO). Samples here were shipped to a central laboratory, so storage may have affected the result. Abbreviations: CHr, reticulocyte hemoglobin content; FG, sodium ferric gluconate complex; Hb, hemoglobin; RBC, red blood cell; TIBC, total iron binding capacity; TSAT, transferrin saturation.

Figure 3. Hemoglobin response. (A): Mean ± standard error increase in Hb from baseline to endpoint (evaluable population; n = 129). a, p = .0092 versus oral iron; b, p = .0044 versus no iron. Note: p = .7695 for oral iron versus no iron. (B): Adjusted mean change in Hb over the course of the study and follow-up period (evaluable population, n = 129). a, p = .0201 versus oral iron at endpoint; b, p = .0017 versus no iron at endpoint. Abbreviations: FG, sodium ferric gluconate complex; Hb, hemoglobin.
Evaluating this issue in patients with chronic kidney disease have shown that oral iron supplementation is inadequate to accommodate the accelerated erythropoiesis that occurs with epoetin alfa therapy [16–18]. Furthermore, the gastrointestinal side effect profile reported with high-dose oral iron is a significant deterrent to using this route of administration [16], as is the required t.i.d. dosing schedule [1]. Both of these issues likely contribute to nonadherence with oral iron administration outside the setting of a clinical trial. Interestingly, despite excellent adherence with oral iron in our study, response rates were remarkably similar between the oral iron and no-iron groups. The anemia of chronic disease may occur in cancer patients and is associated with an increase in hepcidin levels, which decreases oral iron absorption and bone marrow iron utilization, negating any possible effect of oral iron [19]. Given the similar response rates between the oral iron and no-iron groups in this study, one might question the value of administering oral iron at all in this patient population receiving epoetin alfa therapy.

Results of this study are similar to those obtained in studies of patients with chronic kidney disease, that is, that the response to epoetin alfa is improved with IV iron administration but not oral iron [16, 17]. Our findings are similar to those reported in a prospective, multicenter, open-label trial of chemotherapy-related anemia. In that trial, 157 cancer patients receiving epoetin alfa were randomized to receive iron dextran as 100-mg IV boluses, iron dextran total dose infusion, 325 mg of oral iron twice daily, or no iron. Patients treated with IV iron, by bolus or infusion, demonstrated a greater Hb increase ($p < .02$) from baseline to final measurement and a greater Hb response rate ($p < .01$) com-

### Table 3. Change from baseline to endpoint in red blood cell and iron indices

<table>
<thead>
<tr>
<th>Mean ± SD (n)</th>
<th>FG (n = 41)</th>
<th>Oral iron (n = 44)</th>
<th>No iron (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb, g/dl</td>
<td>2.4 ± 1.1</td>
<td>1.6 ± 1.7 (44)*</td>
<td>1.5 ± 1.2 (44)*</td>
</tr>
<tr>
<td>CHr, pg</td>
<td>2.1 ± 3.6</td>
<td>1.4 ± 3.5 (43)</td>
<td>0.3 ± 3.9 (44)</td>
</tr>
<tr>
<td>Transferrin, mg/dl</td>
<td>2.7 ± 32.3 (40)</td>
<td>−5.5 ± 28.6 (44)</td>
<td>11.2 ± 44.4 (44)</td>
</tr>
<tr>
<td>Ferritin, ng/ml</td>
<td>343.7 ± 289.6 (41)</td>
<td>−13.9 ± 305.0 (44)*</td>
<td>−95.8 ± 239.6 (44)*</td>
</tr>
<tr>
<td>Iron, mcg/dl</td>
<td>−3.5 ± 85.2 (41)</td>
<td>−5.5 ± 70.2 (44)</td>
<td>−43.9 ± 96.2 (44)</td>
</tr>
<tr>
<td>TIBC, mg/dl</td>
<td>0.1 ± 40.8 (41)</td>
<td>−5.4 ± 37.4 (44)</td>
<td>21.0 ± 44.5 (44)*</td>
</tr>
<tr>
<td>TSAT, %</td>
<td>−1.8 ± 30.5 (41)</td>
<td>−2.7 ± 24.3 (44)</td>
<td>−13.7 ± 29.7 (44)</td>
</tr>
<tr>
<td>Hypochromic RBCs, %</td>
<td>4.0 ± 11.4 (40)</td>
<td>6.1 ± 10.4 (43)</td>
<td>7.7 ± 12.0 (44)</td>
</tr>
</tbody>
</table>

*a* $p < .01$ versus FG.

*b* $p < .0001$ versus FG.

*c* $p < .01$ versus oral iron.

Abbreviations: CHr, reticulocyte hemoglobin content; FG, sodium ferric gluconate complex; Hb, hemoglobin; RBC, red blood cell; TIBC, total iron binding capacity; TSAT, transferrin saturation.

### Figure 4. Percentage of Hb responders ± 95% confidence interval (evaluable population, $n = 129$). a, $p = .0099$ versus oral iron; b, $p = .0029$ versus no iron. Note: $p = .6687$ for oral iron versus no iron. Abbreviations: FG, sodium ferric gluconate complex; Hb, hemoglobin.

### Figure 5. Mean ± standard error change in TSAT from baseline to endpoint (evaluable population, $n = 129$). Abbreviations: FG, sodium ferric gluconate complex; TSAT, transferrin saturation.
pared with those in oral and no-iron patients, which were not different from each other [8].

In all groups in the current study, TSAT decreased and %HYPO increased, reflecting some degree of iron-restricted hematopoiesis, even in the FG group. Thus, even the cumulative FG dose given may have been inadequate. Auerbach et al. [8] reported efficacy with overall IV iron doses ranging from 1,000 mg to 3,000 mg in a similar patient population. Although TSAT levels during therapy were not described, it seems that greater amounts of IV iron can be safely administered. However, CHr, which is a more immediate indicator of erythropoiesis than TSAT or serum ferritin [14], increased the most in the FG group in the current study, indicating that this group experienced the least iron-restricted erythropoiesis. This finding also raises the question as to what the optimal timing of IV iron therapy would be with respect to epoetin alfa and chemotherapy administration, as well as what the optimal total IV iron dose would be. The answers to these questions are yet to be determined and will likely be the subject of further research. One observational study has shown that 90% of patients who received a daily dose of 62.5 mg of FG for 1 week with a single dose of 40,000 U of epoetin alfa have increased Hb levels after 1 week, with a median increase of 0.73 g/dl from baseline, and that 45% have an Hb increase >1.0 g/dl [20]. In addition, the potential for adequate IV iron therapy to elicit a greater response to epoetin alfa, thereby potentially reducing the overall dose of epoetin alfa required, has yet to be determined, but it is also likely to be the subject of further research to define the optimal protocol for the treatment of anemia with erythropoietic agents and parenteral iron.

Overall, both FG and oral iron were well tolerated, with most adverse events considered mild or moderate in severity. The safety and tolerability of FG in patients with chemotherapy-related anemia are comparable to the tolerability of this iron formulation in patients with chronic kidney disease undergoing hemodialysis [10]. Furthermore, the administration of FG has been associated with fewer and less severe allergic events than iron dextran and can be safely administered in patients with prior iron dextran allergies [9, 21–23]. However, it should be noted that the safety of larger individual doses (≥250 mg) of FG has not been established.

A safety concern often raised when patients are administered parenteral iron is the issue of “iron overload” and the possible risk of developing cancer or infections as a consequence. The highest serum ferritin levels in the present study were 3,586 ng/ml in the FG group, 6,186 ng/ml in the oral iron group, and 3,830 ng/ml in the no-iron group. Current Kidney Disease Outcomes Quality Initiative guidelines recommend that IV iron be withheld if serum ferritin exceeds 800 ng/ml, but this is an opinion-based guideline without substantial evidence [7]. Most of the literature addressing cancer and infections in iron-overloaded patients comes from patients with hemochromatosis or patients who are undergoing hemodialysis. Published reviews on this subject in patients with hemochromatosis report an increase in hepatocellular carcinoma only, and typically only in patients who first developed cirrhosis [24]. Similarly, few data support any increase in common infections [25]. In fact, anemia itself is a risk factor for infections in hemodialysis patients [26]. Moreover, a recent multivariate analysis of associations between iron and mortality in more than 58,000 hemodialysis patients reported no increased death rate for serum ferritin levels as high as 1,200 ng/ml [27].
The results of this study demonstrate the safety and efficacy of FG in cancer patients with chemotherapy-related anemia and functional iron deficiency in optimizing the Hb response to epoetin alfa therapy. The National Comprehensive Cancer Network guidelines for the treatment of cancer and cancer treatment-related anemia support the use of iron supplementation to treat symptomatic patients with Hb <11.3 g/dl and mention that IV iron may be superior to oral iron on the basis of data from the Auerbach et al. study [8, 28]. However, many anemic patients with cancer receive little or no iron therapy, suggesting that the response to erythropoietic therapy in clinical practice is probably similar to our no-iron control group. Although oral iron patients were 93% adherent, there was no significant difference in Hb response or Hb change between the oral iron and no-iron groups, suggesting that oral iron is insufficient to prevent iron-restricted erythropoiesis in these patients. Our findings support the consideration of a more aggressive treatment paradigm that includes IV iron supplementation for patients with cancer and chemotherapy-related anemia who are receiving erythropoietic therapy and have no contraindications to IV iron therapy. Based on our study, such a paradigm would include treatment with 125 mg of FG weekly in patients with TSAT <35% and serum ferritin <900 ng/ml as well as those with absolute iron deficiency (as indicated by baseline TSAT <20% or serum ferritin <100 ng/ml) [7] after ruling out other correctable causes of anemia (e.g., low RBC folate or vitamin B12 deficiency) [29]. Larger controlled trials are warranted to confirm these findings and to characterize optimal dosing strategies.

**Table 4. Adverse events considered possibly, probably, or definitely related to study drug**

<table>
<thead>
<tr>
<th>Adverse event, no. of patients (%)</th>
<th>FG (n = 63)</th>
<th>Oral iron (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>2 (3.2)</td>
<td>11 (18.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (3.2)</td>
<td>3 (4.9)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1 (1.6)</td>
<td>3 (4.9)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (1.6)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Tremor</td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Pain at injection site</td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Back pain</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Taste perversion</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Melena</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Totala</td>
<td>8 (12.7)</td>
<td>19 (31.1)</td>
</tr>
</tbody>
</table>

*Patients may have experienced more than one adverse event. Abbreviation: FG, sodium ferric gluconate complex.*

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This article was written on behalf of the Ferrlecit Study Group.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

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