Perspective

Intravenous iron for treating cancer-induced anemia: meeting an unmet need?

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Recent restrictions on ESA use in cancer and chemotherapy induced anemias (CIA) leave a therapeutic void (1). Regulatory agencies throughout the world now recommend that, ESAs be proscribed when cure is a goal, administration be limited to the lowest dose which avoids transfusions and commencement of therapy be delayed until the hemoglobin level is less than 10 grams per deciliter with discontinuation at higher levels. While transfusion avoidance is the only approved indication for ESAs in oncology patients, these proscriptions are inconsistent with published data suggesting that the maximum quality of life improvements occur between hemoglobin levels of 10 to 13 grams per deciliter (2). For anemic patients receiving chemotherapy or those with anemia of cancer an unmet need is present.

Twelve of twelve studies examining the use of intravenous (IV) iron with (ten) and without (two) concomitant ESA, demonstrated marked improvements in time to target hemoglobin levels, decreased ESA dosing, decreased transfusions and increased response rates. The two studies without ESAs were small but demonstrated a decrease in transfusion requirement with IV iron compared to oral or no iron. In the first of these, Kim *et al*., randomized 75 patients receiving radiation and cisplatin for cervical cancer to either 200 mg of IV iron sucrose weekly or no iron (3). While no baseline or in-study iron parameters were provided, there was a statistically significant reduction in transfusions in the IV iron arm compared to controls. In the second trial, Dangsuwan *et al*., randomized 44 previously transfused patients receiving chemotherapy for gynecologic malignancies to either IV iron sucrose or oral iron (4). Again a significant reduction in transfusions was observed in the IV iron group.

A recent publication by Steinmetz *et al*., the subject of this editorial, is the first large scale study in oncology patients to demonstrate an improvement in hemoglobin levels with IV iron as sole therapy for anemia (5). While neither prospective nor randomized, this observational study provides evidence that IV iron can fill some of the gap in anemia therapy created by the regulatory agencies' limitation of ESA use. It is also the first study to use one of the three newly approved IV iron formulations in CIA, ferric carboxymaltose (Ferinject, Vifor, Switzerland). Ferric carboxymaltose (FCM), like its two competitors, ferumoxytol (Feraheme, AMAG, Boston; AKA Rienso, Takeda, London) and iron isomaltoside, (Monofer, Pharmacosmos, Denmark), uniquely bind the elemental iron more tightly in their individual carbohydrate carriers, such that a large dose can be safely administered in a short period of time.

FCM is the first of the agents to be approved. FCM has demonstrated efficacy in host of conditions associated with iron lack. In a prospective study of 200 patients with inflammatory bowel disease, Kulnigg *et al*. demonstrated that FCM was non-inferior to oral iron and provided rapid improvement in hemoglobin levels when administered as 1000 mg over 15 minutes (6). A subsequent prospective study comparing the efficacy and safety of a novel fixed-dose FCM regimen with individually calculated iron sucrose doses in 485 patients with inflammatory bowel disease and IDA, demonstrated that both treatments improved quality of life scores, but more patients with FCM than with iron sucrose showed full adherence to treatment, and achieved a Hb response ≥20 g/L or Hb normalization (7). The analysis of laboratory measurements at several time points during

the study period showed significantly stronger increases in Hb (from week 2 onwards), transferrin saturation, and serum ferritin (at all time points) in the FCM group (7).

In a hemodialysis population, Covic *et al*., demonstrated that when FCM administered as a 100 or 200 mg bolus on the day of dialysis, significant improvements in hemoglobin levels were observed (8). This also applied to the non-hemodialysis population of chronic kidney disease patients receiving FCM at higher doses (500-1,000 mg) (9).

In a cohort of 477 women with heavy uterine bleeding, VanWyck *et al*. compared FCM to oral iron and showed statistically significant improvements in hemoglobin levels with FCM (10). Similarly, data from 2 prospective studies in 643 women with postpartum anemia showed that FCM was more efficacious in correcting anemia and replenishing iron stores at 6 weeks than oral ferrous sulfate (11,12), although a third one failed in demonstrating these differences (13).

In two series of anemic surgical patients (colon cancer, abdominal hysterectomy, lower limb arthroplasty; 329 patients), preoperative or postoperative administration of FCM was as safe and efficacious as iron sucrose in increasing hemoglobin levels and/or reducing transfusion requirements (14,15).

In this newly published series of Steinmetz at all evaluated 420 and 619 patients in efficacy and safety analyses respectively. In a substantial majority of patients a significant increment of hemoglobin was observed which surpassed the goal to prevent significant anemia progression and transfusion need. The treatment was well tolerated with no significant toxicity. Consistent with previous reports with other formulations, the magnitude of responses was greater in those with lower pretreatment percent transferrin saturations but still significant in those subjects with pretreatment transferrin saturations in the normal range. A similar data set was observed for serum ferritin. These findings seem to confirm that IV iron has no major influence on the regulation of erythropoiesis and suggest that there is no risk of increasing hemoglobin levels beyond recommended ranges as seen with ESAs.

Consistent with the twelve previously published studies in cancer and chemotherapy induced anemia, no significant toxicity was observed. Only one serious adverse event occurred in a patient with advanced metastatic head and neck cancer with pulmonary metastases, probably unrelated to the FCM. However, in 2008 the approval or ferric carboxymaltose was delayed by the United States Food and Drug Administration for hypophosphatemia occurring two weeks post treatment and an imbalance of cardiovascular events and deaths in the treatment arm compared to control. However, inter-group differences in mortality rates were not significant, and none of the deaths were judged to be related to FCM administration by either the investigators or an independent panel of outside experts (16). Phosphate levels were not mentioned in this trial. In all published series extant where hypophosphatemia was observed following treatment with this formulation no clinical sequelae were reported. It would have been reassuring to know that either hypophosphatemia was not present in this population or that its occurrence was clinically insignificant.

Ferric carboxymaltose has been resubmitted for approval in the United States. This new drug application includes additional safety and efficacy data from two large-scale, multi-center, randomized clinical trials in over 3,000 patients (NCT 00981045, NCT 0098207), and we are waiting for the final response from the Food and Drug Administration. A similar formulation, ferumoxytol, has already been approved and is undergoing clinical trials in a host of conditions, including chemotherapy induced anemia, associated with iron lack. Hypophosphatemia does not occur with this formulation or a recently approved competitor, iron isomaltoside (Monofer).

From published series, personal experience (MM) and personal communications with investigators using FCM (MA) the hypophosphatemia appears not clinically significant. This position is notably supported by Laila-Yasmin *et al*., in a population of renal transplant patients where clinically significant hypophosphatemia requiring phosphate replacement was observed but no cardiopulmonary, gastrointestinal or hematologic manifestations were present (17). This is consistent with every other publication on the use of FCM where low phosphorus levels have been reported. This product which allows the rapid administration of a large dose of IV iron in a short period of time provides physicians with an equally efficacious but more convenient means of administration. There are, however, some safety concerns (e.g., hypophosphatemia) and important missing information (e.g., use in children and pregnant women) that need to be addressed. We investigators working with IV iron eagerly await appropriately powered safety studies which will reassure the medical community that self-limited hypophosphatemia, which to date has not required therapy in any of the subjects in the published series, with the exception of one in post-transplant patient, is not of concern, and allow this novel product to be used on both sides of both oceans.

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References

1. Centers for Medicare and Medicaid Services. Decision memo for erythropoiesis stimulating agents (ESAs) for non-renal disease indications (CAG-00383N). http//www.cms.gove/Medicare/Coverage/DeterminationProcess/downloads/id203d.pdf. Accessed July 1, 2012.
2. Crawford J, Cella D, Cleeland CS, et al. Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. Cancer 2002;95:888-95.
3. Kim YT, Kim SW, Yoon BS, et al. Effect of intravenously administered iron sucrose on the prevention of anemia in the cervical cancer patients treated with concurrent chemoradiotherapy. Gynecol Oncol 2007;105:199-204.
4. Dangsuwan P, Manchana T. Blood transfusion reduction with intravenous iron in gynecologic cancer patients receiving chemotherapy. Gynecol Oncol 2010;116:522-5.
5. Steinmetz T, Tschechne B, Harlin O, et al. Clinical experience with ferric carboxymaltose in the treatment of cancer- and chemotherapy-associated anaemia. Ann Oncol 2012. [Epub ahead of print].
6. Kulnigg S, Stoinov S, Simanenkov V, et al. A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. Am J Gastroenterol 2008;103:1182-92.
7. Evstatiev R, Marteau P, Iqbal T, et al. FERGIcor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. Gastroenterology 2011;141:846-53.
8. Covic A, Mircescu G. The safety and efficacy of intravenous ferric carboxymaltose in anaemic patients undergoing haemodialysis: a multi-centre, open-label, clinical study. Nephrol Dial Transplant 2010;25:2722-30.
9. Qunibi WY, Martinez C, Smith M, et al. A randomized controlled trial comparing intravenous ferric carboxymaltose with oral iron for treatment of iron deficiency anaemia of non-dialysis-dependent chronic kidney disease patients. Nephrol Dial Transplant 2011;26:1599-607.
10. Van Wyck DB, Mangione A, Morrison J, et al. Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial. Transfusion 2009;49:2719-28.
11. Van Wyck DB, Martens MG, Seid MH, et al. Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia: a randomized controlled trial. Obstet Gynecol 2007;110:267-78.
12. Seid MH, Derman RJ, Baker JB, et al. Ferric carboxymaltose injection in the treatment of postpartum iron deficiency anemia: a randomized controlled clinical trial. Am J Obstet Gynecol 2008;199:435.e1-7.
13. Breymann C, Gliga F, Bejenariu C, et al. Comparative efficacy and safety of intravenous ferric carboxymaltose in the treatment of postpartum iron deficiency anemia. Int J Gynaecol Obstet 2008;101:67-73.
14. Bisbe E, García-Erce JA, Díez-Lobo AI, et al. A multicentre comparative study on the efficacy of intravenous ferric carboxymaltose and iron sucrose for correcting preoperative anaemia in patients undergoing major elective surgery. Br J Anaesth 2011;107:477-8.
15. Muñoz M, Naveira E, Seara J, et al. Postoperative iron after lower limb arthroplasty:a comparative study of the effects of 300 mg vs. 600 mg IV iron administration on transfusion requirements. Transfus Altern Transfus Med 2011;12:34-35.
16. Muñoz M, Martín-Montañez E. Ferric carboxymaltose for the treatment of iron-deficiency anemia. [corrected]. Expert Opin Pharmacother 2012;13:907-21.
17. Mani LY, Nseir G, Venetz JP, et al. Severe hypophosphatemia after intravenous administration of iron carboxymaltose in a stable renal transplant recipient. Transplantation 2010;90:804-5.

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