Too-Low Iron Doses and Too Many Dropouts in Negative Iron Trial?

TO THE EDITOR: We read with interest the article by Steensma et al1 in the January 1, 2011, issue of Journal of Clinical Oncology on the comparison of parenteral, oral, or no iron supplementation for patients who were treated with darbepoetin alfa for chemotherapy-associated anemia. The results contrast with those of six previously published2-7 and two additionally reported8,9 clinical trials that showed a significant benefit and good tolerability of parenteral iron compared with oral or no iron supplementation in patients with cancer who were receiving a concomitant erythropoiesis-stimulating agent. We believe that the interpretation and understanding of the results of the study by Steensma et al might have been facilitated by reporting some additional information. Both the lack of benefit and the higher number of adverse events in the parenteral iron group may be related to the specific dosing schedule of ferric gluconate in this trial (187.5 mg of iron every 3 weeks).

The low planned total iron dose of 937.5 mg, the second lowest dose among the published trials (750 to 3,000 mg) and the lowest dose when calculated on a weekly basis (62.5 mg/wk), may have limited the potential benefit of parenteral iron supplementation. Furthermore, the iron dose that was actually administered seems to have been even lower, namely 650 mg total iron (43.3 mg/wk), as indicated online by Auerbach.10 In the study by Bastit et al4 that was cited by Steensma et al as similar to their own study, the actually delivered total iron dose was about 400 mg higher.10 The increase of transferrin saturation (TSAT) from baseline to the end of the study that was reported by Steensma et al was substantially lower in the parenteral iron compared with the oral iron group, and even lower than in the placebo group (+1.4%, +8.0%, and +1.7%, respectively). This suggests that the given total dose of parenteral iron was either too low or not effectively used. In this context, Steensma et al mention that patients who were enrolled in the parenteral iron arm were more likely to withdraw consent or discontinue treatment as a result of adverse events. No information is given on how this affected the number of administered iron doses per patient.

In contrast to the low total iron dose throughout the entire study period, the single iron doses administered per treatment as ferric gluconate in adult patients receiving hemodialysis in the United States, and therefore it is in the off-label range. Data from Ferrlecit (sanofi-aventis, Bridgewater, NJ) postmarketing reports indicate that individual doses that exceed 125 mg of iron may be associated with a higher incidence and/or severity of adverse events.11 The high single doses of ferric gluconate in this study may have resulted in oversaturation of transferrin, formation of nontransferrin-bound iron, and deposition of iron in parenchymal tissues (eg, hepatocytes) instead of in the bone marrow. Apart from the increased risk of inducing oxidative stress and thus causing associated adverse events, the described effects may have additionally decreased the amount of iron that was effectively available for erythropoiesis. Therefore, it would be relevant to know more about the time course of TSAT and especially the levels of TSAT 24 hours after ferric gluconate administration.

One aspect that may have affected the statistical power is the low proportion of patients who completed the study per protocol (65% overall; 63% in the placebo and the parenteral iron arm each). Thus, given that more than one third of the patients did not complete the study, a per-protocol analysis would be informative.

In summary, the lack of response to parenteral ferric gluconate in the study by Steensma et al may be attributed to a suboptimal dosing regimen (ie, a low average dose but single doses that were too high) and a high proportion of dropouts rather than a lack of effectiveness per se. The superiority of parenteral iron compared with oral or no iron supplementation in terms of better hematopoietic response and less need for blood transfusions has been confirmed by two recent meta-analyses12,13 that included data from this trial as presented by Steensma et al at the 2009 meeting of the American Society of Hematology.14

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