IRON CORNER

Management of IDA in Cancer and Chemotherapy

The purpose of this review is two-fold. Firstly, we will briefly review the twelve prospective studies on cancer and chemotherapy induced anemia (CIA). Following will be a brief discussion of a recent systematic review and meta-analysis of those studies[1] (Gafter-Gvili Acta Onc). Secondly, based on the review and analysis we will recommend, based on the preponderance of published evidence, a treatment paradigm for those requiring therapy for anemia during cancer care. While the NCCN guidelines recommend the use of IV iron when iron is indicated for CIA, the current ASH/ASCO guidelines state that *"there is insufficient evidence to recommend the routine use of intravenous iron in chemotherapy induced anemia".* It will be our goal in the following paragraph to respectfully recommend a revisit of that recommendation.

Similarly to when erythropoiesis stimulating agents (ESAs) were introduced for dialysis associated anemia, enthusiasm for their use in CIA was far from brisk. However shortly after the seminal paper by Eschbach et al in 1987 (NEJM), demonstrating synergy of IV iron with recombinant erythropoietin (EPO)[2], IV iron became standard for dialysis associated anemia. Not so with CIA. In 2005, Glaspy, in a poignant review, reported that oncologists where spending thrice the amount to achieve half the benefit seen in dialysis populations[3].

The first trial by Auerbach et al[4], demonstrating IV iron's synergy with ESAs randomized iron deficient patients receiving therapy for CIA to either no or oral iron or IV iron administered as 100 mg boluses of low molecular weight iron dextran (LMW ID) or a total dose infusion (TDI) of the same formulation. While ESA alone worked a little with a marginal benefit seen from oral iron, a three-fold benefit in hemoglobin increment was seen with IV iron irrespective of the method of administration. While this study which used as eligibility criteria a ferritin of <200 ng/ml or <300 ng/ml plus a percent transferrin saturation (TSAT) of <19, was criticized for treating exclusively iron deficient patients, subsequent prospective studies (see below) using more rigid criteria for iron repletion, without contradiction to date, supported the original conclusions. These two trials were corroborate by a later study by Auerbach et al[4] demonstrating a benefit of LMW ID irrespective of darbepoietin doses of 300 or 500 ug administered every three weeks[5]. In fact, in this study 300 ug of darbepoietin with IV iron resulted in greater hemoglobin responses than 500 ug of darbepoietin without IV iron.

The first of those trials was published by Henry et al, required that all subjects had as enrollment iron parameters, a ferritin of >100 ng/ml or a TSAT of >15[6] (The Oncologist). While this study used ferric gluconate as the IV iron formulation, the conclusions mirrored those of the first published trial. Shortly thereafter two additional prospective studies, one in anemic subjects with lymphoproliferative malignancies not on chemotherapy[7] (Hedenus et al, Leukaemia) and then another in CIA[8] (Pedrazzoli et al, JCO) supported the same conclusions. In the Hedenus trial, all eligible subjects had stainable iron in a marrow aspirate and in the Pedrazzoli trial, all had both serum ferritin levels greater than 100 ng/ml and TSATs >20%. The same conclusions were drawn. In the same issue of *JCO* as the Pedrazzoli trial, the first prospective study powered to detect a difference in transfusions was published by Bastit et al[9]. Those with absolute iron deficient (ferritin <10 ng/ml and TSATs <15) were excluded. While corroborating the same benefits seen in the other studies, in this study a statistically significant decrement in allogeneic transfusion was observed.

An additional two trials looked at a different subset: patients with gynecologic malignancies receiving chemotherapy or concurrent chemoradiotherapy[10,11] (both in Gynecologic Oncology). What made these two trials unique was the absence of ESAs in the treatment paradigm. In the first of these, Kim et al, randomized patients with cervical cancer receiving radiation and cisplatin chemotherapy, to either 200 mg of IV iron sucrose weekly or no therapy. A statistically significant reduction in transfusions was observed in the IV iron group. In the second trial, Dangsuwan et al, randomized

patients with gynecologic malignancies receiving chemotherapy and had been previously transfused to either IV iron sucrose or oral iron. A statistically significant reduction in transfusion was again observed, corroborating the results of Kim and Bastit.

In a trial with a different design, Anthony et al examined whether IV iron added to ESAs could restore responsiveness in non-responders[12] (Community Oncology). Patients with CIA were treated with ESA alone for 8 weeks and for 12 weeks thereafter responders and non-responders were randomized to IV iron sucrose or ESA alone. Supporting all previously published evidence, both IV iron groups showed statistically significant hemoglobin increments compared to those receiving no IV iron.

Three new formulations have recently been approved in the United States (one) and Europe (two). Corroborating the results of Kim and Dansuwang, ferric carboxymaltose has been shown to alleviate anemia progression and actually result in improvement in hemoglobin levels when administered alone (without ESAs) to patients with CIA[13].

Long term toxicity remains a concern. One study, presented at the 2009 Annual Meeting of the American Society of hematology, by Beguin et al[14] randomized anemic patients who had undergone autologous bone marrow transplant for lymphoproliferative malignancies to ESA alone or ESA plus IV iron sucrose. What made this study unique was the 5 year patient follow-up in the in the data set. While not a primary endpoint, addressing the issue of long term negative effects on cancer outcomes, while similar hemoglobin benefits were observed in the IV iron group, no difference or progression free survival, relapse or overall survival was noted between the two groups.

In the first presentation of the only trial to demonstrate a benefit with IV iron in CIA, Steensma et al[15] (JCO) randomized patients to darbepoietin with or without ferric gluconate. No difference in hemoglobin or quality of life parameters was noted. The investigator measured pre and post-therapy hepcidin levels and in a subsequent re-stratification looking at those randomized to IV iron who actually received at least 80% of the planned dose, once again, a clear benefit for IV iron was observed. These data were presented at the 2011 Annual Meeting of the American Society of Clinical Oncology and reviewed by Dr. Patti Ganz. For those patients with low pretreatment hepcidin levels a greater than 90% response rate with IV iron was observed. While high pre-treatment hepcidin levels did not predict for a failure to respond to IV iron, these provocative data suggest that hepcidin may predict who will response best to the addition iron. As a result of these data, Dr. Ganz posited that if corroborated the ASH/ASCO guidelines may need to be reconsidered.

All of these studies were systematically reviewed by Gafter Gvili et al, who also performed a meta-analysis[1]. While this comprehensive work did not take into consideration the re-stratification of the data in the Steensma trial, they concluded that IV iron significantly increased the hematopoietic response rare to ESAs, that the increase correlated with iron dose regardless of baseline iron status without observing a negative safety signal with IV iron.

Based on these data, comprising thousands of patients with no clinically significant toxicity with IV iron we recommend a change in the current ASH/ASCO guidelines to conform to those of the NCCN. We recommend that ESAs alone are reasonable for CIA if there is no absolute or functional iron deficiency (see section 1 in The Iron Corner). However if either are present IV iron should precede ESA administration and added to the treatment paradigm in all hyporesponsive patients with TSATs <40% and serum ferritins <800, the groups for which there is existing safety data.

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References

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