

Management of IDA in Cancer and Chemotherapy

The purpose of this review is two-fold. Firstly, we will briefly review 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 studies¹ (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 paragraphs 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 were spending thrice the amount to achieve half the benefit seen in dialysis populations³.

The first trial by Auerbach et al⁴, 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 corroborated by a later study by Auerbach et al⁴ demonstrating a benefit of LMW ID irrespective of darbepoietin doses of 300 or 500 ug administered every three weeks⁵. 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 published by Henry et al, required that all subjects had as enrollment iron parameters, a ferritin of >100 ng/ml or a TSAT of >15⁶ (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 chemotherapy⁷ (Hedenus et al, Leukaemia) and then another in CIA⁸ (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 al⁹. 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



IRON CORNER

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-responders¹² (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 CIA¹³.

Long term toxicity remains a concern. One study, presented at the 2009 Annual Meeting of the American Society of Hematology, by Beguin et al¹⁴ 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 in 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 al¹⁵ (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 pretreatment hepcidin levels did not predict for a failure to respond to IV iron, these provocative data suggest that hepcidin may predict who will respond 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-analysis¹. 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 rate to ESAs, that the increase correlated with iron dose regardless of and baseline iron status without observing a negative safety signal with IV iron.

Based on these and other data, several organizations have developed recommendations on iron monitoring and replacement in cancer patients.¹⁶ **The National Comprehensive Cancer Network**, (NCCN) recommends monotherapy with iron (preferably IV) for absolute iron deficiency (ferritin <30 ng/mL and transferrin saturation (TS) <20%) and in patients using ESAs with ferritin between 30 and 800 ng/mL and TS between 20 and 50%. IV iron can reduce the number of transfusions in patients with functional iron deficiency.

The European Society for Medical Oncology (ESMO) recommends iron profile monitoring. IV iron replacement is recommended in patients with iron deficiency to produce an increment in hemoglobin and reduce the need for transfusion.

The European Organization for Research and Treatment of Cancer (EORTC) recommends iron replacement to be restricted to patients with absolute or functional iron deficiency.

In a position paper published in 2017 in Expert Review in Hematology, Barni and colleagues published a series of recommendations on managing iron deficiency in adult cancer patients. The Grade 1 (strong) and Grade 2 (weaker) recommendations. A subset of these recommendations are shown below:¹⁷

IRON CORNER

Recommendation: In all cancer patients, but especially in those scheduled for cytotoxic chemotherapy, radiotherapy, or surgery, the presence of anemia and/or iron deficiency should be investigated before and during treatment, to plan the most appropriate therapeutic strategy.

Recommendation: Initial laboratory screening in cancer patients should include, at least, full blood count with reticulocytes, serum ferritin, transferrin saturation, creatinine, and C-reactive protein (CRP).

Recommendation: In non-anemic ID cancer patients, iron supplements should be administered until serum iron parameters are normalized and iron store replenished, to avoid development of anemia.

Recommendation: New oral iron products may be efficacious in patients who are intolerant or non-responsive to conventional iron salts, and in those with contraindications for IV iron.

Recommendation: For anemic cancer patients with ID, who should not receive ESAs, iron supplementation as monotherapy is recommended

Recommendation: Regardless of the need for RBCT administration, anemia should be appropriately treated. If indicated, iron and/or ESAs are recommended to treat iron deficit or/and chemotherapy-induced anemia.

Recommendation: In cancer patients with absolute or functional ID, iron supplementation may reduce RBCT and ESA requirements and associated costs.

Based on these data, comprising thousands of patients with no clinically significant toxicity with IV iron, as well as the recent recommendations just discussed, we recommend a change in the current ASH/ASCO guidelines in alignment with those of the NCCN, the ESMO, the EORTC and the position paper published in 2017 referenced in this discussion. We recommend IV iron alone as first line therapy if iron deficiency is present. If the patient is unresponsive to IV iron alone, IV iron should precede ESA administration and be 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.

December 2018

References

1. Gafter-Gvili A, Rozen-Zvi B, Vidal L, Leibovici L, Vansteenkiste J, Gafter U, Shpilberg O. Intravenous iron supplementation for the treatment of chemotherapy-induced anaemia - systematic review and meta-analysis of randomised controlled trials. *Acta Oncol.* 2013 Jan;52(1):18-29
2. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med.* 1987 Jan 8;316(2):73-8.
3. Glaspy JA. Cancer patient survival and erythropoietin. *J Natl Compr Canc Netw.* 2005 Nov;3(6):796-804
4. Auerbach M, Ballard H, Trout JR, McIlwain M, Ackerman A, Bahrain H, Balan S, Barker L, Rana J. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: an multicenter, open-label, randomized trial. *J Clin Oncol.* 2004 Apr 1;22(7):1301-7.
5. Auerbach M, Silberstein PT, Webb RT, Averyanova S, Ciuleanu TE, Shao J, Bridges K. Darbepoetin alfa 300 or 500 µg once every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. *Am J Hematol.* 2010 Sep;85(9):655-63.
6. Henry DH, Dahl NV, Auerbach M, Tchekmedyan S, Laufman LR. Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. *Oncologist.* 2007 Feb;12(2):231-42.
7. Hedenus M, Birgegård G, Näsman P, Ahlberg L, Karlsson T, Lauri B, Lundin J, Lårfars G, Osterborg A. Addition of intravenous iron to epoetin beta increases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: a randomized multicenter study. *Leukemia.* 2007 Apr;21(4):627-32.
8. Pedrazzoli P, Farris A, Del Prete S, Del Gaizo F, Ferrari D, Bianchessi C. Randomized trial of intravenous iron supplementation in patients with chemotherapy-related anemia without iron deficiency treated with darbepoetin alpha. *J Clin Oncol.* 2008 Apr 1;26(10):1619-25.
9. Bastit L, Vandebroek A, Altintas S, Gaede B, Pintér T, Suto TS, Mossman TW, Smith KE, Vansteenkiste JF. Randomized, multicenter, controlled trial comparing the efficacy and safety of darbepoetin alpha administered every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. *J Clin Oncol.* 2008 Apr 1;26(10):1611-8.
10. Kim YT, Kim SW, Yoon BS, Cho HJ, Nahm EJ, Kim SH, Kim JH, Kim JW. Effect of intravenously administered iron sucrose on the prevention of anemia in the cervical cancer patients treated with concurrent chemoradiotherapy. *Gynecol Oncol.* 2007 Apr;105(1):199-204.
11. Danguwan P, Manchana T. Blood transfusion reduction with intravenous iron in gynecologic cancer patients receiving chemotherapy. *Gynecol Oncol.* 2010 Mar;116(3):522-5.
12. Anthony LB, Gabrail NY, Ghazal H, et al. IV iron sucrose for cancer- and/or chemotherapy-induced anemia in patients treated with erythropoiesis-stimulating agents. *Comm Oncol.* 2011;8(6):270-278



IRON CORNER

13. Steinmetz T, Tschechne B, Harlin O, Klement B, Franzem M, Wamhoff J, Tesch H, Rohrberg R, Marschner N. Clinical experience with ferric carboxymaltose in the treatment of cancer- and chemotherapy-associated anaemia. *Ann Oncol*. 2013 Feb;24(2):475-82.
14. Beguin Y, Maertens J, De Prijck B, Schots R, Seidel L, Bonnet C, Hafraoui K, Willems E, Vanstraelen G, Servais S, Jaspers A, Fillet G, Baron F. Darbepoetin-alfa and I.V. iron administration after autologous hematopoietic stemcell transplantation: A prospective multicenter randomized trial. *Am J Hematol*. 2013 Jul 22 [epub ahead on print]
15. Steensma DP, Sloan JA, Dakhil SR, et al. Phase III, randomized study of the effects of parenteral iron, oral iron, or no iron supplementation on the erythropoietic response to darbepoetin alfa for patients with chemotherapy-associated anemia. *J Clin Oncol*. 2011;29(1):97-105
16. Naoum FA. Iron Deficiency in Cancer Patients. *Rec Bras Hematol Hemoter*. 2106;38(4):325-330.
17. Barni S et al. Position paper on management of iron deficiency in adult cancer patients. *Expert Rev of Hematology*, 2017
DOI:10.1080/17474086.2017.1343140

Disclaimer

This content is covered by an important disclaimer that can be found at www.iron.sabm.org. Please read this disclaimer carefully before reviewing this content.