Managing Chemotherapy and Cancer-Related Anemia with Iron Supplementation

Iron Corner
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SUMMARY

- Anemia of cancer and treatment is very common of which iron deficiency both absolute and functional is a major cause.
- Anemia of cancer leads to poor quality of life, unnecessary exposure to transfusion risk, and may cause delay in cancer treatment.
- Intravenous (IV) iron can be given as monotherapy or with erythropoiesis-stimulating agents (ESAs) but is often underutilized due to unfounded safety concerns.

How Prevalent Is Anemia?

The prevalence of anemia in cancer is 40% and can exceed 90% for those on treatment.

What Is the Impact of Anemia?

Anemia impacts quality of life by contributing to fatigue, which is the leading patient reported symptom, can lead to treatment delays, and expose patients to unnecessary transfusion risks.

Why Does Anemia Often Go Untreated?

Anemia is often untreated or suboptimally treated due to concerns about the safety of both ESAs and IV iron.

What Are the Causes of Anemia in Cancer?

Cancer-associated anemia can be caused by nutritional deficiencies, hemolysis, blood loss, and chemotherapy or radiation induced myelosuppression. The underlying pathophysiology directly related to the malignancy includes:

- Impaired proliferation and differentiation in erythroid precursors
- Blunted erythropoietin response
- Inflammatory cytokine release
- Impaired iron regulation leading to functional iron deficiency

This functional iron deficiency results in part from an increased expression of hepcidin with downregulation of iron absorption and impaired recycling of iron from macrophages.

How Should Iron Be Tested?

Only 1/3 patients with cancer-related anemia (CRA) have iron studies ordered. The most frequently used tests to assess iron status are ferritin and transferrin saturation (TSAT). When the ferritin is low, absolute iron deficiency is present. Because ferritin is also an inflammatory biomarker it can make diagnosing of functional iron deficiency challenging. A TSAT under 20% suggests functional iron deficiency, both of which can be treated with IV iron.

	ABSOLUTE IRON DEFICIENCY	FUNCTIONAL IRON DEFICIENCY	IRON REPLETE
Ferritin ng/ml	<20	30-800	>800
TSAT %	<30	20-50	>50

What Treatments Should Be Considered?

The anemia of cancer is very often treated with transfusions without first assessing iron status or considering the use of either IV iron or ESA. Iron deficiency can be absolute (usually related to bleeding) with low iron stores, or functional iron deficiency. Iron-restricted erythropoiesis can occur when ESA therapy stimulates erythropoiesis without adequate iron delivery from storage sites.

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The ESA are effective in increasing hemoglobin levels and decreasing transfusion requirements in chemotherapy-induced anemia but data has linked their use to inferior survival and worse cancer outcomes so are not recommended to be used in anemic cancer patients not on treatment or in whom treatment is given with the intent to cure. This may be an opportunity to use iron supplementation.

Which Is More Effective – Oral Iron or Intravenous Iron?

Although oral iron is more convenient and less expensive it may not be tolerated due to gastrointestinal side effects, may not be absorbed in functional iron deficiency, and may be incapable of rapidly repleting iron stores.

There have been multiple clinical trials that have been published using IV iron either as monotherapy or in combination with ESAs to treat CRA. These studies have demonstrated improved hemoglobin levels, reduced transfusions, and improved quality of life.

Is IV Iron Safe?

Any of the current IV iron preparations can be used with relative safety. Minor infusion reactions occur about 1 in 200 infusions with major infusion reactions 1 in 200,000. There were no deaths attributed to IV iron nor increase in infections.

Expert Guidelines

Several organizations have developed recommendations on iron monitoring and replacement in cancer patients.

- **American Society of Hematology (ASH) and American Society of Clinical Oncology (ASCO)**
  The evidence suggests that adding iron supplementation to ESA therapy improves hematopoietic response and reduces the likelihood of RBC transfusions.
- The **National Comprehensive Cancer Network**, (NCCN) recommends monotherapy with iron (preferably IV) for absolute iron deficiency (ferritin <30 ng/mL and TSAT <20%) and in patients using ESAs with ferritin between 30 and 800 ng/mL and TSAT 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.

Recommended References

These review articles provide summaries to better understand the anemia of cancer and iron supplementation.

Highly Recommended Article
Rodgers GM. Update on iron supplementation in patients with cancer-related anemia. Expert Review of Hematology 2024 17 (8), 505-514.

1. Gilreath JA and Rodgers GM. How I treat cancer- associated anemia. Blood 2020:136 (7):801-813.
2. Ganz T. Anemia of Inflammation. N Engl J Med 2019:381:1148-1157.

3. Anand S, Burkenroad A ,Glaspy J. Workup of Anemia in Cancer. Clinical Advances in Hematology & Oncology. 2020 ;18 (10)640-646

4. Avni T, Bieber A et al. The safety of intravenous iron preparations: systematic review and meta-analysis. Mayo Clin Proc. 2015:90(1):12-23.

Additional References

1. Knight K, Wade, S Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. Am J Med. 2004: 116 (suppl 7A) 11S-26S.

2. Macciò A, Madeddu C, Gramignano G, et al. The role of inflammation, iron, and nutritional status in cancer-related anemia: results of a large, prospective, observational study. Haematologica 2015; 100:124.

3. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005; 352:1011.

4. Ganz T. Anemia of Inflammation. N Engl J Med 2019; 381:1148.

5. Coyne D. Iron indices: what do they really mean? Kidney Int Suppl. 2006: (101): S4-S8.

6. Goodnough LT. Iron deficiency syndromes and iron restricted erythropoiesis. Transfusion. 2012;52(7):1584-1592.

7. Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev 2012; 12:CD003407.

8. Bohlius J, Bohlke K, Castelli R, et al. Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents: ASCO/ASH Clinical Practice Guideline Update. J Clin Oncol 2019; 37:1336.

9. Rodgers GM, Gilreath JA. The role of intravenous iron in the treatment of anemia associated with cancer and chemotherapy. Acta Haematol. 2019:142(1):13-21.

10. Jang JH, Kim Y, Park S, et al. Efficacy of intravenous iron treatment for chemotherapy-induced anemia A prospective phase II pilot clinical trial in South Korea. Plos Med. 2020:17(6);e1003091

11. Gilreath JA, Makharadze T, Boccia RV, et al. Efficacy and safety of ferric carboxymaltose injection in reducing anemia in patients receiving chemotherapy for non-myeloid malignancies: A phase 3, placebo controlled study (IRON CLAD) (abstract) Blood 2019:134. Abstract 3535

12. Rodgers GM. Update on iron supplementation in patients with cancer-related anemia. Expert Review of Hematology 2024 17 (8), 505-514.

13. Avni T, Bieber A et al. The safety of intravenous iron preparations: systematic review and meta-analysis. Mayo Clin Proc. 2015:90(1):12-23.

14. Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents: ASCO/ASH Clinical Practice Guideline Update. Bohlius J, Bohlke K, Castelli R, et al. Blood Advances. 2019;3(8):1197-1210

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