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REVIEW

Cancer-Associated Anemia in Patients with β-Thalassemia Minor: Time to Rethink Current Management?

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Abstract

Background: Cancer-associated anemia (CAA) is a frequent complication of systemic anticancer therapy that adversely affects quality of life, treatment adherence, and clinical outcomes. Current management recommendations are largely based on evidence from the general oncology population and do not address patients with β-thalassemia minor, an inherited hemoglobinopathy characterized by chronic microcytosis and altered erythropoiesis. This review examines whether current approaches to CAA management are fully applicable to this unique patient population.
Methods: A narrative review of the available literature was conducted, focusing on international clinical guidelines, studies evaluating erythropoiesis-stimulating agents (ESAs), transfusion strategies, and the biological mechanisms of erythropoiesis in β-thalassemia minor. Existing evidence regarding the interaction between chemotherapy, anemia, and β-thalassemia minor was critically assessed to identify current knowledge gaps and future research priorities.
Results: Current ASCO/ASH and NCCN recommendations provide no disease-specific guidance for managing CAA in patients with β-thalassemia minor. Limited clinical observations suggest that responses to chemotherapy and ESA therapy may differ from those of the general oncology population, potentially due to altered erythropoiesis, fetal hemoglobin induction, and unique erythroid biology. However, available evidence is sparse and largely derived from small observational studies or experimental models, precluding changes to current clinical practice.
Conclusions: Patients with concomitant cancer and β-thalassemia minor represent an underrecognized subgroup for whom evidence-based supportive care recommendations remain lacking. Although current data do not justify modification of existing anemia management guidelines, they highlight an important unmet need for prospective clinical studies and translational research. Addressing this evidence gap may facilitate the development of more individualized supportive care strategies and advance the concept of precision supportive oncology.

Keywords: Cancer-associated anemia; β-thalassemia minor; Erythropoiesis-stimulating agents; Chemotherapy

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Introduction

Cancer-associated anemia (CAA) remains one of the most common complications of systemic anticancer therapy and represents a major challenge in supportive oncology. Depending on tumor type, disease stage, and treatment regimen, anemia affects approximately 40% to over 90% of patients receiving chemotherapy [1-4]. It contributes substantially to fatigue, impaired functional capacity, dyspnea, diminished quality of life, treatment delays, chemotherapy dose reductions, and increased healthcare utilization [1-6]. Although red blood cell transfusions provide rapid symptomatic relief, they consume considerable healthcare resources and are associated with transfusion reactions, alloimmunization, infectious complications, iron overload, and repeated hospital visits [5-7]. Consequently, optimizing anemia management has become a fundamental component of comprehensive cancer care.

Current management strategies are largely based on recommendations from the American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH), and the National Comprehensive Cancer Network (NCCN) [6-8]. Initial evaluation

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focuses on identifying potentially reversible causes of anemia, including iron deficiency, vitamin B12 or folate deficiency, renal dysfunction, bleeding, and chronic inflammation. Red blood cell transfusion remains the preferred treatment for patients with severe or symptomatic anemia requiring rapid correction, whereas iron supplementation is recommended only for selected patients with documented absolute or functional iron deficiency receiving erythropoiesis-stimulating agents (ESAs) [6–9].

ESAs have significantly reduced transfusion requirements in appropriately selected patients with chemotherapy-induced anemia by stimulating erythroid progenitor proliferation and maturation [10-12]. However, enthusiasm for their widespread use has declined following evidence linking ESAs to an increased risk of thromboembolic events and concerns regarding reduced survival or tumor progression in certain malignancies [13-17]. These observations prompted major revisions of international guidelines, restricting ESA use primarily to patients receiving palliative myelosuppressive chemotherapy after careful discussion of the potential benefits and risks [7, 16]. Importantly, these recommendations are derived from randomized clinical trials conducted in the general oncology population and therefore assume relatively homogeneous erythropoietic physiology.

An important exception may be patients with β-thalassemia minor. This inherited hemoglobinopathy affects millions of individuals worldwide and is particularly prevalent in Mediterranean countries, the Middle East, North Africa, South Asia, and regions surrounding the Caspian Sea, where carrier frequencies may approach 10% [18-21]. Given this high prevalence, the coexistence of cancer and β-thalassemia minor is likely to become an increasingly common clinical scenario rather than an exceptional finding.

Unlike individuals without hemoglobinopathies, patients with β-thalassemia minor exhibit lifelong microcytosis, mild chronic anemia, ineffective erythropoiesis, altered globin-chain synthesis, compensatory erythroid expansion, and variable fetal hemoglobin (HbF) expression [22-25]. Although most carriers remain clinically asymptomatic, these hematologic characteristics may influence responses to chemotherapy, transfusion therapy, and ESAs. Nevertheless, current oncology guidelines provide no disease-specific recommendations regarding transfusion thresholds, target hemoglobin levels, or ESA use in this patient population [6-8].

This lack of guidance reflects a substantial evidence gap rather than evidence of equivalent treatment responses. The absence of disease-specific recommendations should not be interpreted as confirmation that patients with β-thalassemia minor respond similarly to the broader oncology population. Instead, it highlights the paucity of clinical research addressing the intersection between inherited hemoglobinopathies and supportive cancer care.

One of the few observations suggesting biological differences was reported by Del Mastro and colleagues,

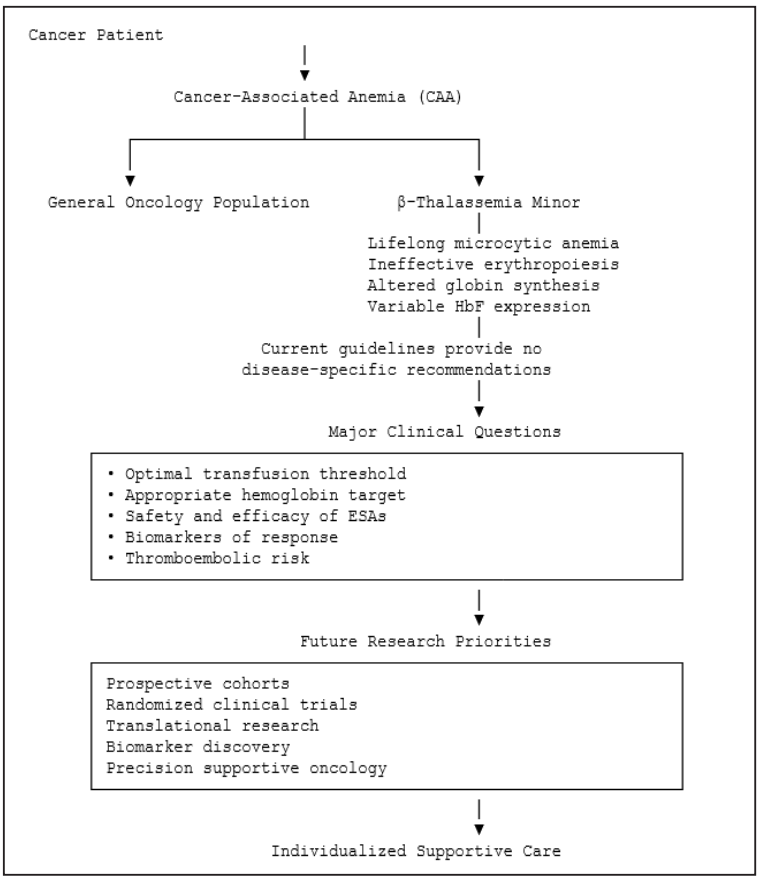

Figure 1. Current Management and Future Directions for Cancer-Associated Anemia in Patients with β-Thalassemia Minor

who unexpectedly described stabilization or even improvement of hemoglobin concentrations during cytotoxic chemotherapy in four patients with breast cancer and β-thalassemia minor [26]. Although the study was exploratory and included only four patients, the findings challenged the conventional assumption that chemotherapy invariably exacerbates anemia.

Several biological mechanisms have been proposed to explain this unexpected observation. Cytotoxic agents may induce HbF production through stress erythropoiesis, a mechanism previously described with hydroxyurea and several other pharmacologic agents [11, 22]. Alternatively, chemotherapy-induced alterations in erythroid differentiation may preferentially stimulate burst-forming unit–erythroid (BFU-E) progenitors or accelerate erythroid maturation in individuals with altered globin synthesis [26]. Other investigators have suggested that selective suppression of ineffective erythropoietic clones could paradoxically improve erythropoiesis under certain conditions [27]. However, these hypotheses remain speculative, and none has been validated in prospective clinical studies involving patients with β-thalassemia minor receiving chemotherapy.

The possibility that ESAs may exert distinct biological effects in β-thalassemia minor is equally intriguing but remains insufficiently investigated. In addition to stimulating erythroid proliferation through erythropoietin receptor signaling, erythropoietin activates anti-apoptotic pathways involving members of the BCL-2 family, promotes erythroid maturation, and reduces oxidative stress within erythrocytes [11, 28]. Experimental studies have demonstrated increased intracellular glutathione concentrations, reduced reactive oxygen species, and improved erythrocyte survival following erythropoietin exposure in thalassemic models [28]. These findings raise the possibility that ESA therapy may influence ineffective erythropoiesis through mechanisms extending beyond simple stimulation of red blood cell production.

Nevertheless, biological plausibility should not be equated with clinical efficacy. Existing evidence derives predominantly from laboratory investigations or studies involving patients with transfusion-dependent β-thalassemia major or β-thalassemia intermedia rather than β-thalassemia minor [28-30]. Whether these observations can be extrapolated to patients with β-thalassemia minor undergoing chemotherapy remains unknown. Similarly, it is unclear whether potential improvements in hemoglobin levels would translate into clinically meaningful outcomes, including reduced transfusion requirements, improved quality of life, or uninterrupted chemotherapy delivery. Furthermore, the well-established thromboembolic risks associated with ESAs in oncology cannot be assumed to differ in patients with β-thalassemia minor in the absence of adequately designed clinical studies [13-17]. Although hypercoagulability has been well documented in β-thalassemia major and intermedia, evidence regarding thrombotic risk among β-thalassemia carriers receiving ESAs during active cancer treatment remains limited [31].

These uncertainties underscore a broader challenge in supportive oncology. While modern oncology increasingly embraces precision medicine, supportive care recommendations often remain generalized despite substantial biological heterogeneity among patients. Precision supportive oncology should therefore extend beyond tumor biology to incorporate inherited host characteristics that may influence treatment tolerance, erythropoietic recovery, and therapeutic response. β-Thalassemia minor represents one such host factor deserving systematic investigation.

At present, the evidence base is limited by the absence of prospective cohort studies, randomized clinical trials, subgroup analyses from major ESA trials, and validated transfusion thresholds specific to patients with β-thalassemia minor. Likewise, optimal hemoglobin targets, predictive biomarkers of treatment response, comparative effectiveness of transfusion versus ESA therapy, and patient-reported outcomes including fatigue, exercise tolerance, and dyspnea remain poorly characterized. Consequently, clinicians managing patients with both cancer and β-thalassemia minor continue to rely largely on evidence extrapolated from oncology populations without inherited hemoglobinopathies.

Future Research Priorities

Rather than prompting immediate changes to clinical practice, these knowledge gaps should provide the basis for a coordinated research agenda. Prospective multicenter observational studies are needed to characterize the natural history of chemotherapy-induced anemia in patients with β-thalassemia minor across different malignancies, treatment regimens, and diverse geographic populations. Building on these observational data, well-designed randomized controlled trials should evaluate the efficacy and safety of erythropoiesis-stimulating agents (ESAs) compared with contemporary transfusion strategies while incorporating standardized assessments of fatigue, functional status, quality of life, and other patient-reported outcomes. In parallel, translational research investigating fetal hemoglobin (HbF) induction, erythropoietin receptor signaling, oxidative stress, erythroid progenitor biology, iron metabolism, and inflammatory pathways may help identify biomarkers capable of predicting treatment response and facilitating more individualized supportive care. Careful monitoring of thromboembolic events, together with comprehensive cost-effectiveness analyses, will also be essential before disease-specific management recommendations can be incorporated into future clinical guidelines.

At present, the available evidence does not support modification of current ASCO/ASH or NCCN recommendations for the management of cancer-associated anemia in patients with β-thalassemia minor. However, the absence of disease-specific evidence should not be interpreted as evidence that existing management strategies are optimal for this patient population. Individuals with concomitant cancer and β-thalassemia minor represent an underrecognized subgroup at the intersection of hematology and oncology, in whom inherited alterations in erythropoiesis may influence

responses to supportive care interventions in ways that remain poorly understood. Addressing this important evidence gap offers an opportunity not only to optimize anemia management for a substantial global patient population but also to advance the broader concept of precision supportive oncology, in which supportive care strategies are individualized according to both tumor biology and host biology (Figure 1).

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Key Messages

• Current international guidelines for cancer-associated anemia do not provide specific recommendations for patients with β-thalassemia minor.

• Limited clinical evidence suggests that erythropoietic responses to chemotherapy may differ in patients with β-thalassemia minor compared with the general oncology population.

• The efficacy and safety of erythropoiesis-stimulating agents (ESAs) in patients with concomitant cancer and β-thalassemia minor remain uncertain because of the lack of disease-specific clinical evidence.

• Prospective observational studies and randomized clinical trials are needed to establish evidence-based recommendations for anemia management in this unique patient population.

• Precision supportive oncology should incorporate inherited hematologic characteristics, such as β-thalassemia minor, alongside tumor biology when individualizing supportive care strategies.

References

1. Pourali L, Taghizadeh A, Akhoundi MR, Varshoei F, Zarifian A, Andalibi MSS. Frequency of Chemotherapy Induced Anemia in Breast Cancer Patients. 2015 Nov 11;:e4672. https://doi.org/10.17795/ijcp-4672
2. Kitano T, Tada H, Nishimura T, Teramukai S, Kanai M, Nishimura T, Misawa A, et al. Prevalence and incidence of anemia in Japanese cancer patients receiving outpatient chemotherapy. International Journal of Hematology. 2007 07;86(1):37-41. https://doi.org/10.1532/IJH97.07040
3. Dicato M, Plawny L, Diederich M. Anemia in cancer. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2010 Oct;21 Suppl 7:vii167-172. https://doi.org/10.1093/annonc/mdq284
4. Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. The American Journal of Medicine. 2004 04 05;116 Suppl 7A:11S-26S. https://doi.org/10.1016/j.amjmed.2003.12.008
5. Ludwig H, Van Belle S, Barrett-Lee P, Birgegård G, Bokemeyer C, Gascón P, Kosmidis P, et al. The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. European Journal of Cancer. 2004 Oct;40(15):2293-2306. https://doi.org/10.1016/j.ejca.2004.06.019
6. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Cancer- and Chemotherapy-Induced Anemia. Plymouth Meeting (PA): NCCN; 2025.
7. Bohlius J, Bohlke K, Castelli R, Djulbegovic B, Lustberg MB, Martino M, Mountzios G, et al. Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents: ASCO/ASH Clinical Practice Guideline Update. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2019 05 20;37(15):1336-1351. https://doi.org/10.1200/JCO.18.02142
8. Aapro M, Beguin Y, Bokemeyer C, Dicato M, Gascón P, Glaspy J, Hofmann A, et al. Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2018 Oct 01;29(Suppl 4):iv271. https://doi.org/10.1093/annonc/mdy323
9. 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 Oncologica. 2013 01;52(1):18-29. https://doi.org/10.3109/0284186X.2012.702921
10. Glaspy JA. Erythropoietin in cancer patients. Annual Review of Medicine. 2009;60:181-192. https://doi.org/10.1146/annurev.med.60.050307.110718
11. Perrine SP. Fetal globin induction--can it cure beta thalassemia?. Hematology. American Society of Hematology. Education Program. 2005;:38-44. https://doi.org/10.1182/asheducation-2005.1.38
12. Del Mastro L, Venturini M, Lionetto R, Garrone O, Melioli G, Pasquetti W, Sertoli MR, et al. Randomized phase III trial evaluating the role of erythropoietin in the prevention of chemotherapy-induced anemia. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 1997 07;15(7):2715-2721. https://doi.org/10.1200/JCO.1997.15.7.2715
13. Bohlius J, Langensiepen S, Schwarzer G, Seidenfeld J, Piper M, Bennett C, Engert A. Recombinant human erythropoietin and overall survival in cancer patients: results of a comprehensive meta-analysis. Journal of the National Cancer Institute. 2005 04 06;97(7):489-498. https://doi.org/10.1093/jnci/dji087
14. Bennett CL, Silver SM, Djulbegovic B, Samaras AT, Blau CA, Gleason KJ, Barnato SE, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA. 2008 02 27;299(8):914-924. https://doi.org/10.1001/jama.299.8.914
15. Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, Hyde C, et al. Erythropoietin or darbepoetin for patients with cancer. The Cochrane Database of Systematic Reviews. 2012 Dec 12;12(12):CD003407. https://doi.org/10.1002/14651858.CD003407.pub5
16. Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Arcasoy MO, Spivak JL, Bennett CL, et al. American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. Blood. 2010 Nov 18;116(20):4045-4059. https://doi.org/10.1182/blood-2010-08-300541
17. Leyland-Jones B. Breast cancer trial with erythropoietin terminated unexpectedly. The Lancet. Oncology. 2003 08;4(8):459-460. https://doi.org/10.1016/s1470-2045(03)01163-x
18. Rahim F, Abromand M. Spectrum of β-thalassemia mutations in various ethnic regions of Iran. Pak J Med Sci. 2008;24(3):410–5...
19. Weatherall DJ, Clegg JB. The Thalassaemia Syndromes. 4th

ed. Oxford: Blackwell Science; 2001...
20. Taher AT, Musallam KM, Cappellini MD. β-Thalassemias. The New England Journal of Medicine. 2021 02 25;384(8):727-743. https://doi.org/10.1056/NEJMra2021838
21. Angastiniotis M, Eleftheriou A, Galanello R, Harteveld CL, Petrou M, Traeger-Synodinos J, Giordano P, et al. Prevention of Thalassaemias and Other Haemoglobin Disorders: Volume 1: Principles. 2013;.
22. Rund D, Rachmilewitz E. Beta-thalassemia. The New England Journal of Medicine. 2005 09 15;353(11):1135-1146. https://doi.org/10.1056/NEJMra050436
23. Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V, editors. Guidelines for the Management of Transfusion Dependent Thalassaemia. 4th ed. Nicosia: Thalassaemia International Federation; 2021.
24. Musallam KM, Rivella S, Vichinsky E, Rachmilewitz EA. Non-transfusion-dependent thalassemias. Haematologica. 2013 06;98(6):833-844. https://doi.org/10.3324/haematol.2012.066845
25. Cao A, Galanello R. Beta-thalassemia. Genetics in Medicine: Official Journal of the American College of Medical Genetics. 2010 02;12(2):61-76. https://doi.org/10.1097/GIM.0b013e3181cd68ed
26. Del Mastro L, Venturini M, Costantini M, Garrone O, Sertoli MR, Bertelli G, Machì AM, Rosso R. Paradoxical effect of cytotoxic chemotherapy on anemia in cancer patients with beta-thalassemia minor. Journal of the National Cancer Institute. 1997 03 19;89(6):455-456. https://doi.org/10.1093/jnci/89.6.455
27. Venturini M, Del Mastro L, Aitini E, Baldini E, Caroti C, Contu A, Testore F, et al. Dose-dense adjuvant chemotherapy in early breast cancer patients: results from a randomized trial. Journal of the National Cancer Institute. 2005 Dec 07;97(23):1724-1733. https://doi.org/10.1093/jnci/dji398
28. Amer J, Dana M, Fibach E. The antioxidant effect of erythropoietin on thalassemic blood cells. Anemia. 2010;2010:978710. https://doi.org/10.1155/2010/978710
29. Rachmilewitz EA, Aker M. The role of recombinant human erythropoietin in the treatment of thalassemia. Annals of the New York Academy of Sciences. 1998 06 30;850:129-138. https://doi.org/10.1111/j.1749-6632.1998.tb10470.x
30. Di Iorio B, De Nicola L, Bellizzi V, Minutolo R, Zamboli P, Rubino R, Fuiano G, Conte G. Efficacy of erythropoietin on dialysis in patients with beta thalassemia minor. Blood Purification. 2004;22(5):453-460. https://doi.org/10.1159/000080729
31. Eldor A, Rachmilewitz EA. The hypercoagulable state in thalassemia. Blood. 2002 01 01;99(1):36-43. https://doi.org/10.1182/blood.v99.1.36