guideline summary

Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents: ASCO/ASH Clinical Practice Guideline Update

Julia Bohlius, MD, MScPH[1]; Kari Bohlke, ScD[2]; and Alejandro Lazo-Langner, MD, MSc[3]

Use of erythropoiesis-stimulating agents (ESAs) to manage anemia increases hemoglobin levels and reduces the need for RBC transfusions but increases the risk of thromboembolic events.[1,2] Studies have also reported decreased survival, increased mortality during active study phase, and/or an increased risk of cancer progression or recurrence with the use of ESAs in patients with cancer.[3-6] The risks of ESAs prompted multiple regulatory actions by the US Food and Drug Administration (FDA) between 2004 and 2009, and in 2010 the FDA approved a Risk Evaluation and Mitigation Strategy for ESA use in patients with cancer. In 2017, the FDA determined that the Risk Evaluation and Mitigation Strategy was no longer necessary: prescribers demonstrated acceptable knowledge of the risks of ESAs and the need to counsel patients about the risks, and utilization data suggested an increase in appropriate prescribing practices.[7] The risks of ESAs remain, however, highlighting the ongoing importance of appropriate use. ESAs are indicated in patients with cancer who are receiving myelosuppressive chemotherapy with noncurative intent and anemia that cannot be adequately managed with transfusion support.

ASCO and the American Society of Hematology first published a joint evidence-based clinical practice guideline for the use of ESAs in adults with cancer and anemia in 2002,[8] with updates in 2007[9] and 2010.[10] Since the 2010 update, additional information has emerged about the safety and efficacy of ESAs in patients with metastatic breast cancer and about the role of iron in conjunction with ESAs. Treatment options have also expanded with the 2018 FDA approval of a biosimilar of epoetin alfa, warranting a guideline update.[11] Additional information is available at www.asco.org/supportive-care-guidelines. Patient information is available at www.cancer.net.

AFFILIATIONS

[1]University of Bern, Bern, Switzerland
[2]American Society of Clinical Oncology, Alexandria, VA
[3]Western University, London, Ontario, Canada

CORRESPONDING AUTHOR

American Society of Clinical Oncology, 2318 Mill Road, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

Reprint Requests: 2318 Mill Road, Suite 800, Alexandria, VA 22314; guidelines@asco.org

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JOP.19.00111.

AUTHOR CONTRIBUTIONS

Conception and design: Julia Bohlius, Alejandro Lazo-Langner
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents: ASCO/ASH Clinical Practice Guideline Update was developed and written by Julia Bohlius, Kari Bohlke, Roberto Castelli, Benjamin Djulbegovic, Maryam B. Lustberg, Massimo Martino, Giannis Mountzios, Namrata Peswani, Laura Porter, Tiffany N. Tanaka, Gianluca Trifirò, Hushan Yang, and Alejandro Lazo-Langner.

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on March 18, 2019 and published at jop.ascopubs.org on June 4, 2019: DOI https://doi.org/10.1200/JOP.19.00111

THE BOTTOM LINE

Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents: American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update

Guideline Question When and how should erythropoiesis-stimulating agents (ESAs) be used to manage anemia in adults with cancer?

Target Population Adults with cancer and anemia.

Target Audience Oncologists, hematologists, oncology nurses, oncology pharmacists, other health care professionals who care for patients with cancer, and patients with cancer.

Methods An Expert Panel was convened to update clinical practice guideline recommendations on the basis of a systematic review of the medical literature.

Recommendations

Clinical Question 1

To reduce the need for RBC transfusions, should ESAs be offered to patients who have chemotherapy-associated anemia?

Recommendation 1.1. Depending on clinical circumstances ESAs may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose hemoglobin has declined to less than 10 g/dL. RBC transfusion is also an option, depending on the severity of the anemia or clinical circumstances. (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong)

Recommendation 1.2. ESAs should not be offered to patients with chemotherapy-associated anemia whose cancer treatment is curative in intent. (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong)

Clinical Question 2

To reduce the need for RBC transfusions, should ESAs be offered to patients with anemia who are not receiving concurrent myelosuppressive chemotherapy?

Recommendation 2.1. ESAs should not be offered to most patients with non–chemotherapy-associated anemia. (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: strong)

Recommendation 2.2. ESAs may be offered to patients with lower risk myelodysplastic syndromes and a serum erythropoietin level of 500 IU/L or less. (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate)

Clinical Question 3

What special considerations apply to adult patients with nonmyeloid hematologic malignancies who are receiving concurrent myelosuppressive chemotherapy?

Recommendation 3. In patients with myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia, clinicians should observe the hematologic response to cancer treatment before considering an ESA. Particular caution should be exercised in the use of ESAs concomitant with treatment strategies and diseases where risk of thromboembolic complications is increased (see Recommendations 4 and 6). In all cases, blood transfusion is a treatment option that should be considered. (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate)

Clinical Question 4

What examinations and diagnostic tests should be performed before making a decision about using an ESA, to identify patients who are likely to benefit from an ESA?

Recommendation 4. Before offering an ESA, clinicians should conduct an appropriate history, physical examination, and diagnostic tests to identify alternative causes of anemia aside from chemotherapy or an underlying hematopoietic malignancy. Such causes should be appropriately addressed before considering

(continued on following page)

THE BOTTOM LINE (CONTINUED)

the use of ESAs. Suggested baseline investigations are listed in Table 1. (Type of recommendation: informal consensus; Evidence quality: intermediate; Strength of recommendation: strong)

Clinical Question 5
Among adult patients who receive an ESA for chemotherapy-associated anemia, do darbepoetin, epoetin beta and alfa originator, and currently available biosimilars of epoetin alfa differ with respect to safety or efficacy?

Recommendation 5. The Expert Panel considers epoetin beta and alfa, darbepoetin, and biosimilar epoetin alfa to be equivalent with respect to effectiveness and safety. (Type of recommendation: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate)

Clinical Question 6
Do ESAs increase the risk of thromboembolism?

Recommendation 6. ESAs increase the risk of thromboembolism, and clinicians should carefully weigh the risks of thromboembolism and use caution and clinical judgment when considering use of these agents. (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong)

Clinical Question 7
Among adult patients who will receive an ESA for chemotherapy-associated anemia, what are recommendations for ESA dosing and dose modifications?

Recommendation 7. It is recommended that starting and modifying doses of ESAs follow FDA guidelines (see Table 2 for specific dosing information). (Type of recommendation: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate)

Clinical Question 8
Among adult patients who will receive an ESA for chemotherapy-associated anemia, what is the recommended target hemoglobin (Hb) level?

Recommendation 8. Hb may be increased to the lowest concentration needed to avoid or reduce the need for RBC transfusions, which may vary by patient and condition. (Type of recommendation: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate)

Clinical Question 9
Among adult patients with chemotherapy-associated anemia who do not respond to ESA therapy ($<$ 1 to 2 g/dL increase in Hb or no decrease in transfusion requirements), does continuation of ESA therapy beyond 6 to 8 weeks provide a benefit?

Recommendation 9. ESAs should be discontinued in patients who do not respond within 6 to 8 weeks. Patients who do not respond to ESA treatment should be re-evaluated for underlying tumor progression, iron deficiency, or other etiologies for anemia. (Type of recommendation: informal consensus; Evidence quality: intermediate; Strength of recommendation: strong)

Clinical Question 10
Among adult patients with chemotherapy-associated anemia, does iron supplementation concurrent with an ESA reduce transfusion requirements*?*

Recommendation 10. Iron replacement may be used to improve hemoglobin response and reduce RBC transfusions for patients receiving ESA with or without iron deficiency. Baseline and periodic monitoring of iron, total iron binding capacity, transferrin saturation, or ferritin levels is recommended. (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: weak)

Additional Resources More information, including a Data Supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at https://www.asco.org/supportive-care-guidelines. Patient information is available at www.cancer.net. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline update.

ASCO and ASH believe that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

REFERENCES

1. Grant MD, Piper M, Bohlius J, et al: AHRQ comparative effectiveness reviews: Epoetin and darbepoetin for managing anemia in patients undergoing cancer treatment—Comparative effectiveness update. Rockville, MD, US Agency for Healthcare Research and Quality, 2013
2. Tonia T, Mettler A, Robert N, et al: Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev 12:CD003407, 2012
3. Leyland-Jones B, Semiglazov V, Pawlicki M, et al: Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: A survival study. J Clin Oncol 23:5960-5972, 2005
4. Thomas G, Ali S, Hoebers FJ, et al: Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. Gynecol Oncol 108:317-325, 2008
5. Untch M, von Minckwitz G, Konecny GE, et al: PREPARE trial: A randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel, and CMF versus a standard-dosed epirubicin-cyclophosphamide followed by paclitaxel with or without darbepoetin alfa in primary breast cancer—Outcome on prognosis. Ann Oncol 22:1999-2006, 2011
6. Leyland-Jones B, Bondarenko I, Nemsadze G, et al: A randomized, open-label, multicenter, phase III study of epoetin alfa versus best standard of care in anemic patients with metastatic breast cancer receiving standard chemotherapy. J Clin Oncol 34:1197-1207, 2016
7. US Food and Drug Administration: Information on erythropoiesis-stimulating agents (ESA) epoetin alfa (marketed as Procrit, Epogen), darbepoetin alfa (marketed as Aranesp), 2017. https://www.fda.gov/Drugs/DrugSafety/ucm109375.htm
8. Rizzo JD, Lichtin AE, Woolf SH, et al: Use of epoetin in patients with cancer: Evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. J Clin Oncol 20:4083-4107, 2002
9. Rizzo JD, Somerfield MR, Hagerty KL, et al: Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. J Clin Oncol 26:132-149, 2008
10. Rizzo JD, Brouwers M, Hurley P, et al: American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. J Clin Oncol 28:4996-5010, 2010
11. US Food and Drug Administration: FDA approves Retacrit as a biosimilar to Epogen/Procrit. 2018. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm607723.htm

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents: ASCO/ASH Clinical Practice Guideline Update

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jop/site/ifc/journal-policies.html.

Alejandro Lazo-Langner
Research Funding: Alexion Pharmaceuticals (Inst), Bayer (Inst), Daiichi Sankyo (Inst), Pfizer (Inst), Bristol-Myers Squibb (Inst)

No other potential conflicts of interest were reported.