Recommendations for the Use of White Blood Cell Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update

By Thomas J. Smith, MD, FACP, FASCO, FAAHPM, Kari Bohlke, ScD, and James O. Armitage, MD

The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; American Society of Clinical Oncology, Alexandria, VA; and University of Nebraska Medical Center, Omaha, NE

Neutropenia and its complications, including febrile neutropenia and infection, are major toxicities associated with myelosuppressive systemic cancer chemotherapy.[1-3] In a nationwide prospective cohort study, first-cycle febrile neutropenia occurred in 6% of adults with solid tumors being treated with myelosuppressive chemotherapy.[2] Among patients with metastatic solid tumors, incidence of febrile neutropenia during myelosuppressive chemotherapy ranged from 13% to 21% in a large retrospective study.[3] Neutropenic complications require prompt evaluation and treatment with empiric antibiotics and often require hospitalization. The risk of such complications increases in direct proportion to the severity and duration of neutropenia.[4] Hematopoietic colony-stimulating factors (CSFs) have been shown to reduce the duration and severity of neutropenia and the risk of febrile neutropenia[5] and enable delivery of more intensive or dose-dense chemotherapy when indicated. However, concerns with respect to adverse events and costs led ASCO to develop clinical practice guidelines for the use of CSFs in 1994 and on four occasions since then. This guideline represents the first major update since 2006 and addresses the strengths and limitations of the use of CSFs across a range of settings in clinical oncology practice on the basis of an exhaustive review of the medical literature. The purpose of these guidelines is to foster the appropriate use of these agents based on high-quality evidence from controlled clinical trials and a comprehensive understanding of the specific patient, disease, and treatment factors associated with the risk of neutropenic complications.

Full Guideline Authors

Recommendations for the Use of White Blood Cell Growth Factors: ASCO Clinical Practice Guideline Update was developed and written by Thomas J. Smith, Kari Bohlke, Gary H. Lyman, Kenneth R. Carson, Jeffrey Crawford, Scott J. Cross, John M. Goldberg, James L. Khatcheressian, Natasha B. Leighl, Cheryl L. Perkins, George Somlo, James L. Wade, Antoinette J. Wozniak, and James O. Armitage.

Authors' Disclosures of Potential Conflicts of Interest

Disclosures provided by the authors are available with this article at jop.ascopubs.org.

Author Contributions

Conception and design: Thomas J. Smith, Kari Bohlke

Administrative support: Thomas J. Smith, Kari Bohlke

Collection and assembly of data: Thomas J. Smith, Kari Bohlke

Data analysis and interpretation: Thomas J. Smith, James O. Armitage

Manuscript writing: All authors

Final approval of manuscript: All authors

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

DOI: 10.1200/JOP.2015.006742; published online ahead of print at jop.ascopubs.org on July 21, 2015.

References

1. Bennett CL, Djulbegovic B, Norris LB, et al: Colony-stimulating factors for febrile neutropenia during cancer therapy. N Engl J Med 368:1131-1139, 2013

2. Culakova E, Thota R, Poniewierski MS, et al: Patterns of chemotherapy-associated toxicity and supportive care in US oncology practice: A nationwide prospective cohort study. Cancer Med 3:434-444, 2014

3. Weycker D, Li X, Edelsberg J, et al: Risk and consequences of chemotherapy-induced febrile neutropenia in patients with metastatic solid tumors. J Oncol Pract 10:47-54, 2014

4. Bodey GP, Buckley M, Sathe YS, et al: Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 64:328-340, 1966

5. Crawford J, Ozer H, Stoller R, et al: Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med 325:164-170, 1991

THE BOTTOM LINE

Recommendations for the Use of White Blood Cell Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update

Guideline Question

How should CSFs be used in patients with cancer?

Target Population

Adults or children with a solid tumor or lymphoma treated with chemotherapy.

Target Audience

Medical oncologists, hematologists, oncology nurses, other clinicians who care for patients with cancer, and patients

Methods

An Update Committee was convened to update clinical practice guideline recommendations based on a systematic review of the medical literature.

Key Points

- Primary prophylaxis with a CSF starting with the first cycle and continuing through subsequent cycles of chemotherapy is recommended in patients who have an approximately 20% or higher risk for febrile neutropenia based on patient-, disease-, and treatment-related factors. Primary CSF prophylaxis should also be given in patients receiving dose-dense chemotherapy when considered appropriate. Consideration should be given to alternative, equally effective and safe chemotherapy regimens not requiring CSF support when available. (Type: Evidence based, benefits outweigh harms. Evidence quality: High. Strength of recommendation: Strong.)
- Secondary prophylaxis with CSFs is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose or treatment delay may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative. (Type: Evidence based, benefits outweigh harms. Evidence quality: High. Strength of recommendation: strong.)
- CSFs should not be routinely used for patients with neutropenia who are afebrile. (Type: Evidence based, benefits outweigh harms. Evidence quality: High. Strength of recommendation: Strong.)
- CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSFs should be considered in patients with fever and neutropenia who are at high risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. (Type: Evidence based, benefits outweigh harms. Evidence quality: High. Strength of recommendation: Strong.)
- Dose-dense regimens with CSF support should be used only if supported by convincing efficacy data or within an appropriately designed clinical trial. Efficacy data support the use of dose-dense chemotherapy in the adjuvant treatment of high-risk breast cancer, and the use of high-dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin in urothelial cancer. There are limited and conflicting data on the value of dose-dense regimens with CSF support in non-Hodgkin lymphoma, and it cannot routinely be recommended at this time. (Type: Evidence based, benefits outweigh harms. Evidence quality: High for breast cancer and lymphoma, intermediate for urothelial cancer. Strength of recommendation: Strong for breast cancer and lymphoma, moderate for urothelial cancer.)
- CSFs may be used alone, after chemotherapy, or in combination with plerixafor to mobilize peripheral-blood progenitor cells. Choice of mobilization strategy depends in part on type of cancer and type of transplantation. (Type: Evidence based, benefits outweigh harms. Evidence quality: High. Strength of recommendation: Strong.)
- CSFs should be administered after autologous stem-cell transplantation in order to reduce the duration of severe neutropenia. (Type: Evidence based, benefits outweigh harms. Evidence quality: High. Strength of recommendation: Strong.)
- CSFs may be administered after allogeneic stem-cell transplantation in order to reduce the duration of severe neutropenia. (Type: Evidence based. Evidence quality: Low. Strength of recommendation: Weak.)
- Prophylactic CSF for patients with diffuse aggressive lymphoma age 65 years and older treated with curative chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab) should be considered, particularly in the presence of comorbidities. (Type: Evidence based, benefits outweigh harms. Evidence quality: Intermediate. Strength of recommendation: Moderate.)
- The use of CSFs in pediatric patients will almost always be guided by clinical protocols. As in adults, the use of CSFs is reasonable for the primary prophylaxis of pediatric patients with a high likelihood of febrile neutropenia. Similarly, the use of CSFs for secondary prophylaxis or for therapy should be limited to high-risk patients. (Type: Evidence based, benefits outweigh harms. Evidence quality: High. Strength of recommendation: Strong.)
- For pediatric indications in which dose-intense chemotherapy is known to have a survival benefit, such as Ewing sarcoma, CSFs should be used to enable the administration of these regimens. (Type: Evidence based, benefits outweigh harms. Evidence quality: High. Strength of recommendation: Strong.)
- CSFs should not be used in pediatric patients with non-relapsed acute lymphoblastic leukemia or non-relapsed acute myeloid leukemia who do not have an infection. (Type: Informal consensus. Evidence quality: Intermediate. Strength of recommendation: Moderate.)

(continued on following page)

THE BOTTOM LINE (CONTINUED)

- Pegfilgrastim, filgrastim, tbo-filgrastim, and filgrastim-sndz (and other biosimilars, as they become available) can be used for the prevention of treatment-related febrile neutropenia. The choice of agent depends on convenience, cost, and the clinical situation. There have been no further data comparing granulocyte-CSF and granulocyte macrophage–CSF since the 2006 update; therefore, there is no change in the recommendation regarding their therapeutic equivalency. (Type: Evidence based, benefits outweigh harms. Evidence quality: Strong. Strength of recommendation: High.)
- Current recommendations for the treatment of patients exposed to lethal doses of whole-body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs, includes the prompt administration of CSF or pegylated granulocyte-CSF. (Type: Formal consensus [by others], benefits outweigh harms. Evidence quality: Intermediate. Strength of recommendation: Moderate.)

Qualifying Statements

The Update Committee did not provide recommendations regarding the use of CSFs in adult patients with acute myeloid leukemia or myelodysplastic syndromes.

Additional Resources

The full guideline was published in *Journal of Clinical Oncology* and includes information about the dosing and administration of CSFs. Additional information, including a Data Supplement with evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/guidelines/wbcgf and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net

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

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Recommendations for the Use of White Blood Cell Growth Factors: American Society of Clinical Oncology 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 jop.ascopubs.org/site/misc/ifc.xhtml.

Thomas J. Smith

Stock or Other Ownership: UnitedHealthcare

Kari Bohlke

No relationship to disclose

James O. Armitage

Leadership: Tesaro

Consulting or Advisory Role: GlaxoSmithKline, Roche, Spectrum Pharmaceuticals, ZIOPHARM Oncology, Conatus, Celgene