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Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update

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ABSTRACT

Purpose
To update the 2006 American Society of Clinical Oncology guideline on the use of hematopoietic colony-stimulating factors (CSFs).

Methods
The American Society of Clinical Oncology convened an Update Committee and conducted a systematic review of randomized clinical trials, meta-analyses, and systematic reviews from October 2005 through September 2014. Guideline recommendations were based on the review of the evidence by the Update Committee.

Results
Changes to previous recommendations include the addition of tbo-filgrastim and filgrastim-sndz, moderation of the recommendation regarding routine use of CSFs in older patients with diffuse aggressive lymphoma, and addition of recommendations against routine dose-dense chemotherapy in lymphoma and in favor of high–dose-intensity chemotherapy in urothelial cancer. The Update Committee did not address recommendations regarding use of CSFs in acute myeloid leukemia or myelodysplastic syndromes in adults.

Recommendations
Prophylactic use of CSFs to reduce the risk of febrile neutropenia is warranted when the risk of febrile neutropenia is approximately 20% or higher and no other equally effective and safe regimen that does not require CSFs is available. Primary prophylaxis is recommended for the prevention of febrile neutropenia in patients who are at high risk on the basis of age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. Dose-dense regimens that require CSFs should only be used within an appropriately designed clinical trial or if supported by convincing efficacy data. Current recommendations for the management of patients exposed to lethal doses of total-body radiotherapy, but not doses high enough to lead to certain death as a result of injury to other organs, include the prompt administration of CSFs.

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INTRODUCTION

Neutropenia and its complications, including febrile neutropenia and infection, remain 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 the American Society of Clinical Oncology (ASCO) to develop a clinical practice guideline for the use of CSFs in 1994 and updates on four occasions since then. This guideline represents the first major update since 2006 and addresses the strengths and

THE BOTTOM LINE

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Guideline Question
How should colony-stimulating factors (CSFs) be used in people 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 people 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 administered 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 a CSF 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 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 only be used 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: strong. Strength of recommendation: high.)

THE BOTTOM LINE (CONTINUED)

- CSFs should be administered after autologous stem-cell transplantation 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 to reduce the duration of severe neutropenia. (Type: evidence based. Evidence quality: low. Strength of recommendation: weak).

- Prophylactic CSFs for patients with diffuse aggressive lymphoma age $\geq$ 65 years 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 as primary prophylaxis for 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 nonrelapsed acute lymphoblastic leukemia or nonrelapsed acute myeloid leukemia who do not have an infection. (Type: informal consensus. Evidence quality: intermediate. Strength of recommendation: moderate.)

- 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 clinical situation. There have been no additional data comparing granulocyte CSFs and granulocyte-macrophage CSFs since the 2006 update; therefore, there is no change in the recommendation regarding their therapeutic equivalency. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

- Current recommendations for the management of patients exposed to lethal doses of total-body radiotherapy, but not doses high enough to lead to certain death resulting from injury to other organs, include the prompt administration of CSFs or pegylated granulocyte CSFs. (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
More information, including a Data Supplement with additional 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. 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.

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 this guideline 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.

GUIDELINE QUESTIONS

This clinical practice guideline considered the following clinical questions: (1) In adults treated with chemotherapy for a solid tumor or lymphoma, what factors should clinicians consider when selecting patients for primary prophylaxis of febrile neutropenia with a CSF? (2)

In adults treated with chemotherapy for a solid tumor or lymphoma, what factors should clinicians use to select patients for secondary prophylaxis of febrile neutropenia with a CSF? (3) Are there circumstances in which CSFs should be considered for the treatment of neutropenia in adults with cancer? (4) In what settings should CSFs be used to increase chemotherapy dose density? (5) What is the role of CSFs as adjuncts to progenitor-cell transplantation? (6) What is the role of CSFs in the setting of acute leukemia or myelodysplastic syndromes? (7) Should CSFs be avoided in patients receiving concomitant chemotherapy and radiation therapy? (8) Are there CSF recommendations that apply specifically to older adults and that differ from recommendations in younger adults? (9) How should CSFs be used in the pediatric population? (10) What are recommendations for the initiation, duration, dosing, and administration of CSFs? (11) Do CSFs differ in efficacy? (12) What is the role of CSFs in the treatment of radiation injury?

METHODS

Guideline Update Development Process

The Update Committee (members listed in Appendix Table A1, online only) met twice via Webinar and corresponded through e-mail. On the basis of the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. Members of the Update Committee were responsible for reviewing and approving the final version of guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Update Committee and the ASCO Clinical Practice Guidelines Committee before publication.

The recommendations were developed by an Update Committee with multidisciplinary representation using a systematic review (October 1, 2005, through September 30, 2014) of phase III randomized controlled trials (RCTs), meta-analyses, systematic reviews, and clinical experience. When recommended by Update Committee members, results from selected phase II trials were considered. Articles were selected for inclusion in the systematic review of the evidence on the basis of the following criteria:

- Population: adults or children with cancer.
- Intervention: granulocyte CSFs (G-CSFs) and granulocyte macrophage CSFs (GM-CSFs) used to prevent or treat febrile neutropenia among patients treated with chemotherapy, to allow the delivery of dose-dense chemotherapy, to mobilize stem cells for transplantation, or to treat radiation injury.

Articles were excluded from the systematic review if they were meeting abstracts not subsequently published in peer-reviewed journals; editorials, commentaries, letters, news articles, case reports, or narrative reviews; or published in a language other than English. Excluded interventions were as follows: topical CSFs, CSFs as immunotherapy or vaccine adjuvant, perioperative CSFs, CSFs in allogeneic donors, CSFs for the prevention of mucositis, and granulocyte transfusion. Also excluded were studies in which the treatment arms received different anticancer drugs.

Outcomes of interest varied by clinical question and included neutropenia- and infection-related outcomes, progression-free and overall survival (OS), and outcomes related to stem-cell mobilization or transplantation.

The guideline recommendations were crafted, in part, using GLIDES (Guidelines Into Decision Support) methodology. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation. Detailed information about the methods used to develop this guideline update is available in the Methodology Supplement at www.asco.org/guidelines/wbcgf, which includes an overview (eg, Update Committee composition, development process, and revision dates), literature search and data extraction information, the recommendation development process, and a quality assessment.

The ASCO Committee and guidelines staff will work with co-chairs to monitor the medical literature and determine the need for future updates. This is the most recent information as of the publication date. For updates, the most recent information, and to submit new evidence, please visit www.asco.org/guidelines/wbcgf and the ASCO Guidelines Wiki (www.asco.org/guidelineswiki).

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with the ASCO Conflict of Interest Management Procedures for Clinical Practice Guidelines (summarized at www.asco.org/rwc). Members of the panel completed the ASCO disclosure form, which requires disclosure of financial and other interests relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include Employment; Leadership; Stock or Other Ownership; Honoraria, Consulting or Advisory Role; Speaker's Bureau; Research Funding; Patents, Royalties, Other Intellectual Property; Expert Testimony; Travel, Accommodations, Expenses; and Other Relationships. In accordance with these procedures, the majority of the members of the panel did not disclose any such relationships.

RESULTS

Characteristics of Studies Identified in the Literature Search

A total of 66 publications met eligibility criteria and form the evidentiary basis for the guideline recommendations. Evidence tables for each clinical question are provided in Data Supplement 1. Forty-one of the publications were RCTs, a majority of which were classified as having either a low or intermediate risk of bias. These classifications are provided in Data Supplement 2.

CLINICAL QUESTION 1

In adults treated with chemotherapy for a solid tumor or lymphoma, what factors should clinicians consider when selecting patients for primary prophylaxis of febrile neutropenia with a CSF?

Recommendation 1

Primary prophylaxis with a CSF starting in 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 on the basis of patient-, disease-, and treatment-related factors. Primary CSF prophylaxis should also be administered 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.)

Literature Review Update and Analysis

Of the 16 publications that addressed primary prophylaxis (eight meta-analyses, three clinical practice guidelines, three RCTs, and two systematic reviews), none prompted a change in the level of febrile neutropenia risk warranting primary prophylaxis with a CSF.[6-21] The 20% cutoff for febrile neutropenia risk has been maintained from the 2005 guideline based on the evidence from randomized trials, especially the trial of CSFs in patients with breast cancer,[22] in which the baseline risk for febrile neutropenia was 17%. Independent systematic reviews of eight trials with 2,156 patients with breast cancer confirmed that CSFs reduce the risk of febrile neutropenia, with possible reductions in the need for hospitalization and all-cause mortality, but with no effect on infection-related mortality.[18] Subsequent studies have shown that CSFs can reduce the risk of hospitalization for febrile neutropenia in elderly patients (age > 65 years) with solid tumors from 9% in all cycles to 5%,[7] but no other differences, such as in mortality, have been reported to justify treating a large number of patients who would not benefit and would experience potential toxicities and costs.

However, recent publications have provided additional information about the likely benefits of primary prophylaxis. Meta-analyses of RCTs conducted in varying patient populations have confirmed that primary prophylaxis with a CSF reduces the risk of febrile neutropenia during chemotherapy for a solid tumor or lymphoma.[8,9,12,13,18,19] Primary prophylaxis may also reduce the risk of hospitalization[18] and infection.[8,19] Results for all-cause or infection-related mortality are less consistent. A meta-analysis of 59 RCTs among patients with solid tumors or lymphoma reported that primary prophylaxis with a G-CSF was associated with a modest reduction in all-cause mortality compared with no primary prophylaxis (risk ratio [RR], 0.93; 95% CI, 0.90 to 0.96; absolute risk difference, −3.2%; 95% CI, −2.1% to −4.2%).[14] The greatest benefit was observed among patients who received dose-dense chemotherapy. In studies that evaluated the same dose and schedule of chemotherapy in different treatment arms, primary prophylaxis did not have a statistically significant effect on mortality.[14] Another large meta-analysis considered 148 RCTs of primary prophylaxis in children or adults who were receiving cancer chemotherapy or undergoing stem-cell transplantation (SCT).[19] Only RCTs

in which all study arms received the same chemotherapy or SCT conditioning regimen were included. On the basis of the 80 trials with all-cause mortality results, short-term all-cause mortality was 7.6% with primary prophylaxis and 8.0% without primary prophylaxis (RR, 0.95; 95% CI, 0.84 to 1.08). Results for infection-related mortality were also null (RR, 0.82; 95% CI, 0.66 to 1.02).[19] In contrast, the addition of a G-CSF was associated with a statistically significant reduction in infection-related mortality in a 2011 meta-analysis of 12 RCTs in adults with a solid tumor or lymphoma; risk was 1.5% among patients who received primary prophylaxis with a CSF, compared with 2.8% among patients who did not receive primary prophylaxis (RR, 0.55; 95% CI, 0.34 to 0.90).[12]

Adverse effects of CSFs include bone pain, but a randomized trial of naproxen versus placebo suggested that nonsteroidal anti-inflammatory drugs may reduce the incidence, duration, and severity of bone pain among CSF-treated patients.[11] Naproxen was administered at a dose of 500 mg twice per day starting on the day of pegfilgrastim administration and continuing for 5 to 8 days.

Clinical Interpretation

In addition to the risk of neutropenic complications associated with chemotherapy regimens in patients who are eligible for clinical trials, the risk and consequences of neutropenic complications may be increased in the elderly, those previously treated with chemotherapy or radiation therapy, and those with medical comorbidities (Table 1). Primary CSF prophylaxis has been consistently associated with significant reductions in the risk of febrile neutropenia and infectious complications and also enables delivery of full-dose chemotherapy on schedule when considered important in patient management.[14] Findings regarding infection-related and all-cause mortality have been less consistent. The ASCO Panel looks forward to reviewing validated and tested, user-friendly risk prediction tools when they are available, but at present, none can be fully recommended.

CLINICAL QUESTION 2

Among adults treated with chemotherapy for a solid tumor or lymphoma, what factors should clinicians use to select patients for secondary prophylaxis of febrile neutropenia with a CSF?

Table 1. Patient Risk Factors for Febrile Neutropenia
Risk Factor
In addition to chemotherapy regimen and type of malignancy, consider the following factors when estimating patient's overall risk of febrile neutropenia[23-25]:
Age ≥ 65 years
Advanced disease
Previous chemotherapy or radiation therapy
Preexisting neutropenia or bone marrow involvement with tumor
Infection
Open wounds or recent surgery
Poor performance status or poor nutritional status
Poor renal function
Liver dysfunction, most notably elevated bilirubin
Cardiovascular disease
Multiple comorbid conditions
HIV infection

Recommendation 2

Secondary prophylaxis with CSFs is recommended for patients who experienced a neutropenic complication from a previous cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose or treatment delay may compromise disease-free or OS 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.)

Literature Review Update and Analysis

The systematic review provided no new data. In particular, there were no new data supporting the use of CSFs to maintain dose-intensity in the treatment of metastatic disease, and the review found no demonstrable benefit in patients with metastatic lung, small-cell lung, colorectal, hormone-refractory prostate, or breast cancer.[26] To date, there have been no improvements in disease-free or OS reported for any common cancer with the use of CSFs to maintain dose-intensity, instead of dose reduction. The ASCO Panel recognizes that there may be individual patients who will not tolerate effective doses of chemotherapy without CSFs, as noted in the Guideline Disclaimer section.

Clinical Interpretation

No changes have been made to the 2006 recommendations.

CLINICAL QUESTION 3

Are there circumstances in which CSFs should be considered for the treatment of neutropenia in adults with cancer?

Recommendation 3.1

Therapy for patients with afebrile neutropenia. 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.)

Recommendation 3.2

Therapy for febrile patients with neutropenia. 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. High-risk features include expected prolonged (> 10 days) and profound ($< 0.1 \times 10^9$/L) neutropenia, age > 65 years, uncontrolled primary disease, pneumonia, hypotension and multiorgan dysfunction (sepsis syndrome), invasive fungal infection, or hospitalization at the time of fever development. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

Literature Review Update and Analysis

New data regarding therapeutic use of CSFs were provided by a single 2014 meta-analysis.[27] Treatment of febrile neutropenia with antibiotics plus a CSF did not reduce overall mortality compared with antibiotics alone (hazard ratio [HR], 0.74; 95% CI, 0.47 to 1.16).[27] However, the addition of a CSF did shorten the duration of neutropenia, fever, and antibiotic use and reduce the number of hospital stays > 10 days.

Table 2. Patient Risk Factors for Poor Clinical Outcomes Resulting From Febrile Neutropenia or Infection[28]

Risk Factor
Sepsis syndrome
Age > 65 years
Profound neutropenia (absolute neutrophil count < 0.1 × 10⁹/L)
Neutropenia expected to last > 10 days
Pneumonia
Invasive fungal infection
Other clinically documented infections
Hospitalization at time of fever
Prior episode of febrile neutropenia

Clinical Interpretation

No changes have been made to the 2006 recommendations. Table 2 lists factors associated with poor clinical outcomes or complications resulting from febrile neutropenia or infection.[28]

CLINICAL QUESTION 4

In what settings should CSFs be used to increase chemotherapy dose density?

Recommendation 4

Dose-dense regimens with CSF support should only be used within an appropriately designed clinical trial or if supported by convincing efficacy data. Efficacy data support the use of CSFs with dose-dense chemotherapy in the adjuvant treatment of high-risk breast cancer and with high–dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (HD-M-VAC) in urothelial cancer. There are limited and conflicting data on the value of dose-dense regimens with CSF support in non-Hodgkin lymphoma (NHL), and this 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.)

Literature Review Update and Analysis

Twenty publications were identified (16 RCTs, two meta-analyses, one clinical practice guideline, and one single-arm phase II trial).[14,16,29-46] In nonmetastatic breast cancer, a 2010 meta-analysis reported that dose-dense chemotherapy (administered with CSFs) improves disease-free and OS, particularly among women with hormone receptor–negative disease.[30] A benefit was observed in three trials of so-called conserved dose-dense chemotherapy (similar doses of drugs in two treatment arms; HR, 0.84; 95% CI, 0.72 to 0.98) and in six trials of so-called modified dose-dense chemotherapy (different drugs or doses in two arms; HR, 0.85; 95% CI, 0.75 to 0.96). A survival benefit of dose-dense chemotherapy was also observed in a phase III clinical trial among women with $\geq$ four positive lymph nodes.[41] Compared with conventionally scheduled epirubicin and cyclophosphamide followed by paclitaxel every 3 weeks, an intense dose-dense schedule of sequential epirubicin, paclitaxel, and cyclophosphamide every 2 weeks increased the toxicity of treatment but improved event-free and OS (OS: HR, 0.76; 95% CI, 0.59 to 0.97). More recently,

doxorubicin plus cyclophosphamide every 2 weeks followed by paclitaxel every 2 weeks was compared with continuous doxorubicin plus cyclophosphamide and/or weekly paclitaxel in the phase III SWOG (Southwest Oncology Group) S0221 trial. Disease-free survival was similar across treatment arms, but OS was highest with dosing every 2 weeks.[31] However, not all studies have reported a benefit of dose-dense chemotherapy in nonmetastatic breast cancer. Dose-dense sequential epirubicin and paclitaxel followed by intensified CMF treatment did not improve disease-free or OS compared with concomitant epirubicin and paclitaxel followed by intensified CMF treatment[37]; dose-intense neoadjuvant fluorouracil, doxorubicin, and cyclophosphamide did not improve pathologic complete response rate compared with conventional neoadjuvant fluorouracil, doxorubicin, and cyclophosphamide[29]; and neoadjuvant weekly doxorubicin and daily oral cyclophosphamide did not improve survival or pathologic complete response rate compared with standard neoadjuvant doxorubicin and cyclophosphamide.[35]

Among patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL), two phase III clinical trials reported that a CSF-supported 14-day cycle of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone (R-CHOP-14) was not more effective than the standard 21-day cycle (R-CHOP-21). In a UK study of patients age ≥ 18 years, 2-year OS was 82.7% in the R-CHOP-14 group and 80.8% in the R-CHOP-21 group (HR, 0.90; 95% CI, 0.70 to 1.15).[33] Similarly, in a multinational study of older patients (age 60 to 80 years) with DLBCL, 3-year OS was 69% in the R-CHOP-14 group and 72% in the R-CHOP-21 group (HR, 0.96; 95% CI, 0.73 to 1.26).[34] R-CHOP-14 also failed to improve progression-free or OS in a phase II/III trial of patients with untreated indolent B-cell NHL.[46]

A single phase III study assessed dose-intensified chemotherapy in lung cancer. Among patients with extensive-stage small-cell lung cancer, dose-intensified carboplatin plus etoposide every 21 days did not improve OS or progression-free survival compared with conventional carboplatin plus etoposide every 28 days.[38] Dose-dense or dose-intense therapy supported by G-CSFs also failed to improve OS or progression-free survival in studies of metastatic and locally advanced soft tissue sarcoma (standard *v* dose-intensified doxorubicin, ifosfamide, and dacarbazine),[38] high-grade osteosarcoma (3- *v* 2-week cycles of cisplatin and doxorubicin),[40] and advanced ovarian cancer (standard *v* intensified cyclophosphamide combined with epirubicin and cisplatin).[42]

Promising results with higher dose density or dose-intensity were reported in urothelial cancer. In a 7-year update of a phase III clinical trial, HD-M-VAC improved OS and progression-free survival among patients with advanced urothelial tract tumors. Median and 5-year OS were 15.1 months and 21.8% in the HD-M-VAC arm, compared with 14.9 months and 13.5% in the M-VAC arm (HR, 0.76; 95% CI, 0.58 to 0.99).[43] In a more recent single-arm phase II trial, neoadjuvant dose-dense M-VAC resulted in significant downstaging among patients with muscle-invasive urothelial cancer.[32]

Clinical Interpretation

There are now several trials that support the use of CSFs in the setting of adjuvant dose-dense chemotherapy for high-risk breast cancer and one large study supporting CSF use with HD-M-VAC in urothelial cancer. Outside of a clinical trial, CSF-supported dose-dense chemotherapy should be restricted to these settings. Trials of dose-dense chemotherapy in lymphoma, lung cancer, ovarian cancer, osteosarcoma, and sarcoma have been negative.

CLINICAL QUESTION 5

What is the role of CSFs as adjuncts to progenitor-cell transplantation?

Recommendation 5.1

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: strong. Strength of recommendation: high.)

Literature Review Update and Analysis

Plerixafor, a CXCR4 receptor antagonist approved by the US Food and Drug Administration in 2008, is administered in combination with a G-CSF for the mobilization of stem cells for autologous transplantation in patients with NHL and multiple myeloma. The combination of a G-CSF and plerixafor has been evaluated in two phase III clinical trials.[47,48] Compared with a G-CSF alone, the combination of a G-CSF and plerixafor increased the number of patients who reached optimal CD34+ cell targets within a specified number of apheresis days. The most common adverse events related to plerixafor were GI disorders and injection site reactions.

Clinical Interpretation

The updated recommendation adds the option of a CSF in combination with plerixafor for the mobilization of peripheral-blood progenitor cells.

Recommendation 5.2

CSFs should be administered after autologous SCT to reduce the duration of severe neutropenia. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

Recommendation 5.3

CSFs may be administered after allogeneic SCT to reduce the duration of severe neutropenia. (Type: evidence based. Evidence quality: low. Strength of recommendation: weak.)

Literature Review Update and Analysis

Concerns about use of CSFs after allogeneic transplantation were raised by retrospective studies that reported an increased risk of acute graft-versus-host disease (GVHD) or treatment-related mortality among CSF recipients.[49-51] However, a 2006 meta-analysis of RCTs found that CSF use after allogeneic SCT reduced the risk of documented infections and did not have a statistically significant effect on grade 2 to 4 acute GVHD or treatment-related mortality.[52] In the combined group of autologous and allogeneic transplantation recipients, CSF use reduced duration of hospitalization, days of parenteral antibiotics, and risk of documented infection, although the association with documented infection was of borderline statistical significance ($P = .05$). CSFs did not reduce the risk of infection-related mortality.

Clinical Interpretation

The updated recommendation adds the option of administering CSFs after allogeneic transplantation. Studies published since the 2006 recommendation have not confirmed previous reports of increased risk of grade 2 to 4 GVHD or mortality in association with CSF use after allogeneic transplantation. Data are limited, however, and benefits of CSF use in this setting seem to be modest. A strong recommendation regarding CSF use after allogeneic transplantation was not possible at this time.

CLINICAL QUESTION 6

What is the role of CSFs in the setting of acute leukemia or myelodysplastic syndromes?

Recommendation 6

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

CLINICAL QUESTION 7

Should CSFs be avoided in patients receiving concomitant chemotherapy and radiation therapy?

Recommendation 7

CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, therapeutic use of CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected. (Type: evidence based. Evidence quality: high. Strength of recommendation: strong.)

Literature Review Update and Analysis

There were no new data.

Clinical Interpretation

No changes have been made to the 2006 recommendations.

CLINICAL QUESTION 8

Are there CSF recommendations that apply specifically to older adults and that differ from recommendations in younger adults?

Recommendation 8

Prophylactic CSFs for patients with diffuse aggressive lymphoma age ≥ 65 years treated with curative chemotherapy (CHOP-R) should be considered, particularly in the presence of comorbidities. (Type: evidence based, benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate.)

Literature Review Update and Analysis

A single RCT evaluated the efficacy of primary prophylaxis among older patients. The trial enrolled patients age ≥ 65 years with performance status of 0 to 2 and either a solid tumor or NHL.[7] Patients received either pegfilgrastim starting with cycle one for all cycles or pegfilgrastim initiated after cycle one at the physician's discretion. Pegfilgrastim administered during all cycles reduced the risk of febrile neutropenia. Among patients with a solid tumor, the risk of febrile neutropenia across all cycles was 10% in the physician-discretion arm and 4% in the arm receiving pegfilgrastim in all cycles ($P = .001$).

Given the low risk of febrile neutropenia in this group, most would not have qualified for CSFs outside of the clinical trial. For these patients at low risk of febrile neutropenia, CSFs should not be routinely prescribed. However, among patients with NHL, risk of febrile neutropenia across all cycles was 37% in the physician-discretion arm and 15% in the arm receiving pegfilgrastim in all cycles ($P = .004$), justifying the use of a CSF as primary prophylaxis to prevent febrile neutropenia and hospitalization. However, the use of pegfilgrastim in all cycles did not result in fewer chemotherapy dose reductions or delays.

Clinical Interpretation

The study by Balducci et al[7] provides support for the administration of pegfilgrastim in patients age ≥ 65 years who have a high enough risk of febrile neutropenia to justify CSF use, such as those with lymphoma. Whether patients would achieve as good or better results with prophylactic antibiotics is uncertain.[53-55]

CLINICAL QUESTION 9

How should CSFs be used in the pediatric population?

Recommendation 9.1

The use of CSFs in pediatric patients will almost always be guided by clinical protocols. As in adults, a CSF is reasonable as the primary prophylaxis for pediatric patients with a high likelihood of febrile neutropenia. Similarly, a CSF as secondary prophylaxis or therapy should be limited to high-risk patients. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

Literature Review Update and Analysis

A single meta-analysis evaluated the efficacy of prophylactic G-CSFs among children with a range of tumor types.[56] Prophylactic G-CSFs reduced the incidence of febrile neutropenia and the duration of severe neutropenia, hospitalization, and antibiotic use among children treated with myelosuppressive chemotherapy. However, prophylactic G-CSFs did not decrease documented infections.

Clinical Interpretation

The 2006 study continues to be the benchmark for children receiving myelosuppressive chemotherapy. Although there were no differences in the rates of infection on the basis of CSF use, many pediatric regimens and pediatric clinical trials depend on rapid count recovery to allow for intensive treatment. For such regimens and such trials, CSFs should still be used if appropriate.

Recommendation 9.2

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.)

Literature Review Update and Analysis

Chemotherapy intensification through interval compression was evaluated in an RCT of patients age < 50 years with newly diagnosed, localized Ewing sarcoma.[57] Chemotherapy consisted of alternating cycles of vincristine, doxorubicin, and cyclophosphamide and of ifosfamide plus etoposide administered every 21 or 14 days. All patients

received filgrastim. Primary tumor treatment was provided after four cycles in the standard arm and after six cycles in the intensified arm. Intensified treatment improved event-free survival; 5-year event-free survival was 73% in the intensified arm and 65% in the standard arm ($P = .048$). OS was also higher in the intensified arm, although this result was of borderline statistical significance; 5-year OS was 83% in the intensified arm and 77% in the standard arm ($P = .056$). Toxicity was similar in the two groups.

Clinical Interpretation

In North America, as a result of these findings, the current standard of care for pediatric patients with Ewing sarcoma outside of a clinical trial is myelosuppressive chemotherapy every 2 weeks when tolerated. This is not feasible without CSF support.

Recommendation 9.3

CSFs should not be used in pediatric patients with nonrelapsed acute lymphoblastic leukemia (ALL) or nonrelapsed acute myeloid leukemia (AML) who do not have an infection. (Type: informal consensus. Evidence quality: intermediate. Strength of recommendation: moderate.)

Literature Review Update and Analysis

Evidence regarding the effects of prophylactic G-CSFs in pediatric ALL or AML is limited, but a 2007 randomized trial reported few benefits with prophylactic G-CSFs after induction therapy for de novo pediatric AML. G-CSFs shortened the duration of neutropenia but did not decrease the risk of febrile neutropenia, microbiologically documented infections, or infection-related mortality.[58] In the intent-to-treat analysis, 5-year event-free survival was 58% with G-CSFs and 59% without G-CSFs ($P = .66$).

Clinical Interpretation

The previous ASCO guideline noted that use of CSFs in children with ALL should be considered with caution. There is little new evidence for or against the use of CSFs in ALL, although we can extrapolate from the AML experience. There is a theoretic concern that CSF use could stimulate the growth of leukemic blasts or leukemic stem cells, particularly in AML, and increase resistance to therapy and disease progression or relapse in both ALL and AML. The 2007 study[58] did not demonstrate an increased risk of relapse with CSF use among pediatric patients with AML, but exclusion criteria limit the generalizability of these results. Furthermore, CSF use did not decrease the risk for infectious complications. The routine use of CSF cannot be recommended for children with de novo AML and, by extension, for children with ALL.

CLINICAL QUESTION 10

What are recommendations for the initiation, duration, dosing, and administration of CSFs?

Recommendations

Recommendations for the administration of filgrastim, tbo-filgrastim, filgrastim-sndz, pegfilgrastim, and sargramostim are summarized in Table 3.

Literature Review Update and Analysis

Recent randomized trials have addressed issues related to the duration and timing of G-CSF prophylaxis. The importance of continuing prophylaxis through all cycles of chemotherapy was assessed among women with breast cancer. Women who received pegfilgrastim prophylaxis during only the first two cycles of chemotherapy were more likely to develop febrile neutropenia than women who received pegfilgrastim prophylaxis during all six cycles of chemotherapy (36% v 10%, respectively).[59] The timing of pegfilgrastim (same day as chemotherapy v next day) was evaluated in randomized phase II trials of patients with breast cancer and lymphoma. Same-day pegfilgrastim resulted in a longer but statistically noninferior duration of severe neutropenia compared with next-day pegfilgrastim.[60] Administration of pegfilgrastim on day 2 versus day 4 was evaluated in a small trial

Agent	Dosing and Administration
Filgrastim	Filgrastim should be started 1 to 3 days after administration of myelotoxic chemotherapy; in setting of high-dose therapy and autologous stem-cell rescue, filgrastim can be started 1 to 5 days after administration of high-dose therapy; filgrastim should be continued until reaching ANC $\geq$ 2 to 3×10^9/L; for PBPC mobilization, filgrastim should be started $\geq$ 4 days before first leukapheresis procedure and continued until last leukapheresis
	In adults, recommended filgrastim dose is 5 μg/kg per day for all clinical settings other than PBPC mobilization; in setting of PBPC mobilization, dose of 10 μg/kg per day may be preferable; preferred route of filgrastim administration is subcutaneous
Filgrastim-sndz	Same as for filgrastim
Tbo-filgrastim	Tbo-filgrastim should be started 1 to 3 days after administration of myelotoxic chemotherapy; in adults, recommended tbo-filgrastim dose is 5 μg/kg per day; preferred route of tbo-filgrastim administration is subcutaneous
Pegfilgrastim	Pegfilgrastim 6 mg should be administered once 1 to 3 days after chemotherapy if possible; because some patients will not be able to return for dose of pegfilgrastim because of distance or immobility, for instance, alternatives to consider may include self-administered filgrastim or tbo-filgrastim or same-day pegfilgrastim, recognizing that although same-day pegfilgrastim is not as effective as later pegfilgrastim, it is better than no pegfilgrastim; pegfilgrastim is also available in a timed automated-inject device that delivers 6 mg of pegfilgrastim subcutaneously, 27 hours after it is placed on skin and activated; pegfilgrastim is not currently indicated for stem-cell mobilization; 6-mg formulation should not be used in infants, children, or small adolescents who weigh < 45 kg
Sargramostim	Because GM-CSFs have been licensed specifically for use in mobilization and after transplantation of autologous PBPCs, after autologous or allogeneic bone marrow transplantation, and for AML, manufacturer's instructions for administration are limited to those clinical settings; GM-CSFs should be initiated on day of bone marrow infusion and not < 24 hours after last chemotherapy and 12 hours after most recent radiotherapy; GM-CSFs should be continued until ANC > 1.5×10^9/L for 3 consecutive days is achieved; drug should be discontinued early or dose reduced by 50% if ANC increases to > 20×10^9/L; recommended dose for adults is 250 μg/m^2 per day

Table 3. Dosing and Administration of CSFs

Abbreviations: AML, acute myeloid leukemia; ANC, absolute neutrophil count; CSF, colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; PBPC, peripheral-blood progenitor cell.

of older patients with aggressive NHL[61] and a larger trial of women with node-positive breast cancer.[62] Although the NHL trial suggested that day-4 pegfilgrastim may reduce the incidence of severe leukocytopenias, the breast cancer trial reported that day-2 and day-4 pegfilgrastim produced similar rates of febrile neutropenia, infection, and grade 4 leukopenia.

Clinical Interpretation

The recommendation for pegfilgrastim administration includes off-label use (administration of pegfilgrastim on same day as chemotherapy in certain circumstances). Evidence suggests that pegfilgrastim administered 1 to 3 days after chemotherapy results in a lower risk of infection than pegfilgrastim administered on the same day as chemotherapy,[60] but clinicians should not be prohibited from using same-day pegfilgrastim if it provides the only feasible means of CSF administration for certain patients.

CLINICAL QUESTION 11

Do CSFs differ in efficacy?

Recommendation 11

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 clinical situation. There have been no additional data comparing G-CSF and GM-CSF since the 2006 update; therefore, there has been no change in the recommendation regarding their therapeutic equivalency. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

Literature Review Update and Analysis

In a 2011 meta-analysis of primary G-CSFs in adults undergoing chemotherapy for a solid tumor or lymphoma, filgrastim, pegfilgrastim, and lenograstim (which is not currently available in United States) each significantly reduced the risk of febrile neutropenia.[9] A comparison of pegfilgrastim and filgrastim was based on five clinical trials and suggested that pegfilgrastim was more effective than filgrastim at reducing the risk of febrile neutropenia (RR, 0.66; 95% CI, 0.44 to 0.98).[9] A number of small RCTs comparing pegfilgrastim and filgrastim have also been conducted in other patient populations, including pediatric patients[63,64] and adults who have undergone autologous SCT.[65-67] A statistically significant benefit of pegfilgrastim over filgrastim in the incidence of febrile neutropenia was reported after a study of patients with multiple myeloma who had undergone autologous peripheral-blood SCT, but the sample size and the differing timing of G-CSF administration limit the conclusions that can be drawn from this study; pegfilgrastim was started on day 1 after stem-cell infusion, and filgrastim was started on day 5 after stem-cell infusion.[67]

Tbo-filgrastim, a nonglycosylated recombinant methionyl human granulocyte colony-stimulating growth factor, was approved by the US Food and Drug Administration in 2012 for reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia. RCTs conducted in patients with breast cancer, lung cancer, and NHL have suggested that the safety and efficacy of tbo-filgrastim are similar to those of

filgrastim.[68-71] In a meta-analysis of the three trials, the adjusted difference in the rate of first-cycle febrile neutropenia between tbo-filgrastim and filgrastim was 1.7% (95% CI, −3.8% to 7.1%), again demonstrating no statistically significant difference between the two drugs for this outcome.[71]

Filgrastim-sndz, approved in March 2015, was the first biosimilar product approved in the United States. Approval was based on structural and functional characterization, animal data, human pharmacokinetic and pharmacodynamic data, clinical immunogenicity data, and other clinical safety and effectiveness data. Filgrastim and filgrastim-sndz were compared in a phase III noninferiority trial. Full results from the trial had not been published at the time the ASCO guideline was submitted for publication. However, an abstract was published as part of the 56th Annual Meeting of the American Society of Hematology (online publication only).[72] The study enrolled women who were eligible for neoadjuvant or adjuvant docetaxel, doxorubicin, and cyclophosphamide chemotherapy for breast cancer. Study participants were randomly assigned to one of four groups: filgrastim-sndz in all cycles; filgrastim-sndz in cycle one, then alternating filgrastim and filgrastim-sndz in subsequent cycles; filgrastim in cycle one, then alternating filgrastim-sndz and filgrastim in subsequent cycles; or filgrastim in all cycles. Filgrastim-sndz was noninferior to filgrastim with respect to duration of severe neutropenia after cycle one chemotherapy. Switching between the two drugs did not seem to affect efficacy or safety.

Clinical Interpretation

Filgrastim, tbo-filgrastim, filgrastim-sndz, and pegfilgrastim are all effective in the reduction of the risk of febrile neutropenia. Choice of agent will depend on factors such as convenience and cost and may in some cases be dictated by the patient's treatment plan (eg, weekly chemotherapy).

CLINICAL QUESTION 12

What is the role of CSFs in the treatment of radiation injury?

Recommendation 12

Current recommendations for the management of patients exposed to lethal doses of total-body radiotherapy, but not doses high enough to lead to certain death as a result of injury to other organs, include the prompt administration of CSFs or pegylated G-CSFs.[73-75] (Type: formal consensus [by others], benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate.)

Literature Review Update and Analysis

This question has not been addressed by placebo-controlled trials in humans and, because of ethical considerations, is unlikely to be addressed. An expert panel convened by the WHO in 2009 considered data from animal experiments, case series and case reports, and studies of patients treated with chemotherapy and made a strong consensus recommendation for the administration of GM-CSFs or G-CSFs in the management of hematopoietic syndrome resulting from exposure to ionizing radiation.[73] The panel noted that health care providers "should consider initiating cytokine therapy for exposures of ≥ 2 Gy and/or a significant decrease in the absolute lymphocyte count, or when it is anticipated that neutropenia of less than 0.5×10^9 cells per liter will persist for ≥ 7 days."[73p6] The recommended timing of cytokine initiation was within 24 hours of exposure.

Clinical Interpretation

Accidental or intentional (eg, resulting from terrorist attack or war) total-body radiation leads to probable or certain death resulting from bone marrow failure at doses of 3 to 10 Gy without supportive care, CSFs, and/or bone marrow transplantation.[76-78] Doses below that level are almost always survivable with excellent nursing care; higher doses are lethal because of injury to other organs, such as the GI tract. The chance of mortality from any radiation dose rises with combined injuries to the skin, lungs, and so on.[79]

Hematopoietic growth factors can increase the survival, proliferation, amplification, and differentiation of granulocyte progenitors to produce neutrophils. Although no prospective randomized trials have been carried out to determine the benefit of hematopoietic growth factors in humans exposed to accidental or intentional radiation injury, they have been used in radiation accident victims, and neutrophil recovery seems to have been hastened in 25 of 28 patients (from Radiation Emergency Assistance Center/Training Site registry). In animal models, prompt administration of hematopoietic growth factors after otherwise lethal total-body radiation exposure has dramatically increased survival.[80-85]

PATIENT AND CLINICIAN COMMUNICATION

For adults with a solid tumor or lymphoma who receive chemotherapy regimens that carry a high risk of febrile neutropenia ($\geq 20\%$), primary prophylaxis substantially reduces the risk of a serious treatment complication and is recommended for most patients. However, for many commonly used chemotherapy regimens, the risk of febrile neutropenia is $< 20\%$, and more individualized decisions about CSF use are required. The risk of neutropenic complications and the importance of primary prophylaxis will vary with factors such as age, comorbidity, and other treatment-related considerations. It is important that in addition to understanding the evidence-based benefits and other risks of treatment, patients learn about the risk of febrile neutropenia as part of routine chemotherapy education.

The most common adverse effect of G-CSFs is bone pain, and patients should be encouraged to report this and other adverse effects to their treatment team. Acetaminophen and nonsteroidal anti-inflammatory drugs are common first-line options for the prevention or treatment of G-CSF–related bone pain in adults. Other approaches that may be considered include antihistamines, opioids, and G-CSF dose reduction.[86]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/ethnic minorities disproportionately experience comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[87] Many other patients lack access to care because of their geographic location or distance from appropriate treatment facilities. Analyses of SEER-Medicare data suggest that first-cycle CSF use among women with breast cancer is less common in nonwhites[88] and women of low socioeconomic status[89] and varies substantially by geographic region.[88] Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations regarding the treatment of patients with multiple chronic conditions can be challenging. Patients with multiple chronic conditions are a complex and heterogeneous population and are frequently excluded from clinical trials.

In the case of febrile neutropenia, observational studies have provided important information about the impact of comorbidity. A 2014 systematic review reported that the presence of comorbid conditions increased the risk of febrile neutropenia among patients with cancer treated with chemotherapy.[23] Both the number and types of comorbidities may be important to consider. Among patients with breast, lung, prostate, or colorectal cancer in the SEER-Medicare database, the risk of febrile neutropenia increased with the number of comorbid conditions.[24] Compared with patients with no comorbid conditions, patients with $\geq$ three comorbid conditions had an 81% increased risk of febrile neutropenia. The presence of renal, hepatic, or cardiovascular disease has been associated with febrile neutropenia or febrile neutropenia–related hospitalization in patients with NHL treated with CHOP-based chemotherapy.[90,91] The optimal approach to incorporating comorbidity information in risk prediction tools continues to be explored, but comorbidity remains an important predictor of febrile neutropenia, even after accounting for factors such as cancer type and age.[25]

COST IMPLICATIONS

Although the 2006 Update Committee extensively discussed the cost of CSFs, it recommended CSF use when the febrile neutropenia rate was approximately $\geq 20\%$ based on clinical impact alone, because of the consensus that reduction in febrile neutropenia itself was an important clinical outcome. Since the 2006 update, original data from randomized trials have been limited.

Cost-effectiveness analyses of primary versus secondary prophylaxis with G-CSFs have produced varying results. In a model that considered three different strategies (no primary prophylaxis, 10 days of filgrastim, or one dose of pegfilgrastim) among patients receiving R-CHOP-21 for DLBCL, primary prophylaxis was not cost effective from the perspective of a publicly funded health care system. Costs associated with no primary prophylaxis, filgrastim prophylaxis, and pegfilgrastim prophylaxis were Canadian $7,314, $13,947, and $16,290, respectively.[92] The incremental cost effectiveness for primary prophylaxis with filgrastim versus no primary prophylaxis was Canadian $5,796,000 per quality-adjusted life-year, far outside accepted bounds. In a United Kingdom–based model of cost among patients with breast cancer, the most cost-effective strategy (primary prophylaxis, secondary prophylaxis, or no G-CSFs) depended on patient characteristics and risk of febrile neutropenia. Of the three types of G-CSFs evaluated, pegfilgrastim seemed to be more cost effective than

filgrastim or lenograstim.[93] A cost benefit may be more apparent in the United States, as a result of higher health care costs,[94] but cost effectiveness will vary by factors such as the risk of febrile neutropenia.

Randomized trials have assessed the efficacy of reduced dosages or less frequent administration of prophylactic G-CSFs. A study in the United Kingdom randomly assigned 172 patients with breast cancer to primary prophylaxis with a G-CSF during all six cycles of chemotherapy or during just the first two cycles. Prophylactic G-CSF during only the first two cycles of chemotherapy was cost saving but resulted in a higher rate of febrile neutropenia than a G-CSF during all cycles (36% v 10%, respectively).[95] A reduced dose of lenograstim (50 μg/body) was evaluated in a small cross-over study of patients with NHL in Japan and compared favorably with a 75-μg/body dose of filgrastim.[96] In the absence of more definitive data, the consensus of the 2015 Update Committee is that clinicians should adhere to current product labeling.

There do seem to be opportunities to improve G-CSF use in the community. The overuse of CSFs was one of the 2012 ASCO Choosing Wisely recommendations: "Don't use white cell stimulating factors for primary prevention of febrile neutropenia for patients with less than 20% risk for this complication."[97p3] To reduce CSF use in patients receiving low-risk chemotherapy regimens, Fishman et al[98] instituted real-time peer-to-peer consultation regarding pegfilgrastim use. Among patients receiving low-risk chemotherapy regimens, pegfilgrastim use decreased from 52 units in the fourth quarter of 2009 to 15 units in the third quarter of 2010 (71% decrease) with no adverse consequences.

Although questions remain about the cost effectiveness of G-CSFs in certain settings, the 2015 Update Committee has reiterated the position that G-CSF prophylaxis should be driven by clinical considerations and not by cost. CSF use is recommended when the febrile neutropenia rate is ≥ 20% based on clinical impact alone, because of the consensus that reduction in febrile neutropenia itself is an important clinical outcome. The 2015 Update Committee has recognized, again, that these are expensive agents with the potential for overuse. As stated, when alternative regimens are available that offer equivalent efficacy without the need for CSF support, these alternative regimens should be used.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

ADDITIONAL RESOURCES

More information, including a Data Supplement with additional 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. Patient information is available at www.cancer.net. Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update

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Appendix

Table A1. Update Committee Membership	
Member	Affiliation/Location
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NOTE. American Society of Clinical Oncology staff: Kari Bohlke, ScD.
Abbreviation: PGIN, Practice Guideline Implementation Network.