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Release date: January 10, 2020; Expiration date: January 10, 2021

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Hematopoietic Growth Factors
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Hematopoietic Growth Factors

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/disclosures/guidelinepanellisting.aspx.

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Hematopoietic Growth Factors, Version 1.2020

Featured Updates to the NCCN Guidelines

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ABSTRACT

Management of febrile neutropenia (FN) is an integral part of supportive care for patients undergoing cancer treatment. The NCCN Guidelines for Hematopoietic Growth Factors provide suggestions for appropriate evaluation, risk determination, prophylaxis, and management of FN. These NCCN Guidelines are intended to guide clinicians in the appropriate use of growth factors for select patients undergoing treatment of nonmyeloid malignancies. These NCCN Guidelines Insights highlight important updates to the NCCN Guidelines regarding the incorporation of newly FDA-approved granulocyte-colony stimulating factor biosimilars for the prevention and treatment of FN.

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

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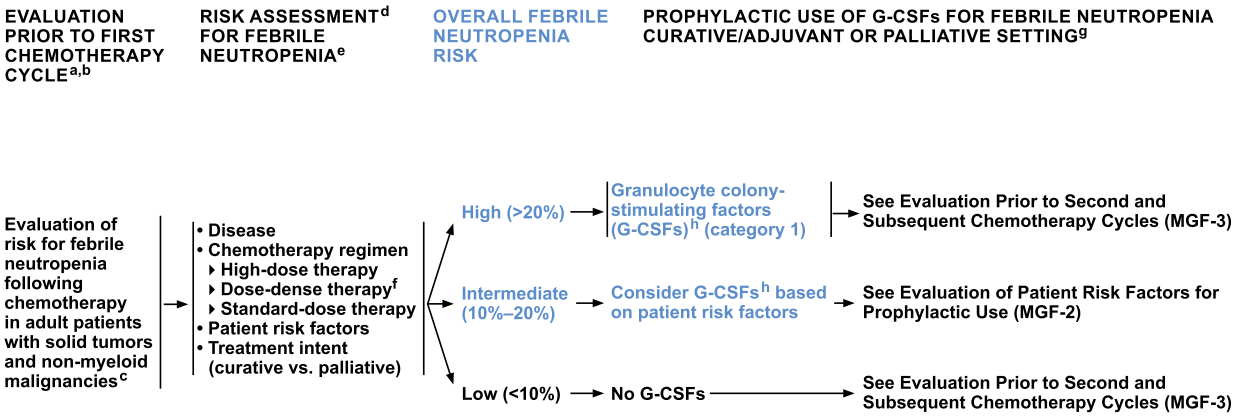


[a]The NCCN Guidelines for Hematopoietic Growth Factors were formulated in reference to adult patients.
[b]Patients receiving cytotoxic chemotherapy as part of a clinical trial may be evaluated for prophylaxis with myeloid growth factor (MGF) as clinically indicated, unless precluded by trial specifications.
[c]For use of growth factors in myelodysplastic syndromes (MDS), see the NCCN Guidelines for Myelodysplastic Syndromes; in acute myeloid leukemia (AML), see the NCCN Guidelines for Acute Myeloid Leukemia; and in chronic myeloid leukemia (CML), see the NCCN Guidelines for Chronic Myeloid Leukemia.
[d]There are many factors that need to be evaluated to determine a patient's risk categorization; these include type of chemotherapy regimen (See MGF-A) and patient risk factors (See MGF-2).
[e]Febrile neutropenia is defined as single temperature: ≥38.3 °C orally or ≥38.0 °C over 1 h; neutropenia: <500 neutrophils/mcL or <1,000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[f]In general, dose-dense regimens require MGF support to maintain dose intensity and schedule.
[g]See Toxicity Risks with Myeloid Growth Factors (MGF-D).
[h]See G-CSFs for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B).

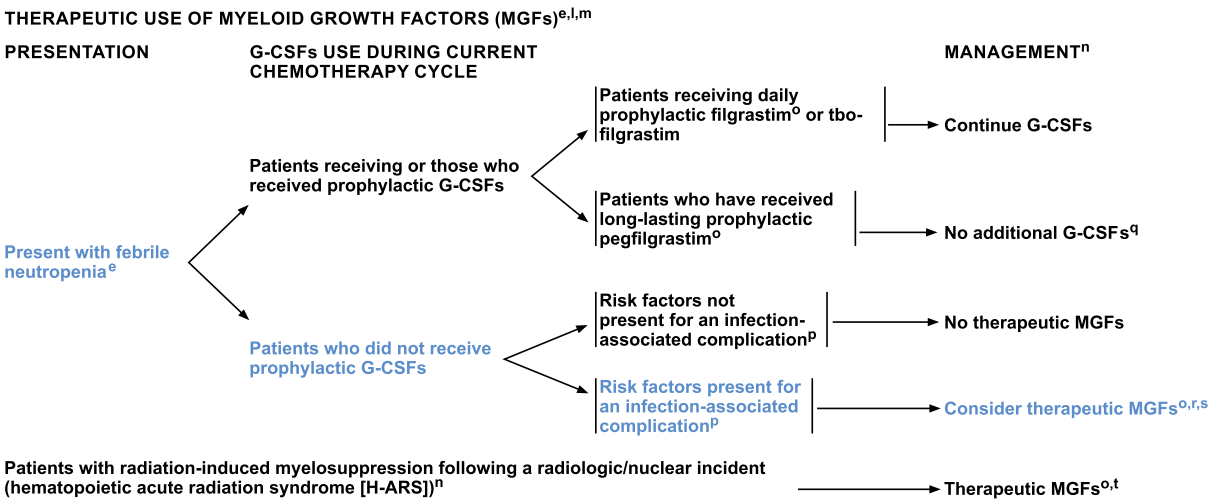
MGF-1

Overview

Myeloid growth factors (MGFs), such as granulocyte colony-stimulating factors (G-CSFs), are hematopoietic growth factors (HGFs) that regulate the growth and differentiation of cells in the myeloid lineage.[1] Pharmacologic G-CSFs, such as filgrastim and pegfilgrastim, are primarily used to reduce the incidence of febrile neutropenia (FN) in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy. FN is a major dose-limiting toxicity of many chemotherapy regimens. Patients who develop FN often require prolonged hospitalizations and treatment with broad-spectrum antibiotics.[2] Development of FN increases treatment costs and can prompt dose reductions or treatment delays, which may compromise clinical outcome.[3] Management and prevention of FN is an integral part of supportive care for many patients undergoing cancer treatment. Unfortunately, biologics such as filgrastim and pegfilgrastim are costly, which has limited their accessibility for many patients.

In 2009, the Biologics Price Competition and Innovation Act established an abbreviated licensure pathway for biosimilars with the goal of reducing expenditure for costly biologic drugs.[4,5] A biosimilar is a biologic product that is highly similar to the FDA-approved originator biologic product, with the exception of minor differences in clinically inactive components and no clinically meaningful differences with respect to efficacy, safety, and purity.[6] The first drug granted FDA approval on the biosimilar pathway was filgrastim-sndz in 2015.[7] The increased need for cost-effective HGFs recently led to the rapid approval of additional biosimilars (Table 1).[8–13]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for HGFs provide recommendations for the evaluation, prevention, and management of FN and cancer- and chemotherapy-induced anemia (CIA). The purposes of these guidelines are to operationalize the evaluation and treatment of FN and CIA in adult patients with cancer, especially those receiving chemotherapy, and enable the patient and clinician to assess management options for FN and CIA in the context of an individual patient's condition, including options for prevention of FN in patients receiving chemotherapy. These NCCN Guidelines Insights highlight important updates to the NCCN Guidelines for HGFs regarding the incorporation of newly FDA-approved biosimilar G-CSFs for the management of



[e]Febrile neutropenia is defined as single temperature: ≥38.3 °C orally or ≥38.0 °C over 1 h; neutropenia: <500 neutrophils/mcL or <1,000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[l]For antibiotic therapy recommendations for fever and neutropenia, see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[m]The decision to use MGFs in the therapeutic setting is controversial. See Discussion for further details.

nFarese AM, MacVittie TJ. Filgrastim for the treatment of hematopoietic acute radiation syndrome. Drugs Today (Barc) 2015;51:537-48.

[o]An FDA-approved biosimilar is an appropriate substitute for filgrastim and pegfilgrastim.

[p]Risk factors/possible indications for therapeutic MGFs include sepsis syndrome, age >65 years, absolute neutrophil count [ANC] <100/mcL, neutropenia expected to be >10 days in duration, pneumonia or other clinically documented infections, invasive fungal infection, hospitalization at the time of fever, and prior episode of febrile neutropenia.

[q]There are no studies that have addressed therapeutic use of filgrastim for febrile neutropenia in patients who have already received prophylactic pegfilgrastim. However, pharmacokinetic data of pegfilgrastim demonstrated high levels during neutropenia and suggest that additional G-CSFs may not be beneficial; however, in patients with prolonged neutropenia additional G-CSFs may be considered.

[r]See Discussion for further details. Pegfilgrastim (or biosimilars) have only been studied for prophylactic use. Filgrastim (or biosimilars), tbo-filgrastim, or sargramostim may be used therapeutically with initial dosing and discontinued at time of neutrophil recovery.

[s]Filgrastim (or biosimilars) or tbo-filgrastim: daily dose of 5 mcg/kg; Sargramostim: used in clinical trials at a dose of 250 mcg/m^2 per day. Continue therapeutic MGFs until post-nadir ANC recovery to normal or near-normal levels by laboratory standards.

[t]Therapeutic options include filgrastim (or biosimilars), tbo-filgrastim, pegfilgrastim (or biosimilars), and sargramostim.

MGF-4

FN. The most recent and complete version of these guidelines is available at NCCN.org.

Biosimilars

FDA approval of biosimilars is based on review of evidence, including analytical studies for structural and functional characterization, animal toxicity studies, and comparative clinical studies assessing immunogenicity, pharmacokinetics, and pharmacodynamics.[14,15] FDA-approved biosimilars have the same amino acid sequence as the parent compound; however, differences may be seen in the 3-dimensional structure, glycosylation sites, isoform profiles, and the level of protein aggregation.[6] Therefore, pharmacokinetic and pharmacodynamic studies are essential in evaluating biologic activity, efficacy, and safety.[5,16] Because biosimilars are supported by limited clinical data at the time of approval, data must be extrapolated to support the use of biosimilars for additional indications of the originator product. Scientific justification is required for extrapolation, including mechanism-of-action studies in each indication, as well as pharmacokinetic, immunogenicity, and toxicity assessments in

Table 1. FDA-Approved Hematopoietic Growth Factor Biosimilars

Biosimilar	FDA Approval Date	Indications
Filgrastim-sndz[8]	March 2015	FN prophylaxis and treatment; mobilization of hematopoietic progenitor cells in the transplant setting
Epoetin alfa-epbx[9]	May 2018	Anemia due to chronic kidney disease, chemotherapy, or treatment with zidovudine in patients with HIV infection; to reduce RBC transfusions in patients undergoing elective, noncardiac, nonvascular surgery
Pegfilgrastim-jmdb[10]	June 2018	FN prophylaxis
Filgrastim-aafi[11]	July 2018	FN prophylaxis and treatment; mobilization of hematopoietic progenitor cells in the transplant setting
Pegfilgrastim-cbqv[12]	November 2018	FN prophylaxis
Pegfilgrastim-bmez[13]	November 2019	FN prophylaxis

Abbreviation: FN, febrile neutropenia.

G-CSFs FOR PROPHYLAXIS OF FEBRILE NEUTROPENIA AND MAINTENANCE OF SCHEDULED DOSE DELIVERY

- **Filgrastim[b] (category 1) or tbo-filgrastim[a] (category 1)**
  - **Daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits) until post-nadir ANC recovery to normal or near-normal levels by laboratory standards.**
  - **Start the next day or up to 3–4 days after completion of myelosuppressive chemotherapy and treat through post-nadir recovery.[c,d]**
- **Pegfilgrastim[b] (category 1)**
  - **One dose of 6 mg**
    - ◊ **Based on clinical trial data, pegfilgrastim[b] should be administered the day after myelosuppressive chemotherapy (category 1).[e]**
    - ◊ **There should be at least 12 days between the dose of pegfilgrastim[b] and the next cycle of chemotherapy.**
    - ◊ **If the treatment cycle includes chemotherapy administration on days 1 and 15, pegfilgrastim[b] may be given after each chemotherapy treatment.**
    - ◊ **For patients who cannot return to the clinic for next-day administration, there is an FDA-approved delivery device available that can be applied the same day as chemotherapy in order to deliver the full dose of pegfilgrastim the following day (approximately 27 hours after application).[f,g]**
    - ◊ **Administration of pegfilgrastim[b] up to 3–4 days after chemotherapy is also reasonable based on trials with filgrastim.**
  - **There is evidence to support use for chemotherapy regimens given every 3 weeks (category 1).**
  - **There are phase II studies that demonstrate efficacy for chemotherapy regimens given every 2 weeks.**
  - **There are insufficient data to support use for cytotoxic chemotherapy regimens administered every week; therefore, pegfilgrastim should not be used.**
- **Subcutaneous route is preferred for all G-CSFs listed above.**
- **For information regarding prophylactic anti-infectives (ie, viral, fungal, bacterial), see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.**

See Toxicity Risks with Myeloid Growth Factors (MGF-D)

[a]Tbo-filgrastim is a human G-CSF approved by the FDA through an original biologic license application. All of these G-CSFs are indicated for reducing the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy associated with a clinically significant incidence of febrile neutropenia.

[b]An FDA-approved biosimilar is an appropriate substitute for filgrastim and pegfilgrastim. See Discussion for more details.

[c]Studies suggest that shorter durations of G-CSFs may be less efficacious. (Weycker D, Li X, Tzivelekis S, et al. Burden of chemotherapy-induced febrile neutropenia hospitalizations in US clinical practice, by use and patterns of prophylaxis with colony-stimulating factor. Support Care Cancer 2017;25:439-447.)

[d]Neutrophil counts should be monitored, as indicated, appropriate to the setting.

[e]Lyman GH, Allcott K, Garcia J, et al. The effectiveness and safety of same-day versus next-day administration of long-acting granulocyte colony-stimulating factors for the prophylaxis of chemotherapy-induced neutropenia: a systematic review. Support Cancer Care 2017;25:2619-2629.

[f]Rarely, there is a failure to inject that requires further medical attention.

[g]Yang BB, Morrow PK, Wu X, et al. Comparison of pharmacokinetics and safety of pegfilgrastim administered by two delivery methods: on-body injector and manual injection with a prefilled syringe. Cancer Chemother Pharmacol 2015;75:1199-1206.

MGF-B

different patient populations.[17] If overall safety and efficacy are equivalent, biosimilars may be approved for the same indications and can be substituted for the originator product.

Switching between the biosimilar and the originator product without the intervention of a healthcare provider is permitted if a biosimilar is designated as interchangeable.[6] Concerns regarding interchangeability include enhanced immunogenicity, compromised safety, and diminished efficacy. Although no biosimilars have been designated as interchangeable by the FDA, limited data suggest that patients can alternate between the biosimilar and the originator biologic without any clinically meaningful differences in efficacy or safety.[18] Another concern is the potential for product drift that may arise during the manufacturing process of biologics and biosimilars, which could result in differences in efficacy and safety over time. Continued postmarketing surveillance of all biologic products is necessary for long-term monitoring of these agents. Healthcare providers should be aware of the FDA's nomenclature for biosimilars (originator biologic name followed by a random 4 letter suffix), which is important for the pharmacovigilance of specific products.

In March 2015, the FDA approved the first biosimilar, filgrastim-sndz, for all indications of the originator filgrastim.[7,8] This approval was based on review of data demonstrating a highly similar protein structure to filgrastim with near-identical pharmacokinetics, pharmacodynamics, and immunogenicity in healthy volunteers and patients with cancer.[8,19–21] Data have shown filgrastim-sndz to have identical mass, size, charge, and hydrophobicity to the originator product.[19] Pharmacokinetic and pharmacodynamic modeling have further confirmed that the mechanism of action is the same and occurs through binding to the G-CSF receptor.[20] Clinical data leading to the approval of filgrastim-sndz were predominately from healthy volunteers and patients with cancer in the context of the prevention of chemotherapy-induced neutropenia. Although a potential concern regarding immunogenicity exists with biosimilars, immunogenicity is anticipated to be low to nonexistent with filgrastim biosimilars based on the lack of immunogenicity seen with the parent filgrastim biologics and the nature of filgrastim as an unglycosylated protein. Filgrastim-sndz was evaluated in limited clinical studies of healthy volunteers and patients with cancer, with the incidence of antibodies binding to filgrastim reaching 3% (11 of

333 patients).[8] Further analysis of these patients showed no evidence of neutralizing antibodies, suggesting that there is no increased risk of immunogenic adverse events or reduction of efficacy.[21] A phase III trial of 218 patients with breast cancer receiving myelosuppressive chemotherapy with TAC (docetaxel/doxorubicin/cyclophosphamide) showed no clinically meaningful differences in efficacy, safety, or immunogenicity between filgrastim and filgrastim-sndz, even in patients who alternated between the 2 in subsequent chemotherapy cycles.[18] A recently published combined analysis of this and another phase III trial on the safety of filgrastim-sndz in patients with breast cancer concluded that filgrastim-sndz has a safety profile consistent with previous studies of reference filgrastim.[22] Several retrospective studies also report similar efficacy between filgrastim-sndz and filgrastim for prophylaxis of chemotherapy-induced neutropenia.[23–26] Based on these data, filgrastim-sndz is included in the NCCN Guidelines as an appropriate substitute for filgrastim.

It should be noted that tbo-filgrastim was approved as an original biologic in the United States, and therefore has a more restricted indication than filgrastim biosimilars.[27] Several studies have demonstrated similar outcomes with the use of tbo-filgrastim compared with filgrastim for the prevention of FN. One trial randomly assigned 348 patients with breast cancer receiving docetaxel/doxorubicin therapy to either tbo-filgrastim, filgrastim, or placebo,[28] and found that tbo-filgrastim was equivalent to filgrastim and superior to placebo in reducing the duration of severe neutropenia and incidence of FN. Two other randomized studies in patients with lung cancer and non-Hodgkin's lymphoma (NHL) receiving chemotherapy also reported similar efficacy and toxicity for tbo-filgrastim and filgrastim.[29,30] A meta-analysis of these 3 trials concluded that tbo-filgrastim was noninferior to filgrastim in reducing the incidence of FN.[31] Studies in healthy subjects demonstrated similar pharmacokinetic and pharmacodynamic profiles.[32,33] Tbo-filgrastim has demonstrated low immunogenicity in patients with cancer receiving chemotherapy, with no evidence showing the development of neutralizing antibodies or immunogenic adverse events.[34]

Based on the new FDA approvals, filgrastim-aafi and pegfilgrastim-jmdb, pegfilgrastim-cbqv and pegfilgrastim-bmez were recently included in the NCCN Guidelines as appropriate substitutions for originator filgrastim and pegfilgrastim, respectively, for prevention of FN. In addition, epoetin alfa-epbx has also been included as an appropriate substitute for epoetin alfa, an erythropoiesis-stimulating agent (ESA), for management of anemia in patients being treated with myelosuppressive chemotherapy. The FDA's approval of these biosimilars was based on review of evidence, including structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamic data, clinical immunogenicity data, and other clinical safety and effectiveness data.

Filgrastim-aafi

In July 2018, the FDA approved a second filgrastim biosimilar, filgrastim-aafi, for the same indications as filgrastim.[11,35] A phase III randomized equivalence study in 279 patients receiving docetaxel/doxorubicin for breast cancer found filgrastim-aafi to be bioequivalent to filgrastim in terms of efficacy and safety, with similar incidence of FN, treatment-related bone pain, and mean time to neutrophil recovery.[36] The prospective, noninterventional, longitudinal VENICE study, which observed the tolerability, safety, and efficacy of filgrastim-aafi in 386 patients receiving chemotherapy, concluded that filgrastim-aafi was effective and well-tolerated in both the primary and secondary prophylactic settings.[37] Most patients (95.6%) experienced no change in chemotherapy dose or schedule due to FN, and fewer than one-third (29.8%) experienced ≥1 treatment-related adverse events. Two other noninterventional studies reached similar conclusions regarding the bioequivalence of filgrastim-aafi to reference filgrastim in both the prophylactic and therapeutic settings.[38,39]

Pegfilgrastim-jmdb, Pegfilgrastim-cbqv, and Pegfilgrastim-bmez

In 2018, the FDA approved the first pegfilgrastim biosimilars, pegfilgrastim-jmdb and pegfilgrastim-cbqv, for the same indications as pegfilgrastim based on data showing highly similar pharmacokinetics, pharmacodynamics, and safety in healthy volunteers.[10,12,40–44] Pegfilgrastim-jmdb has been shown to have high analytical and functional similarity to pegfilgrastim, with similar structure, molecular mass, physicochemical characteristics, and G-CSF receptor binding affinity.[45,46] A phase I randomized equivalence trial concluded that pegfilgrastim-jmdb demonstrated similar pharmacokinetics, pharmacodynamics, and safety to pegfilgrastim in healthy volunteers.[40] In a multicenter randomized phase III efficacy and safety trial, patients with breast cancer receiving myelosuppressive chemotherapy with pegfilgrastim-jmdb support showed no difference in duration of severe neutropenia, time to absolute neutrophil count (ANC) nadir, duration of postnadir recovery, or treatment-related adverse events compared with patients receiving reference pegfilgrastim.[47] Pegfilgrastim-jmdb has also demonstrated low immunogenic potential in healthy volunteers and patients with cancer receiving myelosuppressive chemotherapy.[48] Although data are limited, a multicenter randomized crossover study in 122 healthy volunteers demonstrated that pegfilgrastim-cbqv had a similar safety profile and similar bioequivalent pharmacokinetics and pharmacodynamics to pegfilgrastim.[41,42]

No serious treatment-related adverse events were observed with the use of pegfilgrastim-cbqv.

In late 2019, the FDA approved the third pegfilgrastim biosimilar, pegfilgrastim-bmez, for the same indications as pegfilgrastim.[13,49] Pegfilgrastim-bmez showed similar pharmacokinetics and pharmacodynamics to pegfilgrastim in healthy volunteers, with no clinically meaningful differences in safety, tolerability, or immunogenicity.[50] Two randomized phase III trials (PROTECT-1 and PROTECT-2) demonstrated equivalent efficacy and safety between pegfilgrastim-bmez and pegfilgrastim in patients with breast cancer receiving myelosuppressive chemotherapy.[51,52] In PROTECT-1, patients randomized to receive pegfilgrastim-bmez had equivalent duration of severe neutropenia during cycle 1 of chemotherapy as those receiving pegfilgrastim (difference, 0.07 days; 95% CI: –0.12 to 0.26).[52] This was confirmed in PROTECT-2, which reported a difference in duration of severe neutropenia of 0.16 days (95% CI, –0.40 to 0.08).[51] Pegfilgrastim-bmez also demonstrated highly similar safety and tolerability to pegfilgrastim across both trials, with no significant difference in adverse events reported.[53]

Epoetin alfa-epbx

Cancer-related anemia is prevalent, occurring in 30% to 90% of patients with cancer.[54] In select patients undergoing treatment with myelosuppressive chemotherapy, administration of ESAs such as epoetin alfa, with or without iron supplementation, may improve anemia. In May 2018, the FDA approved the first epoetin alfa biosimilar, epoetin alfa-epbx, for anemia associated with administration of myelosuppressive chemotherapy, chronic kidney disease (CKD), or treatment of HIV, or to prevent the need for RBC transfusions in patients undergoing surgery.[9,55] Analytical studies and clinical pharmacology data from healthy volunteers have shown epoetin alfa-epbx to have highly similar protein structure, stability, pharmacokinetics, and pharmacodynamics to epoetin alfa.[56] Epoetin alfa-epbx was also shown to have similar efficacy, safety, and mechanism of action to epoetin alfa in 2 randomized phase III clinical trials involving patients with anemia secondary to CKD.[56] Additionally, the results of 3 independent studies conducted in patients with CKD and healthy volunteers showed similar rates and titers of antidrug antibodies for both products, indicating there is no clinically meaningful difference in immunogenicity risk for epoetin alfa-epbx as compared with epoetin alfa. Although there are limited data on the efficacy of epoetin alfa-epbx in treating CIA, 2 studies concluded that there were no clinically meaningful differences in efficacy or safety between epoetin alfa-epbx and epoetin alfa in the treatment of anemia in patients with CKD.[57,58] Therefore, the FDA approved extrapolation of epoetin alfa-epbx for the treatment of anemia in patients undergoing treatment with myelosuppressive chemotherapy, as well as all other indications for the originator.[9]

NCCN Recommendations for Management of FN

Prophylactic Use of G-CSFs

Risk of developing FN is related to the chemotherapy regimen, delivered dose intensity, treatment intent, and patient-specific comorbidity factors. Based on the chemotherapy regimen, the patient is assigned to an overall high-risk group (>20% risk of FN), intermediate-risk group (10%–20% risk), or low-risk group (<10% risk). Patients in the high-risk group should receive prophylactic G-CSF (see MGF-1, page 14). This recommendation is based on the results of several large randomized trials that have documented a significant reduction in FN incidence following primary G-CSF prophylaxis when the risk of FN without prophylaxis is >20%.[59,60] In one such example, a randomized, placebo-controlled phase III trial in patients with breast cancer receiving TC (docetaxel/cyclophosphamide) found that the incidence of FN was significantly lower for patients who received prophylactic G-CSF versus placebo (1.2% vs 68.8%, respectively; $P<.001$).[59] Patients in the G-CSF group also had lower rates of hospitalization and antibiotic use. Furthermore, prophylactic use of G-CSFs was associated with a 46% reduction in the relative risk of developing FN in a systematic review of 17 randomized controlled trials involving 3,493 patients with solid tumors or malignant lymphoma receiving systemic chemotherapy.[60]

For patients receiving intermediate-risk chemotherapy regimens, the panel recommends individualized consideration of prophylactic G-CSF use based on the presence of ≥1 patient-specific comorbidity factors, such as age >65 years, prior exposure to chemotherapy or radiotherapy, persistent neutropenia, bone marrow involvement by the tumor, poor performance status, recent surgery and/or open wounds, renal or liver dysfunction, and/or HIV infection.[61,62] Most of these have been confirmed as independent risk factors for the development of neutropenic complications in a risk model developed by Lyman et al[61] that was validated in a study population of 3,760 patients with cancer beginning chemotherapy. This model and its associated risk factors have been retrospectively validated both internally and externally in an independent patient population.[63] When the intent of chemotherapy is palliative, use of G-CSF is a difficult decision and requires careful discussion between the physician and patient. If the increased risk for FN is due to patient-specific risk factors, G-CSF use is reasonable. However, if the risk is due to the chemotherapy regimen, the panel feels that alternatives such as

dose reduction or the use of less myelosuppressive chemotherapy, if of comparable benefit, should be explored. For patients receiving low-risk chemotherapy regimens, routine use of G-CSF prophylaxis is not recommended but may be appropriate if the patient is receiving therapy with curative intent and is at significant patient-specific risk for the development of FN.

Based on review of the evidence and FDA-approvals, the panel decided to include filgrastim-sndz and the newly approved biosimilars filgrastim-aafi and pegfilgrastim-jmdb, pegfilgrastim-cbqv, and pegfilgrastim-bmez as appropriate substitutes for filgrastim/tbo-filgrastim and pegfilgrastim, respectively, for FN prophylaxis (see MGF-B, page 16). All options are category 1 recommendations in this setting. Initial doses of filgrastim, tbo-filgrastim, or filgrastim biosimilars should be administered subcutaneously the next day or up to 3 to 4 days after completion of myelosuppressive chemotherapy in a daily dose of 5 mcg/kg until postnadir ANC recovery to normal or near-normal levels by laboratory standards. The dose may be rounded to the nearest vial size by institution-defined weight limits. The NCCN panel recommends treatment of patients through postnadir recovery, because studies have shown shorter durations of G-CSF treatment to be less efficacious.[64]

Pegfilgrastim, pegfilgrastim-jmdb, pegfilgrastim-cbqv, and pegfilgrastim-bmez are pegylated versions of filgrastim designed to have a longer half-life, which allows for a single administration of 6 mg to be sufficient. Based on clinical trial data, the panel recommends that pegfilgrastim be administered the day following myelosuppressive chemotherapy.[65] The rationale for not giving same-day pegfilgrastim is the potential for exacerbation of neutropenia resulting from stimulation of hematopoietic progenitor cells at the time of cytotoxic chemotherapy active in dividing cells, resulting in loss of the progenitors.[65,66] Based on review of these data, the panel endorsed the next-day administration of pegfilgrastim biosimilars. Administration of pegfilgrastim or pegfilgrastim biosimilars up to 3 to 4 days after myelosuppressive chemotherapy is also reasonable based on trials of filgrastim. In addition, panelists recognized that some institutions have administered pegfilgrastim on the same day as chemotherapy for logistical reasons and to minimize travel burdens on long-distance patients.[67] The recent FDA approval of a delivery device that can be applied the same day as chemotherapy and set to deliver the full dose of pegfilgrastim the following day (approximately 27 hours after application) offers an alternative to same-day administration for patients who cannot return to the clinic for next-day administration of pegfilgrastim.[68] However, this on-body delivery device is currently only available for use with originator pegfilgrastim and not pegfilgrastim biosimilars. The panel also discussed the use of pegfilgrastim and pegfilgrastim biosimilars in chemotherapy regimens of different cycle lengths. In general, there should be at least 12 days between the dose of pegfilgrastim and the next cycle of chemotherapy. If the treatment cycle includes chemotherapy administration on days 1 and 15, pegfilgrastim or a biosimilar may be given after each chemotherapy treatment. Based on phase III clinical trials,[69,70] use of pegfilgrastim for chemotherapy regimens given every 3 weeks is a category 1 recommendation. Pegfilgrastim use is a category 2A recommendation for chemotherapy regimens given every 2 weeks, based on phase II studies.[71–76] Data supporting the use of pegfilgrastim for weekly regimens are insufficient, and therefore pegfilgrastim should not be used. The panel has extended these recommendations to pegfilgrastim biosimilars.

Therapeutic Use of G-CSFs

Compared with prophylactic use, there is less evidence supporting the therapeutic use of G-CSF for FN. Although there are clinical benefits to G-CSF therapy for FN, such as shorter time to neutrophil recovery and shorter length of hospitalization, it remains unclear whether these benefits translate into a survival advantage.[77,78] The NCCN panel recommends that patients presenting with FN who are receiving or have previously received prophylactic filgrastim, tbo-filgrastim, filgrastim-sndz, or filgrastim-aafi should continue G-CSF. However, because pegfilgrastim, pegfilgrastim-jmdb, pegfilgrastim-cbqv, and pegfilgrastim-bmez are long-acting, patients who have received these agents prophylactically should not be treated with additional G-CSF.[79] No studies have addressed the therapeutic use of filgrastim for FN in patients who have already received prophylactic pegfilgrastim or a pegfilgrastim biosimilar. Pharmacokinetic data following treatment with pegfilgrastim demonstrate high levels during neutropenia and suggest that additional G-CSF use may not be beneficial. However, additional G-CSF support may be considered in patients with prolonged neutropenia (beyond 12–14 days), because the pegylated products are unlikely to endure beyond this window.

For patients presenting with FN who have not received prophylactic G-CSF, the panel recommends an evaluation of risk factors for infection-related complications or poor clinical outcome. Features associated with poor outcome include age >65 years, sepsis syndrome, ANC <100 neutrophils/mcL, anticipated prolonged (>10 days) neutropenia, pneumonia or other clinically documented infection, invasive fungal infections, hospitalization at the time of fever, and prior episodes of FN. If risk factors are present, therapeutic G-CSF should be considered. Filgrastim, tbo-filgrastim, filgrastim-sndz, or filgrastim-aafi may be administered

in the therapeutic setting at a daily dose of 5 mcg/kg (see MGF-4, page 15). Treatment should continue through postnadir recovery. Because pegfilgrastim has only been studied for prophylactic use, the panel does not recommend pegfilgrastim-jmdb, pegfilgrastim-cbqv, or pegfilgrastim-bmez for therapeutic use at this time.

Summary

These NCCN Guidelines Insights highlight important recent updates to the NCCN Guidelines for HGFs. The panel recently provided updated recommendations regarding the inclusion of FDA-approved G-CSF biosimilars for the management of FN and other indications, as well as the erythropoietin biosimilar for treatment of anemia. Development and availability of new G-CSF biosimilars for management of FN have increased in recent years. The incorporation of biosimilars into the NCCN Guidelines represents an opportunity to reduce healthcare expenditures while ensuring the receipt of high-quality care for patients with cancer. Because biosimilars are supported by limited clinical data at the time of approval, clinicians must make decisions on the appropriate incorporation of biosimilars into clinical practice while relying on fewer comprehensive studies. Increased education and awareness of the FDA approval process for biosimilars, including enhanced understanding of the evidence required to verify the safety and efficacy of these products, will help ensure the acceptance and use of biosimilars in clinical oncology care.[80]

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References

1. Hauke RJ, Tarantolo SR. Hematopoietic growth factors. Lab Med 2000;31:613–618.
2. Lyman GH, Kuderer NM. Epidemiology of febrile neutropenia. Support Cancer Ther 2003;1:23–35.
3. Lalami Y, Klastersky J. Impact of chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN) on cancer treatment outcomes: an overview about well-established and recently emerging clinical data. Crit Rev Oncol Hematol 2017;120:163–179.
4. U.S. Food & Drug Administration. Implementation of the Biologics Price Competition and Innovation Act of 2009. Available at: https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/ucm215089.htm. Accessed March 18, 2019.
5. Lyman GH, Zon R, Harvey RD, et al. Rationale, opportunities, and reality of biosimilar medications. N Engl J Med 2018;378:2036–2044.
6. U.S. Food & Drug Administration. Biosimilar and Interchangeable Products. Available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580419.htm. Accessed February 28, 2019.
7. Awad M, Singh P, Hilas O. Zarxio (filgrastim-sndz): the first biosimilar approved by the FDA. P&T 2017;42:19–23.
8. U.S. Food & Drug Administration. Filgrastim-sndz label information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125553lbl.pdf. Accessed October 9, 2019.
9. U.S. Food & Drug Administration. Epoetin alfa-epbx label information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125545s000lbl.pdf. Accessed October 9, 2019.
10. U.S. Food & Drug Administration. Pegfilgrastim-jmdb label information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761075s000lbl.pdf. Accessed October 9, 2019.
11. U.S. Food & Drug Administration. Filgrastim-aafi label information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761080s000lbl.pdf. Accessed October 9, 2019.
12. U.S. Food & Drug Administration. Pegfilgrastim-cbqv label information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761039s000lbl.pdf. Accessed October 9, 2019.
13. U.S. Food & Drug Administration. Pegfilgrastim-bmez label information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761045lbl.pdf. Accessed November 8, 2019.
14. U.S. Food & Drug Administration. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Available at: https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf. Accessed April 16, 2019.
15. U.S. Food & Drug Administration. Biosimilar Development, Review, and Approval. Available at: https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval. Accessed April 16, 2019.
16. Kleinberg M, Mosdell KW. Current and future considerations for the new classes of biologicals. Am J Health Syst Pharm 2004;61:695–708.
17. U.S. Food & Drug Administration. FDA Medical Imaging Drugs Advisory Committee and the Oncologic Drugs Advisory Committee Briefing Materials. Tbo-filgrastim. Available at: https://wayback.archive-it.org/7993/20170405222000/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM350157.pdf. Accessed January 18, 2019.
18. Blackwell K, Gascon P, Krendyukov A, et al. Safety and efficacy of alternating treatment with EP2006, a filgrastim biosimilar, and reference filgrastim: a phase III, randomised, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy. Ann Oncol 2018;29:244–249.
19. Sörgel F, Lerch H, Lauber T. Physicochemical and biologic comparability of a biosimilar granulocyte colony-stimulating factor with its reference product. BioDrugs 2010;24:347–357.
20. U.S. Food & Drug Administration. Oncologic Drugs Advisory Committee Meeting. BLA 125553. EP2006, a proposed biosimilar to Neupogen (filgrastim). Available at: https://wayback.archive-it.org/7993/20170405222922/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM428780.pdf. Accessed February 28, 2019.
21. Mellstedt H. Anti-neoplastic biosimilars—the same rules as for cytotoxic generics cannot be applied. Ann Oncol 2013;24(Suppl 5):v23–28.
22. Harbeck N, Gascón P, Krendyukov A, et al. Safety profile of biosimilar filgrastim (Zarzio/Zarxio): a combined analysis of phase III studies. Oncologist 2018;23:403–409.
23. Zecchini J, Yum K, Steinberg A, et al. A single-center, retrospective analysis to compare the efficacy and safety of filgrastim-sndz to filgrastim for prophylaxis of chemotherapy-induced neutropenia and for neutrophil recovery following autologous stem cell transplantation. Support Care Cancer 2018;26:1013–1016.
24. Schwartzberg LS, Lal LS, Balu S, et al. Incidence of febrile neutropenia during chemotherapy among patients with nonmyeloid cancer receiving filgrastim vs a filgrastim biosimilar. Clinicoecon Outcomes Res 2018;10:493–500.
25. Schwartzberg LS, Lal LS, Balu S, et al. Clinical outcomes of treatment with filgrastim versus a filgrastim biosimilar and febrile neutropenia-associated costs among patients with nonmyeloid cancer undergoing chemotherapy. J Manag Care Spec Pharm 2018;24:976–984.
26. Chen X, Agiro A, Barron J, et al. Early adoption of biosimilar growth factors in supportive cancer care. JAMA Oncol 2018;4:1779–1781.
27. U.S. Food & Drug Administration. Tbo-filgrastim label information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125294s0000lbl.pdf. Accessed January 18, 2019.
28. del Giglio A, Eniu A, Ganea-Motan D, et al. XM02 is superior to placebo and equivalent to Neupogen in reducing the duration of severe

neutropenia and the incidence of febrile neutropenia in cycle 1 in breast cancer patients receiving docetaxel/doxorubicin chemotherapy. BMC Cancer 2008;8:332.

29. Engert A, Griskevicius L, Zyuzgin Y, et al. XM02, the first granulocyte colony-stimulating factor biosimilar, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with non-Hodgkin lymphoma receiving chemotherapy. Leuk Lymphoma 2009;50:374–379.
30. Gatzemeier U, Ciuleanu T, Dediu M, et al. XM02, the first biosimilar G-CSF, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with small cell or non-small cell lung cancer receiving platinum-based chemotherapy. J Thorac Oncol 2009;4:736–740.
31. Engert A, del Giglio A, Bias P, et al. Incidence of febrile neutropenia and myelotoxicity of chemotherapy: a meta-analysis of biosimilar G-CSF studies in breast cancer, lung cancer, and non-Hodgkin's lymphoma. Onkologie 2009;32:599–604.
32. Lubenau H, Bias P, Maly AK, et al. Pharmacokinetic and pharmacodynamic profile of new biosimilar filgrastim XM02 equivalent to marketed filgrastim Neupogen: single-blind, randomized, crossover trial. BioDrugs 2009;23: 43–51.
33. Lubenau H, Sveikata A, Gumbrevicius G, et al. Bioequivalence of two recombinant granulocyte colony-stimulating factor products after subcutaneous injection in healthy volunteers. Int J Clin Pharmacol Ther 2009;47:275–282.
34. Zou L, Buchner A, Field JA, et al. Immunogenicity assessment of tbo-filgrastim in cancer patients receiving chemotherapy. Bioanalysis 2018;10: 1221–1228.
35. The Center for Biosimilars. FDA approves second Neupogen biosimilar, Nivestym. Available at: https://www.centerforbiosimilars.com/news/fda-approves-second-neupogen-biosimilar-nivestym. Accessed February 28, 2019.
36. Waller CF, Semiglazov VF, Tjulandin S, et al. A phase III randomized equivalence study of biosimilar filgrastim versus Amgen filgrastim in patients receiving myelosuppressive chemotherapy for breast cancer. Onkologie 2010;33:504–511.
37. Fruehauf S, Otremba B, Stötzer O, et al. Compatibility of biosimilar filgrastim with cytotoxic chemotherapy during the treatment of malignant diseases (VENICE): a prospective, multicenter, non-interventional, longitudinal study. Adv Ther 2016;33:1983–2000.
38. Brito M, Esteves S, André R, et al. Comparison of effectiveness of biosimilar filgrastim (Nivestim™), reference Amgen filgrastim and pegfilgrastim in febrile neutropenia primary prevention in breast cancer patients treated with neo(adjuvant) TAC: a non-interventional cohort study. Support Care Cancer 2016;24:597–603.
39. Frederic M, Stephane L, Didier K, et al. Biosimilar filgrastim in the treatment and the prevention of chemotherapy-induced neutropenia: the next study [abstract]. J Geriatr Oncol 2014;5:S71. Abstract P100.
40. Waller CF, Tiessen RG, Lawrence TE, et al. A pharmacokinetics and pharmacodynamics equivalence trial of the proposed pegfilgrastim biosimilar, MYL-1401H, versus reference pegfilgrastim. J Cancer Res Clin Oncol 2018;144:1087–1095.
41. Glaspy JA, O'Connor PG, Tang H, et al. Randomized, single-blind, crossover study to assess the pharmacokinetic and pharmacodynamic bioequivalence of CHS-1701 to pegfilgrastim in healthy subjects [abstract]. J Clin Oncol 2017;35(Suppl):Abstract e21693.
42. O'Conner P, Tang H, Civoli F, et al. Proposed pegfilgrastim biosimilar CHS-1701 demonstrates pharmacokinetic and pharmacodynamic similarity to marketed pegfilgrastim in a rat neutropenia model and in healthy subjects. Presented at the 22nd Congress of the European Hematology Association; June 22–25, 2017; Madrid, Spain. Abstract E1147.
43. U.S. Food & Drug Administration. FDA approves first biosimilar to Neulasta to help reduce the risk of infection during cancer treatment. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm609805.htm. Accessed February 28, 2019.
44. The Center for Biosimilars. FDA approves Coherus' pegfilgrastim biosimilar, Udenyca. Available at: https://www.centerforbiosimilars.com/news/fda-approves-coherus-pegfilgrastim-biosimilar-udenyca. Accessed February 4, 2019.
45. Hoy SM. Pegfilgrastim-jmdb/MYL-1401H: a pegfilgrastim biosimilar. BioDrugs 2019;33:117–120.
46. Sankaran PK, Palanivelu DV, Nair R, et al. Characterization and similarity assessment of a pegfilgrastim biosimilar MYL-1401H. J Clin Oncol 2018; 36(Suppl):e19028.
47. Waller CF, Ranganna GM, Pennella EJ, et al. Randomized phase 3 efficacy and safety trial of proposed pegfilgrastim biosimilar MYL-1401H in the prophylactic treatment of chemotherapy-induced neutropenia. Ann Hematol 2019;98:1217–1224.
48. Waller C, Ranganna GM, Pennella E, et al. Comparison of immunogenicity between the proposed pegfilgrastim biosimilar MYL-1401H and reference pegfilgrastim. Blood 2017;130:3568.
49. The Center for Biosimilars. FDA approves Sandoz's pegfilgrastim biosimilar, Ziextenzo. Available at: https://www.centerforbiosimilars.com/news/fda-approves-sandozs-pegfilgrastim-biosimilar-ziextenzo. Accessed November 8, 2019.
50. Nakov R, Gattu S, Wang J, et al. Proposed biosimilar pegfilgrastim shows similarity in pharmacokinetics and pharmacodynamics to reference pegfilgrastim in healthy subjects. Br J Clin Pharmacol 2018;84: 2790–2801.
51. Blackwell K, Donskih R, Jones CM, et al. A comparison of proposed biosimilar LA-EP2006 and reference pegfilgrastim for the prevention of neutropenia in patients with early-stage breast cancer receiving myelosuppressive adjuvant or neoadjuvant chemotherapy: pegfilgrastim randomized oncology (supportive care) trial to evaluate comparative treatment (PROTECT-2), a phase III, randomized, double-blind trial. Oncologist 2016;21:789–794.
52. Harbeck N, Lipatov O, Frolova M, et al. Randomized, double-blind study comparing proposed biosimilar LA-EP2006 with reference pegfilgrastim in breast cancer. Future Oncol 2016;12:1359–1367.
53. Harbeck N, Wang J, Otto GP, et al. Safety analysis of proposed pegfilgrastim biosimilar in phase I and phase III studies. Future Oncol 2019;15: 1313–1322.
54. Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. Am J Med 2004;116(Suppl 7A)11S–26S.
55. U.S. Food & Drug Administration. FDA approves first epoetin alfa biosimilar for the treatment of anemia. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm607703.htm. Accessed February 28, 2019.
56. U.S. Food & Drug Administration. FDA Oncologic Drugs Advisory Committee Briefing Materials: "Epoetin Hospira," a proposed biosimilar to US-licensed Epogen/Procrit. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM561560.pdf. Accessed July 10, 2018.
57. Fishbane S, Singh B, Kumbhat S, et al. Intravenous epoetin alfa-epbx versus epoetin alfa for treatment of anemia in end-stage kidney disease. Clin J Am Soc Nephrol 2018;13:1204–1214.
58. Thadhani R, Guilatco R, Hymes J, et al. Switching from epoetin alfa (Epogen(R)) to epoetin alfa-epbx (RetacritTM) using a specified dosing algorithm: a randomized, non-inferiority study in adults on hemodialysis. Am J Nephrol 2018;48:214–224.
59. Kosaka Y, Rai Y, Masuda N, et al. Phase III placebo-controlled, double-blind, randomized trial of pegfilgrastim to reduce the risk of febrile neutropenia in breast cancer patients receiving docetaxel/cyclophosphamide chemotherapy. Support Care Cancer 2015;23: 1137–1143.
60. Kuderer NM, Dale DC, Crawford J, et al. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol 2007;25:3158–3167.
61. Lyman GH, Kuderer NM, Crawford J, et al. Predicting individual risk of neutropenic complications in patients receiving cancer chemotherapy. Cancer 2011;117:1917–1927.
62. Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: a systematic review. Crit Rev Oncol Hematol 2014;90:190–199.
63. Lyman GH, Poniewierski MS. A patient risk model of chemotherapy-induced febrile neutropenia: lessons learned from the ANC study group. J Natl Compr Canc Netw 2017;15:1543–1550.
64. Weycker D, Li X, Tzivelekis S, et al. Burden of chemotherapy-induced febrile neutropenia hospitalizations in US clinical practice, by use and patterns of prophylaxis with colony-stimulating factor. Support Care Cancer 2017;25:439–447.
65. Lyman GH, Allcott K, Garcia J, et al. The effectiveness and safety of same-day versus next-day administration of long-acting granulocyte colony-stimulating factors for the prophylaxis of chemotherapy-induced neutropenia: a systematic review. Support Care Cancer 2017;25:2619–2629.
66. Meropol NJ, Miller LL, Korn EL, et al. Severe myelosuppression resulting from concurrent administration of granulocyte colony-stimulating factor and cytotoxic chemotherapy. J Natl Cancer Inst 1992;84:1201–1203.

67. American Society of Clinical Oncology. Letter to CMS regarding "Neulasta administered same day as chemotherapy". Available at: http://www.asco.org/sites/default/files/letter_to_cms_rac_audit_on_neulasta_110912_lthd.pdf. Accessed February 28, 2019.
68. Yang BB, Morrow PK, Wu X, et al. Comparison of pharmacokinetics and safety of pegfilgrastim administered by two delivery methods: on-body injector and manual injection with a prefilled syringe. Cancer Chemother Pharmacol 2015;75:1199–1206.
69. Green MD, Koelbl H, Baselga J, et al. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. Ann Oncol 2003;14:29–35.
70. Vogel CL, Wojtukiewicz MZ, Carroll RR, et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. J Clin Oncol 2005;23:1178–1184.
71. Watanabe T, Tobinai K, Shibata T, et al. Phase II/III study of R-CHOP-21 versus R-CHOP-14 for untreated indolent B-cell non-Hodgkin's lymphoma: JCOG 0203 trial. J Clin Oncol 2011;29:3990–3998.
72. Hecht JR, Pillai M, Gollard R, et al. A randomized, placebo-controlled phase ii study evaluating the reduction of neutropenia and febrile neutropenia in patients with colorectal cancer receiving pegfilgrastim with every-2-week chemotherapy. Clin Colorectal Cancer 2010;9:95–101.
73. Brusamolino E, Rusconi C, Montalbetti L, et al. Dose-dense R-CHOP-14 supported by pegfilgrastim in patients with diffuse large B-cell lymphoma: a phase II study of feasibility and toxicity. Haematologica 2006;91:496–502.
74. Burstein HJ, Parker LM, Keshaviah A, et al. Efficacy of pegfilgrastim and darbepoetin alfa as hematopoietic support for dose-dense every-2-week adjuvant breast cancer chemotherapy. J Clin Oncol 2005;23:8340–8347.
75. Jones RL, Walsh G, Ashley S, et al. A randomised pilot phase II study of doxorubicin and cyclophosphamide (AC) or epirubicin and cyclophosphamide (EC) given 2 weekly with pegfilgrastim (accelerated) vs 3 weekly (standard) for women with early breast cancer. Br J Cancer 2009;100:305–310.
76. Pirker R, Ulsperger E, Messner J, et al. Achieving full-dose, on-schedule administration of ACE chemotherapy every 14 days for the treatment of patients with extensive small-cell lung cancer. Hai 2006;184:279–285.
77. Estcourt LJ, Stanworth SJ, Hopewell S, et al. Granulocyte transfusions for treating infections in people with neutropenia or neutrophil dysfunction. Cochrane Database Syst Rev 2016;4:CD005339.
78. Clark OA, Lyman GH, Castro AA, et al. Colony-stimulating factors for chemotherapy-induced febrile neutropenia: a meta-analysis of randomized controlled trials. J Clin Oncol 2005;23:4198–4214.
79. Johnston E, Crawford J, Blackwell S, et al. Randomized, dose-escalation study of SD/01 compared with daily filgrastim in patients receiving chemotherapy. J Clin Oncol 2000;18:2522–2528.
80. Lyman GH, Balaban E, Diaz M, et al. American Society of Clinical Oncology statement: biosimilars in oncology. J Clin Oncol 2018;36:1260–1265.