Colony Stimulating Factors
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Cancer patients receiving myelosuppressive chemotherapy *(To reduce incidence of infection (febrile neutropenia)*	Acute Myeloid Leukemia (AML) patients receiving chemotherapy *(Following induction or consolidation chemotherapy to reduce time to neutrophil recovery and the duration of fever in adults)*	Bone Marrow Transplant (BMT)	Peripheral Blood Progenitor Cell Collection and Therapy	Severe Chronic Neutropenia *(To reduce the incidence and duration of neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia)*	Hematopoietic Syndrome of Acute Radiation Syndrome *(To Increase survival in patients acutely exposed to myelosuppressive doses of radiation)*
filgrastim (Neupogen®)[1]	Amgen	X	X	X[a]	X	X	X
filgrastim-aafi (Nivestym™)*[2]	Pfizer	X	X	X[a]	X	X	--
filgrastim-sndz (Zarxio®)*[3]	Sandoz	X	X	X[a]	X	X	--
pegfilgrastim (Neulasta®)[4]	Amgen	X	--	--	--	--	X
pegfilgrastim-cbqv (Udenyca™)†[5]	Coherus	X	--	--	--	--	--
pegfilgrastim-jmdb (Fulphila™)†[6]	Mylan	X	--	--	--	--	--
sargramostim (Leukine®)[7]	Sanofi	--	X	X[b]	X	--	X
tbo-filgrastim (Granix®)[8]	Teva	X	--	--	--	--	--

* Filgrastim-aafi (Nivestym) and filgrastim-sndz (Zarxio) are biosimilars to the originator filgrastim (Neupogen), approved through the FDA 351(k) biosimilar pathway.

† Pegfilgrastim-cbqv (Udenyca) and pegfilgrastim-jmdb (Fulphila) are biosimilars to the originator pegfilgrastim (Neulasta), approved through the FDA 351(k) biosimilar pathway.

[a] In cancer patients receiving BMT to reduce duration of neutropenia and febrile neutropenia

[b] For acceleration of myeloid reconstitution after PBPC/BMT; treatment of delayed neutrophil recovery or graft failure after BMT

OVERVIEW

Myelosuppressive chemotherapy can induce neutropenia (< 500 neutrophils/µL or < 1,000 neutrophils/µL and a predicted decline to ≤ 500/µL during the 48 hours after the dose) and febrile neutropenia (≥ 38.3°C orally or ≥ 38°C sustained over 1 hour) which is a dose-limiting toxicity of chemotherapy.[9] Febrile neutropenia can cause increased diagnostic and treatment costs, prolonged hospitalizations, and broad-spectrum antibiotic use which may necessitate chemotherapy dose reductions, treatment delays, and may ultimately compromise treatment outcomes. The risk of febrile neutropenia is dependent on treatment and dose intensity, which is often underreported. Colony stimulating factors (CSF) are hematopoietic growth factors that have been shown to decrease the likelihood of neutropenic complications resulting from chemotherapy and to improve relative chemotherapy dose intensity. Prophylactic CSF use can reduce the severity, risk, and duration of febrile neutropenia and decrease rates of infection and hospitalizations. Filgrastim (Neupogen), filgrastim-aafi (Nivestym), filgrastim-sndz (Zarxio), pegfilgrastim (Neulasta), pegfilgrastim-cbqv (Udenyca), pegfilgrastim-jmdb (Fulphila), and tbo-filgrastim (Granix) are granulocyte colony-stimulating factors (G-CSF). Sargramostim (Leukine) is a granulocyte-macrophage colony stimulating factor (GM-CSF). Colony stimulating factors act on hematopoietic cells and stimulate proliferation, differentiation commitment, and some end-cell functional activation.

The National Comprehensive Cancer Network (NCCN) v2.2019 practice guidelines for Myeloid Growth Factors base recommendations on evidence derived mainly from G-CSF studies and patients with solid tumors and lymphoid blood cancers.[10] Safety data appear similar between filgrastim (Neupogen), pegfilgrastim (Neulasta), and their biosimilars and the subcutaneous (SC) route is preferred for all agents. To date, there are insufficient head-to-head comparative studies on the clinical benefits of G-CSFs and GM-CSFs. Subcutaneous filgrastim and its biosimilars, tbo-filgrastim, and pegfilgrastim have a category 1 recommendation stating there is high-level evidence from randomized controlled clinical trials and there is uniform NCCN consensus that they prophylactically reduce the risk of febrile neutropenia. Pegfilgrastim-jmdb and pegfilgrastim-cbqv have been designated a category 2A (lower level evidence, there is uniform consensus that the intervention is appropriate). Filgrastim, filgrastim biosimilars, and tbo-filgrastim can be administered the day after chemotherapy, up to 3 to 4 days after chemotherapy, and through post-nadir recovery. Based on data from clinical trials, pegfilgrastim and its biosimilars should be administered the day after chemotherapy (category 1); however, administration up to 3 to 4 days after chemotherapy is also reasonable according to the NCCN guidelines. For patients unable to return to the clinic the next day for medication administration, a delivery device, (Neulasta Onpro®), is available that allows for the device to be applied to patient the same day as chemotherapy administration, but the device does not release the medication until approximately 27 hours after application. There is evidence to support the use of chemotherapy regimens every 3 weeks with pegfilgrastim or its biosimilars (category 1). Efficacy data exist for pegfilgrastim products in chemotherapy regimens given every 2 weeks (category 2A). There are insufficient data to support dose/schedule of weekly chemotherapy regimens; therefore, pegfilgrastim products should not be used. Sargramostim is no longer recommended for prophylactic use in patients with solid tumors receiving myelosuppressive chemotherapy. Prophylactic use of CSF in patients taking chemotherapy and radiation concurrently has not been studied; therefore, the NCCN guidelines do not recommend CSF use in such patients.

Compared to prophylactic use, there is less evidence to support the CSFs for therapeutic use and the guidelines note that it remains unknown whether CSF use translates into survival advantage. The NCCN

guidelines recommend therapeutic treatment based on the patient's prophylactic therapy use. However, since pegfilgrastim and its biosimilars are long-acting, patients who received prophylactic pegfilgrastim products should not receive additional CSF. For patients who have not received prophylactic CSF, the guidelines recommend an evaluation of risk factors related to infection complications or poor clinical outcomes; if risk factors are present, then CSF should be considered. Filgrastim, filgrastim biosimilars, tbo-filgrastim, and sargramostim have a 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate) for therapeutic use and can be used until post-nadir absolute neutrophil count (ANC) recovery to normal or near-normal levels. Pegfilgrastim and its biosimilars have only been studied for prophylactic use.

The NCCN practice guidelines stratify patients into 3 risk groups based on the chemotherapy regimen and patient-related risk factors: high risk (> 20% risk of developing febrile neutropenia), intermediate risk (10% to 20% risk of developing febrile neutropenia), and low risk (< 10% risk of developing febrile neutropenia).[11] It is the recommended that high-risk patients receive prophylactic CSF regardless of the intent of treatment (category 1). If the patient falls into the intermediate risk group, NCCN recommends individualized consideration of CSF based on the likelihood of developing febrile neutropenia, consequences of developing febrile neutropenia, and the implications of interfering with chemotherapy treatments. Patients with ≥ 1 risk factor (e.g., ≥ 65 years old, prior exposure to chemotherapy/radiation, poor performance status, recent surgery and/or open wounds, persistent neutropenia) should be considered for prophylactic therapy, whereas patients with no risk factors should be observed. Lastly, NCCN does not recommend the routine use of CSF in patients with low risk of developing febrile neutropenia due to lack of cost effectiveness and availability of alternative treatments. However, choosing to administer a CSF may be considered if the treatment is curative or adjuvant and the patient is at serious medical consequences of febrile neutropenia.

The updated v2.2019 NCCN Hematopoietic Growth Factors guidelines also address the role of biosimilars.[12] The guidelines note that a biosimilar is a biological product that is highly similar to the FDA-approved originator product with very small, clinically inactive differences but no difference in efficacy, safety, or purity. The first biosimilar, filgrastim-sndz, was approved in March 2015 with a second filgrastim biosimilar, filgrastim-aafi, being approved in 2018. However, tbo-filgrastim was approved in 2012 as a biologic rather than a biosimilar in the United States; in Europe, tbo-filgrastim is available as a biosimilar to filgrastim. The first pegfilgrastim biosimilars, pegfilgrastim-jmdb and pegfilgrastim-cbqv, were approved in 2018. Studies have shown these products have similar safety and efficacy profiles as the originator product. The guidelines state if overall safety and efficacy are equivalent, biosimilars may be substituted for the originator product. However, the guidelines note that current biosimilars are not interchangeable; therefore, alternating between a biosimilar and it's originator in not recommended. The guidelines also note that the use of biosimilars may provide opportunities for cost containment. The panel endorses the use of filgrastim-sndz, filgrastim-aafi, tbo-filgrastim, pegfilgrastim-jmdb, and pegfilgrastim-cbqv for myelosuppressive doses of radiation. For mobilization of hematopoietic progenitor cells in the autologous setting, the use of concurrent filgrastim (or 1 of its biosimilars) with sargramostim (category 2B) or single agent filgrastim, filgrastim-sndz, filgrastim-aafi, or tbo-filgrastim is recommended (category 2A). According to the guidelines, the World Marrow Donor Association (WMDA) recommends filgrastim (NCCN category 2A; preferred) or filgrastim biosimilars (NCCN category 2B) for the mobilization of peripheral blood progenitor cells in healthy donors in the allogeneic setting. The NCCN Panel does not recommend pegfilgrastim or its biosimilars for mobilization at this time.

The American Society of Clinical Oncology (ASCO) published an updated set of guidelines in 2015 for the use of white blood cell growth factors. They note the ability of these agents to reduce the duration and severity of neutropenia and febrile neutropenia and allow more intensive or dose-dense chemotherapy.[13] The guidelines made no recommendation regarding the equivalency of the 2 colony-stimulating agents, granulocyte CSFs, and granulocyte-macrophage CSFs. Pegfilgrastim, filgrastim, filgrastim-sndz, and tbo-filgrastim can be used for the prevention of treatment-related febrile neutropenia. The choice of agent should be based on the clinical situation, convenience, and cost (Type: evidence-based, benefit outweigh harms; Evidence quality: high; Strength of recommendation: strong). The recommendations for the use of CSF for primary prophylaxis include the prevention of febrile neutropenia in patients who are at high risk based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. Clinical trial data support the use of CSF when the risk of febrile neutropenia is ≥ 20% starting with the first cycle and continuing through subsequent cycles of chemotherapy. The decision on whether to use prophylactic CSF should take into consideration concerns such as the optimal chemotherapy regimen, individual patient risk factors, and the intention of treatment, that is, curative, prolongation of life, or symptom control and palliation. Alternative, but equally effective and safe, chemotherapy options not requiring CSFs should be considered (Type: evidence-based, benefit outweigh harms; Evidence quality: high; Strength of recommendation: strong). ASCO recommends secondary prophylaxis with CSF 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 may compromise disease-free, 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). CSF 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). CSF should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSF should be considered in patients with fever and neutropenia who are at high-risk for infection-related complications or who have prognostic factors that are predictive of poor clinical outcomes (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong). High-risk features include expected prolonged (> 10 days) and profound (< 0.1 x 10^9/L) neutropenia, age > 65 years, uncontrolled primary disease, pneumonia, hypotension and multiorgan dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever.

Per the 2015 ASCO guidelines, CSFs can be used during or after chemotherapy or with plerixafor to mobilize peripheral-blood progenitor cells (PBPC) depending on the type of cancer and transplantation (Type: evidence-based, benefit outweigh harms; Evidence quality: strong; Strength of recommendation: high). CSF should be administered after autologous stem-cell transplantation (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong) and may be administered after allogenic stem-cell transplantation (Type: evidence-based; Evidence quality: low; Strength of recommendation: weak). They recommend filgrastim-sndz; future biosimilars may be used for the prevention of neutropenia. ASCO recommends that the choice of agent depend on convenience, cost, and clinical situation. ASCO's dosing and administration recommendations for filgrastim-sndz are identical to those for filgrastim.

PHARMACOLOGY[14,15,16,17,18,19,20,21]

Sargramostim (Leukine) is a recombinant human GM-CSF produced by recombinant DNA technology in yeast. GM-CSF is a hematopoietic growth factor, which triggers proliferation and differentiation of hematopoietic progenitor cells. GM-CSF is included in a group of growth factors termed CSF that promote survival, clonal expansion, and differentiation of hematopoietic progenitor cells. GM-CSF induces partially-committed progenitor cells to divide and differentiate in the granulocyte-macrophage pathways which include neutrophils, monocytes/macrophages, and myeloid derived dendritic cells. GM-CSF also has the capability of activating mature granulocytes and macrophages. GM-CSF is a multilineage factor and, in addition to dose-dependent effects on the myelomonocytic lineage, can encourage the proliferation of megakaryocytic and erythroid progenitors.

Filgrastim (Neupogen), filgrastim-aafi (Nivestym), filgrastim-sndz (Zarxio), pegfilgrastim (Neulasta), pegfilgrastim-cbqv (Udenyca), pegfilgrastim-jmdb (Fulphila), and tbo-filgrastim (Granix) are G-CSFs that are produced by recombinant technology using *Escherichia coli*. G-CSF acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating differentiation, commitment, proliferation, and end cell functional activation. Filgrastim, filgrastim-aafi, filgrastim-sndz, and tbo-filgrastim stimulate the growth and development of neutrophils within the bone marrow. Labeling for filgrastim, filgrastim-aafi, and filgrastim-sndz report a shift towards earlier granulocyte progenitor cells (left shift), including the appearance of promyelocytes and myeloblasts, usually during neutrophil recovery following the chemotherapy-induced nadir; this shift is not reported in the labeling for tbo-filgrastim. Studies on cellular proliferation, receptor binding, and neutrophil function demonstrate that filgrastim and pegfilgrastim have the same mechanism of action. Pegfilgrastim, pegfilgrastim-cbqv, and pegfilgrastim-jmdb are conjugates of filgrastim and monomethoxypolyethylene glycol. Neutrophil receptor binding is an important component of the clearance of pegfilgrastim, pegfilgrastim-cbqv, and pegfilgrastim-jmdb; serum clearance is directly related to the number of neutrophils. Filgrastim-aafi (Nivestym) and filgrastim-sndz (Zarxio) are biosimilars for filgrastim (Neupogen); pegfilgrastim-cbqv (Udenyca) and pegfilgrastim-jmdb (Fulphila) are biosimilars to pegfilgrastim (Neulasta).

PHARMACOKINETICS[22,23,24,25,26,27,28,29]

Drug	Half-Life Intravenous Administration	Half-Life Subcutaneous Administration
filgrastim (Neupogen)	231 minutes	210 minutes
filgrastim-aafi (Nivestym)		
filgrastim-sndz (Zarxio)		
pegfilgrastim (Neulasta)	--	15–80 hours
pegfilgrastim-cbqv (Udenyca)		
pegfilgrastim-jmdb (Fulphila)		
sargramostim (Leukine)	3.84 hours	1.4 hours
tbo-filgrastim (Granix)	--	3–3.5 hours

CONTRAINDICATIONS/WARNINGS[30,31,32,33,34,35,36,37]

filgrastim (Neupogen), filgrastim-aafi (Nivestym), filgrastim-sndz (Zarxio), pegfilgrastim (Neulasta), pegfilgrastim-cbqv (Udenyca), pegfilgrastim-jmdb (Fulphila), and tbo-filgrastim (Granix)

Filgrastim, filgrastim-aafi, filgrastim-sndz, pegfilgrastim, pegfilgrastim-cbqv, pegfilgrastim-jmdb, and tbo-filgrastim (Granix) are contraindicated in patients with known hypersensitivity to *E. coli*-derived proteins, filgrastim products, pegfilgrastim products, or any other component of medication.

Uses of filgrastim, filgrastim biosimilars, pegfilgrastim, pegfilgrastim biosimilars, and tbo-filgrastim have reported allergic-type reactions during initial or subsequent treatments, including anaphylactic reactions. However, a majority of allergic type reactions occurred with initial exposure. These have generally been characterized by systemic symptoms involving at least 2 body systems, most often skin (e.g., rash, urticaria, facial edema), cardiovascular (e.g., hypotension, tachycardia), and respiratory (e.g., wheezing, dyspnea). In rare cases following administration of pegfilgrastim, filgrastim, or their biosimilars, allergic reactions, including anaphylaxis, recurred within days after the initial anti-allergic treatment was discontinued; recurrence is not discussed in the labeling for tbo-filgrastim. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days. Administration of steroids, bronchodilators, antihistamines, and/or epinephrine may reduce the severity of symptoms. If rechallenged, symptoms recurred in more than half the patients. Filgrastim, filgrastim biosimilars pegfilgrastim, pegfilgrastim biosimilars, and tbo-filgrastim should be permanently discontinued in patients with serious allergic reactions. The needle cap for the single-dose prefilled syringe contains latex; therefore, persons with latex allergies should not administer pegfilgrastim, filgrastim, or filgrastim-sndz.

Splenic rupture, including fatal cases, has been reported following the administration of filgrastim, filgrastim biosimilars, pegfilgrastim, pegfilgrastim biosimilars, and tbo-filgrastim. Patients receiving any agent who report left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

The on-body injector (Neulasta Onpro) for pegfilgrastim (Neulasta) delivery kit uses acrylic adhesive; therefore, its use may result in serious reactions in patients who have allergies to acrylic adhesives. Patients should avoid activities such as traveling, driving, or operating heavy machinery 26 to 29 hours following application of the on-body injector for pegfilgrastim. This includes the 45-minute delivery period, plus 1 hour post-delivery. A caregiver should be close by for the first use. Use of the on-body injector is not recommended for patients with H-SARS and it has not been studied in pediatric patients. Missed or partial doses of pegfilgrastim have been reported with the on-body injector. Patients should be aware to notify their healthcare professional (HCP) immediately if they suspect a missed or partial dose has been delivered in order to get replacement medication. The pegfilgrastim on-body injector is intended to be used in an electromagnetic environment; however, do not expose the on-body injector to medical imaging studies (e.g., X-ray scan, MRI, CT scan, ultrasound), oxygen-rich environments (e.g., hyperbaric chambers), or radiation treatment, as it may cause injector damage or patient injury. The injector must be at least 4 inches away from electrical equipment, including cell phones, cordless telephones, microwaves, and other common appliances, as these may interfere with operation and can lead to a missed or incomplete dose. The pegfilgrastim injector should not be used in hot tubs, saunas, and whirlpools. Direct sunlight should be avoided and the injector should be worn under clothing.

Patients should not sleep on the injector or apply pressure during wear. Lotions, creams, oils, and cleaning agents can loosen the adhesive and should be avoided near the injector.

Acute respiratory distress syndrome (ARDS) has been reported in patients receiving filgrastim, filgrastim biosimilars, pegfilgrastim, pegfilgrastim biosimilars, and tbo-filgrastim, and it is suggested to be secondary to an invasion of neutrophils to sites of inflammation in the lungs. Patients receiving filgrastim, filgrastim biosimilars, pegfilgrastim, pegfilgrastim biosimilars, or tbo-filgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. If ARDS occurs, filgrastim, filgrastim biosimilars, pegfilgrastim, pegfilgrastim biosimilars, and tbo-filgrastim should be discontinued and/or withheld until resolution of ARDS, and patients should receive appropriate medical management.

Healthy donors undergoing PBPC mobilization have reported alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis and have required hospitalization. Hemoptysis resolved with discontinuation of filgrastim products. The use of filgrastim or filgrastim biosimilars for PBPC mobilization in healthy donors is not an approved indication. In cancer patients using filgrastim or its biosimilars, the medication should be discontinued if the leukocyte count is > 100,000/mm^3. Pegfilgrastim products and tbo-filgrastim are not indicated for PBPC mobilization.

Severe sickle cell crisis, some cases resulting in death, have been associated with the use of filgrastim, filgrastim biosimilars, pegfilgrastim, pegfilgrastim biosimilars, and tbo-filgrastim in patients with sickle cell disorders. After careful consideration of the potential risks and benefits, only physicians qualified by specialized training or experience in the treatment of patients with sickle cell disorders should prescribe filgrastim, filgrastim biosimilars, pegfilgrastim, pegfilgrastim biosimilars, or tbo-filgrastim for such patients. Patients experiencing a sickle cell crisis should discontinue therapy.

The G-CSF receptor that filgrastim, pegfilgrastim, and tbo-filgrastim act upon has been found on tumor cell lines. It is possible that filgrastim, pegfilgrastim, and tbo-filgrastim act as growth factors for any tumor type; however, more data are needed since the limited data that are available are inconclusive. This also applies to biosimilar products of filgrastim and pegfilgrastim. The safety of filgrastim and its biosimilars in treating chronic myeloid leukemia (CML) and myelodysplasia has not been established.

The safety and efficacy of filgrastim products used concurrently with chemotherapy have not been established. However, due to the sensitivity of rapidly dividing myeloid cells during chemotherapy, the use of filgrastim products should be avoided for 24 hours before and through 24 hours after chemotherapy. Concurrent therapy with radiation should also be avoided.

The safety and efficacy of filgrastim and its biosimilars have not been established in the treatment of neutropenia due to other hematopoietic disorders, such as myelodysplastic syndrome (MDS). The diagnosis of Severe Chronic Neutropenia (SCN) should be confirmed prior to initiating therapy with filgrastim or its biosimilars since cytogenetic abnormalities and transformation to MDS and acute myeloid leukemia (AML) have been observed in patients treated with filgrastim products for SCN. The risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia. Eventual development of myeloid leukemia has been associated with abnormal cytogenetics and MDS. The effect of filgrastim or its biosimilars on the development of abnormal cytogenetics and the effect of their continued administration in patients with abnormal cytogenetics or MDS are unknown. The risks and benefits of continuing filgrastim and its biosimilars should be carefully considered if a patient with SCN develops abnormal cytogenetics or myelodysplasia.

Cases of moderate to severe cutaneous vasculitis have been reported in patients taking filgrastim products. These cases most often occurred in patients with SCN receiving long-term filgrastim products. Therapy with filgrastim, including its biosimilars, should be held if cutaneous vasculitis occurs and may be restarted at a reduced dose when symptoms resolve and the ANC has decreased.

Thrombocytopenia has been reported in patients taking filgrastim products; therefore, platelet counts should be monitored.

Capillary leak syndrome (CLS) can occur in patients using human GCSFs. Symptoms include hypotension, hypoalbuminemia, edema, and hemoconcentration and can be life-threatening, especially if treatment is delayed. Patients who develop symptoms of CLS should be monitored closely and receive symptomatic treatment.

Glomerulonephritis has occurred in patients taking filgrastim products, including pegfilgrastim and its biosimilars, based on findings of azotemia, hematuria, proteinuria, and renal biopsy. Reducing the dose or discontinuing filgrastim or pegfilgrastim products should result in resolution of glomerulonephritis.

White blood cell (WBC) counts of ≥ 100,000/mm^3 were observed in approximately 2% of patients taking filgrastim at doses > 5 mcg/kg/day when receiving myelosuppressive chemotherapy and have been reported in patients receiving pegfilgrastim products (WBC ≥ 100 x 10^9/L) and tbo-filgrastim (WBC > 100,000 x 10^6/L). In order to avoid potential risks of excessive leukocytosis, it is recommended that filgrastim, filgrastim biosimilars, and tbo-filgrastim be stopped if the ANC surpasses 10,000/mm^3 after the chemotherapy-induced ANC nadir occurs. Dosages of filgrastim, filgrastim biosimilars, or tbo-filgrastim that increase ANC > 10,000/mm^3 may not result in additional clinical benefit. Patients using filgrastim, filgrastim biosimilars, and tbo-filgrastim should have their complete blood count (CBC) monitored at least twice weekly during therapy. Monitoring of CBC is also recommended for pegfilgrastim products, although a monitoring schedule is not specified. Discontinue filgrastim and its biosimilars if the leukocyte count becomes > 100,000/mm^3 during the period of administration for PBPC mobilization.

When interpreting bone-imaging results, it should be noted that increased hematopoietic activity of bone marrow in response to growth factor has been associated with transient positive bone-imaging changes.

Aortitis has been reported in patients taking filgrastim and pegfilgrastim products as early as the first week of therapy. Signs and symptoms of aortitis include fever, abdominal pain, malaise, back pain, and increased inflammatory markers. If suspected, product should be discontinued.

sargramostim (Leukine)

Sargramostim (Leukine) is contraindicated in patients with a history of serious allergic reactions to human granulocyte-macrophage colony stimulating factor, yeast-derived products, or any component of the product; anaphylactic reactions have been reported.

Sargramostim should not be administered simultaneously with cytotoxic chemotherapy or radiotherapy or within 24 hours preceding or following chemotherapy or radiotherapy due to the potential sensitivity of rapidly dividing hematopoietic progenitor cells.

Sargramostim contains benzyl alcohol in the liquid formulations and in the bacteriostatic water for injection diluent. Benzyl alcohol has been reported to be associated with a fatal “gasping syndrome” in premature and low birth weight infants. Formulations containing benzyl alcohol should not be

administered to neonates. Instead, administer lyophilized sargramostim reconstituted with sterile water for injection.

Reports of fluid retention (11%), edema, capillary leak syndrome (< 1%), and pleural (1%) and/or pericardial effusion (4%) have been reported in patients after sargramostim administration. In patients with pre-existing pleural and pericardial effusions, the use of sargramostim may worsen fluid retention; however, fluid retention linked with or worsened by sargramostim has been reversible after interruption or dose reduction of sargramostim, with or without diuretic therapy. Patients with pre-existing fluid retention, pulmonary infiltrates, or congestive heart failure should use sargramostim with caution.

Transient supraventricular arrhythmia has been reported in uncontrolled studies during sargramostim administration especially in patients with a history of cardiac arrhythmia. These arrhythmias have been reversible after discontinuation of sargramostim. Use sargramostim with caution in patients with pre-existing cardiac disease.

Respiratory distress, hypoxia, flushing, hypotension, syncope, and/or tachycardia have been reported following the first administration of sargramostim in a particular treatment cycle. These signs have resolved with symptomatic treatment and usually do not reappear with successive doses in the same cycle of treatment. If a patient displays symptoms, reduce the rate of infusion by 50% and discontinue if symptoms still persist.

Stimulation of marrow precursors may cause an increase in white blood cell (WBC) count. If the absolute neutrophil count (ANC) exceeds 20,000 cells/mm^3 sargramostim therapy should be stopped or the dose reduced in half. Within 3 to 7 days following therapy termination, excessive blood counts should return to normal or baseline levels. Twice weekly complete blood count (CBC) with differential levels should be performed thereafter.

Sargramostim primarily stimulates normal myeloid precursors but may act as a growth factor for any tumor type including myeloid malignancies; therefore, caution should be used when prescribing sargramostim in patients with any malignancy with myeloid characteristics. If disease progression occurs during sargramostim therapy, the medication should be discontinued.

DRUG INTERACTIONS[38,39,40,41,42,43,44,45]

Interactions between agents in this class and other drugs have not been fully evaluated.

Drugs that may potentiate the myeloproliferative effects of these agents, such as lithium and corticosteroids, should be used with caution. Patients receiving lithium and these agents should have more frequent monitoring of neutrophil counts.

ADVERSE EFFECTS[46,47,48,49,50,51,52,53]

Drug	Bone (Skeletal) Pain	Pyrexia	Skin Rash	Edema
filgrastim (Neupogen), filgrastim-aafi (Nivestym), filgrastim-sndz (Zarxio) cancer patients receiving chemotherapy	11 (6)	48 (29)	14 (5)	reported
pegfilgrastim (Neulasta), pegfilgrastim-cbqv (Udenyca), pegfilgrastim-jmdb (Fulphila)	31 (26)	reported	reported	reported
sargramostim (Leukine) patients with AML	21 (5)	81–95 (74–96)	44–70 (38–73)	13–34 (11–35)
tbo-filgrastim (Granix)	3.4 (1.4)	8 (nr)	reported	reported

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

Lactate dehydrogenase and alkaline phosphatase occurred in 6% of 294 patients receiving filgrastim following chemotherapy treatment.

There is a potential for immunogenicity when using therapeutic proteins; however, the incidence of antibody development in patients taking filgrastim, filgrastim-aafi, filgrastim-sndz, or tbo-filgrastim has not been adequately determined. In clinical studies, the incidence of antibodies binding to filgrastim was 3% but no evidence of a neutralizing response was observed. In clinical trials the incidence of binding antibodies to tbo-filgrastim was 1.4 % in patients who received prior chemotherapy; no cross-reactive antibodies were detected and all antibody responses were transient and of low titers. In studies, evidence of binding antibodies was detected (< 1%) with pegfilgrastim use but there was no evidence of neutralizing antibodies. Cytopenias resulting from an antibody response to exogenous growth factor have been reported rarely. Antibody studies involving patients with Crohn's disease, melanoma in complete remission (unapproved use), and a variety of other diseases revealed that 1.3%, 82.9%, and 2.3%, respectively, had neutralizing anti-sargramostim antibodies detected.

Adverse reactions with ≥ 2% higher incidence in filgrastim and its biosimilars compared to placebo-treated patients for AML include epistaxis, back pain, extremity pain, erythema, maculopapular rash, diarrhea, constipation, and transfusion reaction. Adverse reactions with ≥ 5% higher incidence in filgrastim and its biosimilars patients compared to placebo-treated patients for BMT include rash, hypersensitivity, thrombocytopenia, anemia, hypertension, sepsis, bronchitis, and insomnia. Adverse reactions for the treatment of PBPC when using filgrastim or its biosimilars include bone pain (30%), pyrexia (16%), alkaline phosphatase increases (11%), and headache (10%). Adverse reactions with ≥ 5% higher incidence in patients treated with filgrastim, or its biosimilars, compared to placebo when treating SCN include arthralgia, bone pain, back pain, muscle spasms, musculoskeletal pain, extremity pain, splenomegaly, anemia, upper respiratory tract infection, urinary tract infection, epistaxis, chest pain, diarrhea, hypoesthesia, and alopecia.

The incidence of anti-sargramostim neutralizing antibodies may be related to duration of exposure to the product.

Monitoring

For cancer patients receiving myelosuppressive chemotherapy, obtain CBC and platelet count prior to chemotherapy and at regular intervals (twice weekly) during treatment with filgrastim or pegfilgrastim products; if ANC increases beyond 10,000/mm^3 therapy termination should be considered. For cancer patients receiving BMT, frequent CBC and platelet counts are recommended during filgrastim therapy, including biosimilars.

For patients with severe chronic neutropenia, serial CBC with differential, platelet counts, and an evaluation of bone marrow morphology and karyotype should be performed prior to starting therapy. Twice weekly CBC with differential and platelet counts should be obtained during the initial 4 weeks of therapy with filgrastim or its biosimilars and during the 2 weeks following any dose adjustment. Once a patient is clinically stable, a monthly CBC with differential and platelet count should be performed during the first year of therapy with filgrastim or its biosimilars. Thereafter, quarterly CBC with differential and platelet counts is recommended.

Patients using filgrastim, filgrastim-aafi, or filgrastim-sndz for PBPC mobilization should have their neutrophil counts monitored after 4 days of therapy and discontinued therapy if the WBC count increases > 100,000/mm^3.

For Hematopoietic Syndrome of Acute Radiation Syndrome, a baseline CBC and serial CBC should be taken approximately every third day until the ANC remains > 1,000/mm^3 for 3 consecutive CBCs when using filgrastim or sargramostim. Filgrastim and sargramostim therapy should not be delayed if a CBC is not readily available. Filgrastim and sargramostim therapy should continue until the ANC remains > 1,000/mm^3 for 3 consecutive CBCs or exceeds 10,000/mm^3 after radiation-induced nadir. When using pegfilgrastim, a baseline CBC should be obtained. However, therapy should not be delayed if a CBC is not readily available. The amount of radiation absorbed should be estimated based on information from public authorities, biodosimetry, or clinical findings, such as time to onset of vomiting or lymphocyte depletion kinetics.

With sargramostim, a CBC is recommended twice per week to avoid excessive leukocytosis (WBC > 50,000 cells/mm^3; ANC > 20,000 cells/mm^3). Patients with pre-existing renal or hepatic dysfunction should have their renal and hepatic function monitored at least biweekly during sargramostim therapy. Patient hydration and body weight should be monitored carefully during therapy.

SPECIAL POPULATIONS[54,55,56,57,58,59,60,61]

Pediatrics

The safety and efficacy of filgrastim (Neupogen), filgrastim-aafi (Nivestym), filgrastim-sndz (Zarxio), pegfilgrastim (Neulasta), pegfilgrastim-cbqv (Udenyca), pegfilgrastim-jmdb (Fulphila), tbo-filgrastim (Granix), and sargramostim have been established in the treatment of pediatric patients. The pharmacokinetics of filgrastim in pediatric patients after chemotherapy are similar to those in adults receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of this product. Similarly, there are no overall differences in safety between adults and pediatrics based on postmarketing surveillance and review of scientific literature when using pegfilgrastim. Pharmacokinetics and safety of tbo-filgrastim in pediatrics is similar to what is seen in adults. Safety and efficacy of sargramostim have been established in pediatrics ≥ 2 years, based on clinical studies in adults for autologous peripheral blood progenitor cells and bone marrow

transplantation, allogenic bone marrow transplantation, and treatment of delayed neutrophil recovery or graft failure. The adverse reactions were consistent with those reported in adults. Approval of sargramostim for pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation was based on animal studies since human studies with H-ARS could not be conducted due to ethical and feasibility reasons.

The Neulasta on-body injector has not been studied in pediatrics.

Pregnancy

For all agents in this class review, data on use during pregnancy are insufficient to inform prescribers of the drug-associated risk; the benefits of the drug should outweigh the risks when prescribing to pregnant women. Filgrastim-sndz is designated Pregnancy Category C; the drug labels for filgrastim, filgrastim-aafi, tbo-filgrastim, pegfilgrastim, pegfilgrastim-cbqv, pegfilgrastim-jmdb, and sargramostim comply with the Pregnancy and Lactation Labeling Rule (PLLR).

DOSAGES[62,63,64,65,66,67,68,69]

Drug	Cancer patients receiving myelosuppressive chemotherapy	Acute Myeloid Leukemia (AML) patients receiving chemotherapy	Bone Marrow Transplant (BMT)	Peripheral Blood Progenitor Cell Collection and Therapy	Severe Chronic Neutropenia	Hematopoietic Syndrome of Acute Radiation Syndrome	Availability
filgrastim (Neupogen)	5 mcg/kg/day, administered as a single daily injection by SC bolus, by short IV infusion (15 to 30 minutes), or continuous IV infusion; doses may be increased by increments of 5 mcg/kg for each chemotherapy cycle according to the duration and severity of the ANC nadir	5 mcg/kg/day as single daily injection by SC injection, short IV infusion (15 to 30 minutes), or continuous IV infusion; doses may be increased by increments of 5 mcg/kg for each chemotherapy cycle according to the duration and severity of the ANC nadir	10 mcg/kg/day given as an IV infusion no longer than 24 hours; during periods of neutrophil recovery, the daily dose should be titrated against the neutrophil response dosing schedule	10 mcg/kg/day SC; give for at least 4 days before the first leukapheresis procedure and continued until the last leukapheresis	Starting Dose: Congenital Neutropenia: 6 mcg/kg SC twice daily Idiopathic or Cyclic Neutropenia: 5 mcg/kg SC daily	10 mcg/kg as single daily SC injection; administer as soon as possible after suspected/ confirmed exposure to radiation doses > 2 gray (Gy)	Single-dose vials: 300 mcg/1 mL, 480 mcg/1.6 mL Prefilled single-use syringes (SingleJect®): 300 mcg/0.5 mL, 480 mcg/0.8 mL
filgrastim-aafi (Nivestym)						--	Single-dose vials: 300 mcg/1 mL, 480 mcg/1.6 mL Prefilled syringe: 300 mcg/0.5 mL, 480 mcg/0.8 mL
filgrastim-sndz (Zarxio)						--	Prefilled single-dose syringes: 300 mcg/0.5 mL, 480 mcg/0.8 mL

Dosages (continued)

Drug	Cancer patients receiving myelosuppressive chemotherapy	Acute Myeloid Leukemia (AML) patients receiving chemotherapy	Bone Marrow Transplant (BMT)	Peripheral Blood Progenitor Cell Collection and Therapy	Severe Chronic Neutropenia	Hematopoietic Syndrome of Acute Radiation Syndrome	Availability
pegfilgrastim (Neulasta)	6 mg SC once per chemotherapy cycle; pediatric (weight < 45 kg) dosing is weight-based per dosing schedule in drug PI	--	--	--	--	2 doses, 6 mg each, given SC 1 week apart; pediatric (weight < 45 kg) dosing is weight based per dosing schedule in drug PI; first dose given as soon as possible after suspected / confirmed radiation exposure of > 2 gray; second dose given 1 week after	Neulasta: single-use prefilled syringe for manual use: 6 mg/0.6 mL Neulasta Onpro® Delivery Kit: single-use delivery kit: 1 prefilled syringe (6 mg/0.6 mL) copackaged with 1 on-body injector for HCP administration
pegfilgrastim-cbqv (Udenyca)						--	Single-dose prefilled syringe: 6 mg/0.6 mL
pegfilgrastim-jmdb (Fulphila)						--	Single-dose prefilled syringe: 6 mg/0.6 mL

Dosages (continued)

Drug	Cancer patients receiving myelosuppressive chemotherapy	Acute Myeloid Leukemia (AML) patients receiving chemotherapy	Bone Marrow Transplant (BMT)	Peripheral Blood Progenitor Cell Collection and Therapy	Severe Chronic Neutropenia	Hematopoietic Syndrome of Acute Radiation Syndrome	Availability
sargramostim (Leukine)	--	250 mcg/m^2/day given IV over 4 hours starting approximately day 11 or 4 days following completion of induction chemotherapy, if the day 10 bone marrow is hypoplastic with < 5% blasts	250mcg/m^2/day given IV over 2 hours beginning 2 to 4 hours after bone marrow infusion, and not < 24 hours after the last dose of chemotherapy or radiotherapy; therapy should not begin until post-marrow infusion ANC is < 500 cells/mm^3 and continued until ANC is > 1,500 cells/mm^3 for 3 consecutive days; treatment of BMT failure or engraftment delay: 250 mcg/m^2/day given IV over 2 hours for 14 days	Mobilization/collection: 250 mcg/m^2/day IV over 24 hours or SC once daily; continue at same dose through PBPC collection, usually after 5 days; if WBC > 50,000 cells/mm^3 reduce dose by 50% Transplantation: 250 mcg/m^2/day IV over 24 hours or SC once daily until ANC > 1,500 cells/mm^3 for 3 consecutive days	--	Administer weight-based dose as SC injection once daily after suspected or confirmed exposure to radiation doses > 2 gray; continue until ANC > 1,000/mm^3 for 3 consecutive CBCs or exceeds 10,000/mm^3 after radiation induced nadir Adults/pediatrics > 40 kg: 7 mcg/kg; pediatrics 15 kg to 40 kg: 10 mcg/kg; and pediatrics < 15kg: 12 mcg/kg	Single-dose vial: 250 mcg

Dosages (continued)

Drug	Cancer patients receiving myelosuppressive chemotherapy	Acute Myeloid Leukemia (AML) patients receiving chemotherapy	Bone Marrow Transplant (BMT)	Peripheral Blood Progenitor Cell Collection and Therapy	Hematopoietic Syndrome of Acute Radiation Syndrome	Severe Chronic Neutropenia	Availability
tbo-filgrastim (Granix)	5 mcg/kg/day as a SC injection until expected neutrophil nadir is passed and neutrophil count is in normal range; administer no earlier than 24 hours following myelosuppressive chemotherapy	--	--	--	--	--	Single-use, preservative-free, prefilled syringes: 300 mcg/0.5 mL, 480 mcg/0.8 mL with needle guard (HCP-administered); without needle guard (self- or caregiver-administered) Single use vials: 300 mcg/1 mL, 480 mcg/1.6 mL

PI=Prescribing Information

Due to the potential sensitivity of rapidly dividing myeloid cells to chemotherapy, filgrastim, filgrastim biosimilars, and tbo-filgrastim should not be administered within 24 hours before administration of chemotherapy. These products should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy. Administer filgrastim, or its biosimilars daily for up to 2 weeks or until the ANC has reached 10,000/mm^3 following the expected chemotherapy-induced neutrophil nadir. Daily dosing of tbo-filgrastim should continue until the expected neutrophil nadir is passed and the ANC has recovered to the normal range; in clinical trials tbo-filgrastim was given for up to 14 days or until and ANC > 10,000 x 10^6/L after the nadir. The duration of filgrastim and filgrastim biosimilar therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive capabilities of the chemotherapy regimen being used. Discontinue filgrastim or its biosimilars if the ANC exceeds 10,000/mm^3 after the expected chemotherapy-induced neutrophil nadir.

The first dose of filgrastim or its biosimilars for patients receiving BMT should be administered at least 24 hours after chemotherapy treatment and at least 24 hours after bone marrow infusion. Pegfilgrastim and pegfilgrastim biosimilars should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

The filgrastim-aafi and filgrastim-sndz single-dose prefilled syringe are not designed to allow for direct administration of doses < 0.3 mL. The spring-mechanism interferes with the visibility of the graduation markings for doses < 0.3 mL. As a result, patient administration of doses < 0.3 mL is not recommended.

Pegfilgrastim, pegfilgrastim-cbqv, and pegfilgrastim-jmdb prefilled syringes are not designed to allow for direct administration of doses < 0.6 mL as they do not bear the necessary graduation marks. Direct administration to patients needing doses < 0.6 mL is not recommended due to potential dosing errors. Pediatric dosage of 0.1 mg/kg should be used for those weighing < 10 kg.

The prefilled syringe co-packaged with pegfilgrastim (Neulasta Onpro) kit should only be used with the on-body injector as it contains additional solution to compensate for liquid loss during delivery through the on-body injector. If the prefilled syringe co-packaged in the Neulasta Onpro kit is used for manual subcutaneous injection, overdose will occur. Likewise, if the manual single-use prefilled syringe is used with the on-body injector, the patient will be underdosed. The on-body injector should not be used with any other drugs and it is not recommended for patients with hematopoietic subsyndrome of acute radiation syndrome (ARS).

A HCP must fill the on-body injector with pegfilgrastim using the prefilled syringe and apply the injector to the patient's intact, non-irritated skin (abdomen or back of arm). The back of the arm may only be used if there is a caregiver available to monitor the status of the on-body injector. An HCP may initiate administration with the on-body injector on the same day as the administration of chemotherapy, as long as the injector delivers pegfilgrastim no less than 24 hours after administration of chemotherapy. Approximately 27 hours after the on-body injector is applied to the patient's skin, pegfilgrastim will be delivered over approximately 45 minutes.

Like the single-use manual syringes, the single-use pegfilgrastim (Neulasta) delivery kits should be refrigerated until ready for use. Because the on-body injector for pegfilgrastim is at room temperature during use, the kit should not be held at room temperature for more than 12 hours prior to use. The kit should be discarded if stored at room temperature > 12 hours and the prefilled syringe should be discarded if stored at room temperature > 48 hours. The injector should be kept dry for the last 3

hours prior to the beginning of dose delivery in order to identify potential leaks. It is waterproof for up to 8 feet for 1 hour. Do not reapply if the on-body injector falls off.

For neutrophil recovery after chemotherapy in AML, if a second cycle of induction is needed, sargramostim should be administered approximately 4 days after the completion of chemotherapy if bone marrow is hypoplastic with < 5% blasts. Sargramostim should be continued until the ANC is > 1,500 cells/mm^3 for 3 consecutive days; not to exceed 42 days. Do not administer sargramostim within 24 hours preceding or following chemotherapy or radiation. For bone marrow transplantation failure or engraftment delay, another dose can be administered after 7 days off therapy if engraftment has not occurred; if engraftment still does not occur, a third course of 500 mcg/m^2/day for 14 days can be used after another 7 days off therapy; additional dose escalation is unlikely to be beneficial.

Sargramostim treatment should be interrupted or the dose reduced by half if the ANC exceeds 20,000 cells/mm^3 in order to avoid complications of excessive leukocytosis or if WBC is > 50,000 cells/mm^3. If a severe reaction occurs, the sargramostim dose can be decreased by 50% or temporarily discontinued until the reaction goes away. If leukemic regrowth, disease progression, or blast cells appear, sargramostim should be discontinued.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class for FDA-approved indications. Randomized, controlled, double-blind, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Biosimilars must demonstrate that there are no clinically meaningful differences in safety or effectiveness from the reference product. Often biosimilars are compared to products that are not available in the US. In this therapeutic class review, only biosimilar clinical studies that meet the above search criteria and compare the biosimilar product to an FDA-approved reference product will be included.

Pegfilgrastim-cbqv (Udenyca) was compared to pegfilgrastim (Neulasta) for immunogenicity, adverse reactions, safety, pharmacokinetics, and pharmacodynamics; no significant differences were found.[70]

Pegfilgrastim-jmdb (Fulphila) was compared to European-sourced pegfilgrastim in a phase 3 trial, but not an FDA-approved product.[71] The FDA states approval is based on review of evidence that included extensive structural and functional characterization, animal study data, human pharmacokinetic and

pharmacodynamic data, clinical immunogenicity data, and other clinical safety and effectiveness data that demonstrates pegfilgrastim-jmdb (Fulphila) is biosimilar to pegfilgrastim (Neulasta).[72]

Three open-label studies compared filgrastim-aafi (Nivestym) and US-sourced filgrastim (Neupogen). No significant difference was found between the products regarding pharmacokinetics, pharmacodynamics, safety, and immunogenicity.[73,74]

filgrastim (Neupogen) and pegfilgrastim (Neulasta)

Pegfilgrastim 6 mg SC once per chemotherapy cycle (every 21 days) and filgrastim 5 mcg/kg SC daily were compared in 157 patients with breast cancer (stage II–IV).[75] The placebo and filgrastim injections were given daily until the absolute neutrophil count was > 10 x 10^9/L or a total of 14 days. This randomized, double-blind, multicenter study evaluated patients for duration of grade 4 neutropenia, depth of neutrophil nadir, incidence of febrile neutropenia, time to neutrophil recovery, and safety data. Patients received doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 chemotherapy. A total of 152 patients were evaluated for efficacy. Pegfilgrastim and filgrastim had similar efficacy for all efficacy measures for all cycles. The incidence of severe neutropenia was 83% with filgrastim therapy and 84% with pegfilgrastim during cycle 1. The duration of severe neutropenia during cycle 1 was 1.6 days with filgrastim and 1.8 days with pegfilgrastim. The incidence of febrile neutropenia was 20% with filgrastim and 13% with pegfilgrastim. The median time of recovery to an ANC of > 2 x 10^9 mm^3 in all cycles for both treatment groups was 9 days. The most frequently reported adverse effect was bone pain (37% pegfilgrastim; 42% filgrastim).

A randomized, double-blind, non-inferiority study compared the safety and efficacy of filgrastim and pegfilgrastim in 310 patients with advanced breast cancer (stage II-IV) receiving chemotherapy.[76] Patients were randomized to filgrastim 5 mcg/kg body weight once daily or pegfilgrastim 100 mcg/kg body weight once every 21-day chemotherapy cycle plus placebo injection once daily. G-CSF therapy began 24 hours post-chemotherapy. Patients received doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 for up to 4 cycles. Daily injections of filgrastim or placebo were given until the ANC was 10 x 10^9/L or a total of 14 days. The primary outcome was duration of grade 4 neutropenia (ANC < 500 in cycle 1); the percentage of patients experiencing grade 4 neutropenia in cycle 1 was 79% and 77% for filgrastim and pegfilgrastim, respectively (p>0.5). The mean duration of grade 4 neutropenia for cycle 1 was 1.8 and 1.7 days for filgrastim and pegfilgrastim, respectively (p>0.5). For subsequent cycles (2 through 4), the mean duration of severe neutropenia for cycles 2, 3, and 4 were 0.7, 0.6, and 0.9 days for pegfilgrastim and 1.1, 1.2, and 1.3 days for filgrastim (p≤0.001 cycles 2 and 3, p=0.019 cycle 4). The incidence of febrile neutropenia (defined as fever > 38.2^o C with ANC < 0.5 x 10^9/L) was 12% with filgrastim and 7% with pegfilgrastim during the first cycle. Incidence of febrile neutropenia over the entire study period was 18% with filgrastim and 9% with pegfilgrastim (p=0.029). Time to ANC recovery was 9.7 days with filgrastim and 9.3 days with pegfilgrastim (95% confidence interval [CI], -0.88 to 0.08). Adverse event profiles were similar in both groups. The pegfilgrastim dose is different from the current FDA-approved labeling dose of 6 mg as a single dose.

filgrastim (Neupogen) and sargramostim (Leukine)

A randomized, double-blind, multicenter study compared sargramostim and filgrastim in the treatment of chemotherapy-induced myelosuppression in 181 afebrile cancer patients with ANC levels < 500/µL.[77] Patients received daily SC injections of either agent until ANC levels reached at least 1,500/µL. There was no statistical difference between treatment groups in the mean number of days to

reach an ANC of 500/µL, but the mean number of days to reach ANC levels of 1,000/µL and 1,500/µL was approximately 1 day less in patients receiving filgrastim. Fewer patients in the sargramostim arm were hospitalized, and they had a shorter mean length of hospitalization, mean duration of fever, and mean duration of intravenous antibiotic therapy compared with patients who received filgrastim. Both growth factors were well tolerated. Sargramostim and filgrastim have comparable efficacy and tolerability in the treatment of standard-dose chemotherapy-induced myelosuppression in community practice.

A randomized, double-blind, multicenter study in 137 cancer patients receiving myelosuppressive chemotherapy compared the tolerability of sargramostim and filgrastim in the prevention or treatment of chemotherapy-induced neutropenia.[78] Patients received sargramostim SC 300 mcg daily or filgrastim SC 480 mcg daily starting 1 to 2 days after completion of chemotherapy. The drugs were given prophylactically to 82% of patients within 48 hours; the other patients (18%) received the drugs when the ANC decreased to < 500/mL. No statistically significant differences in the incidence or severity of adverse events were detected with the exception of a slightly higher incidence of grade 1 fever (< 38.1 degrees C) with sargramostim. The study was not designed to evaluate efficacy, but it was noted that there were no statistically significant differences between treatment groups in total days of growth factor therapy, days of hospitalization, or days of intravenous antibiotics during the treatment period.

filgrastim-sndz (Zarxio) and filgrastim (Neupogen)

The efficacy and safety of filgrastim-sndz were evaluated in a multicenter, phase 3, randomized, double-blind, active-control, noninferiority study in 218 adult, female breast cancer patients receiving adjuvant myelosuppressive chemotherapy (TAC: docetaxel, doxorubicin, cyclophosphamide).[79] A notable inclusion criterion was adequate bone marrow function, while exclusion criteria included: history of myelogenous leukemia, myelodysplastic syndrome, or concomitant sickle cell disease; concurrent or prior radiotherapy within 4 weeks of randomization; and use of prophylactic antibiotics, prior chemotherapy, or anticancer treatment of breast cancer, or previous G-CSF therapy. Patients were randomized 1:1:1:1 to 4 treatment arms prior to 6 cycles of chemotherapy: (1) filgrastim-sndz, (2) reference filgrastim, (3) alternating filgrastim-sndz and reference filgrastim each cycle, or (4) alternating reference filgrastim and filgrastim-sndz each cycle. Chemotherapy was administered on day 1 of each cycle and given every 3 weeks for 6 cycles. The assigned filgrastim agent (5 mcg/kg/day) was administered daily as a SC injection beginning on day 2 of each cycle until the ANC recovered to 10,000/mm^3 following the nadir or for a maximum of 14 days. The primary endpoint was duration of severe neutropenia, defined as a difference in mean DSN (number of consecutive days from ANC < 500/mm^3 to ≥ 500/mm^3) between the 2 filgrastim agents during cycle 1. Filgrastim-sndz was defined as noninferior if the lower 97.5% CI for the DSN mean difference in the per-protocol population was larger than -1 day. The mean DSN for the per-protocol population in cycle 1 was 1.17 days (95% CI, 0.95 to 1.39) in the biosimilar group (n=101) and 1.2 days (95% CI, 1 to 1.4) in the reference arm (n=103). The DSN mean difference was 0.04 days, and the lower 97.5% CI was -0.26 days. Thus, filgrastim-sndz met the noninferiority requirement. Results in the full analysis set for cycle 1 were similar to the per-protocol analysis. The authors found no clinically meaningful differences between the 2 agents across all cycles in secondary efficacy measures, including incidence of febrile neutropenia (FN), hospitalization secondary to FN, infection incidence, and extent and timing of nadir.

META-ANALYSIS

A meta-analysis evaluated a total of 5 head-to-head studies comparing pegfilgrastim and filgrastim for reducing chemotherapy-induced neutropenia among a total of 617 patients with solid tumors and malignant lymphomas.[80] Studies included used the approved doses as indicated in the package insert. Although only 1 study had a statistically significant difference in febrile neutropenia reductions favoring pegfilgrastim over filgrastim (relative risk [RR] reduction of 50%; p=0.027), the pooled RR showed a statistically significant favorable result for pegfilgrastim (RR, 0.64; 95% CI, 0.43 to 0.97). Grade 4 neutropenia rates (for cycle 1: RR, 0.99; 95% CI, 0.91 to 1.08; cycle 2: RR, 0.88; 95% CI, 0.7 to 1.11; cycle 3: RR, 0.80; 95% CI, 0.47 to 1.36; cycle 4: RR, 0.9; 95% CI, 0.71 to 1.13), time to ANC (95% CI, -0.34 to 0.56), and incidence of bone pain (RR, 0.95; 95% CI, 0.76 to 1.19) were similar between the 2 G-CSFs. A single dose of pegfilgrastim performed better than a median of 10 to 14 days of filgrastim in reducing febrile neutropenia rates for patients undergoing myelosuppressive chemotherapy.

SUMMARY

Myelosuppressive chemotherapy can induce neutropenia and febrile neutropenia, which can lead to increased healthcare costs and poor patient health outcomes. Clinical trials have shown that prophylactic use of colony stimulating factors (CSFs) promote the recovery of neutrophils following myelosuppressive chemotherapy and decrease the likelihood of neutropenic complications. Limited comparative data suggest that filgrastim (Neupogen) and pegfilgrastim (Neulasta) have similar efficacy, tolerability, and adverse drug reaction profiles. However, though data are limited, pegfilgrastim may have a slightly higher rate of reducing febrile neutropenia compared to filgrastim. In comparison to other products, pegfilgrastim and pegfilgrastim biosimilar administration frequency may be viewed as more favorable since it only requires a single subcutaneous injection per chemotherapy cycle, whereas filgrastim, filgrastim-aafi (Nivestym), filgrastim-sndz (Zarxio), tbo-filgrastim (Granix), and sargramostim (Leukine) administration requires daily subcutaneous injection. Additionally, the pegfilgrastim delivery kit (Neulasta Onpro) offers an alternative delivery option with the on-body injector. Several biosimilars to the originator products, filgrastim (filgrastim-aafi and filgrastim-sndz) and pegfilgrastim (pegfilgrastim-cbqv and pegfilgrastim-jmdb), are now available; tbo-filgrastim was not approved as a biosimilar. Further clinical trials comparing clinical activity, toxicity, cost-effectiveness, and long-term outcomes of these products are warranted since head-to-head trials are extremely limited.

The v2.2019 NCCN practice guidelines for hematologic growth factors indicate there is higher level evidence supporting the use of filgrastim, filgrastim-aafi, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim (category 1) for prophylaxis use against febrile neutropenia. Pegfilgrastim-cbqv and pegfilgrastim-jmdb are rated a category 2A and sargramostim is no longer recommended in this setting. However, the guidelines also acknowledge that there are insufficient head-to-head comparative studies on the clinical benefits of G-CSFs and GM-CSFs. A delivery device for pegfilgrastim is also available that impacted NCCN guidelines for pegfilgrastim use eliminating same day pegfilgrastim/chemotherapy therapy recommendations. The 2019 NCCN guidelines also address the use of biosimilars. The guidelines note that biosimilars are biological products that are highly similar to their FDA-approved originator product with very small, clinically inactive differences but have no difference in efficacy, safety, or purity. The guidelines state if overall safety and efficacy are equivalent, biosimilars may be substituted for the originator product and may provide opportunities for cost containment; however, at this time the FDA does not consider an biosimilar to be interchangeable (substitutable without physician involvement) with its originator product. To conclude, the NCCN

guidelines recommend clinicians assess the patient and treatment-related risk factors for the development of neutropenic complications and clinicians should use independent judgment when considering appropriate therapy.

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