

Therapeutic Class Overview Colony-Stimulating Factors

Therapeutic Class

- Overview/Summary:** There are two types of colony-stimulating factors (CSFs) commercially available in the United States, the granulocyte CSFs (G-CSFs) and the granulocyte-macrophage CSF (GM-CSF). Filgrastim (Neupogen[®]) and pegfilgrastim (Neulasta[®]) are the two G-CSFs available, whereas sargramostim (Leukine[®]) is the only GM-CSF available. There is currently no generic product available in the United States. These agents primarily differ in their Food and Drug Administration-approved indications, which are outlined below in Table 1.¹⁻³ The G-CSFs are generally used in cancer patients to reduce the incidence of adverse events associated with chemotherapy including febrile neutropenia. GM-CSF is commonly used to accelerate myeloid recovery in patients who have received myeloablative chemotherapy and/or stem cell transplantation. Several retrospective studies have compared the efficacy of CSFs in reducing the risk of chemotherapy-induced neutropenia and results have demonstrated that pegfilgrastim was associated with fewer hospitalizations for febrile neutropenia compared to filgrastim and/or sargramostim.⁴⁻⁶ An earlier, randomized controlled trial demonstrated that there were no clinically significant differences between filgrastim and pegfilgrastim.⁷ Presently, the National Comprehensive Cancer Network states that both filgrastim and pegfilgrastim have stronger evidence than sargramostim supporting their use.⁸ The American Society of Clinical Oncology and the European Organization for Research and Treatment of Cancer make no recommendation on which of the G-CSFs is preferred.^{9,10}

Table 1. Current Medications Available in Therapeutic Class¹⁻³

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Filgrastim (Neupogen [®])	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs, to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with acute myeloid leukemia, to reduce the duration of neutropenia and neutropenia-related clinical sequelae in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation, for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis, for chronic administration to reduce the incidence and duration of sequelae of neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia or idiopathic neutropenia	Prefilled syringe (preservative-free): 300 µg/0.5 mL 480 µg/0.8 mL Single-dose vial (preservative-free): 300 µg/mL 480 µg/1.6 mL	-
Pegfilgrastim (Neulasta [®])	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs	Prefilled single use syringe: 6 mg/0.6 mL	-
Sargramostim (Leukine [®])	For the mobilization of hematopoietic progenitor cells into the peripheral blood	Liquid for injection (preserved solution):	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	for collection by leukapheresis, to reduce time to neutrophil recovery and the incidence of severe and life-threatening infections and infections resulting in death in older adult patients with acute myelogenous leukemia following induction chemotherapy, to accelerate myeloid recovery in patients with non-Hodgkin lymphoma, acute lymphoblastic leukemia and Hodgkin disease undergoing autologous bone marrow transplantation, to accelerate myeloid recovery in patients undergoing allogeneic bone marrow transplantation from human leukocyte antigen-matched related donors, in patients who have undergone allogeneic or autologous bone marrow transplantation in whom engraftment is delayed or has failed	500 µg/mL Powder for reconstitution (preservative-free): 250 µg	

Evidence-based Medicine

- Two retrospective trials evaluated the efficacy of filgrastim and pegfilgrastim in patients with nonmyeloid malignancies who received chemotherapy. In Almenar et al, pegfilgrastim was associated with fewer episodes of febrile neutropenia compared to filgrastim (10.7 vs 24.3%; *P* value not reported) as well as fewer hospitalizations for febrile neutropenia (9.3 vs 19.8%; *P* value not reported).⁴ Results from Weycker et al also demonstrated that the risk of hospitalization for febrile neutropenia or infection was lower with pegfilgrastim compared to filgrastim (odds ratio, 0.64; 95% confidence interval, 0.48 to 0.85; *P*=0.002).⁵
- One retrospective, case-controlled cohort study was conducted to compare filgrastim, pegfilgrastim and sargramostim in reducing the risks of neutropenia-related hospitalizations in cancer patients receiving chemotherapies. The results showed that the use of pegfilgrastim was associated with fewer hospitalizations for neutropenic complications compared to filgrastim and sargramostim (1.1, 2.1 and 2.5%, respectively; *P*<0.001 for both filgrastim and sargramostim compared to pegfilgrastim).⁶
- A recent meta-analysis of twenty studies by Cooper et al demonstrated that there was a significantly lower risk of febrile neutropenia following treatment with pegfilgrastim compared to filgrastim (relative risk, 0.66; 95% CI, 0.44 to 0.98).¹¹
- Additional randomized controlled trials are needed to provide stronger evidence to determine whether differences in safety and efficacy are present between the agents for the various other approved indications.

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Colony-stimulating factors (CSFs) should be used as primary prophylaxis when the risk of febrile neutropenia is >20% in patients with cancer who are receiving myelosuppressive chemotherapy, as assessed by the type of chemotherapy regimen and patient risk factors.⁸⁻⁹
 - Filgrastim and pegfilgrastim are considered to have more evidence than sargramostim supporting their use as prophylaxis of febrile neutropenia.⁸
 - When febrile neutropenia develops, patients who are receiving prophylactic filgrastim or sargramostim should continue with CSF therapy until resolution of neutropenia. Patients who are not receiving a CSF prophylactically should start CSF therapy if they are at risk for infection-related complications or poor clinical outcomes.^{8,9}

- CSF therapy is the current standard of care to mobilize peripheral blood stem cells and after autologous peripheral blood stem cell transplantation.⁹
- CSF therapy may be considered in the elderly with acute myeloid leukemia once chemotherapy is completed to reduce time to neutrophil recovery.¹²
- CSF therapy is effective in the treatment of cyclic, congenital and idiopathic neutropenia.⁸
- Other Key Facts:
 - The CSFs are only available as branded agents.
 - There are differences in dosing schedules between the agents with pegfilgrastim being administered at a fixed dose (6 mg subcutaneously once per chemotherapy cycle), while both filgrastim and sargramostim are dosed daily based on patient body weight.¹⁻³

References

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Therapeutic Class Review Colony-Stimulating Factors

Overview/Summary

Colony-stimulating factors (CSFs) fall under the naturally occurring glycoprotein cytokines, one of the primary groups of immunomodulators and are vital to the proliferation and differentiation of hematopoietic progenitor cells.¹⁻³ Two types of CSFs available in the United States are the granulocyte CSF (G-CSF) and the granulocyte-macrophage CSF (GM-CSF). The two G-CSFs available are filgrastim (Neupogen[®]) and pegfilgrastim (Neulasta[®]), and the only GM-CSF available is sargramostim (Leukine[®]). The Food and Drug Administration (FDA)-approved indications differ between the agents. Both filgrastim and pegfilgrastim are FDA-approved to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy associated with a significant incidence of severe neutropenia with fever. In addition, filgrastim also has several other indications. There are differences in dosing schedules between the agents with pegfilgrastim being administered at a fixed dose (6 mg subcutaneously once per chemotherapy cycle), while both filgrastim and sargramostim are dosed daily based on patient body weight.⁴⁻⁷

The G-CSFs are generally used in patients with cancer to reduce the incidence of adverse events associated with chemotherapy, such as febrile neutropenia, infections and delayed neutrophil recovery time. Neutrophils are the body's defense system against infection and play a key role in the process of acute inflammation.⁸ Chemotherapy and radiation can affect neutrophil function and decrease the production of neutrophils in the bone marrow. Neutropenia is defined as an absolute neutrophil count (ANC) below 1,500 cells/ μ L. Patients with severe neutropenia (ANC <500 cells/ μ L) are at high risk for infection.⁸ Endogenous G-CSF is produced by monocytes, fibroblasts and endothelial cells and acts upon the bone marrow to increase the production of neutrophils. In addition to increasing neutrophil production, G-CSF also enhances phagocytic and cytotoxic actions of mature neutrophils.^{1,2} Filgrastim and pegfilgrastim are produced by recombinant deoxyribonucleic acid (DNA) technology via the insertion of the human G-CSF gene into *Escherichia coli* (*E coli*) bacteria.^{4,5} Pegfilgrastim, a long-acting formulation of filgrastim, is produced by conjugating filgrastim with polyethylene glycol, thereby increasing the molecular weight and delaying kidney excretion.⁵

GM-CSF is primarily used to accelerate myeloid recovery in oncology patients following myelosuppressive treatment regimens. Endogenous GM-CSF is predominantly found in T lymphocytes, monocytes, macrophages, fibroblasts and endothelial cells.¹ In addition to increasing the production of neutrophils, GM-CSF also increases other white blood cells including monocytes, macrophages and eosinophils in the bone marrow promotes their function. Like the G-CSFs, sargramostim is also produced utilizing recombinant DNA technology; however, it is derived in yeast (*Saccharomyces cerevisiae*) rather than *E coli* bacteria.⁶

Current treatment guidelines regarding the general use of CSFs from the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) recognize the importance of preventing and limiting the duration of febrile neutropenia. Similarly, both guidelines recommend primary prophylaxis with a CSF when the risk of febrile neutropenia is >20%. Therapeutic use of a CSF may be considered only when a patient with febrile neutropenia is at high risk of infection-related complications based on prognostic factors.^{9,10}

The results of several retrospective studies comparing the efficacy of CSFs in reducing the risk of neutropenic complications have demonstrated that pegfilgrastim may be associated with fewer hospitalizations for febrile neutropenia compared to filgrastim and/or sargramostim, while an earlier prospective, randomized trial demonstrated comparable clinical efficacy between filgrastim and pegfilgrastim.¹¹⁻¹⁴ There is currently no general consensus with regard to choosing between specific CSFs. The NCCN states that when choosing an agent for prophylaxis of febrile neutropenia, filgrastim and pegfilgrastim are considered to have stronger data to support their use compared to sargramostim.^{9,15} The European Organization for Research and Treatment of Cancer recommends the use of filgrastim and

pegfilgrastim while stating that there is some evidence showing G-CSF and GM-CSF are comparable in efficacy.¹⁶ The ASCO state that due to the lack of information, no recommendation can be made with regards to the equivalency of the two G-CSFs.¹⁰

Adverse events commonly reported with all of the CSFs include nausea, vomiting and bone pain. Warnings associated with G-CSFs include splenic rupture, acute respiratory distress syndrome, allergic reactions (e.g., anaphylaxis, angioedema or urticaria), sickle cell crisis and alveolar hemorrhage and hemoptysis in healthy donors undergoing peripheral blood progenitor cell mobilization.^{4,5} Warnings for sargramostim include fluid retention (e.g., edema, capillary leak syndrome and pleural and/or pericardial effusion), respiratory syndromes, arrhythmias, elevation of serum creatinine or hepatic enzymes and fatal gasping syndrome in premature infants associated with the use of benzyl alcohol.⁶

Medications

Table 1. Medications Included Within Class Review⁴⁻⁶

Generic Name (Trade name)	Medication Class	Generic Availability
Filgrastim (Neupogen [®])	Granulocyte colony stimulating factor	-
Pegfilgrastim (Neulasta [®])	Granulocyte colony stimulating factor	-
Sargramostim (Leukine [®])	Granulocyte-macrophage colony stimulating factor	-

Indications

Table 2. Food and Drug Administration-Approved Indications⁴⁻⁶

Indication	Filgrastim	Pegfilgrastim	Sargramostim
To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever	✓	✓	
To reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with acute myeloid leukemia	✓		
To reduce the duration of neutropenia and neutropenia-related clinical sequelae (e.g., febrile neutropenia) in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation	✓		
For the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis	✓		✓
For chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia or idiopathic neutropenia	✓		
For use following induction chemotherapy in older adult patients with acute myelogenous leukemia to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death			✓
For acceleration of myeloid recovery in patients			✓

Indication	Filgrastim	Pegfilgrastim	Sargramostim
with non-Hodgkin's lymphoma, acute lymphoblastic leukemia, and Hodgkin's disease undergoing autologous bone marrow transplantation			
For acceleration of myeloid recovery in patients undergoing allogeneic bone marrow transplantation from human leukocyte antigen-matched related donors			✓
In patients who have undergone allogeneic or autologous bone marrow transplantation in whom engraftment is delayed or has failed			✓

Filgrastim has been used off-label for the treatment of graft failure following bone marrow transplantation, neutropenia associated with myelodysplastic syndrome, hairy cell leukemia, aplastic anemia, acquired immune deficiency syndrome and zidovudine- and other drug-induced neutropenia. Pegfilgrastim has been used to decrease the risk of infection and febrile neutropenia in pediatric patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy. Sargramostim has been most commonly used off-label to treat Crohn's disease, melanoma, neutropenia associated with myelodysplastic syndrome, aplastic anemia, oral mucositis, pulmonary alveolar proteinosis, sepsis and neutropenia in the newborn, stomatitis, zidovudine- and other drug-induced neutropenia and wound healing.^{7,17}

Pharmacokinetics

The pharmacokinetics of filgrastim were comparable in both healthy subjects and cancer patients, and the elimination half-lives for intravenous and subcutaneous administration were similar. Pegfilgrastim was administered in 379 cancer patients and was found to exhibit nonlinear pharmacokinetics. The clearance of pegfilgrastim is directly proportional to the number of neutrophils, and the clearance decreases with increases in dose.⁴⁻⁶

Table 3. Pharmacokinetics^{4-6,17}

Generic Name	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Filgrastim	Not reported	Administered intravenously or subcutaneously	Not reported	Not reported	Intravenous and subcutaneous, 3.5
Pegfilgrastim	Not reported	Administered subcutaneously	Not reported	Not reported	Subcutaneous, 15 to 80
Sargramostim	Not reported	Administered intravenously or subcutaneously	Not reported	Not reported	Intravenous, 1; subcutaneous, 2 to 3

Clinical Trials

There are numerous placebo-controlled and head-to-head trials for filgrastim to pegfilgrastim; however, there few comparative trials between the granulocyte colony-stimulating factors (G-CSFs) and granulocyte-macrophage colony-stimulating factor (GM-CSF).

One randomized, double-blind, multicenter trial compared filgrastim and sargramostim in 181 patients with chemotherapy-induced febrile neutropenia (absolute neutrophil count [ANC] ≤ 500 cells/ μ L). Patients were given daily subcutaneous injections of either agent until ANC levels reached $\geq 1,500$ cells/ μ L. Overall, the mean number of days patients received filgrastim was significantly shorter than sargramostim (4.60 vs 5.70; $P=0.0001$). There was no significant difference among the treatment groups in the mean number of days to reach an ANC of 500 cells/ μ L (3.60 vs 3.30, respectively; $P=0.32$); however, the mean number of days to reach an ANC of 1,000 and 1,500 cells/ μ L was significantly shorter in the filgrastim group (4.50 and 4.60, respectively) compared to the sargramostim group (5.10 and 5.70, respectively);

$P=0.009$ and $P=0.0001$, respectively). Patients receiving sargramostim had fewer hospitalizations with febrile neutropenia or intravenous antibiotics ($P=0.46$), shorter mean length of hospitalization ($P=0.58$) and shorter mean duration of fever ($P=0.14$) compared to patients in the filgrastim group; however, these differences were not significant. Both agents were well-tolerated and had comparable efficacy and tolerability in the treatment of standard-dose chemotherapy-induced myelosuppression.¹⁸

The results of a second prospective, randomized, double-blind, multicenter trial comparing sargramostim and filgrastim demonstrated that with the exception of a slightly higher incidence of grade one fever (37.1 to 38.0°C) with sargramostim compared to filgrastim (48 vs 26%, respectively; $P=0.01$), there were no statistically significant differences in the incidence or severity of local or systemic adverse events potentially related to CSFs. Although the study was not designed to directly evaluate efficacy, there were also no statistically significant differences between treatment groups in total days of growth factor therapy, days of hospitalization or days of intravenous antibiotic therapy. Both agents were well tolerated and there were no clinically significant differences between treatments.¹⁹

A Cochrane review of 13 randomized, placebo-controlled trials was performed to evaluate the efficacy and safety of G-CSF (filgrastim and lenograstim [not available in the United States]) or GM-CSF (sargramostim) compared to placebo in patients who were receiving nonmyeloablative chemotherapy for malignant lymphomas. The results of sensitivity analyses performed in this review demonstrated that there were no differences between G-CSF and GM-CSF in their effects on overall survival, freedom from treatment failure and risk reduction in incidence of neutropenia or febrile neutropenia.²⁰

A multicenter, randomized, double-blind, active-control trial compared single-dose pegfilgrastim to daily filgrastim in reducing neutropenia in 310 patients who received four cycles of myelosuppressive chemotherapy for high-risk breast cancer. There were no significant differences between treatment groups in the duration of severe neutropenia and the depth of ANC nadir in all cycles. Overall, the incidence of febrile neutropenia was lower in the pegfilgrastim group than in the filgrastim group (9 vs 18%; $P=0.029$). The difference in the mean duration of severe neutropenia between the pegfilgrastim and filgrastim treatment groups was less than one day. Adverse event profiles in the pegfilgrastim and filgrastim groups were similar. A single injection of pegfilgrastim per cycle was as safe and effective as daily injections of filgrastim in reducing neutropenia and its complications in patients who received four cycles of chemotherapy.¹⁴

Two retrospective trials evaluated the differences in efficacy between filgrastim and pegfilgrastim in patients with nonmyeloid malignancies who underwent chemotherapy. In Almenar et al, a multicenter, retrospective, observational trial, pegfilgrastim was associated with fewer episodes of febrile neutropenia compared to filgrastim (10.7 vs 24.3%; P value not reported) as well as fewer hospitalizations for febrile neutropenia (9.3 vs 19.8%; P value not reported).¹¹ Results from Weycker et al also demonstrated that the risk of hospitalization for febrile neutropenia or infection was lower with pegfilgrastim compared to filgrastim (odds ratio, 0.64; 95% confidence interval, 0.48 to 0.85; $P=0.002$).¹² Two retrospective, case-controlled cohort trials were conducted to compare filgrastim, pegfilgrastim and sargramostim in reducing the risks of neutropenia-related hospitalizations in cancer patients receiving chemotherapies. Weycker et al reported that the use of pegfilgrastim was associated with fewer hospitalizations for neutropenic complications compared to filgrastim and sargramostim (1.1, 2.1 and 2.5%, respectively; $P<0.001$ for both filgrastim and sargramostim compared to pegfilgrastim).¹³ Heaney et al found that sargramostim was associated with fewer infection-related hospitalizations compared to filgrastim (12 vs 26%, respectively; $P=0.0422$) and pegfilgrastim (24%; $P=0.0628$). The incidence of hospitalizations for febrile neutropenia was also lower in the sargramostim group compared to the filgrastim and pegfilgrastim groups; however, these differences were not statistically significant.²¹

Additional randomized controlled studies are needed to provide stronger evidence to determine whether differences in safety and efficacy are present between the agents with respect to the different indications.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Acceleration of Myeloid Recovery in Patients with Non-Hodgkin's Lymphoma, Acute Lymphocytic Leukemia and Hodgkin's Disease Undergoing Autologous Bone Marrow Transplant				
<p>Nemunaitis et al²²</p> <p>Sargramostim 250 µg/m²/day IV beginning within four hours of bone marrow reinfusion and continuing for 21 days</p> <p>vs</p> <p>placebo</p> <p>Preparative regimens used before transplantation differed among the participating institutions.</p>	<p>DB, MC, PC, RCT</p> <p>Patients with relapsed NHL, HD and ALL who were undergoing an autologous BMT</p>	<p>N=128</p> <p>100 days</p>	<p>Primary: Neutrophil recovery (ANC of ≥500x10⁶ cells/L)</p> <p>Secondary: Infections, duration of IV antibiotics, duration of hospitalization</p>	<p>Primary: Patients in the sargramostim group had a significantly shorter time to ANC recovery compared to patients in the placebo group (19 vs 26 days; <i>P</i><0.001).</p> <p>Secondary: Patients in the sargramostim group had significantly fewer nonstreptococcal infections compared to patients in the placebo group (<i>P</i><0.004).</p> <p>Patients in the sargramostim group had a significantly shorter duration of IV antibiotic use compared to patients in the placebo group (24 vs 27 days; <i>P</i>=0.009).</p> <p>Patients in the sargramostim group had a significantly shorter duration of hospitalization compared to patients in the placebo group (27 vs 33 days; <i>P</i>=0.01).</p> <p>There was no significant difference in incidence and duration of fever, frequency of other adverse events or 100-day survival rate between groups.</p>
<p>Rabinowe et al²³</p> <p>Sargramostim 250 µg/m²/day IV beginning within four hours of bone marrow reinfusion and continuing for 21 days</p> <p>vs</p> <p>placebo</p>	<p>ES</p> <p>Patients with relapsed NHL, HD and ALL who underwent an autologous BMT and originally participated in an efficacy study conducted by Nemunaitis et al.²²</p>	<p>N=128</p> <p>36 months</p>	<p>Primary: Long-term toxicities, clinical variables likely to predict for the speed of neutrophil engraftment and the independent predictive effect of sargramostim on neutrophil</p>	<p>Primary: There were no significant differences between the sargramostim group and the placebo group in disease-free survival (<i>P</i>=0.58) or in overall survival (<i>P</i>=0.55).</p> <p>Patients with a diagnosis of HD demonstrated delayed neutrophil recovery to both an ANC of ≥100 and ≥500 cells/µL (<i>P</i>=0.07) compared to patients with NHL or leukemia.</p> <p>Patients with HD and previous exposure to stem cell depleting agents experienced a significant delay in neutrophil recovery to an ANC of ≥500/µL compared to placebo (<i>P</i>=0.0008).</p> <p>Sargramostim accelerated neutrophil recovery following marrow infusion regardless of disease type (<i>P</i>=0.0011), previous exposure to agents that</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			recovery Secondary: Not reported	deplete stem cells ($P=0.0028$), prior number of drugs ($P=0.0035$), radiotherapy exposure ($P=0.0024$), marrow purging ($P=0.0028$), type of preparative regimen ($P=0.0023$) or relapse status at autologous BMT ($P=0.0031$) compared to placebo. Secondary: Not reported
Lazarus et al ²⁴ RhGM-CSF 11 µg/kg/day IV beginning three hours after completion of marrow infusion then daily thereafter over four hours until either recovery of both neutrophil count (ANC of >1,500 cells/µL) and platelet count (>50,000 units/µL, untransfused) occurred, or CSF therapy was administered for a total of 30 days vs historical control group Treatment consisted of involved-field radiotherapy, cyclophosphamide 60 mg/kg/day IV for two days, fractionated total body irradiation and autologous BMT.	MC Patients 15 to 60 years of age with histologically confirmed NHL in relapse	N=16 Duration not specified	Primary: Neutrophil recovery (ANC of ≥ 500 cells/mm ³), time to self-sustaining platelet count of >20,000 units/µL, toxicity and hematopoietic reconstitution Secondary: Not reported	Primary: Neutrophil recovery was significantly faster in the rhGM-CSF group compared to the control group (14 vs 20 days; $P=0.00002$). Time to self-sustaining platelet count of >20,000 units/µL was not significantly different between the rhGM-CSF group (23.5 days) and the control group (26 days; $P=0.38$). Toxicities encountered were mild and included fever, chills, hypertension, alopecia, rash, diarrhea, stomatitis, myalgias and synovial (knee) effusions. All patients showed early regeneration of hematopoietic precursors in the bone marrow between days 10 and 22 after transplantation and increased in proportion to peripheral blood counts, but by 30 to 60 days, remained lower than prior to transplant. Neutrophils transiently decreased in 13 of 16 patients (median decrease, 42%) within 24 to 72 hours of discontinuing rhGM-CSF infusions. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Acceleration of Myeloid Recovery in Patients Undergoing Allogeneic Bone Marrow Transplant from Human Leukocyte Antigen-Matched Related Donors				
<p>Nemunaitis et al²⁵</p> <p>Sargramostim 250 µg/m²/day infused over four hours starting on the day of marrow infusion and continuing to day 20</p> <p>vs</p> <p>placebo</p> <p>All patients received HLA-identical sibling marrow, cyclosporine, and prednisone for GVHD prophylaxis.</p>	<p>DB, MC, PC, RCT</p> <p>Patients of all ages and of either sex undergoing HLA-identical sibling BMT for hematologic malignancy</p>	<p>N=109</p> <p>1 year</p>	<p>Primary: Time to myeloid engraftment (ANC of >500 cells/mm³), time to ANC of ≥1,000/mm³ and median days of hospitalization</p> <p>Secondary: Rate of infections, rate of bacteremia and rate of grade three or four mucositis</p>	<p>Primary: The median time to myeloid engraftment was significantly shorter in the sargramostim group compared to the placebo group (13 vs 17 days; <i>P</i>=0.0001).</p> <p>The median time to ANC of ≥1,000/mm³ was significantly shorter in the sargramostim group compared to the placebo group (14 vs 19 days; <i>P</i>=0.0001).</p> <p>The median days of hospitalization were significantly shorter in the sargramostim group compared to the placebo group (25 vs 26 days; <i>P</i>=0.02).</p> <p>Secondary: The rate of infections was significantly lower in the sargramostim group compared to the placebo group (34 vs 51 patients; <i>P</i>=0.001).</p> <p>The rate of bacteremia was significantly lower in the sargramostim group compared to the placebo group (9 vs 19 patients; <i>P</i>=0.043).</p> <p>The rate of grade three or four mucositis was significantly lower in the sargramostim group compared to the placebo group (4 vs 16 patients; <i>P</i>=0.005).</p> <p>There were no significant differences between treatment groups in platelet recovery, erythrocyte recovery, incidence of veno-occlusive disease, GVHD severity, relapse or survival.</p>
Chronic Administration to Reduce Incidence and Duration of Sequelae of Neutropenia in Symptomatic Patients with Congenital, Cyclic or Idiopathic Neutropenia				
<p>Bernini et al²⁶</p> <p>RhG-CSF 5 µg/kg SC once daily until ANC was >1.5x10⁹ cells/L</p> <p>The rhG-CSF dosage,</p>	<p>PRO</p> <p>Children with symptomatic chronic idiopathic neutropenia with an ANC of <0.5x10⁹</p>	<p>N=6</p> <p>Mean of 14 months</p>	<p>Primary: Neutrophil response, clinical response, complications and expense</p>	<p>Primary: Treatment with rhG-CSF 5 µg/kg daily resulted in a mean 44-fold increase (25- to 143-fold increase) in the ANC by the end of the first week of treatment.</p> <p>At 14 months, the minimal rhG-CSF dose requirements ranged from 1 µg/kg once weekly to 5 µg/kg every other day to maintain an ANC of >1x10⁹ cells/L, but all patients were able to maintain this goal.</p>

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<p>interval and amount were then increased and decreased, respectively, in an alternating fashion until the lowest rhG-CSF dose was reached that would maintain the ANC $>1 \times 10^9$ cells/L.</p>	<p>cells/L documented repeatedly (and confirmed as not varying in a cyclic fashion) for less than six months, ≥ 12 infections that required antibiotic therapy within the previous 12 months, use of prophylactic antibiotics to prevent recurrent infections, one or more life-threatening infections or any combination of these factors</p>		<p>comparison Secondary: Not reported</p>	<p>A significant reduction in the incidence of infections was observed following the initiation of rhG-CSF therapy ($P < 0.001$).</p> <p>A significant reduction in number of days of antibiotic therapy and number of clinical visits was observed after the initiation of rhG-CSF therapy ($P < 0.001$ for both).</p> <p>Low-dose rhG-CSF therapy was well tolerated and no adverse events were noted.</p> <p>Although not statistically significant, treatment with the lowest effective dose of rhG-CSF demonstrated a total mean annual expense of \$4,337 compared to the expense of \$12,074 annually prior to rhG-CSF treatment ($P = 0.09$). The mean annual savings per patient was \$12,000 (\$5,124 to \$23,406).</p> <p>Secondary: Not reported</p>
<p>Welte et al²⁷</p> <p>RhGM-CSF 3 to 30 $\mu\text{g}/\text{kg}/\text{day}$ IV for 42 days and subsequently, one to three months later, rhG-CSF 3 to 15 $\mu\text{g}/\text{kg}/\text{day}$ SC for 142 days</p> <p>All patients were started on 3 $\mu\text{g}/\text{kg}/\text{day}$; if no response was seen after 14 days, the dose was increased to the next dose level for 14 days.</p> <p>If after 14 days at the</p>	<p>T</p> <p>Patients >1 month of age with severe congenital neutropenia, normal kidney and liver function as judged by creatinine, bilirubin, transaminases and coagulation function, normal electrocardiogram, not on experimental therapy,</p>	<p>N=5</p> <p>Duration not specified</p>	<p>Primary: Effects of rhGM-CSF and rhG-CSF on blood cells, maintenance therapy, bone marrow, clinical responses and adverse event of treatment</p> <p>Secondary: Not reported</p>	<p>Primary: Treatment with rhGM-CSF increased the ANC count in only one of the five patients in the study (up to 10,296/μL [oscillated between 1,000 and 6,000 cells/μL]). In four patients, the absolute eosinophil count increased from below 1,000 cells/μL to 3,200 to 5,700 cells/μL. AMC increased two to six fold in four of the five patients as well. Other blood cells such as erythrocytes, platelets or lymphocytes did not change significantly during rhGM-CSF treatment (P values not reported).</p> <p>Treatment with rhG-CSF increased ANC levels to $>1,000$ cells/μL in all five patients. The absolute eosinophil count was not significantly augmented in all patients (one patient increased fivefold from baseline [oscillation between 100 and 800 cells/μL]). AMC increased two to eight fold in three of the five patients.</p> <p>Four of the five patients maintained an ANC count of $>1,000$ cells/μL during</p>

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<p>maximal dose no response was observed (no increase in ANC), the therapy was discontinued.</p> <p>All patients also received prophylactic antibiotic therapy with co-trimoxazole, amoxicillin, rifampicin or flucloxacillin.</p>	<p>chemotherapy, hormonal therapy or immunotherapy, absence of serious infections uncontrolled on antibiotic therapy or requiring white cell transfusion and absence of anti-neutrophil antibodies</p>			<p>days 43 to 142 of rhG-CSF therapy.</p> <p>The number of promyelocytes before and during rhGM-CSF treatment did not change significantly in four patients. Two patients in the rhG-CSF showed increases in promyelocytes (2 to 12% and 9 to 12%).</p> <p>All patients experienced recurrent bacterial and fungal infections prior to rhGM-CSF therapy, and after therapy, no new episodes of severe bacterial infections occurred. Two patients had resolved their infections, one patient had no change and one patient developed <i>Staphylococcus aureus</i> induced paronychia. The one patient who had no change in their infection with rhGM-CSF therapy had their infection resolved within six weeks of rhG-CSF therapy. The other four patients did not experience any bacterial infections during rhG-CSF therapy.</p> <p>Both rhGM-CSF and rhG-CSF were well tolerated by all patients. During the highest dose level of rhGM-CSF treatment (30 µg/kg/day), a mild local phlebitis at the infusion site was observed in all patients. The only serious adverse event occurred with rhG-CSF treatment in one patient who suffered from a cutaneous necrotizing vasculitis on both lower legs that resolved with a lowering of the dose.</p> <p>One patient had an increase in serum alkaline phosphatase from 285 U/L before rhG-CSF therapy to 441 U/L after rhG-CSF therapy. The other four patients had no change. Liver and renal functions remained normal.</p> <p>Secondary: Not reported</p>
<p>Decrease Incidence of Infection, as Manifested by Febrile Neutropenia, in Patients with Nonmyeloid Malignancies Receiving Myelosuppressive Anticancer Drugs Associated with Significant Incidence of Severe Neutropenia with Fever</p>				
<p>Bohlius et al²⁰</p> <p>Filgrastim or lenograstim* ≥1 µg/kg/day IV or SC</p> <p>or</p>	<p>MA of 13 PC, RCT</p> <p>Patients >16 years of age with NHL or HD</p>	<p>N=2,607</p> <p>Duration not specified</p>	<p>Primary: Overall survival and freedom from treatment failure</p>	<p>Primary: Compared to placebo, treatment with CSFs had no significant effect on overall survival (HR, 0.97; 95% CI, 0.87 to 1.09) or freedom from treatment failure (HR, 1.11; 95% CI, 0.91 to 1.35).</p> <p>Sensitivity analyses showed that there was no significant difference between</p>

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<p>sargramostim $\geq 1 \mu\text{g}/\text{kg}/\text{day}$ IV or SC</p> <p>vs</p> <p>placebo or no treatment</p> <p>All patients received G-CSF or GM-CSF as primary prophylaxis during standard nonmyeloablative chemotherapy prior to the onset of neutropenia in the first- or second-line treatment of malignant lymphoma.</p> <p>G-CSF and GM-CSF were administered within 72 hours of chemotherapy administration and in each cycle of chemotherapy.</p>			<p>Secondary: Quality of life, risk and duration of neutropenia, risk and duration of febrile neutropenia, infection, risk and duration of IV antibiotic treatment, hospitalization, dose intensity of chemotherapy, mortality during chemotherapy, tumor response, adverse events of CSFs, risk and duration of thrombocytopenia and anemia</p>	<p>G-CSF and GM-CSF in their effects on the primary endpoints.</p> <p>Secondary: No difference in quality of life was detected between CSFs and placebo.</p> <p>Treatment with CSFs was associated with a 33% risk reduction in developing neutropenia compared to placebo (RR, 0.67; 95% CI, 0.60 to 0.73). There was a 26% risk reduction in developing febrile neutropenia with an ANC of $<1 \times 10^9/\text{L}$ (RR, 0.74; 95% CI, 0.62 to 0.89) and a 41% risk reduction in developing neutropenia with ANC of $<0.5 \times 10^9/\text{L}$ (RR, 0.59; 95% CI, 0.48 to 0.72) with CSF compared to placebo. There was no conclusive evidence that CSFs reduce the duration of neutropenia or febrile neutropenia.</p> <p>The risk of developing an infection was reduced by 26% in patients receiving CSF compared to patients receiving placebo (RR, 0.74; 95% CI, 0.64 to 0.85). There was a non-significant risk reduction in requiring IV antibiotic treatment with CSF compared to placebo (RR, 0.82; 95% CI, 0.57 to 1.18).</p> <p>There was no conclusive evidence to detect the effect of CSF on the duration of IV antibiotic treatment, hospitalization or dose intensity of chemotherapy.</p> <p>Between the two treatment groups, there was no difference in mortality during chemotherapy (RR, 0.93; 95% CI, 0.60 to 1.43) or complete tumor response (RR, 1.03; 95% CI, 0.95 to 1.10).</p> <p>Significantly more patients receiving CSF reported bone pain compared to patients receiving placebo (RR, 3.57; 95% CI, 2.09 to 6.12). GM-CSF was associated with a smaller risk of bone pain compared to G-CSF ($P=0.026$). Treatment with CSF did not increase the risk of thromboembolic complications compared to placebo (RR, 1.29; 95% CI, 0.56 to 3.01).</p> <p>There was no conclusive evidence showing that CSF treatment affects incidence or degree of thrombocytopenia or anemia.</p>
<p>Cooper et al²⁸</p> <p>Filgrastim (dose not</p>	<p>MA, SR of 20 RCT</p> <p>Adult cancer</p>	<p>N=not reported</p>	<p>Primary: Incidence of febrile</p>	<p>Primary: There was a significant reduction in the risk of developing febrile neutropenia associated with filgrastim (RR, 0.57; 95% CI, 0.48 to 0.69), lenograstim (RR,</p>

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<p>reported) administered one to three days following the completion of chemotherapy</p> <p>vs</p> <p>lenograstim* (dose not reported) administered one to three days following the completion of chemotherapy</p> <p>vs</p> <p>pegfilgrastim (dose not reported) administered one to three days following the completion of chemotherapy</p> <p>vs</p> <p>no G-CSF primary prophylaxis</p>	<p>patients with solid tumors or lymphomas who were receiving primary G-CSF prophylaxis (pegfilgrastim, filgrastim or lenograstim)</p>	<p>Duration not specified</p>	<p>neutropenia over all chemotherapy cycles</p> <p>Secondary: Not reported</p>	<p>0.62; 95% CI, 0.44 to 0.88) and pegfilgrastim (RR, 0.30; 95% CI, 0.14 to 0.65) compared to receiving no G-CSF prophylaxis.</p> <p>Overall, there was a lower risk of febrile neutropenia when using any G-CSF for primary prophylaxis compared to no primary prophylaxis (RR, 0.51; 95% CI, 0.41 to 0.62).</p> <p>There was a significantly lower incidence of febrile neutropenia following treatment with pegfilgrastim compared to filgrastim (RR, 0.66; 95% CI, 0.44 to 0.98).</p> <p>There were no head-to-head studies comparing lenograstim to either filgrastim or pegfilgrastim.</p> <p>Secondary: Not reported</p>
<p>Grigg et al²⁹</p> <p>Filgrastim 5 µg/kg/day SC from day two of each cycle until an ANC of $\geq 10 \times 10^9$ cells/µL after the expected nadir or for 14 days, whichever occurred first</p> <p>vs</p>	<p>MC, OL, RCT</p> <p>Patients ≥ 60 years of age with NHL requiring treatment with standard CHOP therapy, ECOG performance status ≤ 2, an ANC of $\geq 2 \times 10^9$ cells/µL, platelet count of</p>	<p>N=50</p> <p>6 cycles of chemotherapy</p>	<p>Primary: Duration of grade four neutropenia (ANC of $< 0.5 \times 10^9/L$) in cycle one</p> <p>Secondary: Incidence of febrile</p>	<p>Primary: The mean duration of grade four neutropenia in cycle one was shorter for patients who received cytokine (pegfilgrastim 60 µg/kg, 2.2±1.2 days; pegfilgrastim 100 µg/kg, 1.5±1.0 days; filgrastim 0.8±1.2 days) compared to patients who received no cytokine in cycle one (mean 5.0±2.0 days; <i>P</i> values not reported).</p> <p>Secondary: The incidence of febrile neutropenia throughout the study was as follows: 3% of patients treated with pegfilgrastim 60 µg/kg who received a total of 68 cycles, 0% of patients treated with pegfilgrastim 100 µg/kg who received a</p>

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<p>no cytokine support in cycle one followed by filgrastim 5 µg/kg/day SC in all other cycles</p> <p>vs</p> <p>pegfilgrastim 60 µg/kg on day two of each cycle</p> <p>vs</p> <p>pegfilgrastim 100 µg/kg on day two of each cycle</p> <p>Patients received CHOP therapy repeated every three weeks for up to six cycles provided ANC of $>1 \times 10^9$ cells/µL, and platelet count of $>100 \times 10^9$ units/L.</p>	<p>$\geq 100 \times 10^9$/L, bilirubin concentration $\leq 2 \times$ upper limit of normal and adequate renal function</p>		<p>neutropenia (ANC of $< 0.5 \times 10^9$ cells/µL and temperature $> 38.2^\circ\text{C}$), time to ANC recovery (ANC of $\geq 2.0 \times 10^9$ cells/µL) in cycles one, three and six and the ability to deliver planned dose of chemotherapy on time</p>	<p>total of 62 cycles, 8% patients treated with filgrastim who received a total of 59 cycles and 0% of patients who did not receive cytokine (in cycle one only) who received a total of 43 cycles (<i>P</i> values not reported).</p> <p>The median time to ANC recovery in cycles one, three and six was similar for all patients receiving cytokine support: pegfilgrastim 60 µg/kg, 11 days; pegfilgrastim 100 µg/kg, 10 days and filgrastim, 10 days (<i>P</i> values not reported).</p> <p>In cycles two through six, eight patients experienced a delay in the start of chemotherapy of more than three days; no delays were related to neutropenia. Full dose cyclophosphamide and doxorubicin was given in 94, 96 and 100% of cycles given to filgrastim, pegfilgrastim 60 µg/kg and pegfilgrastim 100 µg/kg patients, respectively. One filgrastim patient received reduced doses due to error and one pegfilgrastim 60 µg/kg patient received reduced doses following febrile episodes. In addition, seven patients had a reduction in vincristine dose due to neuropathy (<i>P</i> values not reported).</p> <p>Pegfilgrastim was well tolerated with a safety profile similar to daily filgrastim. Adverse events (WHO grade one to four) were reported by 95% of filgrastim and 96% of pegfilgrastim patients (<i>P</i> value not reported).</p>
<p>Holmes et al³⁰</p> <p>Filgrastim 5 µg/kg/day SC from day two of each cycle until an ANC of $\geq 10 \times 10^9$/L after the expected nadir or for 14 days, whichever occurred first</p> <p>vs</p> <p>pegfilgrastim 30 µg/kg SC on day two of each cycle</p>	<p>AC, MC, RCT</p> <p>Woman ≥ 18 years of age with high-risk stage II, III or IV breast cancer, ECOG performance status ≤ 2, WBC count of $\geq 4 \times 10^9$ cells/µL, platelet count of $\geq 150 \times 10^9$ units/L, adequate renal, hepatic and cardiac function</p>	<p>N=154</p> <p>4 cycles of chemotherapy</p>	<p>Primary: Duration of grade four neutropenia (ANC of $< 0.5 \times 10^9$ cells/L) in cycle one</p> <p>Secondary: Duration of grade four neutropenia during cycles</p>	<p>Primary: In cycle one, the mean duration of grade four neutropenia for filgrastim was 1.6 days compared to 2.7 days for pegfilgrastim 30 µg/kg, 2.0 days for pegfilgrastim 60 µg/kg and 1.3 days for pegfilgrastim 100 µg/kg (<i>P</i> values not reported).</p> <p>Secondary: The duration of grade four neutropenia in cycles two through four ranged between zero and one day in $\geq 98\%$ of patients receiving pegfilgrastim 100 µg/kg, compared to 86% for pegfilgrastim 60 µg/kg and $\geq 92\%$ for filgrastim (<i>P</i> values not reported). Most patients in the pegfilgrastim 30 µg/kg group were escalated to higher doses of pegfilgrastim in later cycles and these values were not reported.</p>

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<p>vs</p> <p>pegfilgrastim 60 µg/kg SC on day two of each cycle</p> <p>vs</p> <p>pegfilgrastim 100 µg/kg SC on day two of each cycle</p> <p>Patients received doxorubicin and docetaxel chemotherapy repeated every three weeks for up to four cycles provided ANC of $>1 \times 10^9$ cells/µL, and platelet count of $>100 \times 10^9$ units/L.</p>			<p>two through four, ANC profile, time to ANC recovery (ANC of $\geq 2 \times 10^9$ cells/µL) after the expected ANC nadir and rate of febrile neutropenia (ANC of $< 0.5 \times 10^9$ cells/µL and temperature $> 38.2^\circ\text{C}$)</p>	<p>Pegfilgrastim 100 µg/kg had similar ANC profiles as filgrastim in each of the cycles (<i>P</i> value not reported).</p> <p>The mean time to ANC recovery for cycle one was 11 days in the pegfilgrastim 30 µg/kg and 10.3 days for 60 µg/kg treatment groups, compared to 9.5 and 9.4 days for the pegfilgrastim 100 µg/kg and filgrastim 5 µg/kg/day treatment groups, respectively. The mean time to ANC recovery was significantly longer for pegfilgrastim 30 and 60 µg/kg/cycle but not the 100 µg/kg/cycle, compared to filgrastim (<i>P</i> values not reported).</p> <p>Febrile neutropenia was experienced at least once during the study by seven patients (12%) receiving pegfilgrastim 60 µg/kg, five patients (11%) receiving pegfilgrastim 100 µg/kg and two patients (12%) receiving filgrastim. There were no significant differences demonstrated between the groups (<i>P</i> values not reported).</p>
<p>Green et al³¹</p> <p>Filgrastim 5 µg/kg/day SC from day two of each cycle until an ANC of $\geq 10 \times 10^9$ cells/µL after the expected nadir or for 14 days, whichever occurred first</p> <p>vs</p> <p>pegfilgrastim 6 mg SC once on day two of each cycle</p> <p>Patients received doxorubicin and docetaxel chemotherapy repeated every three weeks for up to</p>	<p>DB, MC, RCT</p> <p>Patients >18 years of age with high-risk stage II or stage III/IV breast cancer, ECOG performance status ≤ 2, chemotherapy naïve or adjuvant therapy only or only one chemotherapy regimen for metastatic disease, an ANC of $\geq 1.5 \times 10^9$ cells/µL, platelet count of $\geq 100 \times 10^9$ units/L, and a serum</p>	<p>N=157</p> <p>4 cycles of chemotherapy</p>	<p>Primary: Duration of grade four neutropenia (ANC of $< 0.5 \times 10^9$ cells/µL) in cycle one</p> <p>Secondary: Duration of grade four neutropenia in cycles two through four, depth of the ANC nadir in cycles two</p>	<p>Primary: There was no statistically significant difference in the mean duration of grade four neutropenia in cycle one between the filgrastim group (1.6 ± 1.1 days) and the pegfilgrastim group (1.8 ± 1.4 days; difference of 0.23 days; 95% CI, -0.15 to 0.63).</p> <p>Secondary: The mean duration of grade four neutropenia was not significantly different between the filgrastim and pegfilgrastim groups during cycle two (0.9 ± 1.0 vs 1.1 ± 1.2 days, respectively; difference of 0.13; 95% CI, -0.20 to 0.47), cycle three (0.9 ± 1.1 vs 1.1 ± 1.2 days, respectively; difference of 0.16; 95% CI, -0.20 to 0.51) and cycle four (1.0 ± 1.3 vs 1.0 ± 1.1 days, respectively; difference of 0.00 days; 95% CI, -0.39 to 0.39).</p> <p>The median ANC nadir was significantly different between the two treatment groups (<i>P</i> value not reported).</p> <p>The incidence of febrile neutropenia was not significantly different between</p>

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<p>four cycles provided ANC of $>1 \times 10^9$ cells/μL, and platelet count of $>100 \times 10^9$ units/L.</p>	<p>creatinine <1.5 times upper limit of normal</p>		<p>through four, incidence of febrile neutropenia, time to neutrophil recovery (ANC of $\geq 2 \times 10^9$ cells/μL), incidence of IV antibiotic administration and hospitalizations</p>	<p>patients receiving filgrastim and those receiving pegfilgrastim (13 vs 20%; difference of -7%; 95% CI, -19 to 5).</p> <p>The median time to neutrophil recovery in all cycles was nine days from chemotherapy administration for both the pegfilgrastim group and the filgrastim group (<i>P</i> values not reported).</p> <p>Rates of IV antibiotic administration (21 and 17%) and hospitalizations (31 and 18%) for the filgrastim and pegfilgrastim groups, respectively, were generally consistent with the results obtained for the incidence of febrile neutropenia (<i>P</i> values not reported).</p> <p>The safety profile of pegfilgrastim, assessed by adverse events, antibody formation and changes in laboratory values, was similar between treatment groups.</p>
<p>Holmes et al¹⁴</p> <p>Filgrastim 5 μg/kg/day SC from day two of each cycle until an ANC of $\geq 10 \times 10^9$ cells/μL after the expected nadir or for 14 days, whichever occurred first</p> <p>vs</p> <p>pegfilgrastim 100 μg/kg SC on day two of each cycle</p> <p>Patients received doxorubicin and docetaxel chemotherapy repeated every three weeks for up to four cycles if ANC was $>1 \times 10^9$ cells/μL, and platelet count was $>100 \times 10^9$</p>	<p>DB, MC, RCT</p> <p>Patients >18 years of age with high risk stage II or stage III/IV breast cancer, who were naïve to chemotherapy or received adjuvant therapy and/or completed ≤ 1 regimen of chemotherapy for metastatic disease, completion of previous chemotherapy more than four weeks before randomization, an ECOG performance</p>	<p>N=310</p> <p>4 cycles of chemotherapy</p>	<p>Primary: Duration of grade four neutropenia (ANC of $<0.5 \times 10^9$ cells/μL) in cycle one</p> <p>Secondary: Duration of grade four neutropenia during cycles two through four, the depth of ANC nadir in each cycle (one to four), rates of febrile neutropenia</p>	<p>Primary: In cycle one, there was no significant difference in the duration of grade four neutropenia between the filgrastim group (1.8 days) and the pegfilgrastim group (1.7 days; difference of 0.03 days; 95% CI, -0.36 to 0.30).</p> <p>Secondary: The duration of grade four neutropenia was significantly shorter in the pegfilgrastim group compared to the filgrastim group in cycle two (0.7 vs 1.1 days; <i>P</i>=0.001), cycle three (0.6 vs 1.2 days; <i>P</i>\leq0.001) and cycle four (0.9 vs 1.3 days; <i>P</i>=0.019).</p> <p>The depth of ANC nadir was similar between the two treatment groups over the course of the study (<i>P</i> values not reported).</p> <p>Febrile neutropenia occurred at least once during the study in 9% of patients in the pegfilgrastim group compared to 18% of patients in the filgrastim group (<i>P</i>=0.029).</p> <p>The mean time to ANC recovery was 9.3 days for the pegfilgrastim group compared to 9.7 days in the filgrastim group (difference of -0.40 days; 95% CI, -0.88 to 0.08).</p>

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units/L.	status ≤ 2 , an ANC of $\geq 1.5 \times 10^9/L$, platelet count of $\geq 100 \times 10^9/L$ and adequate hepatic and cardiac function		and the time to ANC recovery in chemotherapy cycles one to four	Adverse event profiles were similar among the pegfilgrastim and filgrastim groups.
<p>Vose et al³²</p> <p>Filgrastim 5 $\mu\text{g}/\text{kg}/\text{day}$ SC starting on day six, one day after completion of chemotherapy and given until ANC of $\geq 10 \times 10^9$ cells/μL after the expected nadir or for 12 days, whichever came first</p> <p>vs</p> <p>pegfilgrastim 100 $\mu\text{g}/\text{kg}$ SC once on day six, one day after completion of chemotherapy, of each cycle</p> <p>Chemotherapy consisted of etoposide, methylprednisolone, cisplatin and cytarabine and repeated every three weeks.</p>	<p>MC, OL, RCT</p> <p>Patients ≥ 18 years of age with an ECOG performance status ≤ 2, an ANC of $\geq 1.5 \times 10^9$ cells/μL, platelet count of $\geq 100 \times 10^9$ cells/μL, and adequate renal function who were diagnosed with relapsed or persistent HD and had treatment failure from ≥ 1 prior chemotherapy regimen or a diagnosis of NHL and relapsed from or were refractory to first-line CHOP chemotherapy</p>	<p>N=66</p> <p>4 cycles of chemotherapy</p>	<p>Primary: Duration of grade four neutropenia (ANC of $< 0.5 \times 10^9$ cells/μL) in cycle one</p> <p>Secondary: Duration of grade four neutropenia in subsequent cycles, ANC profiles, time to ANC recovery, and rates of febrile neutropenia (ANC of $< 0.5 \times 10^9$ cells/μL and temperature $\geq 38.2^\circ\text{C}$) for cycles one and two</p>	<p>Primary: There was no significant difference in the duration of grade four neutropenia in cycle one between patients in the filgrastim and pegfilgrastim groups (68 vs 69%, respectively; <i>P</i> value not reported).</p> <p>Secondary: In subsequent cycles, the mean duration of grade four neutropenia was not significantly different between patients in the filgrastim and pegfilgrastim groups (0.6 vs 0.4 days, respectively; difference of -0.14; 95% CI, -0.73 to 0.44).</p> <p>The geometric mean ANC nadir was 0.208×10^9 cells/μL for patients in the filgrastim group compared to 0.161×10^9 cells/μL for patients in the pegfilgrastim group (95% CI, 0.326 to 1.839).</p> <p>The median time to ANC recovery was not significantly different between the filgrastim group and pegfilgrastim group (15 vs 16 days, respectively; 95% CI, -0.84 to 3.07).</p> <p>The rate of febrile neutropenia was not significantly different between the filgrastim group and pegfilgrastim group (19 vs 21%; 95% CI, -19.4 to 22.0).</p> <p>The incidences of adverse events were similar between the two treatment groups.</p>
<p>Staber et al³³</p> <p>Filgrastim 5 $\mu\text{g}/\text{kg}/\text{day}$ SC</p>	<p>AC, OL, T</p> <p>Patients with</p>	<p>N=54</p> <p>Duration not</p>	<p>Primary: Duration of grade four</p>	<p>Primary: The mean duration of grade four neutropenia was significantly shorter in the pegfilgrastim group compared to the filgrastim group (8.3 vs 9.5 days;</p>

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<p>from day seven after transplantation until ANC was $>10 \times 10^9$ cells/μL</p> <p>vs</p> <p>pegfilgrastim 6 mg SC once on day five after transplantation</p> <p>PBSCT was performed on day zero with unmanipulated peripheral blood stem cells that were harvested using cyclophosphamide and G-CSF prior to the start of the study.</p>	<p>hematological malignancies, an ECOG performance status ≤ 2 and normal cardiac, pulmonary, hepatic and renal function prior to transplantation</p>	<p>specified</p>	<p>neutropenia (ANC of $<0.5 \times 10^9$ cells/μL)</p> <p>Secondary: Incidence of febrile neutropenia (ANC of $<0.5 \times 10^9$ cells/μL and temperature $\geq 38.2^\circ\text{C}$), duration of febrile neutropenia, duration of fever and incidence of documented infections</p>	<p>$P=0.047$).</p> <p>Secondary: The incidence of febrile neutropenia was similar between patients in the filgrastim and pegfilgrastim treatment groups (77 vs 80%, respectively; P value not reported).</p> <p>The mean duration of febrile neutropenia was significantly shorter in the pegfilgrastim group compared to the filgrastim group (1.6 vs 3.0 days; $P=0.017$).</p> <p>The mean duration of fever was significantly shorter in the pegfilgrastim group compared to the filgrastim group (1.73 vs 4.10 days; $P=0.003$).</p> <p>The incidence of documented infections was significantly lower in the pegfilgrastim group compared to the filgrastim group (26 vs 56%; $P=0.02$).</p> <p>Bone pain was the only adverse event considered cytokine related and was reported in six patients (20%) in the pegfilgrastim group and seven patients (23%) in the filgrastim group (P value not reported).</p>
<p>Almenar et al¹¹</p> <p>Filgrastim or lenograstim* administered daily (dosing not specified)</p> <p>vs</p> <p>pegfilgrastim (dosing not specified) administered once</p>	<p>MC, OS, RETRO</p> <p>Patients with nonmyeloid tumors who underwent cytotoxic chemotherapy for tumor types including breast, lung, NHL, multiple myeloma, gastrointestinal, gynecological and others</p>	<p>N=186</p> <p>Duration not specified</p>	<p>Primary: Proportion of patients with proactive vs reactive use of G-CSF, the duration of treatment with daily G-CSF, delay or reduction in chemotherapy dose (>3 days delay with</p>	<p>Primary: The proportion of patients receiving G-CSF as primary and secondary prophylaxis for febrile neutropenia was similar in both the filgrastim and pegfilgrastim groups. Pegfilgrastim was less likely to be used to treat febrile neutropenia compared to filgrastim (17.3 vs 29.7%; P value not reported).</p> <p>The duration of treatment with daily G-CSF was not reported.</p> <p>A similar proportion of patients had a delay in chemotherapy administration in the filgrastim and pegfilgrastim groups (46 and 44%, respectively; P value not reported). However, 20.7% of patients receiving filgrastim had a chemotherapy dose reduction due to neutropenia, compared to 6.7% of patients receiving pegfilgrastim (P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			<p>respect to planned date of administration or <85% of planned dose administered), incidence of febrile neutropenia, incidence of hospitalization, antibiotic use and adverse events</p> <p>Secondary: Not reported</p>	<p>There were fewer incidences of febrile neutropenia and hospitalization due to febrile neutropenia in the pegfilgrastim group compared to the filgrastim group. The incidences of febrile neutropenia in the filgrastim and pegfilgrastim groups were 24.3 and 10.7%, respectively (<i>P</i> value not reported), while the incidences of hospitalization due to febrile neutropenia were 19.8 and 9.3%, respectively (<i>P</i> value not reported).</p> <p>Fewer patients in the pegfilgrastim group received antibiotics due to febrile neutropenia compared to the filgrastim group (8.0 vs 17.1%; <i>P</i> value not reported).</p> <p>Bone pain was reported in 2.7 and 1.3% of patients receiving filgrastim and pegfilgrastim, respectively. Other treatment-related adverse events were reported in 5.4 and 1.3% of patients in the filgrastim and pegfilgrastim groups, respectively (<i>P</i> value not reported).</p> <p>Secondary: Not reported</p>
<p>Weycker et al¹²</p> <p>Filgrastim (dose not specified) for a mean of 4.5±3.3 days</p> <p>vs</p> <p>pegfilgrastim (dose not specified)</p> <p>G-CSFs were administered on or before day five of each chemotherapy cycle.</p>	<p>CO, RETRO</p> <p>Adult patients who received chemotherapy for a primary solid tumor and who received filgrastim or pegfilgrastim during the first course of chemotherapy; the most common types of malignancies were breast cancer, lung cancer and NHL; eligible, unique chemotherapy</p>	<p>N=4,903 (patients with a total of 15,763 chemotherapy cycles)</p> <p>Duration not specified</p>	<p>Primary: Incidence of hospitalization for neutropenia, incidence of hospitalization for febrile neutropenia or infection, incidence of all-cause hospitalization (hospitalizations for neutropenia, febrile neutropenia</p>	<p>Primary: Pegfilgrastim was associated with a significantly lower incidence of hospitalizations for neutropenia compared to filgrastim (1.2 vs 2.1%; OR, 0.55; 95% CI, 0.36 to 0.84; <i>P</i>=0.005).</p> <p>The risk of hospitalization for neutropenic fever or infection was significantly lower with pegfilgrastim compared to filgrastim (3.1 vs 4.8%; OR, 0.64; 95% CI, 0.48 to 0.85; <i>P</i>=0.002).</p> <p>The incidence of all-cause hospitalizations was 6.3% with pegfilgrastim compared to 8.7% for filgrastim (OR, 0.70; 95% CI, 0.56 to 0.86; <i>P</i>=0.001).</p> <p>After adjusting for patient, cancer and chemotherapy characteristics, pegfilgrastim was associated with a significantly lower incidence of hospitalization for neutropenia (adjusted OR, 0.64; 95% CI, 0.41 to 0.99; <i>P</i>=0.043), hospitalization for neutropenic fever or infection (adjusted OR, 0.69; 95% CI, 0.52 to 0.92; <i>P</i>=0.012) and all-cause hospitalization (adjusted OR, 0.73; 95% CI, 0.59 to 0.91; <i>P</i>=0.004) compared to filgrastim.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	cycles were eligible if the first and second cycles were 20 to 59 days apart and if G-CSFs were administered on or before day five of cycle		and infection were identified using corresponding ICD-9 codes) Secondary: Not reported	Secondary: Not reported
Beveridge et al ¹⁸ Filgrastim 5 µg/kg SC daily vs sargramostim 250 µg/m ² SC daily	DB, MC, RCT Patients ≥18 years of age who developed neutropenia within four weeks of chemotherapy regimen (ANC of <500 cells/µL)	N=181 Mean duration of treatment: filgrastim, 4.60±0.14 days; sargramostim, 5.70±0.23 days	Primary: Number of days to reach an ANC of 1,000 and 1,500 cells/µL, number of febrile neutropenic episodes, duration of hospitalization, duration of fever, duration of IV antibiotic therapy, number of episodes of chills or fever, number of events of fever in the morning, evening and four hours after injection of CSF, documented positive	Primary: The number of days to reach an ANC of 1,000 cells/µL was significantly shorter with filgrastim compared to sargramostim (4.50 vs 5.10 days; <i>P</i> =0.009). Filgrastim was associated with fewer number of days to reach an ANC of 1,500 cells/µL compared to sargramostim (4.60 vs 5.70 days; <i>P</i> =0.0001). There was no significant difference between the two treatment groups with regard to the number of days to reach an ANC of 500 cells/µL (3.60 vs 3.30 days; <i>P</i> =0.32). There was no significant difference between filgrastim and sargramostim regarding the proportion of patients with hospitalizations for febrile neutropenia or IV antibiotic therapy (6.3 and 7.8%, respectively; <i>P</i> =0.46). Compared to filgrastim, sargramostim was associated with a nonsignificant reduction in the duration of hospitalization (5.60 vs 4.80 days; <i>P</i> =0.58), fever (3.60 vs 1.60 days; <i>P</i> =0.14) and IV antibiotic therapy (6.30 vs 4.70 days; <i>P</i> value not reported). Two patients (1.9%) in the filgrastim group and one patient (1.2%) from the sargramostim group experienced chills (<i>P</i> =0.60). There was no significant difference between filgrastim and sargramostim treatment with respect to the incidence of grade two fever reported in the morning (10 and 9%, respectively; <i>P</i> =0.53), evening (13.7 and 11.0%, respectively; <i>P</i> =0.41) and four hours following CSF injection (10.7 and 3.8%, respectively; <i>P</i> =0.07). Two patients receiving filgrastim and zero patients receiving sargramostim had

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			bacterial cultures, number of events of sepsis and adverse events Secondary: Not reported	documented positive blood cultures, indicating bacteremia (<i>P</i> value not reported). The incidence of sepsis was not reported. Both filgrastim and sargramostim treatments were well tolerated, and there were no significant differences between the treatment groups with regard to adverse events. Secondary: Not reported
Beveridge et al ¹⁹ Filgrastim 7 µg/kg SC daily vs sargramostim 300 µg SC daily Study drugs were administered starting one to two days following chemotherapy.	AC, DB, MC, RCT Patients ≥18 years of age with a documented Malignancy, ECOG performance status grade ≤2 and who received cytotoxic chemotherapy	N=144 7 days	Primary: Tolerability, hospitalization and use of IV antibiotics Secondary: Not reported	Primary: There were no cases of grade four toxicity during the treatment period in patients receiving either sargramostim or filgrastim and no instances when either treatment had to be discontinued due to toxicity (<i>P</i> values not reported). Grade one fever (37.1 to 38.0°C) occurred in more patients receiving filgrastim compared to sargramostim (36 vs 16 patients; <i>P</i> <0.01). There were no statistically significant differences between the treatment groups in the incidence of local reactions or in the incidence or severity of bone or joint pain, chills, nausea, vomiting, dyspnea or headache (<i>P</i> values not reported). There were no significant differences between the filgrastim and sargramostim treatment groups in the duration of hospitalization (4.0 vs 4.6 days, respectively) or in duration of IV antibiotic therapy (6.0 vs 4.4 days, respectively) during the treatment period (<i>P</i> values not reported). Secondary: Not reported
Milkovich et al ³⁴ Filgrastim vs sargramostim Dosages of the medications	MC, RETRO, XO Patients ≥18 years of age who received chemotherapy for a lung, breast, lymphatic system or ovarian tumor	N=490 12 months	Primary: Frequency and severity of adverse events and the frequency of switching to the alternative CSF	Primary: Significantly more episodes of fever ≥100.4°F occurred in the sargramostim treatment group compared to the filgrastim group (9 vs 4%; <i>P</i> <0.001). Although skeletal muscle pain was the most frequently reported adverse event, there was no significant difference between the filgrastim group and the sargramostim group (11 vs 8%, respectively; <i>P</i> =0.06). Adverse events that occurred significantly more frequently in the sargramostim

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>were at the discretion of the investigator.</p> <p>Mean doses were 369 µg (5.5 µg/kg) for filgrastim and 474 µg (6.9 µg/kg) for sargramostim.</p>			<p>Secondary: Not reported</p>	<p>group compared to the filgrastim group included fatigue (4 vs 2%; <i>P</i><0.05), diarrhea (3 vs 2%; <i>P</i><0.05), injection site reaction (6 vs <1%; <i>P</i><0.01), other dermatologic disorders (3 vs <1%; <i>P</i><0.01) and edema (2 vs <1%; <i>P</i><0.01).</p> <p>Significantly more patients switched from sargramostim to filgrastim compared to the number of patients who switched from filgrastim to sargramostim (29 vs 1%]; <i>P</i><0.001).</p> <p>Secondary: Not reported</p>
<p>Weycker et al¹³</p> <p>Pegfilgrastim (dose not specified)</p> <p>vs</p> <p>filgrastim (dose not specified) for 4.8±3.4 days</p> <p>or</p> <p>sargramostim (dose not specified) for 6.0±4.4 days</p> <p>G-CSFs and GM-CSF were administered on or before day five of each chemotherapy cycle.</p> <p>The most common concomitant chemotherapy regimen was cyclophosphamide and doxorubicin for breast cancer, carboplatin and</p>	<p>CO, RETRO</p> <p>Adult patients who received chemotherapy for solid tumors based on evidence of medical claims; each chemotherapy cycle was a minimum of 20 days; the most common malignancies were breast cancer, lung cancer and NHL; eligible, unique chemotherapy cycles were then identified; cycles were eligible if the first and second cycles were 20 to 59 days apart and if G-CSFs and GM-CSF were administered</p>	<p>N=22,995 (patients with a total of 77,269 chemotherapy cycles)</p> <p>Duration not specified</p>	<p>Primary: Incidence of hospitalization for neutropenia, incidence of hospitalization for neutropenic fever or infection, incidence of all-cause hospitalization within 60 days after the initiation of study drugs (hospitalizations for neutropenia, febrile neutropenia and infection were identified using corresponding</p>	<p>Primary: The risk of hospitalization for neutropenia was significantly higher during chemotherapy cycles in which patients received filgrastim compared to pegfilgrastim (2.1 vs 1.1%; <i>P</i><0.001). Similarly, the same risk was higher in patients who received sargramostim during chemotherapy compared to patients receiving pegfilgrastim (2.5 vs 1.1%; <i>P</i><0.001).</p> <p>Pegfilgrastim was associated with significantly fewer hospitalizations compared to filgrastim (2.6 vs 4.0%; <i>P</i><0.001) and sargramostim (5.1%; <i>P</i><0.001).</p> <p>Patients receiving pegfilgrastim had fewer incidences of all-cause hospitalization compared to filgrastim (5.3 vs 7.9; <i>P</i><0.001) and sargramostim (9.6%; <i>P</i><0.001).</p> <p>After adjusting for patient, cancer and chemotherapy characteristics, filgrastim and sargramostim were still associated with increased risk of hospitalization for neutropenia compared to pegfilgrastim (OR, 1.8 for filgrastim; <i>P</i><0.001; OR, 2.7 for sargramostim; <i>P</i><0.001).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
etoposide for lung cancer and cyclophosphamide, doxorubicin and vincristine for NHL.	on or before day five of cycle; receipt of chemotherapy and diagnoses of malignancies were based on medical insurance claims		ICD-9 codes) Secondary: Not reported	
Heaney et al ²¹ Sargramostim (dose not specified) vs filgrastim (dose not specified) or pegfilgrastim (dose not specified)	CO, RETRO Adult patients with cancer who had received chemotherapy and had ≥2 doses of filgrastim or sargramostim or ≥1 dose of pegfilgrastim; the most common types of malignancies were breast cancer, lung cancer and NHL; patients receiving sargramostim were matched 1:1 with patients receiving filgrastim and pegfilgrastim based and gender and age	N=2,962 Average duration of treatment: filgrastim and sargramostim, 31 days; pegfilgrastim, 58 days	Primary: Incidence of infection-related hospitalization and costs per-patient per-month Secondary: Incidence of febrile neutropenia-related hospitalization	Primary: Sargramostim was associated with significantly fewer infection-related hospitalizations compared to filgrastim (12 vs 26%; RR, 0.46; 95% CI, 0.22 to 0.97; <i>P</i> =0.0422) and pegfilgrastim (12 vs 24%; RR, 0.52; 95% CI, 0.26 to 1.04; <i>P</i> =0.0628). Comparison on febrile neutropenia-related hospitalizations was not performed due to low event rate in each treatment group. The per-patient-per-month costs for sargramostim was 84% lower compared to filgrastim (\$138/patient/month vs \$866/patient/month; <i>P</i> =0.0380) and 62% lower compared to pegfilgrastim (\$138/patient/month vs \$365/patient/month; <i>P</i> =0.01). Secondary: The incidence of hospitalizations was 5% for sargramostim, 8% for filgrastim (RR, 0.58; 95% CI, 0.17 to 1.98; <i>P</i> =0.3837) and 6% for pegfilgrastim (RR, 0.85; 95% CI, 0.26 to 2.75; <i>P</i> =0.0628).
Delayed or Failed Engraftment in Patients Undergone Allogeneic or Autologous Bone Marrow Transplant				
Weisdorf et al ³⁵ Sargramostim 250 µg/m ² /day SC for 14 days	RCT Patients with graft failure after BMT (failure to achieve a	N=47 Duration not specified	Primary: Development of a sustained ANC of ≥500 cells/µL for	Primary: There was no significant difference in development of a sustained ANC of ≥500 cells/µL for three consecutive days between the sargramostim alone group (eight days [two to 61]) and the sequential treatment group (six days [one to 36]; <i>P</i> =0.39).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>vs</p> <p>sargramostim 250 $\mu\text{g}/\text{m}^2/\text{day}$ SC for seven days followed by filgrastim 5 $\mu\text{g}/\text{kg}/\text{day}$ SC for seven days</p>	<p>leukocyte count of ≥ 100 cells/μL by day 21 after transplantation, failure to achieve a leukocyte count ≥ 300 cells/μL or an ANC of ≥ 200 cells/μL by day 28; or failure to maintain a mean ANC of ≥ 500 cells/μL for seven days after having previously achieved an ANC of ≥ 500 cells/μL at any time beyond day 28)</p>		<p>three consecutive days</p> <p>Secondary: Recovery of red cells and platelets to transfusion-independence, adverse reactions to cytokine infusions and 100-day survival</p>	<p>Secondary: There was no significant difference in recovery of red cells to transfusion-independence between the sargramostim alone group (30 days [six to 124]) and the sequential treatment group (42 days [11 to 250]; $P=0.24$).</p> <p>There was no significant difference in recovery of platelets to transfusion-independence between the sargramostim alone group (28 days [six to 127]) and the sequential treatment group (42 days [four to 249]; $P=0.38$).</p> <p>No significant adverse events (e.g., fevers, rash, serositis or bone pain) led to discontinuation of either treatment. The incidence of GVHD was similar in both treatment arms (P values not reported).</p> <p>Significantly fewer patients died in the sargramostim alone group (one of 23 patients) compared to the sequential treatment group (seven of 24 patients; $P=0.026$).</p>
<p>Nemunaitis et al³⁶</p> <p>RhGM-CSF 60 to 1,000 $\mu\text{g}/\text{m}^2/\text{day}$ as a single two-hour IV infusion daily for 14 or 21 days</p> <p>A second course at twice the dose of the first course was allowed if after two weeks from the treatment course, the ANC remained $< 0.500 \times 10^9$ cells/μL and there was no life-threatening toxicity from the rhGM-CSF and no evidence of leukemic relapse.</p>	<p>DE</p> <p>Patients with malignancy or aplastic anemia who underwent allogeneic, autologous or syngeneic BMT and subsequently developed graft failure</p>	<p>N=37</p> <p>Duration not specified</p>	<p>Primary: Patient response (ANC of $\geq 500 \times 10^9$ cells/μL within 14 days of starting the final course of rhGM-CSF) by type of BMT, effect on infection, effects on GVHD, toxicities and survival</p> <p>Secondary: Not reported</p>	<p>Primary: Nine of 15 patients who underwent an allogeneic BMT increased their ANC to $\geq 0.500 \times 10^9$ cells/μL within 14 days of starting rhGM-CSF. Six patients did not respond to therapy.</p> <p>The mean ANC value in the allogeneic BMT subgroup increased from $0.153 \pm 0.140 \times 10^9$ cells/μL (zero to 0.360×10^9 cells/μL) at the start of treatment to a mean of $2.545 \pm 3.944 \times 10^9$ cells/μL (zero to 11.970×10^9 cells/μL) on the last day of the final course ($P=0.03$).</p> <p>Eleven of the 21 autologous BMT patients and one syngeneic BMT patient increased their ANC to $\geq 0.500 \times 10^9$ cells/μL within 14 days of starting rhGM-CSF. Ten patients did not respond to therapy.</p> <p>The mean ANC value in the autologous or syngeneic BMT group increased from $0.104 \pm 0.130 \times 10^9$ cells/μL (zero to 0.472×10^9 cells/μL) at start of treatment to $0.964 \pm 1.010 \times 10^9$ cells/μL (zero to 4.190×10^9 cells/μL) on the last day of the final course of rhGM-CSF ($P=0.00047$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>A maximum of three courses of rhGM-CSF was administered to each patient.</p>				<p>Fevers (temperature >38°C) were present in 13 of 15 allogeneic BMT patients before treatment with rhGM-CSF. Five patients had bacteremia or fungemia, two had viral infections, one had liver, spleen and brain abscesses.</p> <p>Fever was present in 16 of 22 autologous BMT patients and syngeneic BMT patients before treatment with rhGM-CSF. Five of the 22 patients had bacteremia or fungemia, three had pneumonia and one had a cellulitis.</p> <p>Three patients had graft rejection (only host cells in circulation), two of which responded to rhGM-CSF therapy with recovery of host hematopoiesis. Four patients had only donor hematopoietic cells detected at the time of treatment and all responded to rhGM-CSF. Prior to initiating rhGM-CSF therapy, seven patients had evidence of grade I or II GVHD and none had a GVHD exacerbation.</p> <p>Of the seven patients who received chemically purged autologous marrow, none responded to rhGM-CSF therapy.</p> <p>The four autologous BMT patients who were administered doses of rhGM-CSF $\geq 500 \mu\text{g}/\text{m}^2/\text{day}$ developed myalgias and bone pain during the infusion which resolved within two hours after completion of the rhGM-CSF infusion. At doses $\leq 250 \mu\text{g}/\text{m}^2/\text{day}$, toxicity thought to be associated with rhGM-CSF was observed in one patient who developed sternal and joint pain. In addition, bilirubin increased in three patients and diminished in two others.</p> <p>Overall, 19 patients remained alive after follow-up. The actuarial survival of the 37 patients 100 days and one year after the day they received rhGM-CSF was 59% (95% CI, 44 to 75) and 50% (95% CI, 36 to 60), respectively. Three of the nine allogeneic BMT patients who responded to rhGM-CSF and four of the 12 responders after autologous BMT died.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Mobilization of Hematopoietic Progenitor Cells into Peripheral Blood Collection by Leukapheresis				
<p>Putkonen et al³⁷</p> <p>Filgrastim 5 µg/kg/day SC starting on day two following myeloablative therapy until the end of leukapheresis</p> <p>vs</p> <p>pegfilgrastim 6 to 18 mg once on day two following myeloablative therapy</p>	<p>HC, RETRO</p> <p>Patients with lymphoproliferative malignancies (multiple myeloma, lymphomas and chronic lymphocytic leukemia) requiring stem cell mobilization prior to APBSCT and who had successful mobilization with pegfilgrastim</p>	<p>N=114</p> <p>Median duration to leukapheresis onset was 10 days (10 to 18 days)</p>	<p>Primary: Blood CD34+ cell count at the onset of leukapheresis</p> <p>Secondary: Not reported</p>	<p>Primary: The median blood CD34+ cell count at the onset of leukapheresis was comparable between the filgrastim and pegfilgrastim groups (79x10⁶ cells/µL [10 to 390x10⁶/L] vs 64x10⁶ cells/µL [17 to 805x10⁶/L], respectively; <i>P</i>=0.44).</p> <p>The median onset of leukapheresis was similar between the two treatment groups (10 days for both; <i>P</i>=0.75).</p> <p>Fifty-three percent of patients in the pegfilgrastim group obtained target yield of CD34+ cells following one leukapheresis cycle, compared to 36% of patients in the filgrastim group (<i>P</i> value not reported).</p> <p>Secondary: Not reported</p>
<p>Weaver et al³⁸</p> <p>Filgrastim 5 µg/kg/day SC until PBSC harvests were completed</p> <p>vs</p> <p>sargramostim 250 µg/m²/day SC until PBSC harvests were completed</p> <p>vs</p> <p>sargramostim 250 µg/m²/day SC for five days followed by filgrastim 6 µg/kg/day SC until PBSC harvests were completed</p>	<p>MC, OL, RCT</p> <p>Patients with multiple myeloma, breast cancer or lymphoma</p>	<p>N=156</p> <p>Duration not specified</p>	<p>Primary: CD34+ cell yields, hematological recovery, morbidity and resource utilization</p> <p>Secondary: Not reported</p>	<p>Primary: Significantly more CD34+ cells were harvested in the filgrastim alone group (7.1 cells/kg/apheresis) and in the sequential dosing group (5.5 cells/kg/apheresis) compared to the sargramostim group (2.0 cells/kg/apheresis; <i>P</i>=0.0001 and <i>P</i>=0.0002, respectively).</p> <p>ANC recovery was significantly faster in patients who received filgrastim alone compared to sargramostim alone (11 vs 14 days; <i>P</i>=0.001) and for patients who received sequential dosing of filgrastim and sargramostim compared to sargramostim alone (12 vs 14 days; <i>P</i>=0.001).</p> <p>Significantly fewer patients had a temperature >38.5°C in the filgrastim alone group and in the sequential dosing group compared to the sargramostim group (18 and 15 vs 52%; <i>P</i>=0.001 for both comparisons).</p> <p>Significantly fewer patients received IV antibiotics in the filgrastim alone group and in the sequential dosing group compared to the sargramostim group (24 and 25 vs 69%; <i>P</i>=0.001 for both comparisons).</p> <p>Significantly fewer patients had hospital admissions in the filgrastim alone</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Patients received myelosuppressive chemotherapy with either paclitaxel and cyclophosphamide or etoposide and cyclophosphamide.</p>				<p>group and in the sequential dosing group compared to the sargramostim group (20 and 21 vs 42%; $P=0.013$ and $P=0.017$, respectively).</p> <p>Significantly fewer patients received red blood cell transfusions in the filgrastim alone group compared to the sargramostim group (22 vs 46%; $P=0.008$).</p> <p>There were no significant differences between treatment groups in the number of febrile days, number with bacteremia, days of IV antibiotics, days in the hospital, number of receiving platelets and number of days red blood cells were infused (P values not reported).</p> <p>Secondary: Not reported</p>
<p>Reduce Duration of Neutropenia and Neutropenia-Related Sequelae in Patients with Nonmyeloid Malignancies Undergoing Myeloablative Chemotherapy Followed by Marrow Transplantation</p>				
<p>Sebban et al³⁹</p> <p>Filgrastim 5 µg/kg/day starting on day five following transplant until resolution of neutropenia (ANC of $>0.5 \times 10^9$ cells/L)</p> <p>vs</p> <p>pegfilgrastim 6 mg once on day five following transplant</p>	<p>MC, OL, RCT</p> <p>Patients ≥ 18 years of age with myeloma or lymphoma requiring APBSCT with an ANC of $\geq 1.5 \times 10^9$ cells/L, platelet count of $\geq 100 \times 10^9$/L and at least 2×10^6 cryopreserved CD34+ cells/kg</p>	<p>N=151</p> <p>Duration not specified</p>	<p>Primary: Mean duration of febrile neutropenia (ANC of <0.5 g/L and temperature $>38^\circ\text{C}$ at least once a day)</p> <p>Secondary: Duration of filgrastim treatment, duration of hospitalization following transplant, duration of neutropenia, thrombocyto-</p>	<p>Primary: The mean duration of febrile neutropenia was 3.29 days for patients treated with filgrastim compared to 3.07 days in the pegfilgrastim group (P value not reported).</p> <p>Secondary: The mean duration of treatment in the filgrastim group was seven days (range four to 15 days).</p> <p>The mean hospital stay following transplant was 15.48 ± 4.82 days with pegfilgrastim treatment compared to 16.64 ± 9.64 days for filgrastim treatment (P value not reported).</p> <p>The mean number of days with an ANC of <0.5 g/L was similar between patients treated with pegfilgrastim and filgrastim (7.43 ± 3.96 vs 7.17 ± 2.94 days, respectively; P value not reported) as was the number of days with an ANC of <1 g/L (10.05 ± 6.50 vs 11.99 ± 8.81 days, respectively; P value not reported).</p> <p>There was a lower number of days with a platelet count of <20 g/L in the pegfilgrastim treatment group compared to the filgrastim group (3.19 ± 4.14 vs 3.61 ± 7.79, respectively; P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			penia, and fever and number of transfusions	<p>The mean duration fever was 5.65±4.21 days in the pegfilgrastim treatment group compared to 7.12±7.51 days in the filgrastim treatment group (<i>P</i> value not reported).</p> <p>The proportions of patients who received a red blood cell transfusion were 61.3 and 60.8% in the pegfilgrastim and filgrastim treatment groups, respectively, while 100 and 97.3% of these patients required a platelet transfusion.</p>
<p>Martino et al⁴⁰</p> <p>Filgrastim 5 µg/kg/day SC starting on day five following transplant until neutrophil engraftment</p> <p>vs</p> <p>pegfilgrastim 6 mg SC once on day one following transplant</p> <p>All Patients were treated with three cycles of vincristine, adriamycin and dexamethasone, followed by cyclophosphamide and G-CSF and PBSC collection.</p> <p>After PBSC collection, patients received high dose melphalan as the conditioning regimen for the APBSCT.</p>	<p>AC, RCT</p> <p>Patients with a de-novo diagnosis of multiple myeloma, stages II to III Durie–Salmon classification</p>	<p>N=37</p> <p>Duration not specified</p>	<p>Primary: Duration of grade four neutropenia (ANC of <math>0.5 \times 10^9/L</math>)</p> <p>Secondary: Incidence of febrile neutropenia (ANC of <math>2 \times 10^9/L</math> and temperature <math>38.2^\circ C</math>), duration of febrile neutropenia, duration of fever, incidence of documented infections and platelet engraftment</p>	<p>Primary: There was no significant difference in the duration of grade four neutropenia between the pegfilgrastim group and the filgrastim group (5 vs 6 days; <i>P</i> value not reported).</p> <p>Secondary: The incidence of febrile neutropenia was significantly lower in the pegfilgrastim group compared to the filgrastim group (61.1 vs 100%; <i>P</i>=0.003).</p> <p>The duration of febrile neutropenia was significantly shorter in the pegfilgrastim group compared to the filgrastim group (1.5 vs 4.0; <i>P</i>=0.005).</p> <p>The incidence of fever of unknown origin was significantly lower in the pegfilgrastim group compared to the filgrastim group (44.0 vs 84.2%; <i>P</i>=0.029).</p> <p>One patient in each treatment group experienced a catheter-related infection and two patients in each of the treatment groups developed documented infections with positive blood cultures. No patients developed documented fungal infections.</p> <p>There was no significant difference in mean time to platelet engraftment between the pegfilgrastim group and the filgrastim group (11 days for both; <i>P</i> value not reported).</p> <p>Bone pain was the only adverse event considered cytokine-related and was reported in 10% of patients in the pegfilgrastim group and 12% in the filgrastim</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Castagna et al⁴¹</p> <p>Filgrastim 5 µg/kg/day SC starting on day one following transplant until ANC recovery to >0.5x10⁹/L for two consecutive days</p> <p>vs</p> <p>pegfilgrastim 6 mg SC once on day one following transplant</p> <p>All patients were treated with high-dose chemotherapy before receiving APBSCT on day zero.</p> <p>The most utilized chemotherapy regimens in the study were carmustine, etoposide, cytarabine and melphalan for lymphomas and high-dose melphalan 200 mg/m² for multiple myelomas.</p>	<p>MC, OL, RCT</p> <p>Adult patients with hematological malignancies and solid tumors who had an adequate harvest of CD34+ cells (≥3x10⁶/kg)</p>	<p>N=80</p> <p>Duration not specified</p>	<p>Primary: Duration of severe neutropenia (ANC of <0.5x10⁹/L), number of days to achieve an ANC of >0.5x10⁹/L starting on day one</p> <p>Secondary: Number of days to achieve an ANC of >1x10⁹/L starting on day one, number of days with fever >38°C, duration of antibiotic and antimycotic therapy and number of documented infections</p>	<p>group (<i>P</i> value not reported).</p> <p>Primary: Pegfilgrastim was non inferior to filgrastim in the duration of severe neutropenia (6.20 vs 5.97 days, respectively; mean difference, 0.23 days; 95% CI, -0.77 to 1.22) and the number of days needed to achieve an ANC of >0.5x10⁹/L (10.75 vs 11.53 days, respectively; mean difference, -0.78 days; 95% CI, -2.97 to 1.42).</p> <p>Secondary: The filgrastim and pegfilgrastim groups were similar with regard to the time to reach an ANC of >1x10⁹/L (12.16 vs 11.98 days, respectively; <i>P</i> value not reported) and days with fever (1.63 vs 0.95 days, respectively; <i>P</i> value not reported).</p> <p>The duration of antibiotic therapy was comparable between the two treatment groups (4.0 days for filgrastim and 5.7 days for pegfilgrastim; <i>P</i>=0.152).</p> <p>The result on the number of documented infections was not reported.</p>
<p>Mathew et al⁴²</p> <p>Filgrastim 5 µg/kg/day SC starting on day five following transplant</p>	<p>CO, RETRO</p> <p>Adult patients with NHL, HD or multiple myeloma who received an</p>	<p>N=164</p> <p>Mean duration of filgrastim therapy</p>	<p>Primary: Time to neutrophil recovery with ANC of ≥0.5x10⁹/L</p>	<p>Primary: The time to neutrophil recovery was 10.9 days with filgrastim and 9.6 days with pegfilgrastim (<i>P</i><0.0001). The total number of days with an ANC of <0.5x10⁹/L with filgrastim was 7.6 days compared to 6.4 days for pegfilgrastim (<i>P</i><0.001).</p> <p>Pegfilgrastim was associated with fewer incidences of febrile neutropenia</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>vs</p> <p>pegfilgrastim 6 mg SC once on day one following transplant</p> <p>All patients were treated with high-dose chemotherapy before receiving autologous SCT on day zero; regimens differed based on malignancies.</p>	<p>induction chemotherapy followed by autologous SCT</p>	<p>ranged from 5 to 21 days</p>	<p>once, total days with an ANC of $<0.5 \times 10^9$ cells/L, incidence of febrile neutropenia, number of definitive infections, days of IV antibiotic treatment, number of doses of filgrastim and pegfilgrastim given, reported episodes of bone pain and incidence of engraftment syndrome</p> <p>Secondary: Not reported</p>	<p>compared to filgrastim (59 vs 78%; $P=0.012$). The mean duration of febrile neutropenia was similar between the two treatment groups (3.2 days for filgrastim and 2.5 days for pegfilgrastim; $P=0.08$).</p> <p>Patients in the filgrastim and pegfilgrastim treatment groups had similar incidences of definitive infections (32 vs 23%, respectively; $P=0.294$). The duration of IV antibiotic treatment was shorter with pegfilgrastim compared to filgrastim (6.3 vs 9.6 days; $P=0.006$).</p> <p>Patients in the filgrastim group received an average of nine doses of filgrastim, whereas 76 of 82 patients in the pegfilgrastim group received a single dose of pegfilgrastim. Six patients who received pegfilgrastim also received additional filgrastim.</p> <p>Two patients in the pegfilgrastim group and none in the filgrastim group reported bone pain, while engraftment syndrome occurred in one patient in each group.</p> <p>Secondary: Not reported</p>
<p>Samaras et al⁴³</p> <p>Filgrastim 5 $\mu\text{g}/\text{kg}/\text{day}$ SC starting on day five following transplant until ANC recovery to $\geq 0.5 \times 10^9/\text{L}$ for three consecutive days</p> <p>vs</p>	<p>RETRO</p> <p>Patients with NHL or HD receiving high-dose BEAM followed by APBSCT</p>	<p>N=54</p> <p>Duration not specified</p>	<p>Primary: Length of hospital stay, time to engraftment, duration of neutropenia and thrombocytopenia, incidence and</p>	<p>Primary: The length of hospital stay was similar between the filgrastim and pegfilgrastim groups (16.0 vs 16.5 days, respectively; $P=0.27$).</p> <p>No differences were observed between the filgrastim and pegfilgrastim groups with regard to the time to engraftment (9 days for both; $P=0.55$), duration of neutropenia (8 vs 7, respectively; $P=0.13$) and duration of thrombocytopenia (9.5 vs 7.0 days, respectively; $P=0.21$).</p> <p>Fever was reported in 80 and 97% of patients in the filgrastim and</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>pegfilgrastim 6 mg SC once on day one following transplant</p> <p>All patients received high-dose carmustine, etoposide, cytarabine and melphalan followed by APBSCT.</p>			<p>duration of fever, use of IV antibiotics and need for red blood cell and platelet transfusion during hospital stay</p> <p>Secondary: Not reported</p>	<p>pegfilgrastim groups, respectively ($P=0.057$). The duration of fever was two days for in the filgrastim group and 4.5 days in the pegfilgrastim group; $P=0.057$.</p> <p>Similar proportions of patients in the filgrastim and pegfilgrastim groups received IV antibiotics (90 vs 100%, respectively; $P=0.13$). The duration of IV antibiotic treatment was also comparable between the two groups (10 days for filgrastim and 11 days for pegfilgrastim; $P=0.75$). The need for red blood cell and platelet transfusions was similar between the two groups ($P=0.27$ for red blood cell transfusions; $P=0.78$ for platelet transfusions).</p> <p>Secondary: Not reported</p>
<p>Samaras et al⁴⁴</p> <p>Filgrastim 5 µg/kg/day SC starting on day five following transplant until ANC recovery to $\geq 0.5 \times 10^9/L$ for three consecutive days</p> <p>vs</p> <p>pegfilgrastim 6 mg SC once on day one following transplant</p> <p>All patients received high-dose melphalan 200 mg/m² followed by APBSCT.</p>	<p>RETRO</p> <p>Patients with multiple myeloma who received melphalan 200 mg/m² followed by APBSCT</p>	<p>N=72</p> <p>Median duration of filgrastim use was 9 days (3 to 14 days)</p>	<p>Primary: Length of hospital stay, time to engraftment, duration of neutropenia and thrombocytopenia, incidence and duration of fever, use of IV antibiotics, need for red blood cell and platelet transfusion during hospital stay</p> <p>Secondary: Not reported</p>	<p>Primary: Pegfilgrastim treatment was associated with a significantly shorter hospital stay compared to filgrastim treatment (14.5 vs 15.5 days; $P=0.024$).</p> <p>The median time to neutrophil engraftment was significantly shorter with pegfilgrastim treatment compared to filgrastim treatment (9 vs 10 days; $P=0.032$). The median duration of neutropenia was also significantly shorter following treatment with pegfilgrastim compared to filgrastim (5 vs 6 days; $P=0.0079$).</p> <p>The duration of thrombocytopenia was similar between patients receiving filgrastim and pegfilgrastim (3.0 and 3.5 days, respectively; $P=0.39$).</p> <p>Seventy-two and 63% of patients in the filgrastim and pegfilgrastim treatment groups, respectively, reported of fever ($P=0.51$). The median duration of fever was similar between the two treatment groups (2 vs 1 days, respectively; $P=0.13$).</p> <p>The proportion of patients requiring IV antibiotics was similar between the filgrastim and pegfilgrastim treatment groups (89 vs 90%, respectively; $P=0.38$). The median duration of treatment was also comparable between groups (6.0 vs 5.5 days, respectively; $P=0.12$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>There was no statistically significant difference between the two groups in the need for platelet transfusion ($P=0.92$); however, more patients in the filgrastim group required platelet transfusions compared to the pegfilgrastim (0.5 vs 0; $P=0.00065$)</p> <p>Secondary: Not reported</p>
Reducing Time to Neutrophil Recovery and Duration of Fever Following Induction or Consolidation Chemotherapy Treatment of Adults with Acute Myelogenous Leukemia				
<p>Jansen et al⁴⁵</p> <p>Filgrastim 5 µg/kg/day SC from day zero until neutrophil recovery (ANC of $>1,500$ cells/mm³)</p> <p>vs</p> <p>sargramostim 500 µg/kg SC from day zero until neutrophil recovery (ANC of $>1,500$ cells/mm³)</p> <p>Patients underwent chemotherapy treatment with cyclophosphamide and etoposide and all patients started G-CSF 10 mg/kg/day SC followed by PBSCT.</p>	<p>T</p> <p>Patients with metastatic (stage IV) or locally advanced (stage II or III) breast cancer or myeloma who were acceptable candidates for high-dose chemotherapy with PBSC rescue</p>	<p>N=46</p> <p>Duration not specified</p>	<p>Primary: Time to ANC recovery of >500 cells/mm³ and ANC of $>1,000$ cells/mm³, time to platelet recovery of $>20,000$ and $>50,000$, days with growth factor, days with temperature $>38.3^{\circ}\text{C}$, days of IV antibiotic use, number of platelet transfusions and number of red cell units</p> <p>Secondary: Not reported</p>	<p>Primary: Time to ANC recovery of $>500/\text{mm}^3$ was significantly shorter in the filgrastim group compared to the sargramostim group (8.8 ± 1.2 vs 10.5 ± 1.5 days; $P<0.001$). In addition, time to ANC recovery of $>1,000/\text{mm}^3$ was significantly shorter in the filgrastim group compared to the sargramostim group (8.9 ± 2.2 vs 11.0 ± 1.7 days; $P=0.001$).</p> <p>There were no significant differences in time to platelet recovery of $>20,000$ or $>50,000$ in the sargramostim group (9.9 ± 1.1 and 11.8 ± 2.1 days, respectively) compared to the filgrastim group (11.2 ± 4.7 and 14.9 ± 9.3 days, respectively; $P=0.40$ and $P=0.37$, respectively).</p> <p>Patients in the filgrastim group experienced significantly fewer days with growth factor use compared to those in the sargramostim group (10.8 ± 2.1 vs 12.2 ± 1.5 days; $P=0.001$).</p> <p>There was no significant difference in the number of days patients experienced a temperature $>38.3^{\circ}\text{C}$ between the sargramostim and filgrastim groups (2.3 ± 2.4 vs 1.8 ± 2.1 days; $P=0.46$).</p> <p>There was no significant difference in the number of days patients received IV antibiotics between the sargramostim and filgrastim groups (4.3 ± 2.7 vs 4.6 ± 4.3 days; $P=0.84$).</p> <p>There was no significant difference in the number of platelet transfusions received between patients in the sargramostim and filgrastim groups (2.4 ± 1.7 vs 3.1 ± 3.2 days; $P=0.80$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>There was no significant difference in the number of red cell units received between patients in the sargramostim and filgrastim groups (2.8 ± 1.6 vs 2.3 ± 2.2; $P=0.21$).</p> <p>Secondary: Not reported</p>
Shorten Time to Neutrophil Recovery and Reduce Incidence of Infection Following Induction Chemotherapy in Older Adult Patients with Acute Myelogenous Leukemia				
<p>Stone et al⁴⁶</p> <p>GM-CSF 5 µg/kg/day IV given daily until the neutrophil count was $\geq 1,000$ cells/cm³, there was evidence of the re-growth of leukemia or severe toxic effects attributable to the study infusion occurred</p> <p>vs</p> <p>placebo given daily until the neutrophil count was $\geq 1,000$/mm³, there was evidence of the re-growth of leukemia or severe toxic effects attributable to the study infusion occurred</p> <p>Induction chemotherapy consisted of daunorubicin and cytarabine.</p>	<p>DB, MC, PC, RCT</p> <p>Patients ≥ 60 years of age with the diagnosis of primary AML as defined morphologically by the FAB system of classification</p>	<p>N=388</p> <p>Duration not specified</p>	<p>Primary: Rate of complete remission</p> <p>Secondary: Therapeutic failure, overall survival, duration of neutropenia and duration of hospitalization</p>	<p>Primary: There was no significant difference in the rate of complete remission between patients receiving GM-CSF and placebo (51 vs 54%; $P=0.61$).</p> <p>Secondary: The reasons for therapeutic failure of remission (i.e., resistant disease or death during marrow hypoplasia) were similar in both treatment groups ($P=0.79$).</p> <p>The median survival was not significantly different between the treatment groups (9.4 months; 95% CI, 7.6 to 11.2).</p> <p>The median duration of neutropenia was significantly shorter in the GM-CSF group compared to the placebo group (15 vs 17 days; $P=0.02$).</p> <p>The median length of hospitalization was not significantly different between the GM-CSF group and the placebo group (28 vs 30 days; $P=0.11$).</p>
<p>Rowe et al⁴⁷</p> <p>Sargramostim 250 µg/m²</p>	<p>DB, RCT</p> <p>Patients 55 to 70</p>	<p>N=124</p> <p>Duration not</p>	<p>Primary: Hematologic response (ANC)</p>	<p>Primary: The median time to ANC recovery of >500 cells/µL was significantly shorter in the sargramostim group compared to the placebo group (13 vs 17 days;</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>SC daily over four hour until the ANC was >1,500 cells/μL for three consecutive days or for a maximum of 42 days</p> <p>vs</p> <p>placebo</p> <p>Induction consisted of standard daunorubicin and cytarabine.</p>	<p>years of age with adequate hepatic, renal and cardiac function (bilirubin 52 mg/dL; creatinine <2 mg/dL; and normal cardiac left ventricular ejection fraction), no previous cytotoxic or radiation therapy, morphologic proof of AML, no known antecedent myelodysplastic and immunophenotypic analysis performed on prestudy specimens</p>	<p>specified</p>	<p>recovery, platelet recovery and red blood cell recovery) and rate of complete remission</p> <p>Secondary: Treatment-related toxicity, infectious toxicity and median survival</p>	<p>$P=0.001$). Similarly there was a shorter median time to ANC recovery of >1,000 cells/μL for patients treated with sargramostim compared to placebo (14 vs 21 days; $P=0.001$).</p> <p>There was no significant difference between the sargramostim and placebo treatment groups in the median recovery rate of platelets (11 vs 12 days, respectively; $P=0.11$) and red blood cells (13 vs 14 days, respectively; $P=0.39$).</p> <p>Significantly more patients experienced complete remission in the sargramostim group compared to the placebo group (60 vs 45%; $P=0.08$).</p> <p>Secondary: The treatment-related mortality was not significantly different between the sargramostim group compared to the placebo group (6 vs 15%, respectively; $P=0.18$). There were no differences between the groups for any other toxicities, including weight gain, cardiac events, or pulmonary events. No patient withdrew from study drug due to toxicity or leukemia re-growth.</p> <p>Grade four and five infections occurred significantly less frequently in the sargramostim group compared to the placebo group (10 vs 36%; $P=0.002$); however, there was no significant difference in occurrence of the combination of grade three, four and five infections (52 vs 70%, respectively; $P=0.068$). Death associated with pneumonia occurred significantly less in the sargramostim group compared to the placebo group (14 vs 54%; $P=0.046$).</p> <p>The median survival time was significantly longer in the sargramostim group compared to the placebo group (10.6 vs 4.8 months; $P=0.048$).</p>
<p>Büchner et al⁴⁸</p> <p>Sargramostim 250 μg/m²/day continuous IV infusion started on day four</p> <p>vs</p>	<p>HC</p> <p>Adult patients with early relapse less than six months following remission and with multiple relapse, and</p>	<p>N=92</p> <p>Duration not specified</p>	<p>Primary: Complete remission rate</p> <p>Secondary: Death rate, definite nonresponse</p>	<p>Primary: There was no statistically significant difference in complete remission rates between the sargramostim group and the control group (50 vs 32%; $P=0.09$).</p> <p>Secondary: The sargramostim group had significantly fewer early (within six weeks) deaths compared to the control group (14 vs 39%; $P=0.009$); however, there was no significant difference among later hypoplastic deaths between the two groups</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>control group (sequential patients treated by the identical chemotherapy at the same situations)</p> <p>Early or multiple relapses were treated with one course S-HAM and newly diagnosed AML and AML late relapses in the higher age group were treated with TAD9.</p>	<p>patients ≥ 65 years with newly diagnosed AML or late relapse</p>		<p>rate, adverse events and duration of remission</p>	<p>(19 vs 13%; <i>P</i> not reported).</p> <p>There was no significant difference in the number of definite nonresponders between the sargramostim group and the control group (17 vs 16%; <i>P</i> value not reported).</p> <p>Patients in the sargramostim group demonstrated a higher overall frequency, including all grades of decrease in serum protein (<i>P</i>=0.02), prothrombin (<i>P</i>=0.02) and pseudocholinesterase levels (<i>P</i>=0.008). In the control group, elevation of serum transaminases was more frequent overall (<i>P</i>=0.008) and in lower-grade elevations and showed more frequent cardiac events (<i>P</i>=0.018).</p> <p>The duration of remission did not appear to be different with GM-CSF compared to the control group (<i>P</i> value not reported).</p>

*Agent not available in the United States.

Drug regimen abbreviations: IV=intravenous, SC=subcutaneous

Study abbreviations: AC=active control, CI=confidence interval, CO=cohort, DB=double blind, DE=dose-escalation, ES=extension study, HC=historical control, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, OS=observation study, PC=placebo controlled, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, T=trial, XO=crossover

Miscellaneous abbreviations: ALL=acute lymphocytic leukemia, AMC=absolute monocytes count, AML=acute myelogenous leukemia, ANC=absolute neutrophil count, APBSCT=autologous peripheral blood stem cell transplantation, BEAM= carmustine, etoposide, cytarabine, melphalan, BMT=bone marrow transplant, CHOP=cyclophosphamide, doxorubicin, vincristine, prednisolone, CSF=colony-stimulating factor, ECOG=Eastern Cooperative Oncology Group, FAB=French-American-British, G-CSF=granulocyte-colony-stimulating factor, GM-CSF=granulocyte-macrophage-colony stimulating factor, GVHD=graft-vs-host disease, HD=Hodgkin's disease, HLA=human leukocyte antigen, NHL=non-Hodgkin's lymphoma, ICD-9=international classification of disease, PBC=peripheral blood count, PBSC=peripheral blood stem cell, PBSCT=peripheral blood stem cell transplant, rhG-CSF=recombinant human granulocyte colony-stimulating factor, rhGM-CSF=recombinant human granulocyte-macrophage colony-stimulating factor, RR=relative risk, SCT=stem cell transplant, SD=standard deviation, S-HAM=sequential high-dose cytosine arabinoside and mitoxantrone, TAD9=9-day 6-thioguanine with cytosine arabinoside and daunorubicin, WBC=white blood cell, WHO=World Health Organization

Table 5. Special Populations⁴⁻⁶

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Filgrastim	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in neonates have not been established.	Not reported	Not reported	C	Unknown; use caution.
Pegfilgrastim	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	Not studied in hepatic dysfunction.	C	Unknown; use caution.
Sargramostim	Safety and efficacy in elderly patients have not been established.* Safety and efficacy in children have not been established.†	Renal function should be monitored at least every other week during therapy.	Hepatic function should be monitored at least every other week during therapy.	C	Unknown; use caution.

*No adequate or well-controlled trials.

†Liquid sargramostim and reconstituted sargramostim with bacteriostatic water for injection, both of which contain benzyl alcohol, should not be administered to neonates due to association with fatal "gasping syndrome" in premature infants.

Adverse Drug Events

Table 6. Adverse Drug Events^{4-6,17}

Adverse Event	Filgrastim	Pegfilgrastim	Sargramostim
Cardiovascular System			
Cardiac (not-specified)	-	-	23
Chest pain	5	-	15
Edema	-	-	13 to 34
Hemorrhage	-	-	23 to 29
Hypertension	-	-	25 to 34
Hypotension	-	-	13
Peripheral edema	-	12	11 to 15
Tachycardia	-	-	11
Central Nervous System			
Anxiety	-	-	11
Central nervous system disorder	-	-	11
Chills	-	-	19 to 25
Fatigue	11	-	-
Fever	12	-	77 to 96
Headache	7	16	36

Adverse Event	Filgrastim	Pegfilgrastim	Sargramostim
Insomnia	-	-	11
Neuro-clinical	-	-	42
Neuro-motor	-	-	25
Neuro-psych	-	-	15
Neutropenic fever	13	-	-
Paresthesia	-	-	11
Pyrexia	-	23	-
Dermatological			
Alopecia	18	48	37 to 73
Pruritus	-	-	23
Rash	6	-	44 to 70
Skin (not-specified)	-	-	77
Gastrointestinal			
Abdominal pain	-	-	38
Anorexia	9	-	13 to 54
Constipation	5	10	-
Diarrhea	14	29	52 to 89
Dyspepsia	-	-	17
Dysphagia	-	-	11
Gastrointestinal disorder	-	-	37
Gastrointestinal hemorrhage	-	-	11 to 27
Hematemesis	-	-	13
Mucositis	12	-	-
Nausea/vomiting	57	13	46 to 90
Stomatitis	5	-	24 to 62
Laboratory Test Abnormalities			
Bilirubinemia	-	-	30
Blood dyscrasia	-	-	25
Coagulation	-	-	19
High blood urea nitrogen	-	-	23
High cholesterol	-	-	17
Hyperglycemia	-	-	25 to 41
Hypomagnesemia	-	-	15
Increased creatinine	-	-	15
Increased serum glutamic pyruvic transaminase	-	-	13
Leukopenia	-	-	17
Liver damage	-	-	13
Low albumin	-	-	27
Thrombocytopenia	-	-	19
Respiratory			
Allergy	-	-	12
Cough	6	-	-
Dyspnea	9	-	15 to 28
Epistaxis	-	-	17
Lung disorder	-	-	20
Pharyngitis	-	-	23
Pulmonary (not-specified)	-	-	48
Rhinitis	-	-	11
Other			
Arthralgia	-	16	11
Asthenia	-	13	17 to 66

Adverse Event	Filgrastim	Pegfilgrastim	Sargramostim
Bone pain	-	31	21
Eye hemorrhage	-	-	11
Generalized weakness	4	-	-
Infection	-	-	65
Liver (not-specified)	-	-	77
Malaise	-	-	57
Metabolic	-	-	58
Mucous membrane disorder	-	-	75
Myalgia	-	21	-
Pain (not-specified)	2	-	17
Sepsis	-	-	11
Skeletal pain	22	-	-
Sore throat	4	-	-
Urinary tract disorder	-	-	14
Weight loss	-	-	27

- Event not reported or incidence $\leq 2\%$.

Contraindications

Table 7. Contraindications⁴⁻⁶

Contraindication	Filgrastim	Pegfilgrastim	Sargramostim
Concomitant use with chemotherapy and radiotherapy	-	-	✓
History of serious allergic reactions to pegfilgrastim or filgrastim	-	✓	-
Hypersensitivity to <i>Escherichia coli</i> -derived proteins or any component of the product	✓	-	-
Hypersensitivity to granulocyte-macrophage colony-stimulating factor, yeast-derived products or any component of the product	-	-	✓
Patients with excessive leukemic myeloid blasts in the bone marrow or peripheral blood ($\geq 10\%$)	-	-	✓

Warnings/Precautions

Table 8. Warnings and Precautions⁴⁻⁶

Warning/Precaution	Filgrastim	Pegfilgrastim	Sargramostim
Acute respiratory distress syndrome; patients who develop fever, lung infiltrates, or respiratory distress should be evaluated for acute respiratory distress syndrome	✓	✓	✓
Allergic reactions; systemic symptoms have been reported including the skin, respiratory and cardiovascular systems	✓	✓	-
Alveolar hemorrhage and hemoptysis; pulmonary infiltrates and hemoptysis requiring hospitalization have been reported in healthy donors undergoing peripheral blood progenitor cell mobilization	✓	-	-
Cardiovascular symptoms; transient supraventricular arrhythmias have been reported, particularly in patients with a previous history of cardiac arrhythmia	-	-	✓

Warning/Precaution	Filgrastim	Pegfilgrastim	Sargramostim
Concurrent radiation therapy; use has not been evaluated and concomitant administration should be avoided	✓	-	-
Cutaneous vasculitis; cases were moderate to severe and occurred in patients on long-term treatment	✓	-	-
Delayed myelosuppression; treatment has not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression	✓	-	-
Fluid retention; edema, capillary leak syndrome, pleural and/or pericardial effusion have been reported	-	-	✓
Growth factor potential; the possibility of this agent acting as a growth factor for any tumor type cannot be excluded	✓	✓	✓
Immunogenicity; due to the therapeutic protein nature of this product, there is potential for antibody development; however, the incidence has not been adequately determined	✓	-	✓
Leukocytosis; to avoid potential complications of excessive leukocytosis a complete blood cell count is recommended twice weekly during treatment	✓	-	-
Pediatric use; benzyl alcohol is a constituent of sargramostim products and has been associated with fatal "gaspings syndrome" in premature infants	-	-	✓
Premature discontinuation of therapy; for a sustained therapeutic response, therapy should continue following chemotherapy until the post-nadir absolute neutrophil count reaches 10,000/mm ³	✓	-	-
Previous exposure to intensive chemotherapy/radiotherapy; extensive radiotherapy to hematopoietic sites for the treatment of disease in the abdomen or chest, or those who have been exposed to multiple myelotoxic agents may have a limited treatment effect on myeloid reconstitution	-	-	✓
Purged bone marrow; effective in accelerating myeloid recovery in patients receiving bone marrow purged by anti-B lymphocyte monoclonal antibodies	-	-	✓
Renal and hepatic dysfunction; some patients with preexisting renal or hepatic dysfunction enrolled in clinical trials had induced elevation of serum creatinine or bilirubin and hepatic enzymes	-	-	✓
Respiratory symptoms; sequestration of granulocytes in the pulmonary circulation has been documented following infusion, resulting in occasional dyspnea	-	-	✓
Severe chronic neutropenia; treatment of neutropenia due to other hematopoietic disorders	✓	-	-

Warning/Precaution	Filgrastim	Pegfilgrastim	Sargramostim
(e.g., myelodysplastic syndrome) has not been established			
Sickle cell disorders; severe sickle cell crises can occur in patients with sickle cell disorders receiving treatment	✓	✓	-
Splenic rupture; individuals reporting left upper abdominal pain and/or shoulder tip pain should be evaluated for enlarged spleen or splenic rupture, as fatal cases have been reported	✓	✓	-
Use in patients with malignancy undergoing mobilized peripheral blood progenitor cell mobilization collection; limited in vitro data suggest that tumor cells may be released and reinfused into the patient in the leukapheresis product	-	-	✓
Use with chemotherapy and radiation therapy; simultaneous use with chemotherapy has not been established and because of potential sensitivity of rapidly dividing myeloid cells to chemotherapy, do not use this agent for 24 hours before and hours after chemotherapy	✓	-	✓

Drug Interactions

There are no specific drug interactions reported with the use of colony-stimulating factors (CSFs).^{4-6,16} Generally, CSFs should be used with caution when used in combination with other agents, which may potentiate the release of neutrophils, such as lithium and corticosteroids.^{4-6,17}

Dosage and Administration

For patients receiving filgrastim or pegfilgrastim, a complete blood count, platelet and hematocrit should be obtained prior to chemotherapy and be monitored regularly during therapy. Prior to and during therapy with sargramostim, patients should be monitored for their renal and hepatic functions in addition to body weight and hydration status.⁴⁻⁶

Filgrastim and sargramostim should not be administered simultaneously with myelosuppressive chemotherapy or radiotherapy or within 24 hours prior to or following chemotherapy or radiotherapy. Pegfilgrastim should not to be administered within 14 days prior to and 24 hours after administration of a myelosuppressive chemotherapy.⁴⁻⁶

Table 9. Dosing and Administration^{4-6,17}

Generic Name	Adult Dose	Pediatric Dose	Availability
Filgrastim	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever, to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with acute myeloid leukemia: Injection: 5 µg/kg/day IV or SC daily for up to two weeks until the absolute neutrophil count has reached 10,000 mm ³ (may vary	Safety and efficacy in neonates have not been established.	Prefilled syringe (preservative-free): 300 µg/0.5 mL 480 µg/0.8 mL Single-dose vial (preservative-free): 300 µg/mL 480 µg/1.6 mL This medication

Generic Name	Adult Dose	Pediatric Dose	Availability
	<p>depending on needs of patient); doses may be increased by 5 µg/kg/day for each chemotherapy cycle, if applicable, based on the duration and severity of neutropenia</p> <p><u>To reduce the duration of neutropenia and neutropenia-related clinical sequelae (e.g., febrile neutropenia) in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation:</u> Injection: 10 µg/kg/day IV or SC daily, duration varies depending on needs of patient; dose should be adjusted based on absolute neutrophil counts</p> <p><u>For the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis:</u> Injection: 10 µg/kg/day SC daily for at least four days before the first leukapheresis and continued until the last leukapheresis; dose should be adjusted based on neutrophil counts</p> <p><u>For chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia:</u> Injection: 6 µg/kg SC twice daily; maintenance, dose should be individualized based on clinical response</p> <p><u>For chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with cyclic neutropenia or idiopathic neutropenia:</u> Injection: 5 µg/kg SC daily; maintenance, dose should be individualized based on clinical response</p>		<p>should be refrigerated.</p>
Pegfilgrastim	<p><u>To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever:</u> Injection: 6 mg SC as single dose once per chemotherapy cycle</p>	<p>Safety and efficacy in children have not been established.</p>	<p>Prefilled single use syringe: 6 mg/0.6 mL</p> <p>This medication should be refrigerated.</p>
Sargramostim	<p><u>For use following induction chemotherapy in older adult patients with acute myelogenous</u></p>	<p>Safety and efficacy in</p>	<p>Liquid for injection</p>

Generic Name	Adult Dose	Pediatric Dose	Availability
	<p><u>leukemia to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death:</u> Injection: 250 µg/m²/day IV starting on day 11 or four days following the completion of induction chemotherapy if the day 10 bone marrow is hypoplastic with <5% blasts; dose should be adjusted based on neutrophil counts; maximum duration of treatment should be 42 days</p> <p><u>For the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis (mobilization of peripheral blood progenitor cells):</u> Injection: 250 µg/m²/day IV or SC daily through period of blood cell collection; if white blood cells >50,000 cells/mm³, dose should be reduced by 50%</p> <p><u>For the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis (post peripheral blood progenitor cell transplantation):</u> Injection: 250 µg/m²/day IV or SC daily immediately following infusion of progenitor cells and continued until absolute neutrophil count >1,500 cells/mm³ for three consecutive days</p> <p><u>For acceleration of myeloid recovery in patients with non-Hodgkin's lymphoma, acute lymphoblastic leukemia, and Hodgkin's disease undergoing autologous bone marrow transplantation, for acceleration of myeloid recovery in patients undergoing allogeneic bone marrow transplantation from human leukocyte antigen-matched related donors:</u> Injection: 250 µg/m²/day IV beginning two to four hours after bone marrow infusion and not less than 24 hours after the last dose of chemotherapy or radiotherapy and continued until absolute neutrophil count >1,500 cells/mm³ for three consecutive days</p> <p><u>In patients who have undergone allogeneic or autologous bone marrow transplantation in whom engraftment is delayed or has failed:</u> Injection: initial, 250 µg/m²/day IV for 14 days; treatment may be repeated after seven days off therapy; if a third course is necessary, dose is increased to 500 µg/m²/day</p>	<p>children have not been established.</p>	<p>(preserved solution): 500 µg/mL</p> <p>Powder for reconstitution (preservative-free): 250 µg</p> <p>Liquid and reconstituted sargramostim should be refrigerated.</p>

IV=intravenously, SC=subcutaneously

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
<p>National Comprehensive Cancer Network: Myeloid Growth Factors Clinical Practice Guidelines in Oncology (2012)⁹</p>	<p><u>Prophylactic use of colony-stimulating factors (CSFs)</u></p> <ul style="list-style-type: none"> • For patients at high risk of febrile neutropenia, prophylactic CSFs is recommended if the risk of febrile neutropenia is 20% or greater and for any patient considered at high risk, regardless of whether the treatment is intended to be curative, to prolong survival or to manage symptoms. • Patients at intermediate risk of febrile neutropenia: <ul style="list-style-type: none"> ○ Intermediate risk is defined as a 10 to 20% probability of developing febrile neutropenia or a neutropenic event that would compromise treatment. ○ Whether the treatment is intended to be curative, to prolong survival or to manage symptoms, it is recommended that individualized consideration of CSF therapy be based on physician-patient discussion of the risk-benefit ratio of the likelihood of developing febrile neutropenia, the potential consequences of a neutropenic event and the implications of reduced chemotherapy doses. ○ If patient risk factors determine the risk is 10 to 20%, CSF is a reasonable prophylactic option. ○ If the risk is due to the chemotherapy regimen and the treatment is intended to prolong survival or to manage symptoms, other alternatives such as the use of less myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be explored. • Patients at low risk of febrile neutropenia: <ul style="list-style-type: none"> ○ In patients at low risk of febrile neutropenia, defined as <10% risk, routine use of CSFs is not considered cost-effective, and alternative treatment options are appropriate. ○ CSFs may be considered if the patient is receiving curative or adjuvant treatment and is at significant risk for serious medical consequences of febrile neutropenia, including death. • Evaluation of subsequent chemotherapy cycles: <ul style="list-style-type: none"> ○ Patient evaluation should occur prior to each subsequent chemotherapy cycle to determine the risk categorization and treatment intent. ○ If a patient experiences an episode of febrile neutropenia or a dose-limiting neutropenic event despite receiving CSF therapy, it is recommended that a chemotherapy dose reduction or change in treatment regimen occur unless there is an impact on patient survival. • Chemotherapy regimens and risk of febrile neutropenia: <ul style="list-style-type: none"> ○ CSF prophylaxis is recommended when using a chemotherapy regimen with an incidence of >20% of febrile neutropenia. ○ Benefits of pegfilgrastim have not been shown in regimens given under two-week duration; therefore, it should be avoided in patients receiving weekly chemotherapy. <p><u>Therapeutic uses of CSFs</u></p> <ul style="list-style-type: none"> • Patients with febrile neutropenia who are receiving prophylactic filgrastim or sargramostim should continue with CSF therapy. However, since pegfilgrastim is long acting, those who have received prophylaxis

Clinical Guideline	Recommendations
	<p>with pegfilgrastim should not be treated with an additional CSF.</p> <ul style="list-style-type: none"> • Due to the lack of evidence supporting the therapeutic use of pegfilgrastim, only filgrastim and sargramostim should be used in this therapeutic setting. • It is recommended for those who have not received prophylactic CSFs to be evaluated for risk factors for infection-related complications or poor clinical outcome. These include old age (>65 years), sepsis syndrome, severe (absolute neutrophil count [ANC] of <100 cells/μL) or anticipated prolonged (>10 days) neutropenia, pneumonia, invasive fungal infection or other clinically documented infections, hospitalization and prior episode of febrile neutropenia. If risk factors are present, CSFs should be considered. <p><u>Dosing and administration</u></p> <ul style="list-style-type: none"> • Based on available data regarding the CSFs in prophylaxis of febrile neutropenia, when choosing among the myeloid growth factors, filgrastim and pegfilgrastim are considered to have more evidence than sargramostim. • Initial doses of filgrastim are started at a daily dose of 5 μg/kg beginning within one to three days after completion of chemotherapy until post-nadir ANC recovery to normal or near-normal ANC levels by laboratory standards. • There is evidence to support the use of pegfilgrastim 24 hours after completion of chemotherapy given every three weeks in one dose of 6 mg per cycle of treatment. • There are insufficient data support dose and schedule of weekly regimens or schedules less than two weeks and these cannot be recommended. Pegfilgrastim may be administered every two weeks. • Administration of filgrastim or pegfilgrastim within 24 hours after completion of chemotherapy is not recommended. • There is insufficient evidence to support a strong recommendation for sargramostim in nonmyeloid malignancies. • Subcutaneous administration is preferred for filgrastim, pegfilgrastim and sargramostim. <p><u>Severe chronic neutropenia</u></p> <ul style="list-style-type: none"> • Granulocyte CSF (G-CSF) is an established effective treatment for cyclic, congenital and idiopathic neutropenia.
<p>The American Society of Clinical Oncology: 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-based Clinical Practice Guideline (2006)¹⁰</p>	<ul style="list-style-type: none"> • Reduction in febrile neutropenia is an important clinical outcome that justifies the use of CSFs, regardless of their impact on other factors, when the risk of febrile neutropenia is approximately 20% and no other equally effective regimen that does not require CSFs is available. <p><u>Primary prophylactic CSF administration (first and subsequent-cycle use)</u></p> <ul style="list-style-type: none"> • Primary prophylaxis is recommended for the prevention of febrile neutropenia in patients who have a high risk of febrile neutropenia based on age, medical history, disease characteristics and myelotoxicity of the chemotherapy regimen. • For “dose dense” regimens, CSFs are required and recommended. • The standard of care is to use chemotherapy regimens that do not require CSFs because of equal efficacy and lower risk of febrile neutropenia if such regimens are available. • Current data demonstrates effectiveness and supports the use of CSFs

Clinical Guideline	Recommendations
	<p>when regimens that have a febrile neutropenia incidence >20% are used; therefore, this practice is recommended.</p> <p><u>Secondary prophylactic CSF administration</u></p> <ul style="list-style-type: none"> • Secondary prophylaxis with CSFs is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome. <p><u>Therapeutic use of CSF</u></p> <ul style="list-style-type: none"> • CSFs should not be routinely used for patients with neutropenia who are afebrile. • CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with febrile neutropenia. However, CSFs should be considered in patients with febrile neutropenia who are at high-risk for infection associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. <p><u>Use of CSFs to increase chemotherapy dose-intensity and dose-density</u></p> <ul style="list-style-type: none"> • Use of CSFs allows a modest to moderate increase in dose-density and/or dose-intensity of chemotherapy regimens. • A survival benefit is suggested by the current data when CSFs are used with dose-dense regimens in specific settings (e.g., node-positive breast cancer and possibly non-Hodgkin's lymphoma [NHL]), but this data cannot be applied to other diseases. • It is recommended to only use dose-dense regimens within an appropriately designed clinical trial or when use is supported by convincing efficacy data. <p><u>Use of CSFs as adjuncts to progenitor-cell transplantation</u></p> <ul style="list-style-type: none"> • The current standard of care is the administration of CSFs to mobilize peripheral-blood progenitor cell (PBPC) often in conjunction with chemotherapy and their administration after autologous, but not allogeneic, PBPC transplantation. <p><u>Use of CSFs in patients with acute leukemia and myelodysplastic syndromes</u></p> <ul style="list-style-type: none"> • For acute myeloid leukemia (AML), CSF use following initial induction therapy is reasonable, as studies have demonstrated a decrease in neutropenia duration, although there has been no favorable impact on remission rate, remission duration or survival. Patients older than 55 years of age may be most likely to benefit from CSF use. • For priming of leukemia cells in patients with AML, use of CSFs is not recommended. • After the completion of consolidation chemotherapy, CSF use can be recommended to possibly decrease the incidence of infection and eliminate the likelihood of hospitalization in some patients receiving intensive postremission chemotherapy. • Due to the lack of information regarding pegylated CSFs in patients with myeloid leukemia, it is recommended that they not be used in such patients outside of clinical trials. • For myelodysplastic syndromes, intermittent administration of CSFs

Clinical Guideline	Recommendations
	<p>may be considered in certain patients with severe neutropenia and recurrent infection; however, there is a lack of data supporting the routine long-term continuous use of CSFs in these patients.</p> <ul style="list-style-type: none"> • For acute lymphocytic leukemia (ALL), to reduce the duration of neutropenia, CSFs are recommended after the completion of the initial first few days of chemotherapy of the initial induction or first postremission course. • For acute leukemia in relapse, it is recommended that CSFs be used judiciously, or not at all, in patients with refractory or relapsed myeloid leukemia due to the lack of expected response. <p><u>Use of CSFs in patients receiving radiotherapy with or without concurrent chemotherapy</u></p> <ul style="list-style-type: none"> • In those patients who are expected to have prolonged delays in radiation treatment due to neutropenia and are not receiving chemotherapy, CSFs may be considered. • In those patients receiving concurrent chemotherapy and radiation of the mediastinum, CSFs should be avoided. <p><u>Use of CSFs in older patients</u></p> <ul style="list-style-type: none"> • To reduce the incidence of febrile neutropenia and infections, prophylactic CSFs should be given to patients 65 years of age and older with diffuse aggressive lymphoma treated with curative chemotherapy (CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone] or more aggressive regimens). <p><u>Use of CSFs in the pediatric population</u></p> <ul style="list-style-type: none"> • The use of CSFs in pediatric patients will usually be guided by clinical protocols. The use of CSFs is reasonable for the primary prophylaxis of pediatric patients with a likelihood of febrile neutropenia. • The use of CSFs for secondary prophylaxis or for therapy should be limited to high-risk patients. • Due to the potential risk for secondary myeloid leukemia or myelodysplastic syndrome associated with CSFs, their use represents a concern in children with ALL whose prognosis is otherwise excellent. For these reasons, the use of CSFs in children with ALL should be considered with caution. <p><u>CSF initiation, duration, dosing and administration</u></p> <ul style="list-style-type: none"> • CSFs should be given 24 to 72 hours after the administration of myelotoxic chemotherapy and should be continued until the ANC reaches at least 2 to 3x10⁹ cells/L. • For PBPC mobilization, CSFs should be started at least four days before the first leukapheresis procedure and continued until the last leukapheresis. • In adults, the recommended CSF doses are 5 µg/kg/day for G-CSF and 250 µg/m²/day for granulocyte-macrophage CSF (GM-CSF) for all clinical settings other than PBPC mobilization. • In the setting of PBPC mobilization, if G-CSF is used, a dose of 10 µg/kg/day maybe preferable. • The preferred route of CSF administration is subcutaneous. <p><u>Pegylated G-CSF initiation, duration, dosing and administration</u></p>

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • Pegfilgrastim 6 mg should be given once, 24 hours after completion of chemotherapy. • The 6 mg formulation should not be used in infants, children or small adolescents weighing less than 45 kg. <p><u>Special comments on comparative clinical activity of G-CSF and GM-CSF</u></p> <ul style="list-style-type: none"> • No guideline recommendation can be made regarding the equivalency of the two CFSs. • Further trials are recommended to study the comparative clinical activity, toxicity and cost-effectiveness of G-CSF and GM-CSF. <p><u>Special comments on growth factors as a treatment for radiation injury</u></p> <ul style="list-style-type: none"> • Current recommendations for the management of patients exposed to lethal doses of total body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs, includes the prompt administration of CSF or pegylated G-CSF.
<p>European Organization for Research and Treatment of Cancer: 2010 Update of European Organization for Research and Treatment of Cancer Guidelines for the Use of Granulocyte-Colony Stimulating Factor to Reduce the Incidence of Chemotherapy-Induced Febrile Neutropenia in Adult Patients with Lymphoproliferative Disorders and Solid Tumors (2010)¹⁶</p>	<p><u>Patient-related risk factors for increased risk of febrile neutropenia</u></p> <ul style="list-style-type: none"> • Prevention of chemotherapy-induced febrile neutropenia should be considered a clinical priority. • Prior to administering each cycle of chemotherapy, evaluation of patient-related risk factors should be included in the overall assessment. • Other risk factors that should be evaluated for include elderly age (aged 65 and over), advanced stage of disease, experience of previous episode(s) of febrile neutropenia, lack of G-CSF use and lack of antibiotic prophylaxis. • Indiscriminate use of antibiotic prophylaxis is not recommended. <p><u>Chemotherapy regimens associated with increased risk of febrile neutropenia</u></p> <ul style="list-style-type: none"> • Chemotherapy regimens are categorized based on their potential to cause febrile neutropenia (>20%, 10 to 20% and <10%); therefore, this risk should be taken into consideration when using certain chemotherapy regimens. <p><u>G-CSF to support chemotherapy</u></p> <ul style="list-style-type: none"> • G-CSF prophylaxis should be used as supportive treatment in cases when dose-dense or dose-intense chemotherapy regimens have demonstrated survival benefits. • G-CSF should be used as primary prophylaxis to maintain a chemotherapy regimen if dose or intensity reduction has demonstrated poor prognosis when the treatment is potentially curative or intended to prolong survival. • When the treatment is palliative, the use of less myelosuppressive chemotherapy or dose/schedule modification should be considered. <p><u>Impact of the overall febrile neutropenia risk on G-CSF use</u></p> <ul style="list-style-type: none"> • At the beginning of each cycle, each patient should be individually assessed for the risk of complication related to febrile neutropenia, which should include patient-related risk factors, the chemotherapy regimen and associated complications and treatment intent. • Prophylactic G-CSF therapy is recommended in patients whose overall risk of febrile neutropenia is >20%. • When a chemotherapy regimen associated with a febrile neutropenia

Clinical Guideline	Recommendations
	<p>risk of 10 to 20% is used, patient characteristics should be taken into account when reviewing the overall risk of febrile neutropenia.</p> <p><u>G-CSF in patients with existing febrile neutropenia</u></p> <ul style="list-style-type: none"> G-CSF treatment in patients with solid tumors and malignant lymphoma should be reserved for those patients who are not responding to appropriate antibiotic management and who are developing life-threatening infections (such as severe sepsis or septic shock). <p><u>Choice of formulation</u></p> <ul style="list-style-type: none"> Where indicated, filgrastim, lenograstim* and pegfilgrastim are all recommended to prevent febrile neutropenia and febrile neutropenia related complications due to their clinical efficacy and studies demonstrating comparable efficacy.
<p>British Committee for Standards in Hematology: Guidelines on the Use of Colony-stimulating Factors in Hematological Malignancies (2003)⁴⁹</p>	<ul style="list-style-type: none"> Due to the lack of comparative trials and clinical trial data, there seems to be no evidence demonstrating efficacy or outcome differences between the G-CSF and GM-CSF products when administered at recommended doses. These guidelines do not differentiate between the agents. <p><u>Prophylactic and adjunctive use</u></p> <ul style="list-style-type: none"> Primary prophylaxis is not routinely recommended unless the expected incidence of febrile neutropenia is >40%. Secondary prophylaxis cannot be routinely justified because of a lack of available evidence but is indicated for tumors in which dose reduction or dose delay would compromise overall survival. Adjunctive treatment is not recommended for patients with uncomplicated febrile neutropenia but should be considered in patients with poor prognostic factors. <p><u>Use of CSFs in association with chemotherapy</u></p> <ul style="list-style-type: none"> AML: The routine use of CSF is recommended after consolidation chemotherapy. CSF is recommended after induction if it is appropriate to reduce hospital stay or antibiotic usage. ALL: G-CSF is indicated to reduce the severity of neutropenia following intensive phases of therapy. Myelodysplastic syndromes: CSFs are indicated to reduce the severity of neutropenia in patients receiving intensive chemotherapy. CSFs are also recommended on an intermittent basis for patients with neutropenia and infection, but continuous prophylactic use is not routinely justified. Aplastic anemia: There is insufficient evidence to make any general recommendations. Hence, patients should be given CSFs only on an individual therapeutic trial basis. Bone marrow failure syndromes: G-CSF is recommended when improvement of neutrophil count is appropriate. Malignant lymphomas: There is evidence to support the routine use of CSFs to reduce the incidence of infection, chemotherapy delay and hospitalization, especially when the risk of febrile neutropenia exceeds 40%. There is also emerging evidence of improved survival with G-CSF-supported dose intensification in elderly patients with high-grade NHL. At present, this evidence is insufficient to justify a change in policy in all patients with lymphoma, but elderly patients may benefit from G-CSF support.

Clinical Guideline	Recommendations
	<p><u>CSFs for PBPC mobilization</u></p> <ul style="list-style-type: none"> CSFs are indicated for the mobilization of PBPCs. <p><u>CSFs after PBSC and marrow transplantation</u></p> <ul style="list-style-type: none"> CSFs are indicated to accelerate reconstitution after allogeneic and autologous PBPC transplantation or bone marrow transplant.
<p>National Comprehensive Cancer Network: Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (2012)¹⁵</p>	<p><u>Monitoring and supportive care</u></p> <ul style="list-style-type: none"> Growth factors may be considered as a part of supportive care for post-remission therapy. Recommendations regarding the use of cytokines for infection or for slow marrow recovery are left to institutional policy. G-CSF or GM-CSF should be discontinued for a minimum of seven days before obtaining bone marrow to document remission as CSF therapy may confound interpretation of the bone marrow. Growth factors should not be used in patients with acute promyelocytic leukemia.
<p>British Committee for Standards in Hematology: Guidelines on the Management of Acute Myeloid Leukemia in Adults (2006)⁵⁰</p>	<p><u>Growth factors</u></p> <ul style="list-style-type: none"> Growth factors following AML chemotherapy have shown no survival benefit but have demonstrated reduction in the duration of neutropenia, antibiotic use and hospital stay. The cost-benefit advantages of routine growth factor use are uncertain. G-CSF is recommended after induction if it is appropriate to reduce hospital stay or antibiotic usage. The routine use of growth factor therapy in AML is not recommended. <p><u>Standard chemotherapy</u></p> <ul style="list-style-type: none"> There is insufficient evidence to support routine use of G-CSF or GM-CSF with induction chemotherapy in patients over 60 years of age, although this may be appropriate if it is desirable to reduce hospitalization or antibiotic usage. <p><u>Management of AML in patients who are pregnant</u></p> <ul style="list-style-type: none"> Pregnant patients with other forms of AML, other than promyelocytic leukemia-retinoic acid receptor-positive acute promyelocytic leukemia, and with stable disease may defer chemotherapy and be supported with growth factors and blood products until delivery can be safely induced at about 30 weeks.
<p>National Comprehensive Cancer Network: Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (2013)⁵¹</p>	<p><u>Supportive care</u></p> <ul style="list-style-type: none"> Use of G-CSF or GM-CSF is not recommended for routine infection prophylaxis. Use of G-CSF or GM-CSF may be considered in a neutropenic patient who has recurrent or resistant infections. Low-dose G-CSF or GM-CSF may be combined with recombinant human erythropoietin for anemia when indicated, particularly in patients who are not responding to erythropoiesis-stimulating agents and have serum erythropoietin level of 500 mUnits/mL or less.
<p>United Kingdom Myelodysplastic Syndromes Guideline Group: Guidelines for the Diagnosis and Therapy</p>	<p><u>Erythropoietin with or without G-CSF</u></p> <ul style="list-style-type: none"> Many studies have clearly demonstrated that erythropoietin with or without G-CSF can increase hemoglobin levels and reduce or eliminate red blood cell transfusion in selected myelodysplastic syndromes patients.

Clinical Guideline	Recommendations
<p>of Adult Myelodysplastic Syndromes (2003)⁵²</p>	<ul style="list-style-type: none"> It is recommended that patients with refractory anemia and refractory anemia with excess blasts who are not eligible for chemotherapy or stem cell transplantation and are symptomatic of anemia, with no or low transfusion requirement (<2 units/month) and a baseline erythropoietin level <200 units/L who have not responded to a trial of erythropoietin alone for six weeks be considered for daily G-CSF therapy, doubling the dose of erythropoietin or both for six more weeks. The G-CSF dose should be doubled weekly (e.g., 75 µg to 150 µg then to 300 µg) to maintain the white blood cell between 6 and 10x10⁹ cells/L. In patients who respond, once the maximum response has been reached, the G-CSF can be reduced to thrice weekly, and the erythropoietin dose can be reduced by one day a week at four weekly intervals (e.g., five days a week to four days then three days) to the lowest dose that retains response. It is recommended that the combination of erythropoietin and G-CSF be used from the beginning for patients with refractory anemia with excess blasts, symptomatic anemia, baseline erythropoietin levels <500 units/L and a transfusion requirement <2 units/month. Due to the lack of published data, it is encouraged to continue randomized-controlled trials of erythropoietin with or without G-CSF to address the issues of quality of life, survival advantage and pharmacoeconomics. <p><u>Prophylactic management of infection</u></p> <ul style="list-style-type: none"> Prophylactic low-dose G-CSF therapy may be considered in patients who are severely neutropenic in order to maintain a neutrophil count >1x10⁹ cells/L.
<p>European Society for Medical Oncology Hematopoietic Growth Factors: European Society for Medical Oncology Clinical Practice Guidelines (2011)⁵³</p>	<p><u>Incidence of febrile neutropenia, complication rates and mortality</u></p> <ul style="list-style-type: none"> Despite relatively high rates of low neutrophil count during standard-dose chemotherapy regimens for malignancies other than acute leukemia, rates of febrile neutropenia, other complication rates and mortality rates are relatively low for most standard chemotherapies. These rates do not justify the systematic use of hematopoietic growth factors (hGFs) such as G-CSF or its pegylated form (pegfilgrastim) in prophylaxis of chemotherapy-induced neutropenia unless the risk of febrile neutropenia exceeds 20%, a chemotherapy dose reduction is deemed detrimental to the intended outcome or other special circumstances are present. Colony-stimulating growth factors should be avoided in patients who are not at high risk for febrile neutropenia or neutropenic complications. The use of hGFs for treatment of febrile neutropenia is also not recommended, except in settings with increased morbidity and mortality, including sepsis, tissue infection and prolonged neutropenia. These agents should be particularly avoided in patients with infections not related to neutropenia, such as community- or hospital-acquired pneumonia <p><u>Special situations for the use of hGFs as primary prophylaxis</u></p> <ul style="list-style-type: none"> Reduced marrow reserve (e.g., ANC <1.5x10⁹ cells/L) due to radiotherapy >20% marrow. The patient has the human immunodeficiency virus. Patients 65 years of age and older who were treated with curative regimens (cyclophosphamide, adriamycin, vincristine, prednisone or

Clinical Guideline	Recommendations
	<p>more intensive regimens for patients with aggressive NHL).</p> <p><u>Special situations for the use of hGFs as secondary prophylaxis</u></p> <ul style="list-style-type: none"> • Infections during the next chemotherapy treatment cycle are considered to be life threatening. • The chemotherapy dose reduction is below the clinically appropriate threshold. • Without the administration of hGF, there would be a delay in chemotherapy treatment. • There is a lack of protocol adherence if compromising cure rate, overall or disease-free survival. <p><u>Use of G-CSFs in high-risk situations</u></p> <ul style="list-style-type: none"> • Treatment of acute leukemias and autologous or allogeneic stem cell transplantations lead to higher risks of febrile neutropenia and potentially lethal complications. • Administration of hGF may be safely postponed until five to seven following autologous marrow transplant. • Short acceleration of recovery of ANC does not consistently translate into relevant clinical benefit in patients undergoing peripheral blood stem cell transplantation. Use of G-CSF in standard-risk patients outside trials is not recommended. • It is reasonable to administer G-CSF following allogeneic marrow transplant. The clinical benefit is restricted to recovery of ANC and should be started five to seven days following transplant. • In autologous peripheral blood stem cell mobilization, the administration of hGFs with or without chemotherapy is effective. The recommended dose of G-CSF is 10 µg/kg daily for seven to 10 days prior to apheresis, with or without chemotherapy. The hGF-mobilized peripheral blood stem cells are superior in terms of recovery of ANC to marrow stem cells plus post infusion hGFs. • In allogeneic peripheral blood stem cell mobilization, there is a faster ANC recovery following peripheral blood stem cells compared to marrow stem cells. The recommended dose of G-CSF is 10 µg/kg daily for seven to 10 days before apheresis, with or without chemotherapy.

*Agent not currently available in the United States.

Conclusions

Colony-stimulating factors (CSFs) are growth factors that stimulate the production and enhance recovery of neutrophils.⁵⁴ There are currently two types of CSFs available in the United States, granulocyte CSF (G-CSF) and granulocyte-macrophage CSF (GM-CSF). Filgrastim and pegfilgrastim, the currently available G-CSFs and are both Food and Drug administration (FDA)-approved to decrease the incidence of infection in patients with nonmyeloid malignancies receiving chemotherapy regimens associated with severe neutropenia.⁴⁻⁵ In addition to this indication, filgrastim has several other indications including the reduction in time to neutrophil recovery and the reduction in duration of neutropenia in specific patient populations, as well as for mobilization of hematopoietic progenitor cells and chronic administration in patients with specific types of neutropenia.⁴ Sargramostim, is the only GM-CSF currently available and is indicated for the acceleration of myeloid recovery, delayed or failed engraftment after bone marrow transplant and to shorten neutrophil recovery time in patients with acute myelogenous leukemia.⁶

G-CSFs are largely used to prevent and reduce the duration of neutropenia in patients receiving chemotherapy.^{9,10,16,53} Several clinical trials have demonstrated efficacy of the G-CSFs for this indication. A systematic review published in 2007 reviewed 17 randomized controlled trials comparing

primary prophylactic G-CSF to placebo or untreated controls in adult solid tumor and malignant lymphoma patients. The review reported an overall 46% decrease in the risk of febrile neutropenia, a 45% decrease in infection-related mortality and a 40% decrease in all-cause mortality during the chemotherapy period.⁵⁶

Currently the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO) and European Organization for Research and Treatment of Cancer (EORTC) guidelines recommend CSF prophylaxis in patients whose overall risk of febrile neutropenia is >20%.^{9,10,16} Retrospective data has reported a potential advantage of pegfilgrastim in reducing the risk of hospitalizations due to febrile neutropenia when compared to filgrastim and sargramostim, while an earlier prospective, randomized trial demonstrated comparable clinical efficacy between filgrastim and pegfilgrastim for the indication of febrile neutropenia.¹¹⁻¹⁴ The NCCN and the EORTC guidelines currently do not recommend one G-CSF product over another for treatment.^{9,16} Moreover, with the lack of well-designed clinical studies comparing the efficacy of the G-CSFs and GM-CSF, the ASCO guidelines do not provide recommendations regarding the specific types of products, whereas the NCCN states filgrastim and pegfilgrastim have stronger evidence than sargramostim supporting their use.^{9,10} Additional studies are needed to determine the safety and efficacy differences among the G-CSFs and GM-CSF in febrile neutropenia as well as the other FDA-approved indications.

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