Filgrastim and Pegfilgrastim Use in Patients With Neutropenia

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Myelosuppression, the reduction of platelets and red and white blood cells, is the most common side effect of chemotherapy. Filgrastim and pegfilgrastim are used to assist recovery in patients with low white blood cell counts. This article explores the dosing, efficacy, cost, and clinical considerations of filgrastim and pegfilgrastim in neutropenia care. Increased knowledge of the medications may contribute to positive patient outcomes. As the price of hospitalization increases, prophylactic dosing of filgrastim and pegfilgrastim becomes more cost effective. In addition, clinical outcomes are improved through a reduction in length of hospital stays and the need for IV antibiotic administration.

At a Glance

- Filgrastim and pegfilgrastim are colony-stimulating factors that shorten time to neutropenic recovery in patients receiving myelosuppressive chemotherapy.
- Treatment benefits of filgrastim and pegfilgrastim include the prevention of neutropenic fever, the ability to adhere to chemotherapy schedules, and fewer hospital stays.
- Although filgrastim and pegfilgrastim have a high retail value, the rising price of hospital stays may outweigh their cost.

result in neutrophils, not the germ lines of other cells, no information definitively states whether CSFs will or will not promote cancer cell growth.

Pharmacodynamics

Filgrastim and pegfilgrastim have identical effects on the body (Holmes, O'Shaughnessy, et al., 2002). Both CSFs act on the precursors to blood-producing cells in the bone marrow by binding to receptors on the surface of the cells (Amgen Inc., 2007a, 2007b). CSFs promote the division of hematopoietic cells and the production of functioning neutrophils (see Figure 1). Although filgrastim and pegfilgrastim only act on cells that

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makes the molecule too large to pass through the renal system but allows it to act as intended (Bedell, 2003; Curran & Goa, 2002; Waladkhani, 2004). In patients with neutropenia, pegfilgrastim cannot be cleared until the ANC increases. The half-life of pegfilgrastim ranges from 15–80 hours (Amgen Inc., 2007a).

Dosing

Filgrastim, a short-acting CSF, typically is delivered to the patient via subcutaneous injection, although it can be administered by IV injection. Initial dosing for filgrastim is 5 mcg/kg per day and is adjusted according to white blood cell response. The drug is discontinued once ANC is 1,000/mm³ or higher for three consecutive days.

Pegfilgrastim, a long-acting CSF, also is administered via subcutaneous injection. An initial dose of 6 mg is given 24–72 hours after the completion of chemotherapy; the medication is cleared by neutrophils, so only one dose is needed per cycle (NCCN, 2009). A study by Bruns et al. (2006) found no advantage in a 12 mg dose of filgrastim versus the standard 6 mg dose.

Both medications should be administered 24 hours after the completion of chemotherapy; delaying the CSF dose decreases its efficacy (Cappozzo, 2004). CSFs should not be given before the course of chemotherapy (Cappozzo). Pegfilgrastim should not be administered to patients who weigh less than 45 kg; all patients who weigh 45 kg or more should receive a 6 mg dose (Cappozzo; Hussar, 2003).

Indications

According to Turkoski et al. (2007), filgrastim is used for the “stimulation of granulocyte production in chemotherapy-induced neutropenia” (p. 701). Evidence-based indications for the prophylactic use of CSFs were published by NCCN and the American Society of Clinical Oncology (ASCO) (see Figure 2). NCCN (2009) recommends that CSFs be considered adjunct treatment for febrile neutropenia with antibiotic therapy but cites a lack of evidence for improved outcomes. Only the short-acting filgrastim should be used therapeutically because pegfilgrastim has not been studied as adjunct treatment. If a patient has been dosed with pegfilgrastim prophylactically, no additional CSFs should be given (NCCN, 2009).

The ASCO guidelines do not recommend adjunct therapy with CSFs in febrile neutropenia unless the patient’s clinical situation warrants it. A patient who has not been treated with CSFs prophylactically may begin CSF therapy after becoming neutropenic and febrile. The ASCO guidelines do not recommend therapeutic CSFs for patients who become neutropenic but do not develop fever (Smith et al., 2006).

The NCCN guidelines (2009) limit the use of CSFs in chemotherapy-induced neutropenia. In addition, the ASCO guidelines indicate other uses for CSFs, such as in progenitor-cell transplantation, leukemia and myelodysplastic conditions, radiation treatment without chemotherapy, and radiation injury (accidental exposure) (Smith et al., 2006).

Efficacy

CSFs are used to reduce infections in patients with neutropenia. Fever is an indicator of infection in patients with neutropenia; patients with fever need antibiotics and supportive treatment (Dale, 2002). In a phase III study by Vogel et al. (2005), the prophylactic use of pegfilgrastim on the second day of 100 mg/m² docetaxel chemotherapy treatment in patients with breast cancer (n = 928) resulted in a 94% decrease of febrile neutropenia compared to control. In addition, the placebo group (n = 465) had a 17% rate of febrile neutropenia, whereas the pegfilgrastim group had a 1% rate. In another trial by Crawford et al. (1991), patients with small cell lung cancer (N = 199) were randomized to receive either a CSF or placebo on the fourth day of chemotherapy treatment with cyclophosphamide, doxorubicin, and etoposide. The placebo group (n = 104) had a 56% rate of febrile neutropenia, whereas the treatment group (n = 95) had a 28% rate (a 50% reduction). In addition, days of hospitalization were reduced from four days to two days, and the duration of IV antibiotics was reduced from 2.25 days to 1.25 days (Crawford et al.).

The use of CSFs and subsequent reduction in neutropenia may improve outcomes through the delivery of full-dose chemotherapy regimens (Wilson & Gardner, 2007). Febrile complications of neutropenia may delay treatment or reduce dose intensity. Patients with breast cancer who received at least 85% of their planned adjuvant chemotherapy regimen had an increased incidence of relapse-free survival versus patients who received less (Frasci, 2002). Most delays and reductions in treatment were related to neutropenia.

When considering CSFs, the differences between filgrastim and pegfilgrastim must be evaluated, with the major distinction being frequency of injections. Filgrastim requires a daily injection starting about 24 hours after the end of a chemotherapy cycle. Injections continue until the neutrophil count reaches 1,000/mm³. Pegfilgrastim requires one injection about 24 hours after the end of a chemotherapy cycle (Smith et al., 2006). Pegfilgrastim could help patients adhere to treatment schedules because the drug requires fewer injections. However, although both drugs have very few associated adverse reactions, pegfilgrastim has lasting effects.
that may prolong side effects. A study that compared filgrastim administered daily versus pegfilgrastim administered once per cycle in 310 patients receiving chemotherapy found no statistically significant difference in neutrophil recovery between the two drugs (Holmes, O’Shaughnessy, et al., 2002). Similar results were reported in a smaller (N = 157) phase III study comparing the two drugs in adults with stage II, III, or IV breast cancer (Green et al., 2003).

Healthcare providers should consider patient comfort when choosing filgrastim versus pegfilgrastim. Pegfilgrastim requires fewer injections if not contraindicated (Amgen Inc., 2007a, 2007b; NCCN, 2009). Length of time between chemotherapy cycles also should be considered. Filgrastim should be used when time between cycles is less than two weeks because pegfilgrastim has not been studied in shorter cycles (NCCN, 2009; Smith et al., 2006).

Safety and Side Effects

Bone pain, the most common side effect of filgrastim and pegfilgrastim, occurs in about 56% of patients. Bone pain usually is treated successfully with nonopoid analgesics (acetaminophen or nonsteroidal anti-inflammatory inhibitors if not contraindicated), and CSF treatment can continue; bone pain resolves when filgrastim is discontinued or after pegfilgrastim has been cleared (with recovered ANC) (Amgen Inc., 2007a, 2007b; Moore & Crom, 2006). Filgrastim and pegfilgrastim have a low occurrence of fever, petechiae, rash, splenomegaly, increased liver enzymes, epistaxis, hyper- or hypotension, cardiac arrhythmias, headaches, nausea, vomiting, peritonitis, leukocytosis, and transfusion reaction (Turkoski et al., 2007). Patients receiving filgrastim or pegfilgrastim should have biweekly complete blood counts to monitor response to CSF treatment. Patients treated with CSFs should be monitored for acute respiratory distress as well as sickle-cell crisis (Hussar, 2003), as the conditions could manifest with the increased blood viscosity caused by extra circulating white blood cells (Steinberg & Charm, 1971).

In a case report by Hatzimichael et al. (2006), a patient presented with left upper abdominal pain and was diagnosed with splenic hematoma, which occurred one week after receiving pegfilgrastim. Whether CSF caused the hematoma is unclear because the patient also had thrombocytopenia (low platelets) at the time. Patients should be cautioned against any activity that could cause trauma to the abdomen while being treated with a CSF (Hatzimichael et al.).

A study in mice examined hypersplenism and its relationship with thrombocytopenia when used with CSFs (Takamatsu et al., 2007). The results showed that splenomegaly is rare and resolves after CSFs are discontinued. In addition, platelets in the mice dropped during initial CSF use and recovered after the drug was discontinued; thrombocytopenia resolved spontaneously, despite continued therapy in long-term use of CSFs.

Cost

Clinical decisions cannot be made without considering cost. The average length of treatment for filgrastim is 10 or 11 doses per cycle of chemotherapy, and pegfilgrastim is administered as a single dose per chemotherapy cycle (Holmes, Jones, et al., 2002). At www.drugstore.com, 10 vials of filgrastim currently cost $2,180.56, and one dose of pegfilgrastim costs $3,000–$7,000.

Figure 2. Indications for the Use of Colony-Stimulating Factors

Note. Based on information from National Comprehensive Cancer Network, 2009; Smith et al., 2006.

Contraindications

A contraindication for filgrastim and pegfilgrastim is a sensitivity or allergy to any component of *Escherichia coli*. The medications are made through the replication of a strain of *E. coli*, which houses a plasmid containing the genetic code for human endogenous CSF (Amgen Inc., 2007a). Sargramostim (Leukine®, Bayer Healthcare Pharmaceuticals) is a CSF manufactured with yeast instead of bacteria. Sargamostim was found to be equivalent to filgrastim; the medications are interchangeable clinically (Stull, Bilmes, Kim, & Fichtl, 2005). To date, sargramostim is indicated for induction chemotherapy in adult patients aged 55 years or older with acute myelogenous leukemia as well as bone marrow transplantation recipients (Bayer Healthcare Pharmaceuticals, 2008). Sargramostim is recommended by NCCN (2009), but with lower-level evidence than filgrastim and pegfilgrastim. Filgrastim and pegfilgrastim are pregnancy category C and only should be used if the benefits outweigh potential harm. Whether or not CSFs are excreted in human milk is unknown, so extreme caution is warranted (Amgen Inc., 2007b).

Drug Interactions

Concurrent use of lithium with filgrastim and pegfilgrastim requires more frequent monitoring of blood cell levels (complete blood count more than twice per week) because lithium has an additive effect and can increase the release of neutrophils (Amgen 2007b; Hussar, 2003). In addition, CSFs should not be given concurrently with chemotherapy or during radiation treatment because cytotoxic treatments may attack CSF-stimulated proliferating cells (Amgen Inc., 2007b).
per syringe (Neulasta Info, n.d.). Although the cost of hospital stays varies among institutions, prevention should decrease overall expenses.

Because of their high cost, CSFs only were prescribed in the past if a patient’s chemotherapy regimen had at least a 40% risk for febrile neutropenia (NCCN, 2009). However, the cost of hospital stays continue to rise, so prescribing CSF therapy to patients with a 20% or greater risk for febrile neutropenia is cost effective (Eldar-Lissai, Cosler, & Lyman, 2005; Moore & Crom, 2006; NCCN, 2009). ASCO recommends that CSFs be used with chemotherapy regimens that have at least a 20% risk for febrile neutropenia (Smith et al., 2006). However, the costs are difficult to quantify because of variability in the price of outpatient treatment centers, home health nurses, and self-care (Annemans, Van Overbeke, Standaert, & Van Belle, 2005). Additional analyses are needed to determine whether the drugs are economically viable when considering inpatient hospital expenses.

Amgen Inc. participates in a program called Safety Net for patients who are un- or underinsured. If a patient meets income and other eligibility guidelines, Amgen Inc. will replace the provider’s stock of filgrastim or pegfilgrastim after administration. For additional information, visit www.amgen.com.

Considerations

In a small study of patients receiving radiation therapy for head and neck cancer (N = 41), patients who received CSFs had fewer feeding tube placements and less mucositis (Su et al., 2006). The patients were not receiving chemotherapy; typically, CSFs only are approved in chemotherapy-induced neutropenia. In addition, 13 of 19 patients (68%) in the treatment group survived versus 9 of 22 (41%) in the placebo group over 7.25 years. The overall survival in the CSF arm suggests the positive effects of CSFs and warrants replication with a larger sample (Su et al.). Concurrent use with radiation therapy is a contraindication.

Filgrastim has been used in the pediatric population with 5 mcg/kg per day dosing and appears to be well tolerated (Amgen Inc., 2007a). Although data are limited, filgrastim does not appear to inhibit growth or alter sexual maturation in pediatric patients. Some patients with congenital types of neutropenia receiving filgrastim have developed myelodysplastic syndrome or acute leukemia (Amgen Inc., 2007a); whether the complications are connected to filgrastim use is unknown (Amgen Inc., 2007b). Pegfilgrastim is not used in patients weighing less than 45 kg, but may be administered to pediatric patients who weigh 45 kg or more (Amgen Inc., 2007a).

Filgrastim and pegfilgrastim are tolerated equally well in older and younger adult patients (Amgen Inc., 2007a, 2007b). More than 50% of all cancers present in people older than 65 years; 80% present in people older than 55 (Balducci & Carreca, 2002). Older adults, who tend to be undertreated and are less likely to be included in clinical trials, could benefit from CSF prophylaxis (Balducci & Carreca). Older adults are more likely to experience the toxic effects of chemotherapy, and the use of CSFs can increase the likelihood of full-dose chemotherapy treatment. As a result, CSFs have become the standard of care in people older than 70 who are receiving their first round of chemotherapy (Hood, 2003).

Patients with leukemia should be considered for CSF use. Administering a drug that stimulates the growth of white blood cells to people who have cancer of the white blood cells is counterintuitive. However, in a study by Löwenberg et al. (2003), CSFs were used prior to chemotherapy in people with acute myeloid leukemia (N = 640) to determine whether CSFs would increase white blood cells’ sensitivity to chemotherapy (priming). The study determined that the theory is plausible because patients who received CSFs had a 42% rate of disease-free survival at four years versus the placebo group (33% rate). However, the study did not find a statistically significant increase in overall survival. To date, ASCO guidelines do not recommend priming (Smith et al., 2006).

Few studies have examined the effects of CSF administration on quality of life. Shortened or eliminated hospital stays and the avoidance of neutropenic fever as a result of CSF use should improve quality of life (Crawford, 2004). However, no tools exist to measure CSFs’ effect on quality of life in patients with neutropenia, so additional research is needed.

Conclusion

Increased understanding of CSFs’ role in preventing or managing neutropenia will allow nurses to provide better guidance to patients. In addition, using filgrastim and pegfilgrastim can help patients avoid life-threatening infections. Additional study of these medications will further enhance nurses’ knowledge and improve treatment options for patients with neutropenia.

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