Chemotherapy-induced neutropenia (CIN) is a frequent adverse event in patients treated with myelosuppressive chemotherapy. The depth and duration of the neutrophil nadir following chemotherapy correlates with the development of infectious complications. However, minimizing the duration and severity of neutropenia by stimulating the growth and development of neutrophils in the bone marrow is possible by using granulocyte–colony-stimulating factors, such as filgrastim (Welte, Gabriole, Bronchud, Platzer, & Morstyn, 1996). The prophylactic administration of filgrastim can reduce the incidence of febrile neutropenia and decrease hospitalizations and IV antibiotic use, as well as facilitate the delivery of on-time chemotherapy doses (Crawford et al., 1991; Gabriole et al., 1988; Morstyn et al., 1988; Trillet-Lenoir et al., 1993; Zinzani et al., 1997). Clinical data indicate that delivering the chemotherapy dose on time is important to treatment outcomes in certain tumor types (Bonadonna, Valagussa, Moliterni, Zambetti, & Brambilla, 1995; Kwak, Halpern, Olshen, & Horning, 1990).

One of the main drawbacks of filgrastim is that it is a small protein that is rapidly cleared from the body through the kidneys and requires daily IV or subcutaneous injections for up to two weeks (Welte et al., 1996). Daily dosing can necessitate frequent visits to the clinic as well as decrease the number of injections that patients must endure as part of their treatment regimen. Pegfilgrastim also may result in improvements with patient adherence because patients no longer have to rely on caregivers, healthcare providers, or themselves to administer their daily injections. The need to arrange for weekend administration and daily clinic visits is reduced because of the self-regulating nature of the drug.

The Science of Pegylation

The term pegylation refers to the process of attaching a polyethylene glycol (PEG) molecule to another molecule, such as a protein. PEG molecules are pH-neutral, nontoxic, water-soluble polymers that consist of repeating ethylene oxide subunits, each with a molecular weight of 44 daltons (d) and two terminal hydroxyl groups (Bailon & Berthold, 1998). They can be either linear (5–30 kD) or branched (40–60 kD) chain structures. A protein can be pegylated by attaching a single large PEG chain at one site or by attaching several smaller PEG chains at many sites. In the case of pegfilgrastim, a 20 kD PEG chain is covalently attached directly to the N-terminal amino acid of filgrastim, a pegylated form of filgrastim, has been developed and can be administered subcutaneously once per chemotherapy cycle. Once-per-cycle dosing with pegfilgrastim can reduce the number of trips that patients and their caregivers must make to the clinic as well as decrease the number of injections that patients must endure as part of their treatment regimen.

To increase the duration of action, pegfilgrastim, a pegylated form of filgrastim, has been developed and can be administered subcutaneously once per chemotherapy cycle. Once-per-cycle dosing with pegfilgrastim can reduce the number of trips that patients and their caregivers must make to the clinic as well as decrease the number of injections that patients must endure as part of their treatment regimen.

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group of the filgrastim molecule (Molineux et al., 1999) (see Figure 1).

Compared with their unmodified counterparts, pegylated proteins usually have improved pharmacokinetics (e.g., a longer serum half-life, slower clearance, fewer fluctuations in plasma concentrations) and, in some cases, greater in vivo efficacy; thus, these proteins have the potential to improve adherence and patient quality of life (Bailon & Berthold, 1998; Delgado, Francis, & Fisher, 1992; Reddy, 2000).

Properties of Pegfilgrastim

Filgrastim is eliminated from the body primarily through the kidneys. A secondary mechanism of elimination is neutrophil-mediated. Pegylating filgrastim increases its molecular size, which impairs renal clearance and prolongs circulation time and duration of action (Molineux et al., 1999). Because the renal clearance of pegfilgrastim is minimal, the major route of elimination of pegfilgrastim appears to be mediated by receptors on the neutrophils themselves. Elimination by this route in patients with neutropenia also is limited because of the depleted number of mature neutrophils in patients treated with myelosuppressive chemotherapy; therefore, the serum concentration of pegfilgrastim remains elevated until the absolute neutrophil count (ANC) has recovered sufficiently to produce enough mature neutrophils to clear the drug (see Figure 2).

In this way, the clearance of pegfilgrastim is said to be self-regulating (Holmes, Jones, et al., 2002; Johnston et al., 2000; Roskos et al., 1999; Yowell, Crawford, Holmes, Yang, & Liang, 2001). The result is a sustained duration of action that makes dosing once per chemotherapy cycle possible, thereby simplifying the management of CIN.

Clinical Trials of Pegfilgrastim

Pegfilgrastim has been studied in clinical trials in patients with lung cancer (Johnston et al., 2000), lymphoma (Vose et al., 2001), and breast cancer (Green et al., 2001; Holmes, Jones, et al., 2002; Holmes, O’Shaughnessy, et al., 2002). In a dose-finding trial in 13 patients with non-small cell lung cancer, pegfilgrastim caused a rapid and lasting increase in ANC (Johnston et al.). A single, subcutaneous, 30 mcg/kg dose of pegfilgrastim resulted in a median ANC nadir (0.1 x 10^9/l or 100/mm^3) similar to that with daily subcutaneous injections of filgrastim at doses of 5 mcg/kg. Doses of pegfilgrastim 100 and 300 mcg/kg resulted in ANC nadirs of 0.65 x 10^9/l (650/mm^3) and 0.7 x 10^9/l (700/mm^3), respectively. Febrile neutropenia (temperature > 38.2 o C [100.8 o F] and ANC < 0.5 x 10^9/l) did not occur in any patients in this trial (Johnston et al.).

Pegfilgrastim similarly protects patients with non-Hodgkin’s lymphoma or Hodgkin’s disease from the effects of CIN. A single, subcutaneous injection of 100 mcg/kg pegfilgrastim was as effective as daily subcutaneous injections of 5 mcg/kg filgrastim in patients treated with the ESHAP protocol (etoposide, methylprednisolone, cisplatin, and cytarabine). No differences were reported between pegfilgrastim and filgrastim in the incidence or severity of adverse events, including bone pain (Vose et al., 2001).

Clinical Studies in Patients With High-Risk Breast Cancer

A dose-finding study in patients with breast cancer treated with 60 mg/m^2 doxorubicin and 75 mg/m^2 docetaxel found that a single, subcutaneous injection of pegfilgrastim at a dose of 100 mcg/kg per chemotherapy cycle provided protection against CIN similar to that with daily injections of filgrastim over several cycles of chemotherapy (Holmes, Jones, et al., 2002). Pegfilgrastim also was found to have a safety profile similar to that of filgrastim.

Pegfilgrastim has been compared with filgrastim in two randomized, double-blind, phase III trials in patients with breast cancer. The trials were similar in design, enrolling patients with either high-risk, early-stage (stage II) breast cancer or advanced (stage III or IV) breast cancer. The patients all had a good performance status (Eastern Cooperative Oncology Group performance status ≤ 2) and complete blood cell counts within normal limits. The patients were treated with four 21-day cycles of doxorubicin (60 mg/m^2) and docetaxel (75 mg/m^2) (Green et al., 2001; Holmes, O’Shaughnessy, et al., 2002). Pegfilgrastim and filgrastim were given subcutaneously 24 hours after chemotherapy, and daily injections of either placebo or filgrastim continued until ANC was at least
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0.5 x 10^9/l), ANC nadir, ANC recovery, and through four, incidence of febrile neutropenia in cycle one, duration and incidence of severe neutropenia in cycles two through four, incidence of febrile neutropenia (temperature > 38.2°C and ANC < 0.5 x 10^9/l), ANC nadir, ANC recovery, and safety.

The larger of the two trials, involving 310 patients in the United States, compared a single, weight-based dose of pegfilgrastim (100 mcg/kg) with daily doses of filgrastim (5 mcg/kg) (Holmes, O’Shaughnessy, et al., 2002). The smaller, international trial (N = 157) compared a single, fixed dose of pegfilgrastim (6 mg) with daily filgrastim (5 mcg/kg) (Green et al., 2001). Pegfilgrastim provided neutrophil recovery similar to that with filgrastim in both trials. The mean DSN in cycle one ranged from 1.6–1.8 days, and the incidence of severe neutropenia in cycle one ranged from 77%–84% with pegfilgrastim and filgrastim. The ANC nadir values were similar with both agents, but the pegfilgrastim recipients did not have ANC overshoot after the nadir, whereas ANC in the filgrastim recipients continued to increase, reflecting the daily administration schedule. In the fixed-dose study, patients in the pegfilgrastim and filgrastim groups were given similar total chemotherapy doses. Only 5% of patients had dose reductions of greater than or equal to 25% in any cycle. In both of these studies, pegfilgrastim was well tolerated and the incidence of adverse events was similar with pegfilgrastim and filgrastim. No dose-limiting toxic effects were reported with either drug. The most commonly reported cytokine-related adverse event was bone pain, and the incidence and severity of bone pain were the same with pegfilgrastim and filgrastim. No patients developed neutralizing antibodies to pegfilgrastim.

The incidence of febrile neutropenia over all cycles of chemotherapy was lower with pegfilgrastim than with filgrastim in both studies, but the difference was not statistically significant in the study by Green et al. (2001) (9% versus 18%, p = 0.029, in Holmes, O’Shaughnessy, et al., 2002; and 13% versus 20%, p > 0.05, in Green et al.). The median time to ANC recovery was similar in both treatment groups. Of note, however, is that ANC recovery was achieved with a single injection of pegfilgrastim, in contrast to an average of 11 daily injections of filgrastim.

The results from the pegfilgrastim fixed-dose study are encouraging, particularly in terms of simplifying the treatment of CIN. No difference occurred in DSN when the results in the patients who were treated with pegfilgrastim were analyzed by weight group (study patients ranged in weight from 46–125 kg), indicating that a single, 6 mg, fixed dose of pegfilgrastim does not compromise efficacy in heavier patients or tolerability in lighter patients (Green et al., 2001). This should further simplify the management of CIN by eliminating the need for dose calculations based on patient weight. By eliminating the need for individual dose calculations, the risk of dosing errors is reduced and drug inventory, preparation, and administration scheduling are simplified.

Pegfilgrastim Dosage and Administration

The recommended dose of pegfilgrastim is 6 mg per chemotherapy cycle, administered as a single, subcutaneous injection at least 24 hours after the chemotherapy is given. The use of pegfilgrastim within 14 days before a cycle of chemotherapy has not been studied; therefore, pegfilgrastim should not be administered within this period. Further studies are needed to investigate the administration of pegfilgrastim on the day of chemotherapy, as well as its use with weekly chemotherapy regimens (Amgen Inc., 2002).

After the administration of chemotherapy and pegfilgrastim, complete blood cell and platelet counts should be monitored regularly. Because patients will not be seen as frequently during their nadir as they would be if they were receiving filgrastim, they will need instructions regarding when to call the clinic if they have a fever or symptoms of infection. The frequency of monitoring the laboratory tests needs to be determined for each patient on the basis of the need for other growth factors (e.g., epoetin alfa), comorbidities, and the patient’s ability to self-monitor for signs of infections or other complications related to his or her cancer or chemotherapy.

Home instructions should include management of bone pain and assessment for infection. The majority of bone pain can be well managed with 650 mg acetaminophen or 400 mg ibuprofen orally every four to six hours. Patients should be instructed to call the clinic if they experience severe bone pain, injection site reactions, or any other new symptoms. Ensure that patients have a thermometer at home and know how to record their temperatures. Patients may find it useful to record their temperature in a diary twice a day and should notify their healthcare providers if their temperature rises above 38°C (100.4°F).

Storage and Handling

Pegfilgrastim is a sterile, colorless, preservative-free preparation supplied in prefilled syringes that contain pegfilgrastim 6 mg in 0.6 ml. Pegfilgrastim should be refrigerated at 2°C–8°C and protected from light. As with any protein preparation, pegfilgrastim should not be shaken. Pegfilgrastim may be allowed to reach room temperature prior to administration. Because the pegfilgrastim preparations are preservative-free, only one injection per prefilled syringe should be given and any unused portion should be discarded. The injection itself is administered in the same manner as filgrastim. Patients may have slight discomfort during subcutaneous injections, and the injection sites (e.g., outer part of the upper arm, abdomen, thighs) should be rotated (Amgen Inc., 2002).

Summary

Pegfilgrastim is a long-acting, pegylated form of filgrastim that can provide patients who are treated with myelosuppressive chemotherapy with prophylactic protection from neutropenic complications, such as febrile neutropenia and infection. A single, 6 mg dose of pegfilgrastim administered once per chemotherapy cycle is safe and effective in adult patients, regardless of body weight. Once-per-cycle dosing with pegfilgrastim relieves patients of the burden of daily injections, should simplify the management of neutropenia, and may improve patient adherence and well-being.
References


For more information on this topic, visit the following Web sites.

Neupogen® Filgrastim www.neupogen.com


About Neutropenia www.neutropenia.org/about-2.html

Links can be found using ONS Online at www.ons.org.

Rapid Recap

Pegfilgrastim for Chemotherapy-Induced Neutropenia

- Chemotherapy-induced neutropenia (CIN) is a frequent and serious toxic effect of myelosuppressive chemotherapy.
- Pegfilgrastim is a novel, long-acting, pegylated form of filgrastim that can be used as prophylaxis for CIN.
- Pegfilgrastim is a larger molecule than filgrastim, and its use results in reduced clearance by the kidneys and longer duration of action in the body.
- The clearance of pegfilgrastim is self-regulated because its major route of elimination is by receptors on neutrophils; the serum concentration of pegfilgrastim remains elevated until the absolute neutrophil count has recovered, after which the drug is cleared from the body.
- In clinical trials, a 6 mg dose of pegfilgrastim administered subcutaneously once per chemotherapy cycle was safe and effective in adult patients, regardless of body weight.
- Pegfilgrastim administered once per cycle decreases the burden of daily injections, thus simplifying the management of CIN and potentially improving patient adherence and well-being.