

CONTINUING EDUCATION

Optimal Use of Granulocyte–Colony-Stimulating Factor in Patients With Cancer Who Are at Risk for Chemotherapy-Induced Neutropenia

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Purpose/Objectives: To provide an overview of the risks for and occurrence of chemotherapy-induced neutropenia in patients with cancer and its optimal prophylactic management with recombinant human granulocyte–colony-stimulating factor (G-CSF).

Data Sources: Original research, review articles, conference presentations, and published guidelines.

Data Synthesis: Chemotherapy-induced neutropenia is a common serious adverse event, and the risks for it can be predicted on the basis of patient characteristics and the chemotherapy regimen.

Conclusions: Optimal, cost-effective prophylactic management of chemotherapy-induced neutropenia with G-CSF requires the assessment of patient factors and the myelotoxicity of the chemotherapy regimen.

Implications for Nursing: Neutropenia and its complications can be serious adverse events in patients who are treated with chemotherapy. Nurses should be familiar with how to identify patients who are at risk for neutropenia and its complications and should be prepared to discuss the need for first-cycle use of G-CSF with the other members of the treatment team as necessary.

Key Points . . .

- Severe neutropenia and febrile neutropenia are serious side effects of treatment with myelosuppressive chemotherapy that can require hospitalization and IV antibiotics and often result in substantial morbidity and mortality.
- First-cycle use of granulocyte–colony-stimulating factor (G-CSF) for chemotherapy-induced neutropenia is safe and effective.
- First-cycle use of G-CSF is cost effective when it is targeted to patients at higher risk for neutropenia.
- Prophylactic management of neutropenia may be simplified with the use of pegfilgrastim, a long-acting form of G-CSF that is administered only once per chemotherapy cycle and at a fixed dose.

Neutrophils are the crucial first line of defense against pathogens such as bacteria and fungi (Burg & Pilling, 2001). Produced in the bone marrow from blood progenitor cells, neutrophils have a relatively short half-life of about seven to eight hours in the peripheral blood. The high proliferative activity of neutrophil precursors and the high turnover of neutrophils in the periphery make them a target for cytotoxic agents that destroy rapidly proliferating cells in the body. Thus, patients with cancer who are treated with chemotherapy are at high risk for the development of neutropenia.

Neutropenia is a potentially serious side effect of cancer chemotherapy. Because neutrophils are responsible for protecting against infection, the presence of neutropenia may place a patient at serious risk for infection. Febrile neutropenia (temperature $\geq 38.2^{\circ}\text{C}$ and absolute neutrophil count [ANC] $\leq 500 \times 10^6/\text{l}$) (Crawford et al., 1991) is a significant risk factor for life-threatening infections that can require hospitalization and treatment with IV antibiotics. The development of infectious complications associated with neutropenia correlates with the depth and duration of the ANC nadir (Bodey, Buckley, Sathe, & Freireich, 1966). Patients with neutrophil counts below $1.0 \times 10^9/\text{l}$ for one week had a 50% chance of infection and, as the duration of neutropenia increased, the risk of infection neared 100%. These patients had a mortality rate above 50% as long as their counts continued to fall, but

Goal for CE Enrollees:

To enhance nurses' knowledge related to the use of granulocyte–colony-stimulating factor for the prevention of febrile neutropenia in patients with cancer receiving chemotherapy.

Objectives for CE Enrollees:

- On completion of this CE, the participant will be able to
1. Describe the effects of granulocyte–colony-stimulating factor on neutrophils.
 2. Discuss the factors that increase the risk of febrile neutropenia during chemotherapy.
 3. Compare the effects and benefits of filgrastim and pegfilgrastim.

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Digital Object Identifier: 10.1188/04.ONF.569-576

even incremental increases in these counts led to more favorable prognoses. As a result of improved antibiotics and treatment practices, the mortality rate associated with febrile neutropenia has dropped to the current rate of 5%–10% (Feld, 2000). However, mortality rates for patients undergoing treatment for cancer 30 years ago, before modern management, were close to 80%, particularly in association with gram-negative bacteremia (Crawford et al., 1991).

In addition to morbidity and mortality concerns, the presence of neutropenia may lead to chemotherapy dose reductions and delays that have been shown to compromise long-term survival rates (Bonadonna, Valagussa, Moliterni, Zambetti, & Brambilla, 1995; Budman et al., 1998; Kwak, Halpern, Olshen, & Horning, 1990). Therefore, preventing febrile neutropenia is still the best way of decreasing treatment-related morbidity and mortality in patients treated with chemotherapy; the appropriate prevention and management of neutropenia are of fundamental importance in these patients.

Granulocyte-Colony-Stimulating Factor

Granulocyte-colony-stimulating factor (G-CSF), a cytokine produced naturally by the body, regulates the proliferation, differentiation, maturation, and functional activation of neutrophils by binding to a specific cell-surface receptor on neutrophil precursors (Welte, Gabrilove, Bronchud, Platzer, & Morstyn, 1996) (see Figure 1). G-CSF has been shown to decrease the duration of the final stage of neutrophil maturation from five days to one day (Dexter & Testa, 1993). Animal studies have shown that both G-CSF and an intact G-CSF receptor are required for producing neutrophils and preventing neutropenia. Mice that lack G-CSF have chronic neutropenia, with peripheral blood neutrophil counts of only 20%–30% of normal, but they are otherwise viable, fertile, and superficially healthy (Lieschke et al., 1994). A single injection of G-CSF in these mice increases their neutrophil counts equal to those in normal mice (Lieschke et al.). Mice that lack the G-CSF receptor have neutrophil counts of only 12% of normal (Liu, Wu, Wesselschmidt, Kornaga, & Link, 1996).

In humans, G-CSF levels increase rapidly after exposure to a pathogen (Cebon, Layton, Maher, & Morstyn, 1994). The data from studies in humans as well as in mice indicate that the increase in neutrophil counts in response to infection is likely to be mediated at least partly by G-CSF. Consequently, G-CSF has been investigated as a way to increase neutrophil counts in patients with neutropenia.

Using Granulocyte-Colony-Stimulating Factor for Prophylaxis of Chemotherapy-Induced Neutropenia

Human G-CSF now is being produced commercially by using recombinant DNA technology. The first recombinant G-

- Stimulates the proliferation of neutrophil progenitor cells
- Stimulates the differentiation of neutrophil progenitor cells
- Reduces the maturation time of neutrophils from five days to one day
- Increases the numbers of mature neutrophils

Figure 1. Actions of Granulocyte-Colony-Stimulating Factor

Note. Based on information from Welte et al., 1996.

CSF approved for clinical use was filgrastim (Neupogen®, Amgen Inc., Thousand Oaks, CA). An injection of filgrastim results in increased neutrophil counts in mice (Fujisawa et al., 1986; Tamura et al., 1987) and humans (Bronchud et al., 1988). Filgrastim has a pharmacologic effect similar to that of endogenous G-CSF, increasing the proliferation, differentiation, and maturation of neutrophil precursors and improving the function and survival of mature neutrophils (Frampton, Lee, & Faulds, 1994). When filgrastim is administered daily to subjects with normal hematopoiesis, their neutrophil counts increase in a dose-dependent manner (Chatta, Price, Stratton, & Dale, 1994). The administration of filgrastim in the first cycle in clinical trials in patients with cancer treated with cytotoxic chemotherapy reduced the duration of severe neutropenia by 50% and also shortened the duration of antibiotic use and hospitalization (Crawford et al., 1991; Trillet-Lenoir et al., 1993).

G-CSF, including recombinant forms such as filgrastim, has a short elimination half-life of only a few hours, owing to its rapid clearance from the plasma through renal and neutrophil-mediated mechanisms (Welte et al., 1996). This rapid clearance means that filgrastim must be given by IV or subcutaneous injection daily for up to two weeks, a requirement that can lower patient acceptability of the treatment and place high demands on healthcare workers and caregivers. A long-acting form of filgrastim, named pegfilgrastim (Neulasta®, Amgen Inc.), has been developed and approved for commercial use. Because of an increase in its molecular size, the renal clearance of pegfilgrastim is minimized, resulting in a longer half-life than that of filgrastim (Molineux et al., 1999). Because renal clearance is minimal, the major route of elimination of pegfilgrastim is neutrophil-mediated. Elimination by this route is limited in patients with neutropenia, and the plasma concentration of pegfilgrastim remains elevated until the ANC has recovered. The clearance of pegfilgrastim thus is self-regulating (Holmes, Jones, et al., 2002; Johnston et al., 2000) (see Figure 2).

Similar to its parent molecule filgrastim, pegfilgrastim stimulates the production of mature neutrophils and reduces the incidence and duration of severe neutropenia in patients treated with myelosuppressive chemotherapy. When studied in healthy volunteers, a single subcutaneous injection of pegfilgrastim (30–300 mcg/kg) produced a dose- and time-dependent increase in neutrophil counts that lasted as long as eight days (Molineux et al., 1999). Similarly, in a dose-escalation trial in 13 patients with non-small cell lung cancer, pegfilgrastim induced a rapid and sustained rise in the ANC (Johnston et al., 2000). In the two phase III pivotal trials in patients treated with myelosuppressive chemotherapy, a single subcutaneous injection of pegfilgrastim (100 mcg/kg or 6 mg) was as safe and effective in reducing the duration of severe neutropenia and its complications as was a course of daily subcutaneous injections of filgrastim 5 mcg/kg, with the most common adverse event being bone pain (25%–37% of patients across all treatment groups) (Green et al., 2003; Holmes, O'Shaughnessy, et al., 2002).

Optimal Use of Granulocyte-Colony-Stimulating Factor in Patients With Chemotherapy-Induced Neutropenia

Filgrastim and pegfilgrastim have shown efficacy in the stimulation and production of neutrophils, and both agents

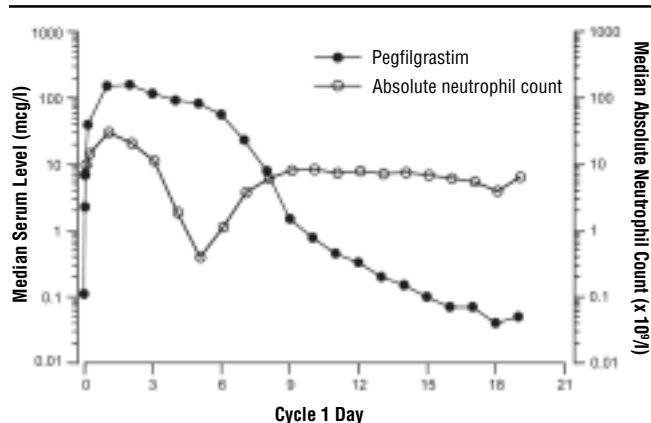


Figure 2. Absolute Neutrophil Count and Serum Levels of Pegfilgrastim After a Single 100 mcg/kg Subcutaneous Injection^a

^a The serum levels remain elevated until the absolute neutrophil count has begun to recover, indicating the self-regulating properties of the agent.

Note. From "Comparable Efficacy and Safety Profiles of Once-Per-Cycle Pegfilgrastim and Daily Injection Filgrastim in Chemotherapy-Induced Neutropenia: A Multicenter Dose-Finding Study in Women With Breast Cancer," by F.A. Holmes, S.E. Jones, J. O'Shaughnessy, S. Vukelja, T. George, M. Savin, et al., 2002, *Annals of Oncology*, 13, p. 903. Copyright 2002 by the European Society for Medical Oncology. Adapted with permission.

reduce the incidence of febrile neutropenia. The most common side effect of filgrastim and pegfilgrastim is medullary bone pain. Prophylactic use of G-CSF (either filgrastim or pegfilgrastim), beginning with the first cycle of chemotherapy, has been shown in clinical trials to be the most effective way to use the product to reduce the incidence of febrile neutropenia. Because febrile neutropenia and its associated infections are difficult to predict in patients who are treated with chemotherapy, selecting the patients at highest risk for neutropenia may be the most efficient and cost-effective strategy for the use of G-CSF. The costs of hospitalization for febrile neutropenia and antibiotic treatment can be significant. One study found that the average daily cost of hospitalization for febrile neutropenia was \$1,675–\$1,892, and the average length of stay ranged from 7.5 ± 0.3 days for patients admitted with few other complications than neutropenia to 16 ± 0.6 days for those with other comorbid conditions (Lyman, Kuderer, Greene, & Balducci, 1998). Using G-CSF in the first cycle can reduce the rate of hospitalization by about 50% (Crawford et al., 1991). The optimal use of G-CSF involves balancing the cost of the drug with the costs of hospitalization and antibiotics as well as patient costs (e.g., loss of earnings and childcare costs) and identifying patients who are most at risk and who therefore would be most likely to benefit from first-cycle use of G-CSF. Quality-of-life issues associated with neutropenia, such as weakness and inability to maintain daily activities of living, also should be considered when determining whether the cost of G-CSF is outweighed by its potential benefits.

Identifying Patients Most at Risk

The key to optimizing the clinical use of G-CSF in a cost-effective manner is to target the patients who are most at risk for neutropenic complications and infections (Bennett et al.,

2001; Lyman et al., 1998). Studies have shown that G-CSF generally is cost effective if patients have a 20%–40% risk of the development of febrile neutropenia (Bennett et al.; Lyman et al., 1998). A number of studies have been conducted to determine the risk factors that can be used to predict the patients in whom neutropenic complications are most likely to occur. Blay et al. (1996) found a lymphocyte count of $\leq 700 \times 10^6/l$ at day 5 after chemotherapy and a high dose of chemotherapy to be predictive of febrile neutropenia. The first-cycle ANC nadir also has been identified as a good predictor of future neutropenic events, with a lower nadir indicating a higher probability of neutropenic events in later cycles (Silber et al., 1998).

Two studies that prospectively evaluated the ANC risk model in patients with breast cancer showed that it could be used to accurately determine which patients are at greater and lesser risk of an episode of neutropenia (Moore et al., 2001; Rivera et al., 2001). Patients with a first-cycle nadir ANC of $\leq 500 \times 10^6/l$ were assigned to the high-risk group and were treated with filgrastim in all subsequent cycles, starting 24 hours after the chemotherapy and continuing until the ANC reached $10,000 \times 10^6/l$. Patients with an ANC greater than $500 \times 10^6/l$ were assigned to the low-risk group and were not treated with filgrastim unless an episode of febrile neutropenia or a dose delay caused by a low ANC occurred (Moore et al.; Rivera et al.). In both studies, 95% of patients treated according to the risk model received greater than or equal to 85% planned dose intensity (Moore et al.; Rivera et al.).

Although these risk models can be used to predict the likelihood of life-threatening neutropenic events in the second or later cycles of chemotherapy, they cannot predict which patients are at the greatest risk in the first cycle. Such conditional models may prove inadequate, particularly when patients have a substantial risk of first-cycle febrile neutropenia, such as in the treatment of hematologic malignancies.

An analysis that correlated pretreatment variables with the ANC nadir and febrile neutropenia in patients with non-Hodgkin's lymphoma (NHL) found that a serum albumin level of ≤ 3.5 g/dl, a serum lactate dehydrogenase level ≥ 460 IU/l, and lymphomatous bone marrow involvement before treatment with chemotherapy were all independent predictors of an ANC of $\leq 500 \times 10^6/l$ and of febrile neutropenia (Intragumtornchai, Sutheesophon, Sutcharitchan, & Swasdikul, 2000; T. Intragumtornchai, personal communication, December 19, 2000) (see Table 1).

Determining the pretreatment factors that are most reliable for predicting neutropenic complications in the first cycle of chemotherapy will require prospective studies. Nevertheless, the factors that thus far have been identified as predictive of neutropenic complications can help to guide healthcare providers in determining which of their patients are at the greatest risk for neutropenic complications and consequently are most likely to receive the greatest benefit from first-cycle use of G-CSF. Nurses can assess patients (see Figure 3) to identify those who are at risk for neutropenia or its complications.

Older Patients

Older patients treated with chemotherapy are at particularly high risk for neutropenia and also have a greater risk of infection during neutropenic episodes (Balducci & Yates, 2000). In all patients, almost three-quarters of the first febrile neutropenia events occur in the first two cycles of chemotherapy (Lyman

Table 1. Patient Characteristics Associated With Absolute Neutrophil Count (ANC) $\leq 500 \times 10^6/l$ or Febrile Neutropenia After Chemotherapy

Characteristic	Patients With ANC $\leq 500 \times 10^6/l$ %*	Patients With Febrile Neutropenia %*
Bone marrow involvement		
Present	77	68
Absent	28	23
Number of extranodal sites		
≥ 2	61	61
< 2	30	21
Serum lactate dehydrogenase level		
> Normal	54	47
$\leq$ Normal	18	13
Disease stage		
I/II	19	15
III/IV	61	53
Performance status		
0/1	23	16
2–4	68	62

*p < 0.001 for all pairwise comparisons.

Note. From “A Predictive Model for Life-Threatening Neutropenia and Febrile Neutropenia After the First Course of CHOP Chemotherapy in Patients With Aggressive Non-Hodgkin’s Lymphoma,” by T. Intragumtornchai, J. Sutheesophon, P. Sutcharitchan, & D. Swasdikul, 2000, *Leukemia and Lymphoma*, 37, pp. 355–356. Copyright 2000 by Taylor and Francis Health Sciences (www.tandf.co.uk/journals). Adapted with permission.

et al., 2002), and in older patients treated with myelosuppressive chemotherapy, the risk of neutropenic infection and death is highest after the first cycle of chemotherapy (Gómez et al., 1998). Older patients are more susceptible in a number of ways. They are more likely to be hospitalized for neutropenia than younger patients, and the length of stay and daily hospitalization costs are greater for patients older than 65 than for younger patients: 9.8 days versus 7.0 days, and \$2,904 versus \$1,915 (Caggiano, Stolshek, Delgado, & Carter, 2001). In particular, patients aged 70 years or older who are treated for NHL with cyclophosphamide, doxorubicin, vincristine, and prednisone or other chemotherapy with equivalent myelosuppressive potential have a high risk of neutropenic complications, and prophylactic G-CSF, beginning in the first cycle of chemotherapy, has been recommended for these patients (Balducci & Yates). Prophylactic G-CSF beginning in the first cycle of chemotherapy also has been recommended in patients aged 60 years or older who are treated with induction or consolidation chemotherapy for acute myelogenous leukemia (Balducci & Yates).

Optimizing Granulocyte-Colony-Stimulating Factor Dosing

G-CSF should be initiated approximately 24 hours after chemotherapy. Delaying its administration to five days after chemotherapy is associated with suboptimal neutrophil recovery (Crawford et al., 1997). Treating patients with G-CSF after severe neutropenia has developed has not been shown to provide the greatest benefit (Beveridge et al., 1998; Hartmann et al., 1997). American Society of Clinical Oncology (ASCO) guidelines do not recommend the routine use of G-CSF in the

treatment of afebrile or febrile patients with neutropenia (Ozer et al., 2000).

The recommended dose of filgrastim in adults is 5 mcg/kg per day administered via IV or subcutaneously (Ozer et al., 2000), which makes calculating the dose size individually for each patient necessary. The ASCO guidelines suggest rounding the calculated dose to the nearest vial or prefilled syringe size (300 mcg or 480 mcg) as a measure to reduce costs and increase convenience without compromising clinical outcome (Ozer et al.). ASCO guidelines also state that continuing daily G-CSF until the ANC is at least $10,000 \times 10^6/l$, as recommended in the prescribing information, is safe and effective, but the guidelines suggest that a shorter course of treatment may be reasonable and could increase patient convenience and reduce costs (Ozer et al.). If febrile neutropenia does develop while a patient is being treated with G-CSF, the G-CSF should be continued until the patient’s postnadir ANC is at a safe level and G-CSF should be used in all subsequent chemotherapy cycles.

The newly approved single-dose formulation, pegfilgrastim, should simplify the prophylactic use of G-CSF. It is supplied in ready-to-use prefilled syringes and can be administered to adult patients as a single, fixed 6 mg dose, regardless of their weight (George et al., 2001; Green et al., 2003). Because pegfilgrastim is given only once per chemotherapy cycle, it should cause minimal disruption to patients’ lives while providing a similar ability as filgrastim to reduce the risk of neutropenia and neutropenic complications. An additional advantage of pegfilgrastim is its self-regulating properties: Because it is eliminated through receptors on the neutrophils, its concentrations remain high throughout the ANC nadir. The elimination of pegfilgrastim is increased when the neutrophil count recovers (Johnston et al., 2000). In addition to providing simplified administration, pegfilgrastim also has been shown to have greater efficacy; although clinical trials show that the clinical effects of pegfilgrastim and filgrastim are similar, in two pivotal trials, treatment with pegfilgrastim has resulted in lower rates of febrile neutropenia (Green et al.; Holmes, Jones, et al., 2002).

Pegfilgrastim should be administered approximately 24 hours after chemotherapy. A single dose of pegfilgrastim provides protection through the ANC nadir. Once prophylactic

If the answer to any of these questions is “yes,” consider using growth factors.

1. Demographic factors
 - Is the travel time from home to clinic more than two hours?
 - Does the patient lack transportation?
 - Is the patient exposed to pathogens, small children, or large groups of people?
 - Is the caregiver outside of the patient’s home?
 - Is the patient unable to afford missing work?
2. Preexisting conditions
 - Does the patient have HIV, diabetes, cardiac complications, or other comorbid conditions?
3. Special risks for elderly patients
 - Does the patient have low serum albumin (≤ 3.5 g/dl)?
 - Does the patient have a higher-than-normal serum lactate dehydrogenase level?
 - Does the patient have lymphomatous bone marrow involvement?
 - Has the patient’s functional status declined?

Figure 3. Patient Assessment for Use of Granulocyte-Colony-Stimulating Factor

G-CSF has been used in a cycle of chemotherapy, it should be continued in all subsequent cycles. Pegfilgrastim may make repeated use in later cycles more acceptable to patients by being less disruptive than filgrastim because it requires fewer injections.

In addition to minimizing the risk of neutropenia and infections, first-cycle use of G-CSF also can increase the likelihood that patients will obtain the maximal benefit of their chemotherapy by receiving the full dose on schedule. Dose reductions are appropriate only when a sustained remission or cure is not the therapeutic intent. The full dose of chemotherapy is important for ensuring the greatest likelihood of long-term survival (Bonadonna & Valagussa, 1981; Kwak et al., 1990). By virtue of the simplified administration of pegfilgrastim—a single 6 mg dose in a prefilled syringe given once per cycle approximately 24 hours after chemotherapy—the issues of dosing and timing should be mitigated in G-CSF therapy.

Nurses, who are responsible for assessing patients before they are treated with chemotherapy as well as for ongoing support of patients, are in an ideal position to identify which patients are at risk for myelosuppression. Nurses also can de-

velop a clinical care pathway for use in their practice to identify patients at risk for neutropenia or its complications. Significant independent predictors for chemotherapy-induced neutropenia and its complications must be identified in prospective studies; once identified, these risk factors can be integrated into practice to more accurately predict neutropenic complications in the first cycle of chemotherapy. Nurses also should discuss the need for hematopoietic support with the other members of the treatment team and prompt for intervention as necessary. In addition, nurses can provide ongoing patient and family education that should include discussions about the treatment, the expected outcomes, and the need to monitor the patient's temperature and ANC, particularly during the expected neutrophil nadir. The introduction of pegfilgrastim can significantly simplify G-CSF therapy for health-care professionals, patients, and their families by giving patients only one injection of G-CSF per chemotherapy cycle.

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