Hematopoietic Support With Moderately Myelosuppressive Chemotherapy Regimens: A Nursing Perspective

Kelley Moore, RN, and Debbie Crom, RN

The proactive use of granulocyte–colony-stimulating factors (G-CSFs) in patients with cancer treated with chemotherapy reduces the incidence of hospitalizations for febrile neutropenia (FN) as well as minimizes chemotherapy dose reductions and delays that could compromise treatment outcomes. In accordance with earlier economic analyses, the guidelines of the American Society of Clinical Oncology recommended the use of G-CSF in the first cycle only with chemotherapy regimens associated with a 40% or greater risk of FN. However, more recent guidelines by the National Comprehensive Cancer Network (NCCN) recommended that the use of G-CSF in the first cycle of chemotherapy be considered for patients at a 20% or higher risk of developing FN or other neutropenic complications. The results of a clinical trial, which led to NCCN’s recommendations, are reviewed in this article. Patients with breast cancer were treated with single-agent docetaxel, a regimen that is associated with a risk of approximately 20% for developing FN. The use of pegfilgrastim in all cycles of chemotherapy caused a significantly lower incidence of FN, fewer hospitalizations as a result of FN, and lowered use of IV anti-infectives than placebo. Thus, when assessing patients before treatment, nurses should consider discussing with the multidisciplinary team the use of growth factor support even with moderately myelosuppressive chemotherapy regimens.

At a Glance

✦ The proactive use of granulocyte–colony-stimulating factors (G-CSFs) in patients with cancer treated with myelosuppressive chemotherapy reduces neutropenic complications and allows for delivery of chemotherapy at full dose and on schedule.

✦ Recent economic analyses indicate that the cost of G-CSF is offset when the risk of febrile neutropenia is lower than 20%.

✦ In clinical trials, benefits of G-CSF have been observed with moderately myelosuppressive regimens associated with a risk of febrile neutropenia of approximately 20%.
antibiotic use and hospitalization (Crawford et al., 1991; Trillet-Lenoir et al., 1993). In other clinical trials, once-per-cycle G-CSF pegfilgrastim was shown to be noninferior to filgrastim in reducing the incidence, duration, and severity of FN (Green et al., 2003; Holmes et al., 2002).

Furthermore, a meta-analysis of four trials of patients treated with G-CSF found significantly fewer chemotherapy dose reductions and delays with G-CSF than with a placebo (odds ratio, 0.32; 95% CI, 0.21–0.47; p = 0.001) (Lyman, Kuderer, & D’Julbegovic, 2002).

Several economic studies have been conducted to determine the risk threshold at which the cost of G-CSF is offset by the reductions in cost resulting from fewer hospitalizations for FN and shorter durations of hospitalization. The resulting clinical decision models have been used to help formulate clinical practice guidelines for the use of G-CSF in patients with cancer. Earlier economic analyses found that the cost of G-CSF filgrastim could be offset when the risk of FN was greater than 40% (Glaspy, Bleecker, Crawford, Stoller, & Strauss, 1993; Lyman, Lyman, Sanderson, & Balducci, 1993). Few commonly used regimens are associated with a risk of FN higher than 40%. As a result, the guidelines of the American Society of Clinical Oncology, which were last updated in 2000, recommended that beginning use of G-CSF in the first cycle should be reserved for patients whose high risk of FN was caused by special circumstances (Ozer et al., 2000).

Economic models of G-CSF use are sensitive to the costs of FN-related hospitalization (Lyman, Kuderer, Greene, & Balducci, 1998). An updated model that uses more recent costs shows that once-per-cycle G-CSF pegfilgrastim is cost-effective when the risk of FN is lower than 20% (Eldar-Lissai, Cosler, & Lyman, 2004). Many common chemotherapy regimens are associated with a risk of FN that is lower than 20%. The clinical benefits of G-CSF with regimens with a 10%–20% risk of FN, however, have not been examined thoroughly. A recent, placebo-controlled, phase III trial evaluated the incidence of FN with pegfilgrastim used with moderately myelosuppressive chemotherapy (Vogel et al., 2005). The design and results of the Vogel et al. trial are summarized in this article.

**Pegfilgrastim With Moderately Myelosuppressive Chemotherapy**

A trial was conducted at 88 sites across North America and Europe in 928 patients (465 in the placebo arm and 463 in the pegfilgrastim arm) with breast cancer who were treated after surgery with IV docetaxel (100 mg/m² every 21 days for as many as four cycles). The incidence of FN in earlier trials of the same regimen without G-CSF support in patients with metastatic or early-stage breast cancer was reported to be between 6% (Chan et al., 1999) and 21% (Bear et al., 2003).

The treatment groups were balanced in regard to disease history and severity and demographics (see Table 1). All but six patients were women, and the mean age was 52 years. The majority of patients (62% in each group) had metastatic disease, which reflects the more common use of single agents for advanced disease and combination regimens for earlier-stage disease. Patients were randomized to pegfilgrastim 6 mg or placebo once per cycle on the day after receiving docetaxel. In a crossover design, any patient who developed FN was given open-label pegfilgrastim in subsequent cycles (see Figure 1). FN was defined as a body temperature of 38.2°C or higher and absolute neutrophil count less than 0.5 × 10⁹/L on the day of the fever or the day after.

The incidence of FN was significantly lower in the group randomized to pegfilgrastim than in the group randomized to placebo (1% versus 17%; p < 0.001), with a 94% reduction in the pegfilgrastim arm compared to the placebo arm. Two-thirds of the instances of FN in the placebo group occurred during the first cycle of chemotherapy. The incidence of hospitalization for FN (1% versus 14%; p < 0.001) and the use of anti-infectives (2% versus 10%; p < 0.001) also were statistically significant (see Figure 2).

The incidence of adverse events such as diarrhea, fever, nausea, and vomiting was similar between treatment groups. Pegfilgrastim generally was well tolerated. Bone pain, a known side effect of pegfilgrastim, was reported by 27% and 31% of patients in the placebo and pegfilgrastim groups, respectively. Bone pain was generally mild to moderate and was managed with non-narcotic analgesics. Six percent of patients in each group required opioids to control the symptom.

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>PLACEBO (N = 465)</th>
<th>PEGFILGRASTIM (N = 463)</th>
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<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Pretreatment absolute neutrophil count (× 10⁹/L)</td>
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<td>3.78&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
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<td>4 1</td>
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<td>Female</td>
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<td>459 99</td>
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<td>307 66</td>
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<td>Hispanic</td>
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<td>Other</td>
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<td>12 3</td>
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<td>128 28</td>
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<td>335 72</td>
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<td>– –</td>
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<td><strong>Chemotherapy in the past two years</strong></td>
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<td></td>
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<tr>
<td>Yes</td>
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<td>297 64</td>
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<td>166 36</td>
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<td>3 1</td>
<td>– –</td>
</tr>
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</table>

<sup>a</sup> n = 462

<sup>b</sup> n = 458

*Note* Because of rounding, not all percentages total 100.

*Note* Based on information from Vogel et al., 2005.
Note. Patients were treated with docetaxel 100 mg/m² on day 1 every 21 days for as many as four cycles and were randomized to pegfilgrastim or placebo on day 2. Patients in whom febrile neutropenia occurred were switched to open-label pegfilgrastim.

**Figure 1. Study Schema**


Other studies of patients with breast cancer also have shown that the use of G-CSF beginning in the first cycle of treatment with a moderately myelosuppressive regimen of docetaxel, doxorubicin, and cyclophosphamide (TAC) may produce clinically significant reductions in the incidence of FN. For example, the incidence of FN with TAC in patients with node-negative breast cancer was 23.8%. After a protocol amendment that specified the use of G-CSF in all cycles, the incidence was 3.5% (Martin et al., 2004). The incidence of FN with TAC and G-CSF given as secondary prophylaxis (i.e., after an occurrence of FN) in patients with node-positive breast cancer was 24% (Nabholtz et al., 2002). The rate of FN per cycle was lower, however, in cycles in which G-CSF was used than in those in which G-CSF was not used (3.1% vs. 6%, respectively) (Vogel, Mackey, & Martin, 2004).

**Nursing Implications**

Nurses should be aware that patients who are treated with moderately myelosuppressive chemotherapy could obtain significant clinical benefits from the use of G-CSF in all cycles. They also should recognize that, in addition to the clinical and economic consequences of FN, hospitalization for FN may have a negative effect on patients’ quality of life (QOL), especially if a prolonged stay or an extensive medical intervention is required. The average length of hospitalization in adult patients with cancer with FN is 11 days (Kuderer et al., 2002), and separation from home and family members can create anxiety (Dale, 2003; Lyman & Kuderer, 2002). Patients who are hospitalized for FN may fear additional nosocomial infections and be concerned about the numerous procedures that they will undergo (Dale; Lyman & Kuderer). Patients and their families also may feel more vulnerable after chemotherapy-induced neutropenia while waiting for the next cycle of chemotherapy to begin (Eggenberger, Krumwiede, Meiers, Blesner, & Earle, 2004; Krumwiede et al., 2004). Patients and families may feel a greater connection with healthcare providers and may need more support from nurses during this time.

Few studies have investigated the effects of FN on QOL; however, two studies have shown that severe chemotherapy-induced neutropenia is related to QOL deficits: Patients reported greater fatigue, distress, and impairment of normal functioning during severe chemotherapy-induced neutropenia. Lower QOL scores correlated with deeper absolute neutrophil count nadirs and the development of FN (Fortner et al., 2002; Okon et al., 2002). Furthermore, analysis of data from three clinical trials in patients with breast cancer treated with chemotherapy showed that the incidence, duration, and severity of adverse events (e.g., abdominal pain, anorexia, asthenia, dehydration, fatigue, rigors, and vomiting) were greater on days when FN occurred (Glaspy, Hackett, Flyer, Dunford, & Liang, 2001). Clearly, appropriate supportive care to reduce the risk of FN and hospitalization for FN also can improve QOL in patients treated with moderately myelosuppressive regimens.

Nurses are responsible for assessing the risk of FN in patients with cancer and for devising supportive care plans. In addition
to the myelosuppressive potential of the chemotherapy regimen, patient factors also can contribute to the risk of FN (Crawford, Dale, & Lyman, 2004). According to the practice guidelines of the American Society of Clinical Oncology (Ozer et al., 2000), patient factors that warrant the use of G-CSF starting in the first cycle of chemotherapy are advanced age, a history of FN, existing neutropenia, previous radiotherapy, extensive prior chemotherapy, poor performance status, advanced cancer, and any other condition that could increase the risk of serious infection (Ozer et al.). Older patients are more susceptible to the complications of neutropenia than younger patients, primarily because of their decreased bone marrow reserves (Balducci & Repetto, 2004). Most complications in older patients occur in the early cycles of chemotherapy. Therefore, NCCN guidelines (2005b) recommended that patients aged 65 years or older be given G-CSFs in all cycles of myelosuppressive chemotherapy.

Nurses also should be aware of the greater risk of FN in the first cycle of chemotherapy. Most instances of FN (67%) in the placebo arm of the study occurred during the first cycle (Vogel et al., 2005), which is consistent with findings in studies of patients with non-Hodgkin lymphoma treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (Lyman & Delgado, 2003; Lyman, Morrison, et al., 2003). Furthermore, studies of practice patterns in early-stage breast cancer and non-Hodgkin lymphoma have shown that a substantial proportion of planned or unplanned chemotherapy dose reductions and delays occurred in the first cycle (Lyman, Dale, & Crawford, 2003; Lyman, Dale, Friedberg, Crawford, & Fisher, 2004). Many studies have highlighted the importance of avoiding chemotherapy dose attenuations as well as the better outcomes that are obtained with chemotherapy given at full dose and on schedule, especially in curable tumors, such as early-stage breast cancer (Bonadonna, Valagussa, Moliterni, Zambetti, & Brambilla, 1995; Bonadonna, Zambetti, Moliterni, Gianni, & Valagussa, 2004; Budman et al., 1998). Therefore, using growth factors is particularly important beginning with the first cycle of chemotherapy with curative intent to avoid FN-related disruptions and to allow delivery of chemotherapy at full dose and on schedule, thus helping to ensure optimal long-term outcomes.

After pretreatment patient assessment, nurses should discuss the need for hematopoietic support with other team members. When devising a care plan, nurses must consider risk factors and the effect that numerous clinic trips will have on patients and their caregivers. A recent survey of adult patients with cancer showed that even visits for brief procedures (e.g., laboratory tests, injections of growth factors) consume substantial time because of travel time to and from the clinic as well as waiting and procedure time. Normal life activities that are disrupted most often include work, community activities, family obligations, and daily activities such as housework and family care (Fortner, Tauer, Zhu, Ma, & Schwartzberg, 2004; Fortner, Tauer, Zhu, Okon, et al., 2004). The management of neutropenia may be simplified for patients and healthcare workers alike with the use of pegfilgrastim, a G-CSF that can be administered only once per chemotherapy cycle, thereby eliminating frequent clinic trips for daily injections of filgrastim. Use of pegfilgrastim is particularly convenient for older adult patients who depend on friends and family members for transportation to a clinic (Hood, 2003). Patient and caregiver time is reduced when pegfilgrastim is used rather than filgrastim (Fortner, Tauer, Zhu, Ma, et al.). Furthermore, with a reduction in the number of clinic visits, the use of pegfilgrastim also can increase the efficiency and reduce the costs of human resources in community oncology practices (Beveridge et al., 2003; Fortner, Okon, et al., 2004).

Nurses should administer pegfilgrastim or filgrastim beginning 24 hours after the dose of chemotherapy in the first cycle and in subsequent cycles. In addition, pegfilgrastim should not be administered fewer than 14 days before the administration of the next cycle of chemotherapy. Patients’ hematologic values, including absolute neutrophil count, hemoglobin level, hematocrit, and platelet counts, should be monitored according to individual practice guidelines. The most common adverse event with G-CSF is bone pain (usually moderate to mild), which generally can be managed with non-narcotic analgesics (Phillips, 2005).

Patients should be educated before the start of chemotherapy and should be informed of the serious clinical consequences of FN, including potentially compromised treatment outcomes if dose reductions or delays are required. Ongoing patient education during chemotherapy should include how and when to take one’s own temperature and how to recognize signs and symptoms that should be reported to a healthcare provider (e.g., fever, shaking chills, bleeding, pain that is not relieved by prescribed medications) (Phillips, 2005). Patient and caregiver education is particularly important for patients who are treated with pegfilgrastim because fewer clinic visits necessitate greater patient and caregiver vigilance (Bedell, 2003).

Nurses are the primary advocates of supportive care for their patients. They also can take a more active role in improving the quality of care provided to patients by participating in continuous quality improvement programs. Nurses often are key members of the multidisciplinary teams that develop and implement guidelines for neutropenia. Several examples exist of nurse-driven programs that resulted in substantial improvements in the management of neutropenia (Donohue & Carbo, 2004; Lenhart, 2004; Maxwell, Winkler, & Lottenberg, 2002; Michelson et al., 2002; White & Keehne-Miron, 2002). To stay connected with other nurses who are interested in improving the management of neutropenia in clinical practice, nurses also can participate in the Neutropenia Special Interest Group sponsored by the Oncology Nursing Society. In addition, nurses should participate in research projects and communicate their experiences and research results in nursing congresses. Other nationwide educational projects, such as the Assessment-Information-Management Higher Initiative, also have been successful in promoting awareness of the importance of supportive care among nurses (Johnson et al., 2005).

**Conclusion**

First- and subsequent-cycle G-CSF significantly reduces the incidence of FN with moderately myelosuppressive regimens. Furthermore, this strategy may be cost-effective by preventing hospitalizations for FN. The use of once-per-cycle pegfilgrastim with moderately myelosuppressive regimens also may improve patient QOL by avoiding hospitalizations and reducing the number of clinic visits for the management of FN and, in
addition, may reduce the number of dose reductions and delays. Therefore, nurses should discuss with other team members the use of growth factors starting in the first cycle with moderately myelosuppressive chemotherapy regimens.

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References


