Published in final edited form as:

Clin J Oncol Nurs. 2010 February ; 14(1): 81–86. doi:10.1188/10.CJON.81-86.

Managing Neutropenia in Older Patients With Cancer Receiving Chemotherapy in a Community Setting

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Abstract

Older patients with cancer who may be more susceptible than younger patients to the myelosuppressive effects of chemotherapy undergo dose delays and reductions that can compromise treatment outcomes. Incidence of neutropenic complications and suboptimal chemotherapy delivery can be reduced with prophylactic colony-stimulating factors; however, their use in older patients with cancer has not been well studied. A randomized, multicenter, community-based trial was designed to compare prophylactic pegfilgrastim use (all cycles of chemotherapy) versus its more common reactive use (at clinicians' discretion) in patients aged 65 years or older with various cancers. Pegfilgrastim use in all cycles reduced the incidence of febrile neutropenia by about 60% and hospitalizations caused by neutropenia and febrile neutropenia by about 50% versus reactive pegfilgrastim use in later cycles. The study showed that older patients with cancer can be treated safely with optimal doses of chemotherapy with appropriate supportive care. Nurses, key collaborators in providing supportive care, can take an active role in identifying older patients who may benefit from pegfilgrastim in all cycles of chemotherapy.

Cancer affects a large number of older adults, with almost 67% of all cases reported in people aged 65 years or older (Jemal et al., 2005) and about 70% of cancer deaths occurring in this age group (Yancik & Ries, 2000). The number of people aged older than 65 has been projected to double from 2000–2030 (Yancik & Ries, 2000) and the burden of cancer in older adults likely will increase.

Gaining a complete picture of an older patient's health is critical to determining appropriate cancer treatment (Balducci & Extermann, 2000). A clinical profile cannot be determined by chronologic age alone. Psychological and physical well-being depend on many factors, including preexisting comorbidities, social support networks, living arrangements, and age-related changes in global bodily functions (Balducci & Extermann, 2000). Older patients with cancer may have preexisting conditions that can increase the likelihood of adverse events related to chemotherapy, such as decreases in renal function. Advanced age and comorbidities often are associated with slower bone marrow recovery following cytotoxic

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chemotherapy administration, which can increase the risk for neutropenia and neutropenic infection (Dale, 2003). A retrospective analysis of patients with non-Hodgkin lymphoma showed that the risk for febrile neutropenia in the first cycle of chemotherapy was twice as high in older patients than in younger patients (Lyman, Dale, & Crawford, 2003).

Neutropenia leading to infection is a major clinical dilemma that often requires hospitalization. Febrile neutropenia in older adults may result in longer hospitalizations and increased risk for complications, including higher rates of inpatient mortality compared with younger adults (Caggiano, Weiss, Rickert, & Linde-Zwirble, 2005; Chrischilles et al., 2002). Several retrospective analyses of patients with breast cancer and non-Hodgkin lymphoma have shown that older patients are consistently treated with lower doses of chemotherapy than younger patients (Lyman, Morrison, et al., 2003; Lyman, Dale, Friedberg, Crawford, & Fisher, 2004; Morrison et al., 2001). In addition, older patients often are treated with less toxic, but less effective, chemotherapy in an effort to reduce the risk for neutropenia (Dale, 2003).

Age alone is not a contraindication to prescribing full-dose, on-schedule, systemic chemotherapy (Muss et al., 2005). Evidence shows that older patients with cancer can safely obtain treatment benefits similar to younger patients when they receive full-dose standard chemotherapy regimens (Christman, Muss, Case, & Stanley, 1992; Hey, 2003; Langer et al., 2002; Muss et al., 2005). However, retrospective analyses have shown that many older patients with cancer receive suboptimal doses of myelotoxic chemotherapy (Dale, McCarter, Crawford, & Lyman, 2003; Lyman, Dale, et al., 2003; Lyman et al., 2004; Muss et al., 2005), likely because physicians are attempting to minimize adverse events (Dale, 2003). Suboptimal dosing is a serious issue because large, randomized clinical trials have demonstrated that the delivery of lower doses or shorter courses of chemotherapy can reduce overall survival in older patients with breast cancer or lymphoma (Bonadonna, Valagussa, Moliterni, Zambetti, & Brambilla, 1995; Budman et al., 1998; Kwak, Halpern, Olshen, & Horning, 1990; Lepage et al., 1993).

Febrile neutropenia risk in patients with cancer may be exacerbated because colony-stimulating factors (CSFs) often are used reactively in response to severe neutropenia or neutropenia-related events, rather than proactively (Meza, Charu, Campos, Davis, & Xie, 2005). A randomized, phase III trial showed that febrile neutropenia incidence was reduced by using pegfilgrastim prophylactically (beginning in the first cycle and continuing in subsequent cycles) in patients with breast cancer who received moderately myelotoxic chemotherapy (Vogel et al., 2005). As a result, international consensus guidelines now agree that adult patients should have primary prophylaxis with CSFs when the chemotherapy regimen chosen is associated with a risk for febrile neutropenia of 20% or higher or when the chemotherapy-associated risk for febrile neutropenia is 10%–20% and the patient has other risk factors for febrile neutropenia (Aapro et al., 2006; National Comprehensive Cancer Network [NCCN], 2008; Smith et al., 2006).

The European Organisation for Research and Treatment of Cancer (EORTC) (Aapro et al., 2006) and NCCN (2008) guidelines recommend giving particular consideration to being aged older than 65 years as a risk factor for febrile neutropenia. However, the clinical

benefits of prophylactic CSFs for older patients with cancer have not been examined thoroughly in clinical trials, largely because of restrictive eligibility criteria that limit enrollment based on function and comorbidity status (Aapro, Kohne, Cohen, & Extermann, 2005). A phase IV trial evaluated how older patients would respond to prophylactic pegfilgrastim (in the first and subsequent cycles of chemotherapy) versus its more common reactive use (Balducci et al., 2007). The design and results of that trial are summarized in this article.

First-Cycle Pegfilgrastim Support for Older Patients With Cancer

This large study of older patients with cancer in the community setting was a collaborative effort between Amgen Inc. and the Geriatric Oncology Consortium, a national, multidisciplinary organization dedicated to improving the representation of older patients with cancer in clinical trials. The phase IV, open-label, randomized, multicenter, community-based trial allowed the enrollment of patients with comorbidities who would have been excluded from most clinical trials. Inclusion criteria were patients aged 65 years or older with lung, breast, or ovarian cancer or aggressive non-Hodgkin lymphoma (NHL), which are common in older patients. Patients with comorbidities generally were accepted. Exclusion criteria were having symptomatic brain metastases, unstable or uncontrolled cardiovascular disease, and infection.

After giving informed consent, patients were randomly assigned to prophylactic or reactive use of pegfilgrastim. In the prophylaxis (pegfilgrastim all cycles) arm, patients received pegfilgrastim in all cycles of chemotherapy, starting in the first cycle. In the reactive (clinician discretion) arm, patients were eligible to receive pegfilgrastim in response to severe neutropenia or neutropenia-related events during chemotherapy. Other options in the reactive arm after cycle 1 were chemotherapy dose delays, dose reductions, or no changes in dose or timing. In both treatment arms, pegfilgrastim, when used, was administered once per cycle as a 6 mg subcutaneous injection 24 hours after chemotherapy administration.

The primary end point of the study was the incidence of febrile neutropenia, defined as a temperature of 38°C or higher and an absolute neutrophil count (ANC) lower than 1,000/mm³. Secondary end points were the incidences of grade 4 febrile neutropenia, defined as a temperature of 38°C or higher and an ANC lower than 500/mm³, grades 3 and 4 neutropenia, chemotherapy dose delays and dose reductions, febrile neutropenia-related hospitalization, and febrile neutropenia-related IV antibiotic use. Dose delays were defined as a delay of seven days or more beyond the first day of the next chemotherapy cycle. Dose reduction was defined as a reduction of any of the chemotherapy agents used in a cycle to lower than 80% of the dose used in cycle 1.

Patient Characteristics and Treatment

A total of 852 patients were enrolled at 192 community cancer centers across the United States from June 2002–November 2004. Fifteen patients with solid tumors and five patients with NHL were excluded from the analysis because they received no chemotherapy or chemotherapy was initiated before informed consent forms were signed. In both groups, about 33% of patients were aged 65–69 years, 33% were aged 70–74, and 33% were aged

75 years or older. About 90% were Caucasian and had an Eastern Cooperative Oncology Group performance status of 0 or 1. Most patients presented with stage III or IV disease (see Table 1).

In the solid tumor group, 686 patients were analyzed (343 in each arm). Fifty-eight percent of patients in the prophylaxis arm and 51% in the reactive arm completed all cycles of their planned chemotherapy, regardless of dose delays or dose reduction. In the reactive arm, 42% received pegfilgrastim at some point, most commonly for grade 3 or 4 neutropenia in a preceding cycle.

In the NHL group, 146 patients were analyzed (73 in each arm). Fifty-two percent in each treatment arm completed their prescribed chemotherapy regimen. In the reactive arm, 64% received pegfilgrastim at some point, usually for grade 3 or 4 neutropenia or febrile neutropenia in an earlier cycle.

Incidence of Febrile Neutropenia

Across all cycles of chemotherapy, the incidence of febrile neutropenia was significantly lower in the prophylaxis arm versus the reactive arm. Proactive administration of pegfilgrastim (prophylaxis arm) led to a 60% reduction in the incidence of febrile neutropenia for patients with solid tumors ($p = 0.001$) and a 59% reduction for patients with NHL ($p = 0.004$). Grade 4 febrile neutropenia was more common in the reactive arm in both groups. Among patients with solid tumors, grade 4 febrile neutropenia incidence was 58% in the reactive arm versus 22% in the prophylaxis arm. Among NHL patients, incidence rates were 86% and 75%, respectively.

The investigators also analyzed the rate of febrile neutropenia in the first cycle alone because most neutropenic events occur in the first cycle of chemotherapy. Among patients with solid tumors, the incidence of febrile neutropenia was 3% in the prophylaxis arm versus 7% in the reactive arm. For patients with NHL, incidence rates were 7% and 25%, respectively.

Incidence and Consequences of Neutropenia

In the solid tumor group, the prophylaxis arm had lower rates of grade 3 or 4 neutropenia, dose delays, dose reductions, hospitalizations, and antibiotic use versus the reactive arm, but the differences were not statistically significant (see Table 2). The findings generally were the same in the NHL group, except the rates of dose delays and dose reductions were higher in the prophylaxis arm than in the reactive arm. A likely explanation is that patients in the prophylaxis arm who developed chemotherapy adverse events had no option but dose modification because they already were receiving growth factor support, whereas most patients in the reactive arm received pegfilgrastim starting in cycle 2 rather than dose modification. Of note, febrile neutropenia–related hospitalizations in both arms were about three times more likely for patients with NHL than for patients with solid tumors. Most hospitalizations occurred during the first cycle in both groups.

Safety

Bone pain was the only serious adverse event related to pegfilgrastim use. Among patients with solid tumors, bone pain occurred more commonly in the prophylaxis arm than in the reactive arm (12% versus 5%, respectively). Among NHL patients, bone pain occurred in 9% of patients in the prophylaxis arm versus 4% in the reactive arm.

Limitations

Although this was the first large trial to evaluate the benefit of growth factor support in older patients with cancer, it did not enroll patients with several other cancers that are commonly observed among older patients (e.g., prostate cancer, pancreatic cancer). In addition, physicians were unwilling to randomize patients with NHL to the reactive arm during the trial because of the high myelosuppressive potential of regimens used to treat the disease. Therefore, fewer patients with NHL were enrolled in the trial than originally planned. Finally, most patients in the trial had advanced-stage disease, in which the benefit of full-dose chemotherapy is under debate.

Nursing Implications

The results demonstrate that prophylactic use of pegfilgrastim (i.e., beginning in the first cycle of chemotherapy and continuing in subsequent cycles) significantly reduced the incidence of febrile neutropenia in older patients with solid tumors or NHL. In addition, prophylactic pegfilgrastim reduced the rates of grade 4 febrile neutropenia, grade 3 or 4 neutropenia, and febrile neutropenia–related hospitalizations and antibiotic use, which are complications that can interfere with delivery of complete courses of chemotherapy as scheduled. Among patients with solid tumors, prophylactic pegfilgrastim reduced the need for dose delays and dose reductions. Administration of pegfilgrastim to older patients was safe, as bone pain was the only serious adverse event and its incidence was low in all treatment arms. The finding is consistent with other reports in which mild to moderate bone pain was the most frequently reported adverse event associated with pegfilgrastim (Kubista et al., 2003). In clinical practice, bone pain is managed with non-narcotic analgesics, such as acetaminophen or nonsteroidal anti-inflammatory drugs; however, narcotic analgesics also may be prescribed for patients who experience severe bone pain (Kirshner, Hicock, & Hofman, 2007).

To date, this is the largest prospective, randomized trial of older patients conducted in a community setting. The patients were receiving an array of mildly to moderately myelotoxic chemotherapy regimens and most had comorbidities, which is typical of patients nurses encounter in the community. As the primary advocates for older patients with cancer, oncology nurses are in a unique position to use the results of this and other clinical trials to influence treatment decisions with regard to supportive care.

Implementing evidence-based guidelines is another way to improve supportive care. Nurses are being encouraged by their peers (Moore & Crom, 2006; Wilson & Gardner, 2007) to familiarize themselves and their colleagues with recently published or revised guidelines regarding the use of granulocyte–colony-stimulating factor (G-CSF). The American Society

of Clinical Oncology, NCCN, and EORTC all recommend that febrile neutropenia risk should be assessed before the first cycle of chemotherapy (Aapro et al., 2006; NCCN, 2008; Smith et al., 2006). The organizations also agree that prophylactic G-CSF is indicated if (a) the chemotherapy regimen is associated with febrile neutropenia risk of 20% or higher; (b) chemotherapy-associated febrile neutropenia risk is 10%–20% and certain patient-related risk factors are present, such as being aged 65 years or older, having poor performance or nutritional status, or having a serious comorbidity; or (c) the aim is to reduce the need for dose reductions or delays during adjuvant therapy, curative therapy, or therapy intended to prolong survival.

A guideline by Repetto et al. (2003) focused on the need for prophylactic G-CSF for older patients receiving myelotoxic chemotherapy. After a comprehensive literature review, the researchers affirmed that prophylactic G-CSF reduces the incidence of chemotherapy-induced neutropenia, febrile neutropenia, and infection in older patients receiving myelotoxic chemotherapy for NHL, small cell lung cancer, or urothelial tumors. Repetto et al. (2003) were unable to review enough data on other cancers to draw conclusions; however, they stated that lack of data should not prevent prophylactic G-CSF use when patients are receiving myelotoxic chemotherapy for malignancies such as breast, colorectal, ovarian, and non-small cell lung cancer. Since EORTC's guidelines were published, a randomized, phase II study has demonstrated that prophylactic pegfilgrastim facilitates full-dose treatment of patients aged 65 years or older who receive adjuvant FEC100 (5-fluorouracil, epirubicin, and cyclophosphamide) for high-risk breast cancer (Romieu et al., 2007).

Nurses can impact patient care by adapting evidence-based guidelines to their specific practice setting. In a survey, most oncologists stated that they believed guidelines were important, agreed with their content, and believed they were useful; however, about 25% found guidelines difficult to apply in daily practice (Bennett et al., 2003). Oncology nurses are beginning to design checklists so that they and other healthcare providers in their practice can standardize assessment for febrile neutropenia risk (Donohue, 2006; Doyle, 2006; White, Maxwell, Michelson, & Bedell, 2005). For example, Dolan, Crombez, and Munoz (2005) and Maxwell and Stein (2006) detailed the development of treatment algorithms and standing orders to enable qualified nurses to participate in deciding whether to administer G-CSF.

Nurse-led initiatives have shown that routine febrile neutropenia risk assessment, followed by prophylactic G-CSF as needed, can improve patient outcomes (Donohue, 2006; Doyle, 2006; Lenhart, 2004; White et al., 2005). One project that began with a retrospective chart review of chemotherapy-induced neutropenia resulted in the development of a febrile neutropenia risk-assessment tool for all patients undergoing chemotherapy (Donohue, 2006). Use of the nurse-developed tool resulted in decreased rates of febrile neutropenia, neutropenia-related hospitalizations, dose delays, and dose reductions in patients treated with chemotherapy (Donohue, 2006).

Nurses also can improve clinical practice by creating patient-care policies for older adults, educating healthcare staff about evidence-based best practices, and, perhaps most

importantly, looking for opportunities to participate in clinical trials focused on older patients. Given the increasing number of trials specifically involving older patients, geriatric oncology is primed for nursing research, and the Geriatric Oncology Consortium strongly supports nurse-led initiatives.

Conclusions

Nurses are uniquely positioned to identify older patients with solid tumors or NHL at increased risk for febrile neutropenia and who could benefit from pegfilgrastim beginning in the first cycle of chemotherapy. Nurse involvement in febrile neutropenia risk assessment is important because prophylactic pegfilgrastim has been shown in a phase IV study to (a) significantly reduce the incidence of febrile neutropenia in this patient population, (b) limit grade 3 or 4 neutropenia and febrile neutropenia–related hospitalizations and antibiotic use, and (c) reduce the need for dose delays and dose reductions in patients with solid tumors.

Data from the study also demonstrated the feasibility of conducting a community-based clinical trial whose participants are older patients with cancer with comorbidities. In addition, a strong need exists for nurses to educate their older patients about the importance of participating in clinical research.

Acknowledgments

The authors take full responsibility for the content of the article but thank Faith Reidenbach and Supriya Srinivasan, PhD, of Scientia Medical Communications, LLC, supported by Amgen Inc., for medical writing support. The study was funded by Amgen Inc. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers or editorial staff.

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At a Glance

- ✦ Older patients with cancer may undergo dose reductions and delays caused by febrile neutropenia (FN) because neutropenia prevention has not been well studied in this population.
- ✦ A randomized, multicenter, community-based trial showed that prophylactic use of pegfilgrastim reduced the incidence of FN, grade 3 or 4 neutropenia, and FN-related hospitalizations and antibiotic use in older patients with solid tumors or non-Hodgkin lymphoma; fewer dose reductions and delays also were observed in patients with solid tumors.
- ✦ Oncology nurses are in a unique position to use evidence-based guidelines and nursing-led initiatives to influence the decision to treat and prevent FN in older patients with cancer.

Table 1

Baseline Characteristics of Patients in the Primary Analysis Set

CHARACTERISTIC	SOLID TUMOR PATIENTS		NHL PATIENTS	
	PEGFILGRASTIM ALL CYCLES (n = 343)	CLINICIAN DISCRETION (n = 343)	PEGFILGRASTIM ALL CYCLES (n = 73)	CLINICIAN DISCRETION (n = 73)
Male sex, n (%)	121 (35)	114 (33)	38 (52)	31 (42)
Race, n (%)				
White	308 (90)	303 (88)	67 (92)	67 (92)
Age, n (%)				
65–69 yrs	127 (37)	122 (36)	21 (29)	20 (27)
70–74 yrs	108 (31)	105 (31)	22 (30)	23 (32)
75–79 yrs	76 (22)	78 (23)	18 (25)	25 (34)
80–84 yrs	22 (6)	30 (9)	9 (12)	4 (5)
85 yrs	10 (3)	8 (2)	3 (4)	1 (1)
Disease stage, n (%)				
I or II or limited	105 (31)	105 (31)	29 (40)	27 (37)
III or IV or extensive	238 (69)	237 (69)	44 (60)	46 (63)
ECOG performance status, n (%)^a				
0	144 (42)	140 (41)	35 (48)	36 (49)
1	167 (49)	158 (46)	33 (45)	32 (44)
2	24 (7)	37 (11)	4 (6)	4 (6)
Tumor type, n (%)				
Lung	193 (56)	190 (55)	—	—
Ovarian	58 (17)	60 (18)	—	—
Breast	92 (27)	93 (27)	—	—
NHL	—	—	73 (100)	73 (100)

^aTwo percent of patients in each arm were missing baseline ECOG performance status scores.

ECOG—Eastern Cooperative Oncology Group; NHL—non-Hodgkin lymphoma

Note. From “Elderly Cancer Patients Receiving Chemotherapy Benefit From First-Cycle Pegfilgrastim,” by L. Balducci, H. Al-Halawani, V. Charu, J. Tam, S. Shahin, L. Dreiling, and W.B. Ershler, 2007, *Oncologist*, 12, p. 1420. Copyright 2007 by AlphaMed Press, Inc. Reprinted with permission.

Table 2

Incidence of Neutropenia and Neutropenia-related events

VARIABLE	SOLID TUMOR		NON-HODGKIN LYMPHOMA	
	PEGFILGRASTIM ALL CYCLES (n = 343) (%)	CLINICIAN DISCRETION (n = 343) (%)	PEGFILGRASTIM ALL CYCLES (n = 73) (%)	CLINICIAN DISCRETION (n = 73) (%)
Febrile neutropenia	4 *	10	15 **	37
Grade 3 or 4 neutropenia	30	80	82	90
Dose delay	16	28	29	23
Dose reduction	7	14	16	8
Hospitalization	5	9	17	37
Antibiotic use	10	28	55	53

*
p = 0.001;**
p = 0.004