Nurses' Guide to Understanding and Implementing the National Comprehensive Cancer Network Guidelines for Myeloid Growth Factors

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Purpose/Objectives: To review and determine the applicability of the 2006 National Comprehensive Cancer Network (NCCN) clinical practice guidelines for the use of myeloid growth factors in adult patients treated with chemotherapy for solid tumors and nonmyeloid malignancies.

Data Sources: Published guidelines, original research, review articles, and conference presentations.

Data Synthesis: Chemotherapy-induced neutropenia is a common adverse effect of myelosuppressive chemotherapy that may lead to life-threatening infections, prolonged hospitalization, increased IV antibiotic use, and dose reductions or delays that affect patients' quality of life and clinical outcomes.

Conclusions: Before treatment begins, nurses should determine which patients are at greater risk for chemotherapy-induced neutropenia and implement an appropriate plan of care.

Implications for Nursing: Nurses are in an ideal position to implement a risk assessment tool and play an integral role in directing the quality of patient care. Implementing the NCCN guidelines is one way to facilitate standardization of care.

Key Points . . .

- The National Comprehensive Cancer Network guidelines focus on assessing risk factors before each chemotherapy cycle, managing neutropenic complications, and implementing intervention measures.
- When determining the appropriate use of colony-stimulating factors for neutropenia, nurses should identify the known risk of febrile neutropenia and severe neutropenia with the regimen to be administered, patient risk factors, and the intent of the cancer treatment.
- Nurses should implement evidence-based guidelines to reduce or manage neutropenic complications in their patient populations and thereby help to ensure the best possible outcomes.
- Risk assessment tools can increase communication between patients and healthcare providers when used before the initiation of therapy.

The National Comprehensive Cancer Network (NCCN) publishes and routinely updates a number of guidelines for the treatment of cancer and the management of its related toxicities to assist healthcare providers in the optimal delivery of cancer care. Each NCCN clinical practice guideline is developed by a multidisciplinary panel of clinical experts. In 2006, NCCN published guidelines to address neutropenic complications, which were defined as a delay in treatment, a dose reduction, or the development of febrile neutropenia. Risk factors for developing neutropenic complications were categorized as chemotherapy regimens and patient risk factors.

The risk of febrile neutropenia is directly related to the side-effect profile and intensity of the chemotherapy regimen (NCCN, 2006). The guidelines defined a chemotherapy regimen as having low, intermediate, or high risk of causing neutropenic events based on documented incidents in clinical trials (see Figure 1). The guidelines defined a high-risk chemotherapy regimen as one in which patients have a 20% or greater probability of experiencing a neutropenic complication. The intermediate risk category is applied to regimens with a 10%–20% probability that patients will have neutropenic complications, and low-risk regimens are those with a risk of less than 10%.

Patient factors are discussed in the guidelines (see Figure 2). An overview of patient-related risk factors for febrile neutropenia is presented in Figure 3. Common patient risk factors are type of cancer, disease stage (e.g., bone marrow involvement in patients with non-Hodgkin lymphoma [NHL]), measures of pretreatment health (e.g., hemoglobin, albumin level), previous neutropenic events, comorbidities (e.g., chronic obstructive pulmonary disease, diabetes), Eastern Cooperative Oncology Group performance status grade 2 or more (see Figure 4), and age greater than 65 years (NCCN, 2006). In addition to assessing risk factors, the NCCN guidelines address treatment intent as a variable for the use of

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High Risk

- Breast cancer
  - Dose dense AC → T (doxorubicin, cyclophosphamide, paclitaxel)
  - AT (doxorubicin, paclitaxel)
  - TAC (docetaxel, doxorubicin, cyclophosphamide)
- Non-Hodgkin lymphoma
  - VAPEC-B (vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, bleomycin)
  - A(N)CVB (doxorubicin or mitoxantrone, cyclophosphamide, vindesine, bleomycin)
  - DHAP (dexamethasone, cisplatin, cytarabine)
  - ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine)
- Non-small cell lung cancer
  - VIG (gemcitabine, ifosfamide, vinorelbine)
  - DP (docetaxel, carboplatin)
- Small cell lung cancer
  - CAE (cyclophosphamide, doxorubicin, etoposide)
  - Topotecan
  - Topotecan/paclitaxel

Intermediate Risk

- Breast cancer
  - Docetaxel
  - AC (doxorubicin, cyclophosphamide)
  - Docetaxel, capecitabine
  - Gemcitabine,* carboplatin
- Non-Hodgkin lymphoma
  - ACOD (doxorubicin, cyclophosphamide, vincristine, prednisone)
  - FM (fludarabine, mitoxantrone)
  - RCHOP (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab)
- Non-small cell lung cancer
  - Cisplatin/paclitaxel
  - Cisplatin/docetaxel
  - Docetaxel/gemcitabine
- Small cell lung cancer
  - Cisplatin/topotecan
  - Etoposide/carboplatin

* Pegfilgrastim should not be used.

Figure 1. National Comprehensive Cancer Network Chemotherapy Regimens With a High or Intermediate Risk of Febrile Neutropenia

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growth factors: curative or adjuvant, life prolongation, and palliative (i.e., symptom management or improvement in quality of life) (Lyman, 2005; NCCN).

The NCCN (2006) guidelines are to be used for conducting individual neutropenic risk assessments. The guidelines emphasize the need to assess the risk of developing neutropenic complications and use of prophylactic growth factors before each chemotherapy cycle—with the first assessment immediately preceding the first cycle. By using the NCCN clinical practice guidelines for myeloid growth factors, nurses can participate in an evidence-based systematic process to improve patient outcomes.

Complications of Chemotherapy-Induced Neutropenia

Febrile neutropenia can lead to life-threatening infections and result in prolonged hospitalization and increased use of broad-spectrum antibiotics (Lyman, 2005; Lyman, Lyman, & Agboola, 2005). Severe and febrile neutropenia also can compromise treatment outcomes by causing or contributing to treatment delays or dose reductions that can adversely affect disease control and survival (Lyman). Data from clinical oncology practices across the United States have shown that a significant proportion of patients are treated with suboptimal chemotherapy related to dose delays and reductions (Lyman, Dale, & Crawford, 2003; Lyman, Dale, Friedberg, Crawford, & Fisher, 2004; Picozzi et al., 2001).

Chemotherapy-induced neutropenia is the primary dose-limiting toxicity associated with systemic chemotherapy in patients with cancer (Lyman, 2005; Lyman, Lyman, et al., 2005; NCCN, 2006). Febrile neutropenia occurred in 20%–24% of more than 5,100 patients with NHL and was associated with significant dose reductions (Lyman et al., 2004; Picozzi et al., 2001). Dose reductions of 15% or greater occurred in 40% of patients, and treatment delays of seven days or more were reported in 24% of patients. As a result, about half of the patients were treated with reduced relative dose intensity (RDI), defined as less than 85% of the standard dose referenced in clinical trials (Lyman et al., 2004). Patient age greater than 60 years was identified as an independent predictor of neutropenic complications in the population, and reduced RDI was more prevalent in those patients, with 60% being treated with an RDI less than 85%. Prophylactic treatment with granulocyte–colony-stimulating factor (G-CSF) was initiated in 12% of patients (n = 541), and initiation with the first cycle reduced the risk of febrile neutropenia (Lyman et al., 2004).

The lack of prophylactic G-CSF was an independent predictor of low RDI in a study of 1,243 patients with early-stage breast cancer. Doses were reduced by 15% or more in approximately 33% of patients, and treatment delays of seven days or more occurred in about 25%. Overall, about two-thirds of the potentially curable patients were treated with an RDI less than 85% (Lyman, Dale, et al., 2003). In 95 older adult patients (i.e., older than age 70) with small cell lung cancer, Ardizzoni et al. (2005) found that, compared to a full-dose regimen of cisplatin and etoposide, partial doses resulted in poor therapeutic outcomes, a 30% reduction in response rate, and a twofold reduction in one-year survival probability.

Data suggest that treatment with full-dose and on-time chemotherapy can improve survival (Budman et al., 1998; Kwak, Halpern, Olshen, & Horning, 1990). CSFs have been

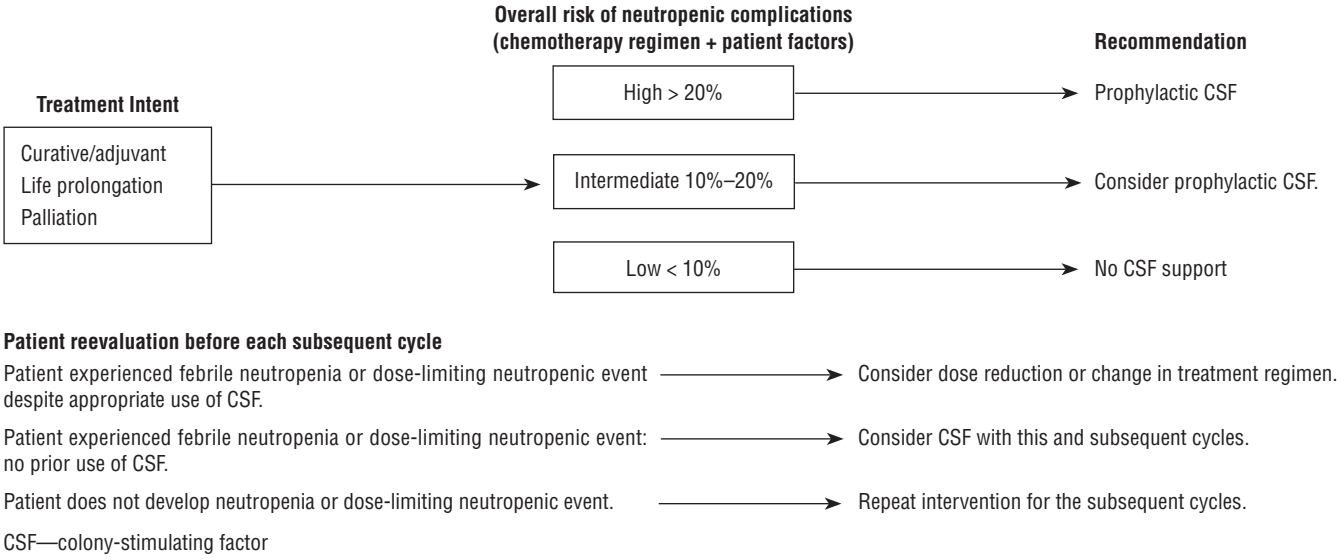

Figure 2. Evaluations for Treatment Intent and Risk Categorization Before Initiation of First-Cycle Chemotherapy and for Patient Risk Factors Before Each Subsequent Cycle

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found to be efficacious in decreasing chemotherapy-induced neutropenia (Kuderer, Crawford, Dale, & Lyman, 2005; Lyman, Morrison, et al., 2003; Vogel et al., 2005); therefore, CSFs may improve prognosis by preventing dose reductions and treatment delays caused by febrile neutropenia.

Consensus Criteria for Myeloid Growth Factors

Reducing the incidence of chemotherapy-induced neutropenia and neutropenic complications is critical in patient management. The efficacy of CSFs in preventing or reducing neutropenic complications in patients with cancer treated with systemic chemotherapy is well established (Kuderer et al., 2005; Lyman, Morrison, et al., 2003; Vogel et al., 2005). Proactive use of CSFs reduces the duration and severity of chemotherapy-induced neutropenia with a subsequent reduction in life-threatening complications. Evidence-based guidelines published by the American Society of Clinical Oncology and the European Organization for Research and Treatment of Cancer are consistent with NCCN guidelines (Repetto et al., 2003; Smith et al., 2006). All three of the major oncology professional organizations have recommended routine prophylaxis with a myeloid growth factor such as G-CSF in adult patients who are at high risk and have indicated that it should be considered for those who are at intermediate risk for chemotherapy-induced febrile neutropenia or other complications of neutropenia.

G-CSF (filgrastim) is a frequently used CSF that stimulates the myeloid line and increases the production of white blood cells after chemotherapy. Pegfilgrastim is a longer-acting G-CSF that is administered once per chemotherapy cycle. Granulocyte macrophage–CSF (GM-CSF) is a multilineage growth factor that increases the production of neutrophils, monocytes, macrophages, and dendritic cells after bone marrow transplantation and chemotherapy. On the basis of NCCN (2006) guideline category 1 consensus (see Table 1), pegfilgrastim and filgrastim are the CSFs of choice in reducing the incidence of febrile neutropenia and are to be administered with the first and subsequent chemotherapy cycles when the chemotherapy regimen or patient-related factors place the patient in the high-risk category.

The NCCN guidelines agree with the U.S. Food and Drug Administration's indication for the use of GM-CSF (sargramostim) in older patients following induction chemotherapy for acute myelogenous leukemia (Berlex, 2006; NCCN, 2006). Because of insufficient evidence, however, NCCN has not recommended the use of sargramostim in the management of neutropenic complications with high- and intermediate-risk regimens.

Evidence-Based Support for Neutropenic Risk Assessment

First- and Subsequent-Cycle Protection

Neutropenic events occur most frequently during the first cycle of chemotherapy when patients are treated with a full-

dose regimen without supportive care (Crawford et al., 2005; Lyman, Crawford, et al., 2005). In all major types of cancer treated with systemic chemotherapy, neutropenic events were reported at an incidence of 56%–79% in a prospective cohort of 3,657 patients in more than 100 U.S. community practices (Crawford et al.). In addition, 56% of the initial neutropenic episodes occurred during the first treatment cycle and the majority of events in later cycles occurred in patients who experienced previous episodes (Lyman, Crawford, et al.). Furthermore, neutropenic events were more likely to occur in the first cycle of chemotherapy than in the three subsequent cycles combined (Crawford et al.). The mean actual dose intensity was 87%, with 34% of patients receiving less than the standard dose intensity during the first four cycles of treatment (Crawford et al.; Lyman, Crawford, et al.). The planned treatment regimen (i.e., drug dose, treatment frequency, and duration) and first-cycle rates of severe and febrile neutropenia were strongly associated ($p < 0.001$) (Lyman, Crawford, et al.). In a study of 928 patients with breast cancer, pegfilgrastim administered in the first and subsequent cycles of chemotherapy significantly reduced the rate of febrile neutropenia across all cycles ($p < 0.001$) and decreased associated complications (hospitalization and IV antibiotic use; $p < 0.001$ for both) (Vogel et al., 2005).

Data from a prospective patient registry that investigated first and subsequent cycles of chemotherapy have been used to develop a prognostic model for severe and febrile neutropenia in patients with cancer treated with systemic chemotherapy (Lyman, Crawford, et al., 2005). The model determined that the key risk factors for the development of severe or febrile neutropenia were advanced age, female gender, poor performance status, poor nutritional status, low baseline and first-cycle nadir blood cell counts, and high chemotherapy dose intensity (Lyman, Lyman, et al., 2005).

Patient Related
- Age over 65 years
- Female gender
- ECOG performance status of 2 or more
- Poor nutritional status (e.g., low albumin)
- Decreased immune function

Cancer Related
- Bone marrow involvement with tumor
- Advanced or uncontrolled cancer
- Elevated lactate dehydrogenase (lymphoma)
- Leukemia
- Lymphoma
- Lung cancer

Treatment Related
- Previous history of severe neutropenia with similar chemotherapy
- Type of chemotherapy (anthracyclines)
- Planned relative dose intensity > 80%
- Preexisting neutropenia (< 1,000) or lymphocytopenia
- Extensive prior chemotherapy
- Concurrent or prior radiation therapy to marrow-containing bone

Comorbidities
- Chronic obstructive pulmonary disease
- Cardiovascular disease
- Liver disease (elevated bilirubin, alkaline phosphatase)
- Diabetes mellitus
- Low baseline hemoglobin

Conditions Associated With Risk of Serious Infection
- Open wounds
- Active tissue infection

ECOG—Eastern Cooperative Oncology Group

Note. The magnitude of all of these risk factors in determining a patient's risk is not clear.

Figure 3. National Comprehensive Cancer Network Risk Factors for Febrile Neutropenia

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Grade 0: fully active, able to carry on all predisease performance without rest

Grade 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)

Grade 2: ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours

Grade 3: capable of only limited self-care; confined to bed or chair more than 50% of waking hours

Grade 4: completely disabled, cannot carry on any self-care; totally confined to bed or chair

Grade 5: dead

Figure 4. Eastern Cooperative Oncology Group Performance Status

Note. From "Toxicity and Response Criteria of the Eastern Cooperative Oncology Group," by M.M. Oken, R.H. Creech, D.C. Tormey, J. Horton, T.E. Davis, E.T. McFadden, et al., 1982, *American Journal of Clinical Oncology, 5,* 649–655. Created by the Eastern Cooperative Oncology Group, Robert Comis, MD, Group Chair.

Patient Risk Factors

Risk models for assessing neutropenia are available, but inconsistencies in the use of risk assessment tools and in documenting findings have made implementing them in all settings difficult. The NCCN (2006) guidelines are evidence based and comprehensive and include the following risk factors: age older than 65, female gender, planned RDI greater than 80%, low pretreatment hemoglobin levels, and comorbidities. Nurses are ideally positioned to synthesize their clinical judgment, the NCCN guideline recommendations, and emerging

Table 1. National Comprehensive Cancer Network Myeloid Growth Factors for Preventing Febrile Neutropenia and Maintaining the Scheduled Dose Delivery

Myeloid Growth Factor	Recommendation
Filgrastim (category 1)	Daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits) until postnadir absolute neutrophil count recovery to normal or near-normal levels by laboratory standards
	Start one to three days after completion of chemotherapy and treat through postnadir recovery.
Pegfilgrastim (category 1)	One dose of 6 mg per cycle of treatment
	Start one to three days after completion of chemotherapy and treat through postnadir recovery.
	There is evidence to support use for chemotherapy regimens given every three weeks (category 1).
	Phase II studies demonstrate efficacy in chemotherapy regimens given every two weeks.
	There are insufficient data to support dose and schedule of weekly regimens or schedules less than two weeks, and these cannot be recommended.
Sargramostim[a] (category 2B)	Used in clinical trials at a dose of 250 mcg/m^2/day (rounding to the nearest vial size by institution-defined weight limits)
	Start one to three days after completion of chemotherapy and treat through postnadir recovery.

- Subcutaneous route is preferred for all three agents.
- There are no data to support alternative dosing schedules in intermediate- and high-risk patients.
- The safety data appear to be similar between filgrastim and pegfilgrastim.
- Prophylactic antibiotics are not recommended (see NCCN Fever and Neutropenia Guidelines [available at www.nccn.org/professionals/physician_gls/PDF/fever.pdf]).

[a] There is category 1 evidence to support filgrastim or pegfilgrastim for the prevention of febrile neutropenia. There is insufficient evidence to recommend sargramostim in this setting. Sargramostim is indicated for use following induction chemotherapy in older adult patients with acute myelogenous leukemia. Studies are ongoing in other areas.

Note. Category 1 indicates uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate. Category 2B indicates nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence, including clinical experience, that the recommendation is appropriate.

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evidence-based literature to assess each patient to ensure that care is tailored to individual needs.

Advanced age has been identified in 10 studies as a risk factor for the development of severe neutropenia (NCCN, 2006). Lyman et al. (2004) reported that being older than 60 was an independent risk factor for the development of febrile neutropenia in patients with NHL who were treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy without CSF. A retrospective case study analysis also determined that patients with NHL (N = 930) who were older than age 65 and treated with CHOP chemotherapy were at greater risk for neutropenic complications (Morrison et al., 2001). In an effort to minimize neutropenic complications, physicians often treat older patients with lower doses of chemotherapy.

Proactive management of the risk of neutropenic complications will increase the likelihood that older patients can be treated with recommended chemotherapy doses (NCCN, 2006). If older patients are treated with recommended doses, they can have outcomes that are equivalent to those of younger patients (Balducci & Repetto, 2004). Another significant risk factor for the development of neutropenic complications is an Eastern Cooperative Oncology Group performance status of grade 2 or more (Lyman, Lyman, et al., 2005; NCCN). Particularly in older patients, poor performance status might be a more accurate predictor of neutropenic risk than chronologic age (NCCN).

In patients with cancer, comorbidities are associated with a greater risk of neutropenia and its complications (Lyman, Lyman, et al., 2005; NCCN, 2006). In patients with NHL, renal and cardiovascular diseases were significantly associated with the risk of febrile neutropenia (Lyman et al., 2004; Lyman, Morrison, et al., 2003). A greater risk of severe or febrile neutropenia was reported in patients with breast cancer and liver, kidney, or cardiovascular disease (NCCN). Hypertension, pulmonary disease, pneumonia, and previous fungal disease also have been shown to increase the risk of neutropenic complications, including prolonged hospitalization and death (Lyman, Lyman, et al.; NCCN).

Many laboratory abnormalities have been found to be predictors for neutropenic complications (Lyman, Lyman, et al., 2005; NCCN, 2006). In patients with early-stage breast cancer, low pretreatment white blood cell counts were predictive of febrile neutropenia and RDI less than 85% (NCCN). In patients with aggressive NHL treated with CHOP, a serum albumin concentration of 3.5 g/dl or less, a lactate dehydrogenase level higher than the upper limit of normal, and bone marrow involvement were significant predictors for febrile neutropenia and life-threatening complications (NCCN).

Recommendations for Risk Assessment Before Every Cycle of Treatment

The NCCN (2006) guidelines have recommended that patients be evaluated before every cycle for treatment intent and risk categorization. Regardless of the patient population, if the regimen is high risk, then the proactive use of CSFs is warranted, beginning with the first cycle. If the regimen risk is intermediate, regardless of treatment intent, the use of CSFs should be considered according to patient risk factors. When the regimen risk is low (i.e., less than a 10%

probability of neutropenic complications), no CSF support is indicated.

Relevance to Nursing

When patients with cancer require chemotherapy, nurses play an important role in patient and caregiver education. Nurses have performed consistent and ongoing patient assessments and have applied evidence-based risk models to help determine the best options for supportive care (Ropka, Padilla, & Gillespie, 2005). A number of studies have reported improvements in patient outcomes through nurse-led adoption of clinical evidence into clinical practice through the implementation of risk assessment models and neutropenia management tools (Donohue, 2006; Maxon, 2005; Maxwell, Winkler, & Lottenburg, 2002; White, Maxwell, Michelson, & Bedell, 2005). Similar strategies can be used in adopting the NCCN guidelines into clinical practice. Healthcare providers can use risk models based on the NCCN (2006) guidelines for the use of myeloid growth factors to evaluate patients' risk of neutropenic complications. Nursing staff should be involved in the development, implementation, and evaluation of practice-specific tools (e.g., risk assessment tools, clinical practice guidelines, standing orders) (Maxwell et al.).

General and advanced practice nurses, in their educators role, inform patients and caregivers about the risk of infection, as well as how to monitor for symptoms of infection (Ropka et al., 2005). Education for patients treated with CSF supportive care must include information about drug administration, such as the injection schedule and the mechanism of action, as well as potential adverse effects and their management (Houston, 1997; White et al., 2005).

Documentation of patient assessment, treatment, and education by nursing staff, as well as improved communications between the nursing staff and the treating physician, will lead to better patient outcomes. Nurses on a multidisciplinary team must use tools in a consistent manner along with practice guidelines and standing orders. Nurses can use the tools to observe and report outcomes that are associated with specific clinical factors and thereby contribute to the formulation of accurate and effective risk models (Ropka et al., 2005; White et al., 2005).

The use of CSFs in all patients treated with myelosuppressive chemotherapy is not economically feasible. Risk assessment models that can determine which patients are at greatest risk for chemotherapy-induced neutropenia will help nurses to efficiently and cost-effectively target the proactive use of CSFs for patients who are most likely to have the greatest benefit (Donohue, 2006). Management protocols and guidelines that use the role of nurses in patient assessment and facilitate communication between nurses and physicians who administer chemotherapy are likely to optimize patient outcomes (Maxon, 2005; Maxwell et al., 2002; Michelson et al., 2002). In a community-based oncology clinic, nurse-driven neutropenia management guidelines, developed in consultation with physicians, advocated for the administration of filgrastim in patients who were at risk for neutropenia-related dose reductions or delays (Maxwell et al.). The use of the guidelines for approximately two years in patients with breast cancer resulted in only 5% of patients receiving less than 85% of the planned dose on time; in addition, 20% of the patient population experienced dose reductions, and 35% experienced dose delays. No patients were hospitalized for febrile neutropenia. The Neutropenia Management Protocol was evaluated for its efficacy in patients treated with chemotherapy for breast cancer or NHL from 1997–2001 at a community oncology clinic. The study's aim was to reduce the incidence of neutropenia while achieving the appropriate dose intensity for optimal clinical outcomes (Michelson et al.). Patients were evaluated for four risk factors: older age, serum albumin level 3.5 g/dl or less, a lactate dehydrogenase level higher than the upper limit of normal serum, and bone marrow involvement. Patients at high risk were given filgrastim as supportive therapy. Implementing the protocol involved nurse assessment of patients, evaluation of conditions that required the notification of a physician or nurse practitioner, implementation of CSF supportive care, monitoring for safety, education of patients and caregivers, and appropriate documentation (Michelson et al.).

Studies have revealed that practical interventions to ensure nurse-driven application of guidelines can affect patient care. A continuous quality improvement program showed that two years after treatment and documentation guidelines were implemented for patients with breast cancer treated with adjuvant chemotherapy, no patients received less than 85% of the planned dose intensity or had febrile neutropenia (White & Keehne-Miron, 2002). Four percent of the patients experienced dose reductions and 28% experienced dose delays.

Conclusion

Myelosuppressive chemotherapy commonly is associated with neutropenia, which can lead to severe infection, result in dose reductions and treatment delays, and, ultimately, adversely affect patient outcomes. Healthcare providers must be able to determine which patients are at risk for neutropenic complications prior to initiation of treatment to ensure appropriate use of CSFs. In addition to identifying high-risk patients, risk assessment tools (when used before the initiation of therapy) increase communication between patients and healthcare providers. Nurses are ideally positioned and qualified to conduct appropriate risk assessments and are committed to playing an integral role in directing the quality of patient care, which may be accomplished by implementing guidelines for the consistent management of neutropenic complications. Evidence-based guidelines should be reviewed thoroughly and implemented by nurses to prevent neutropenic complications. Nurses also can conduct prospective research studies to evaluate the effectiveness of risk models that reduce neutropenic complications. Guidelines from NCCN (2006) on the use of myeloid growth factors provide evidence for nurses to be instrumental in developing risk assessment tools for specific patient populations and in ensuring the best possible patient outcomes while effecting important changes in clinical practice.

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