Neutropenia is defined as a neutrophil count of less than 500 cells per mm$^3$, or a neutrophil count of less than 1000 cells per mm$^3$ with a predicted decrease to less than 500 cells per mm$^3$. Chemotherapy-induced neutropenia (CIN) is the most serious hematologic toxicity of cancer chemotherapy. CIN predisposes patients with cancer to life-threatening infections, particularly from gram-negative bacilli, gram-positive cocci, and fungi by suppression of neutrophil production and by cytotoxic effects on the alimentary tract. Neutrophils comprise the first cellular component of inflammatory response and contribute critically to innate immunity. Because CIN blunts normal inflammatory response, classic signs and symptoms of infection may be absent. Often, patients with neutropenia may present with fever (a single oral temperature of $\geq 38.3^\circ C$ [$101^\circ F$] or a temperature of $\geq 38^\circ C$ [$100.4^\circ F$] for $\geq 1$ hour) as the only indication of infection. The duration of CIN typically is 7 to 10 days. The severity and duration of a neutropenic episode with the presence of a fever, or febrile neutropenia (FN), increase the risk of further infection and of infection-related mortality. CIN also is associated with hospitalization for infection-related morbidity, infection-related mortality, high costs of treatment, and compromised clinical outcomes.

Several risk factors have been identified as significant predictors for neutropenic complications (Table 1). Significant patient-specific risk factors include advanced age, poor performance status, and the presence of comorbidities, such as renal and heart disease. Other patient-specific factors include female sex, poor nutritional status, and elevated alkaline phosphatase and total bilirubin levels. Patients with hematologic malignancies are at greater risk for CIN than patients with solid tumors because of the underlying disease process, in addition to chemotherapy intensity. Advanced disease and uncontrolled cancer also are significant disease-specific predictors of FN and other complications of neutropenia, including death.

CONSEQUENCES OF FEBRILE NEUTROPENIA

Fever without the clinical signs of a localized infection is the most common clinical presentation of infection in patients with neutropenia and is usually considered a medical emergency. The incidence of neutropenia hospitalizations is estimated to be 60 000 cases per year in the United States. These hospitalizations are associated with a high mortality rate; research studies estimate the death rate to be 6.8%, and the rate climbs to 10% for patients with a hematologic malignancy. The Infectious Diseases Society of America has published treatment guidelines for patients with FN, and treatment with intravenous antibiotics, which requires hospitalization, remains a standard of care. These antibiotics are not without toxicity to the gastrointestinal, renal, and dermatologic systems.

Febrile neutropenia has significant economic consequences. Hospitalization for FN varies by cancer type with respect to length of stay and cost. Data from a study evaluating all adult patients with cancer hospitalized with FN between 1995 and 2000 at 115 academic medical centers suggest that length of stay was longer in patients with leukemia than in those patients with lymphoma or solid tumors (19 days vs 10.8 days vs 8.5 days, respectively). The costs of FN follow a similar pattern: the mean costs for leukemia patients were substantially higher than for lymphoma or solid tumor patients ($37 591 vs $19 061 vs $12 302, respectively). A study examining the indirect, non-hospital costs of

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**ABSTRACT**

Chemotherapy-induced neutropenia is the most serious hematologic toxicity of cancer chemotherapy, predisposing patients with cancer to potentially life-threatening infections and other undesired complications. Historical clinical guidelines recommended prophylactic use of colony-stimulating factors (CSF) when the chemotherapy regimen was associated with a 40% or greater incidence of febrile neutropenia (FN). Previous studies supported “watch and wait” approaches to preventing FN after an initial occurrence. Based on recent data, the National Comprehensive Cancer Network issued new guidelines broadening the use of first-cycle CSFs to target patients receiving chemotherapy regimens with a 20% or greater risk of developing FN. These recent guidelines also list important clinical risk factors that place a patient at greater risk of developing FN, independent of the planned chemotherapy regimen. It is vital for oncology nurses, advanced practice nurses, and physician assistants to identify patients at risk as a result of the chemotherapy regimen or other risk factors, to educate patients and families about their risk, and to use CSFs appropriately to decrease the risk of FN and other adverse events. Use of the available evidence enables nurses and other healthcare providers to deliver safe and effective supportive care for patients with cancer.

FN estimated them to be approximately $5000 per hospitalization, most of which were attributed to lost wages.16

Finally, FN adversely affects patients’ quality of life (QOL).2,11 Limited data are available regarding this relationship as FN has been understudied as a secondary outcome in the context of side effects of chemotherapy. Recent data show that patients who developed grade 4 neutropenia during the first cycle of chemotherapy most commonly suffered from fatigue, sleep interruption, myalgias, and pain.11 Other common QOL complaints included interference in daily routines and activities,11,12 negative emotion, and social isolation.11 Further studies are warranted to determine the role of absolute neutrophil counts in QOL and clinical benefits from improved neutropenia management.13

**CURRENT THERAPEUTIC OPTIONS**

Granulocyte colony-stimulating factor (G-CSF) is a major regulator of hemopoiesis and the innate immune system. G-CSF influences the survival, proliferation, and differentiation of all cells in the neutrophil lineage—from hemopoietic stem cells to mature neutrophils—and influences the function of mature neutrophils.14

Randomized trials have demonstrated recombinant G-CSF (filgrastim) to be well tolerated and have shown the benefit of prophylactic use in CIN for the reduction of FN; the incidence, duration, and severity of grade 4 neutropenia; the depth of neutrophil nadir; the number and length of hospitalizations; intravenous antibiotic use15,16 and improved chemotherapy dose intensity.17 Studies have confirmed pegfilgrastim as at least equivalent to filgrastim in efficacy and safety.16,14 The once-per-cycle dosing of pegfilgrastim simplifies CIN management and can improve QOL through fewer injections, fewer clinic visits, lower chances of dosage administration error, and fewer activity disruptions.12,16,18,19

Recent analyses of 10 clinical trials and 2468 patients with lymphomas or solid tumors demonstrated a decreased relative risk of infection-related mortality by 46% when colony-stimulating factors (CSF) were administered (P = 0.13).20 The findings of another recent trial suggest that the use of pegfilgrastim and fluoroquinolones as primary prophylaxis of FN is more effective than filgrastim or pegfilgrastim alone for patients with breast cancer receiving docetaxel/doxorubicin/cyclophosphamide.21 It is important to remember that prophylactic antibiotics do not reduce the incidence of neutropenia, but merely reduce episodes of fever and infection associated with the condition.

Sargramostim, a granulocyte-macrophage CSF, has a similar ability to promote the growth of circulating neutrophils and decrease the risk of neutropenia complications.22 Currently, it is indicated for use in the older adult oncology population (aged >55–70 years) with de novo acute myelogenous leukemia following induction chemotherapy.23

**EMERGING EVIDENCE**

The American Society of Clinical Oncology (ASCO) published evidence-based guidelines for the use of CSFs to prevent FN in patients undergoing chemotherapy. These guidelines were developed from a systematic review of all available published data on the topic. In the initial 1994 publication, the ASCO guidelines recommended primary prophylaxis with G-CSF for patients receiving chemotherapy regimens with a 40% or greater risk of developing FN.24,25 The latest update, issued in 2000, reiterated this prior recommendation based on available cost-effectiveness studies and a lack of outcomes data on chemotherapy regimens with lower risks of FN.26 For regimens below that level of FN incidence, the 2000 ASCO guidelines advocated a “watch and wait” approach. If a patient developed FN, use of CSFs was recommended in the next chemotherapy cycle when treatment intent was curative. For other purposes, dose modifications were considered medically.

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**Table 1. NCCN Patient Risk Factors for Developing Febrile Neutropenia**

<table>
<thead>
<tr>
<th>Treatment-Related</th>
<th>Patient-Related</th>
<th>Cancer-Related</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of severe neutropenia with similar chemotherapy</td>
<td>Age (&gt;65 years)</td>
<td>Bone marrow involvement with tumor</td>
<td>Open wounds</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Female</td>
<td>Advanced/uncontrolled cancer</td>
<td>Active tissue infection</td>
</tr>
<tr>
<td>Planned relative dose intensity ≥85%</td>
<td>COPD</td>
<td>Elevated LDH (non-Hodgkin’s lymphoma)</td>
<td>Cardiovascular Disease</td>
</tr>
<tr>
<td>Pre-existing neutropenia or lymphocytopenia</td>
<td>Poor performance status (ECOG ≥2)</td>
<td>Leukemia</td>
<td>Liver disease (elevated bilirubin/alkaline phosphatase)</td>
</tr>
<tr>
<td>Extensive prior chemotherapy</td>
<td>Poor nutritional status (low albumin)</td>
<td>Lymphoma</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Concurrent or prior radiation therapy to marrow-containing bone</td>
<td>Decreased immune function</td>
<td>Lung cancer</td>
<td>Low baseline hemoglobin</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; NCCN = National Comprehensive Cancer Network.


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acceptable. However, recent research findings contradict the ASCO guidelines because they document the greatest risk for FN occurs in the first cycle of chemotherapy, across several tumor types. In contrast, the National Comprehensive Cancer Network’s (NCCN) clinical practice guidelines are based on evidence and clinical expertise to determine appropriate supportive care for patients with cancer. Appropriate care is determined by assessing the balance between the sum of the benefits compared to the sum of the risks with the intent to provide clinicians with practical tools for day-to-day decision making—even when there are insufficient data. Based on these criteria, and in response to emerging evidence from randomized and observational studies, the NCCN has issued its first set of guidelines devoted to myeloid growth factors.

The pivotal trial in the development of the NCCN’s myeloid growth factor guidelines studied 928 patients with breast cancer who were receiving single-agent docetaxel—a chemotherapy regimen associated with a 10% to 20% incidence of FN in the absence of CSF administration. The trial randomly assigned patients to pegfilgrastim ($n = 463$) or placebo ($n = 465$) given on day 2 of each 21-day chemotherapy cycle. Results demonstrated that CSFs almost eliminated FN when there was a moderate risk: 1% of patients in the pegfilgrastim group developed FN compared to 17% of patients in the placebo group. In addition, only 1% of the pegfilgrastim patients were hospitalized for FN compared to 14% in the placebo group. Two patients died of septic shock in the placebo arm, versus no deaths in the pegfilgrastim arm.

The NCCN panel concluded that the clinical benefit of first and subsequent chemotherapy cycle support with G-CSF was clear for the prevention of FN in patients receiving regimens with a 20% or greater risk of FN. This is regardless of treatment intent—curative, adjuvant, or to enhance QOL or prolong survival. The NCCN panel also redefined the FN risk thresholds; high-risk is now defined as a regimen with a 20% or greater chance of developing FN or a neutropenic event compromising treatment, intermediate-risk is defined as a 10% to 20% chance, and low-risk is defined as a less than 10% chance of developing FN. It is critical to understand these proportions of risk apply to the chemotherapy regimen and not to overall patient risk; the panel identified clinical factors that increase the risk of FN development above a regimen’s published incidence of FN (Table 1).

According to the NCCN panel, first and subsequent cycles of G-CSF are recommended for high-risk patients in most treatment settings. For intermediate-risk patients, G-CSF use should be considered based on treatment intention and the balance of benefit versus harm. Patient-specific and disease-specific risk factors impact the risk of FN and should be thoroughly evaluated in this patient population. G-CSF use in low-risk patients is not recommended in any treatment setting unless the patient is receiving curative or adjuvant treatment and is at a significant risk for serious medical complications of FN.

**NURSING IMPLICATIONS**

Oncology nurses, advanced practice nurses, and physician assistants are in a unique position to provide evidence-based supportive care to patients with cancer. They enjoy sustained contact with patients and are in an optimal position to assess patient risk and monitor patient changes during the course of treatment. In addition, they are the last line of evaluation before the receipt of potentially toxic anticancer therapies; the assessment and interventions nurses make for patients with cancer have profound effects on side effects, complications, and QOL.

Anecdotally, nurses have expressed reluctance to be involved in proactive assessment and management of CIN. However, it is time to build on the advances made in the assessment and management of pain, nausea, and vomiting. Applying the findings and recommendations of the NCCN panel to other clinical settings will decrease variations in interventions, reduce confusion among practitioners, simplify documentation, and most importantly, result in fewer unnecessary hospitalizations and related complications. Tools available to nurses to increase proactive risk assessment and prevention activities include standing orders (ie, interdisciplinary documents with specific inclusion and exclusion criteria to address common clinical occurrences) and guidelines specific to a clinical institution. Institution-specific guidelines provide the opportunity for practice sites to summarize the available literature, develop standards agreed upon by clinicians, and tailor interventions to specific patients. These mechanisms—when developed with nursing leadership—can streamline care, reduce administrative burdens, and deliver better care to patients.

Regardless of the system-level intervention nurses decide to adopt, patients and families must receive adequate education regarding CIN. Essential topics, shown in Table 2, should be shared not only before the first cycle of chemotherapy, but also in all subsequent cycles to assure understanding. Through frequent and clear education messages, the nurse improves the chances that patients will respond appropriately to manage FN, should it occur.

**CONCLUSIONS**

Chemotherapy-induced neutropenia remains the major dose-limiting toxicity of systemic cancer chemotherapy and is associated with significant clinical, economic, and QOL implications. Clinical trials have demonstrated the efficacy and safety of G-CSF to reduce the incidence of CIN and related complications, including FN and infection-related mortality. The recent myeloid growth factor guidelines by the NCCN discuss the most recent data regarding therapeutic efficacy and clinical benefit...
of G-CSF use in patients receiving cancer chemotherapy. As the front-line providers of supportive care, the challenge for oncology nurses is to use the latest evidence and clinical guidelines to accurately identify high-risk patients, provide the appropriate supportive care recommendations, document the rationale and outcomes of those interventions, and educate patients and families as to how to best avoid complications and improve QOL.

ACKNOWLEDGEMENT

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REFERENCES


Table 2. Essential Patient Education Topics for Chemotherapy-Induced Neutropenia

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Fever, Neutropenia</th>
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<tbody>
<tr>
<td>Handwashing, CSFs (administration, mechanism of action, side effects), avoidance of ill persons, temperature checks, complete blood count checks</td>
<td>Preventive measures</td>
</tr>
<tr>
<td>Chills, shortness of breath, new onset of pain, catheter problems, diarrhea, vomiting, changes in skin, urination, mental status</td>
<td>Reportable conditions</td>
</tr>
<tr>
<td>Emergency contacts, closest after-hours medical care, need for rapid access to stabilize and receive broad-spectrum antibiotics</td>
<td>Action plan</td>
</tr>
</tbody>
</table>

CSF = colony-stimulating factors.

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