

# Risks and Consequences of Chemotherapy-Induced Neutropenia

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Neutropenia represents a major dose-limiting toxicity of chemotherapy and is associated with an increased risk of infection, impaired patient quality of life, and interference with the delivery of full-dose chemotherapy. These complications increase not only morbidity and mortality associated with cancer treatment but also the overall cost of care for cancer patients. Conversely, chemotherapy-induced neutropenia as a surrogate for delivered dose intensity has been associated with improved cancer survival. Administration of myeloid growth factors, such as filgrastim and pegfilgrastim, reduces the risk for neutropenic complications and facilitates the delivery of full-dose chemotherapy. There is an ongoing effort to identify patients at increased risk for developing neutropenic complications who would likely benefit from preemptive myeloid growth factor therapy. Appropriate use of myeloid growth factors is associated with reduced neutropenic complications, improved patient quality of life, and potentially improved disease control and long-term survival. (*Clinical Cornerstone*. 2006;8[Suppl 5]; S12–S18). Copyright © 2006 Excerpta Medica, Inc.

Chemotherapy-induced neutropenia represents a major dose-limiting toxicity of systemic cancer chemotherapy. Chemotherapy-induced neutropenia places cancer patients at increased risk for infection, interferes with the delivery of full-dose chemotherapy, and impairs patient quality of life.<sup>1,2</sup> Conversely, recent studies have found that chemotherapy-induced neutropenia as a surrogate for delivered chemotherapy dose intensity is associated with improved survival in cancer patients.<sup>3,4</sup> Myeloid growth factors, including the granulocyte colony-stimulating factors (G-CSFs) filgrastim and pegfilgrastim and the granulocyte-macrophage colony-stimulating factor sargramostim, help forestall many complications associated with neutropenia and help facilitate the optimal use of chemotherapy.

Recently, studies have examined factors that may place patients at increased risk for developing complications from neutropenia.<sup>5,6</sup> Accurate identification of patients at greatest risk for these complications facilitates the most appropriate use of myeloid growth factors. This paper will provide an overview of neutropenia and discuss the compli-

## KEY POINT

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cations associated with this condition, the risk factors for developing these complications, and the use of G-CSFs to reduce these complications, improve patient quality of life, and improve clinical outcomes.

## Overview of Neutropenia

Various definitions of neutropenia have been proposed. For example, the National Cancer Institute defines *severe neutropenia* as an absolute neutrophil count (ANC) of 500 to 1000 cells/mm<sup>3</sup>, and *life-threatening neutropenia*

**TABLE I. NATIONAL CANCER INSTITUTE NEUTROPENIA TOXICITY GRADING SCALE.<sup>7</sup>**

Grade	ANC Level
1 = Mild	LLN–1500 cells/mm <sup>3</sup>
2 = Moderate	1000–<1500 cells/mm <sup>3</sup>
3 = Severe	500–<1000 cells/mm <sup>3</sup>
4 = Life-threatening	<500 cells/mm <sup>3</sup>

ANC = absolute neutrophil count; LLN = lower limit of normal (1200 cells/mm<sup>3</sup>).

as ANC <500 cells/mm<sup>3</sup> (Table I).<sup>7</sup> The Infectious Diseases Society of America defines *febrile fever* as associated with <500 neutrophils/mm<sup>3</sup>, or <1000 neutrophils/mm<sup>3</sup> and a predicted decline to ≤500 neutrophils/mm<sup>3</sup> during the next 48 hours.<sup>8</sup>

In most cases, the nadir in leukocyte count occurs 5 to 14 days after administration of a chemotherapeutic agent. Recovery of the bone marrow generally occurs within 7 to 21 days of chemotherapy, but it can take as long as 4 to 5 weeks. Agents associated with the longest recovery times include the nitrosoureas and mitomycin. The type and dose of chemotherapy affect the degree of bone marrow suppression.<sup>9</sup> Various host factors, such as bone marrow cellularity, marrow reserve, nutritional status, and the ability to metabolize or excrete chemotherapeutic agents also affect the degree of bone marrow suppression.<sup>9,10</sup>

Until recently, neutropenia was viewed primarily as a toxicity of chemotherapy. However, recent studies<sup>3,4</sup> suggest that neutropenia may be a physiologic marker of chemotherapy dose intensity and antitumor efficacy. A pooled analysis of advanced non–small-cell lung cancer studies found that patients developing neutropenia experienced improved survival, with a median survival 10 weeks longer in patients with severe neutropenia compared with patients without neutropenia.<sup>3</sup> Chemotherapy-induced neutropenia has also been correlated with improved survival in breast cancer patients.<sup>4</sup>

### Complications of Neutropenia

While neutropenia may be associated with improved survival as a result of a greater antitumor effect, it is also associated with numerous complications, including infection, infection-related mortality, subsequent reduction in chemotherapy dose intensity, and impaired patient quality of life. These complications result in increased morbidity, mortality, and health care costs.<sup>1,2</sup>

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### Infection

Infection is a major complication of neutropenia in cancer patients. Since neutrophils play an essential role in protecting the body from bacterial and fungal infections, decreased neutrophil counts predispose patients to infection. The further the neutrophil count falls below 1000 cells/mm<sup>3</sup>, the greater the risk of serious infection, including sepsis.

Diagnosing infection in a patient with neutropenia is complicated by the fact that many of the usual signs and symptoms of infection are muted or absent because of the neutropenia. The nonspecific sign of fever (defined as a single temperature >38.3°C taken orally, or an oral temperature ≥38.0°C for 1 hour in the absence of an obvious cause) is often the only sign of an infection in these patients. Although cultures may remain negative in more than half of patients with febrile neutropenia, all patients with neutropenia who develop fever require prompt evaluation and treatment.<sup>11</sup> Since febrile neutropenia may be associated with serious, life-threatening complications, including multiorgan failure, immediate treatment with broad-spectrum antibiotics is required.<sup>2,11</sup>

The costs associated with episodes of febrile neutropenia are substantial.<sup>12</sup> In addition to hospital diagnostic and treatment costs, there are indirect costs related to impaired quality of life.<sup>1,13</sup> Furthermore, an estimated

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5% to 7% of cancer patients who develop febrile neutropenia die during hospitalization.<sup>12,14,15</sup> Factors that have been associated with an increased risk for neutropenic complications are listed in **Table II**.<sup>10,11</sup>

**Reduced Chemotherapy Intensity**

Approximately 50% of cancer patients receive <85% of their planned chemotherapy; in many cases, dose reductions are necessitated by the development of neutropenia or febrile neutropenia.<sup>16,17</sup> Studies suggest that neutropenic complications result in treatment delays in 40% of breast cancer patients and chemotherapy dose reductions in 25% of these patients.<sup>15</sup> Many of the factors that place patients at risk for compromised delivery of the full dose of chemotherapy (eg, advanced age, disease stage, type and dose of chemotherapy, prior treatment, marrow involvement, the presence of multiple comorbidities) are also associated with an increased risk of neutropenia.<sup>1,10,11</sup>

Reductions in chemotherapy dose intensity may result in compromised outcomes.<sup>2,18,19</sup> Recent findings suggest that both chemotherapy dose and intensity may have an impact on long-term outcomes in patients with primary breast cancer.<sup>15</sup> Studies in patients with lymphoma and breast cancer suggest that better survival rates may be observed in patients who receive standard doses of chemotherapy more frequently compared with patients who have longer intervals between doses.<sup>9</sup>

**Impaired Patient Quality of Life**

Studies also have demonstrated that chemotherapy-induced neutropenia and its complications have a nega-

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tive impact on patient quality of life.<sup>20-24</sup> Ashley et al<sup>21</sup> described the results of quality-of-life interviews conducted with 34 cancer patients who developed grade 4 neutropenia. When asked to describe the effects of chemotherapy-induced neutropenia on their daily routine, patients complained of fatigue and noted that the condition resulted in both interference with their daily routines and social isolation.

Calhoun et al<sup>22</sup> evaluated the effects of neutropenia-induced chemotherapy delays on quality of life, psychological response, and general well-being in 138 patients newly diagnosed with cancer, most of whom had breast or ovarian cancer. This group reported that the delays negatively affected their quality of life and diminished their psychological well-being. Patients who experienced a neutropenia-induced chemotherapy delay had substantial increases in tension, depression, anger, and intrusive and avoidant thoughts.

**Myeloid Growth Factors**

Multiple studies have demonstrated that the risk of complications associated with chemotherapy-induced neutropenia can be reduced by using myeloid growth factors. Randomized controlled trials have demonstrated that filgrastim can reduce the risk of febrile neutropenia by ~50%.<sup>25</sup> Pegfilgrastim has demonstrated even greater reductions in the risk of febrile neutropenia among women with breast cancer receiving combination chemotherapy.<sup>26-28</sup> Most recently, a large double-blind, placebo-controlled, randomized trial of breast cancer patients receiving docetaxel demonstrated a reduction in risk of febrile neutropenia of >90%.<sup>29</sup> Myeloid growth factors have been demonstrated to permit the administration of more effective dose-dense chemotherapy regimens and to facilitate the administration of conventional chemotherapy regimens at full dose and on time, while reducing the length and severity of chemotherapy-induced neutropenia; these agents also may prevent life-threatening complications.<sup>1,15,30,31</sup>

**TABLE II. RISK FACTORS FOR COMPLICATIONS OF FEBRILE NEUTROPENIA.<sup>10,11</sup>**

Risk Factor
Inpatient status at the time fever developed
Hematologic malignancies
Significant medical comorbidity or clinically unstable
High temperature and low blood pressure on admission
IV site infection
Prolonged, severe neutropenia
Organ dysfunction
Uncontrolled/progressive cancer
Pneumonia or other complex infection at presentation

Despite the ability of myeloid growth factors to reduce the risk of serious and life-threatening toxicities resulting from chemotherapy treatment, many patients who receive myelosuppressive chemotherapy are not administered myeloid growth factors. For example, only an estimated 30% of US patients receiving adjuvant chemotherapy for breast cancer are treated with myeloid growth factors.<sup>15</sup> It is anticipated that by identifying those patients who are at risk for these complications and who are most likely to benefit from prophylactic myeloid growth factors, the risk of these serious complications may be reduced in an efficient and cost-effective manner. Clinical practice guidelines for the use of these agents have been updated recently; these guidelines may improve the identification of patients who are appropriate candidates for the use of myeloid growth factors.

### KEY POINT

**Myeloid growth factors can reduce the risk of febrile neutropenia by ~50% to >90%.**

#### **Guidelines for Use of Myeloid Growth Factors**

Several organizations, including the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the European Organisation for Research and Treatment of Cancer (EORTC), have recently presented guidelines for the use of myeloid growth factors.

#### **ASCO Guidelines**

Based on the risk of febrile neutropenia as a serious life-threatening toxicity of cancer chemotherapy, as well as multiple trials demonstrating the benefit of myeloid growth factors, the recently updated ASCO guidelines suggest that these agents should be used as primary prophylaxis in patients receiving chemotherapy associated with a risk of febrile neutropenia ~20%, and in those with other special circumstances that place them at increased risk.<sup>32</sup> Special circumstances suggested for myeloid growth factor therapy include age >65 years, comorbid conditions, preexisting neutropenia, a history of recurrent febrile neutropenia while receiving earlier

chemotherapy, and conditions potentially enhancing the risk of serious infection.

The ASCO guidelines also suggest that use of myeloid growth factors may be considered in patients with established febrile neutropenia who are at high risk for infection-associated complications and who have prognostic factors associated with a poor clinical outcome.<sup>33</sup>

#### **NCCN Guidelines**

The recently developed NCCN guidelines suggest that myeloid growth factors should be used routinely in patients with a >20% risk of developing febrile neutropenia or other neutropenic events that would compromise treatment.<sup>34</sup> These guidelines also suggest considering the use of myeloid growth factors in patients with a 10% to 20% risk of developing neutropenic complications if they are at increased risk for poor outcomes due to individual risk factors. While considered a consensus process, the NCCN guidelines were based on the wealth of data available from recent randomized controlled trials.<sup>35</sup>

#### **EORTC Guidelines**

The most recently published guidelines were developed by the EORTC. These guidelines also recommend the use of primary myeloid growth factor prophylaxis in patients at >20% risk of febrile neutropenia.<sup>36</sup> Additionally, in patients receiving chemotherapy that is associated with a 10% to 20% risk of febrile neutropenia, attention should be paid to patient-specific risk factors, such as age >65 years, that may increase the risk of febrile neutropenia. Prophylactic G-CSF is recommended when dose-dense or dose-intense chemotherapy has been shown to have survival benefit. Finally, where a reduction in chemotherapy dose intensity is associated with a poor outcome, primary G-CSF prophylaxis should be used to maintain the chemotherapy regimen.

#### **Risk Factors for Neutropenic Complications**

Despite relatively consistent recommendations among the clinical practice guidelines for use of the myeloid growth factors, the assessment of an individual patient's risk of neutropenic complications still remains a clinical judgment based on training and experience.

The great variability in the occurrence of chemotherapy-induced neutropenia and its complications, including

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febrile neutropenia, suggests that multiple risk factors are associated with the development of these conditions. **Table III**<sup>1,10</sup> lists some of the treatment-, patient-, and disease-related factors that have been associated with the development of neutropenia and febrile neutropenia. Although the treatment regimen and dose are often considered to be the greatest risk factors for febrile neutropenia, a review of clinical trials found great variability in the reported rates of myelosuppression with the same or similar treatment regimens.<sup>37</sup>

The Awareness of Neutropenia in Chemotherapy (ANC) Study Group has examined the incidence of neu-

troponia and its complications in 2500 patients drawn from a registry of 137 randomly selected community oncology practice sites located throughout the United States. In a preliminary analysis of data available from the first 2222 patients,<sup>5</sup> 40% of patients were found to have developed neutropenia (defined as ANC <1000 cells/mm<sup>3</sup>) and 26% had developed severe neutropenia (defined as ANC <500 cells/mm<sup>3</sup>). As previously observed in patients with malignant lymphoma,<sup>38,39</sup> the majority of initial neutropenic events occurred during the first cycle of chemotherapy across all tumor types.<sup>5</sup> Predictors of severe neutropenia include cancer type (highest for breast cancer, lymphoma, and lung cancer), regimen type, baseline neutrophil count, gender, and presence of diabetes or chronic lung disease.<sup>5</sup> The risk of severe neutropenic events (severe neutropenia and febrile neutropenia combined) in the first cycle of chemotherapy was 36% for breast cancer, 20% for lung cancer, 33% for lymphoma, 17% for ovarian cancer, and 8% for colon cancer.<sup>5</sup>

In a further analysis of these data,<sup>6</sup> neutropenia (ANC <1000 cells/mm<sup>3</sup>) was observed in 43% of patients and severe neutropenia (ANC <500 cells/mm<sup>3</sup>) was observed in 24% of patients. More than half of all initial neutropenic events occurred during the first cycle of chemo-

**TABLE III. RISK FACTORS FOR DEVELOPING FEBRILE NEUTROPENIA.**<sup>1,10</sup>

Treatment related	Type of chemotherapeutic agent used (eg, high-dose anthracycline, high-dose cyclophosphamide, etoposide) Dose intensity Extensive prior chemotherapy History of severe neutropenia with similar chemotherapy Concurrent or prior radiation therapy to marrow-containing bone
Patient related	Advanced age (>65 years) Female gender Poor nutritional status Poor performance status Decreased immune function Preexisting neutropenia or lymphocytopenia Conditions associated with risk of serious infection (eg, open wounds, active tissue infection) Comorbidities (eg, chronic obstructive pulmonary disease, cardiovascular disease, hepatic disease, type 2 diabetes, low baseline hemoglobin concentration)
Disease related	Type of cancer (leukemia, lymphoma, lung cancer) Bone marrow involvement Advanced or uncontrolled cancer Elevated lactate dehydrogenase activity (lymphoma)

therapy. Across cancer types, the proportion of neutropenic events occurring in the first cycle ranged from 44% to 75%.

### Risk Models for Predicting Chemotherapy-Induced Neutropenia and Neutropenic Complications

Although the assessment of an individual patient's risk remains a clinical judgment, the goal of the ANC Study Group is to develop and validate objective risk models that may assist clinicians in selecting patients for the use of these agents in an individualized manner. In this way, treatment and supportive care of patients receiving cancer chemotherapy can be optimized. Most of the risk models developed to date have been based on retrospective data measured in various ways under varying clinical conditions, and none have been independently validated.

The ANC Study Group recently presented the results of an initial multivariate risk model for first-cycle severe or febrile neutropenia.<sup>40</sup> Significant independent risk factors included the type of cancer; the patient's age; the presence of hyperglycemia, diabetes, or liver dysfunction; an anthracycline-based regimen; planned full-dose intensity; and a body surface area <2 m<sup>2</sup>. Higher baseline neutrophils, lymphocytes, and platelets, as well as primary prophylaxis with a myeloid growth factor, were associated with a significant reduction in risk. Both internal and external validation of this model are currently under way.

### CONCLUSIONS

Although chemotherapy is frequently associated with dose-limiting neutropenia and its complications, including febrile neutropenia, studies have found that the use of myeloid growth factors can reduce the risk of developing febrile neutropenia, improve patient quality of life, and reduce the need for chemotherapy treatment delays and dose reductions. More appropriate use of myeloid growth factors based on recently presented clinical practice guidelines and validated risk models is likely to result in a further reduction in the risk of these serious and life-threatening toxicities and in improved delivery of cancer chemotherapy. The result will be better clinical outcomes, including improved patient survival and quality of life, along with more efficient and cost-effective use of these agents.

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