Chemotherapy-Induced Neutropenia
Risks, Consequences, and New Directions for Its Management

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Cytotoxic chemotherapy suppresses the hematopoietic system, impairing host protective mechanisms and limiting the doses of chemotherapy that can be tolerated. Neutropenia, the most serious hematologic toxicity, is associated with the risk of life-threatening infections as well as chemotherapy dose reductions and delays that may compromise treatment outcomes. The authors reviewed the recent literature to provide an update on research in chemotherapy-induced neutropenia and its complications and impact, and they discuss the implications of this work for improving the management of patients with cancer who are treated with myelosuppressive chemotherapy. Despite its importance as the primary dose-limiting toxicity of chemotherapy, much concerning neutropenia and its consequences and impact remains unknown. Recent surveys indicate that neutropenia remains a prevalent problem associated with substantial morbidity, mortality, and costs. Much research has sought to identify risk factors that may predispose patients to neutropenic complications, including febrile neutropenia, in an effort to predict better which patients are at risk and to use preventive strategies, such as prophylactic colony-stimulating factors, more cost-effectively. Neutropenic complications associated with myelosuppressive chemotherapy are a significant cause of morbidity and mortality, possibly compromised treatment outcomes, and excess healthcare costs. Research in quantifying the risk of neutropenic complications may make it possible in the near future to target patients at greater risk with appropriate preventive strategies, thereby maximizing the benefits and minimizing the costs. Cancer 2004;100:228–37. © 2003 American Cancer Society.

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Cytotoxic chemotherapy predictably suppresses the hematopoietic system, impairing host protective mechanisms. Neutropenia is the most serious hematologic toxicity of cancer chemotherapy, often limiting the doses of chemotherapy that can be tolerated. The degree and duration of the neutropenia determine the risk of infection (Fig. 1).1,2 The Common Toxicity Criteria of the National Cancer Institute is the most commonly used scale for grading the severity of the cytopenias associated with cancer chemotherapy; it delineates neutropenia into 4 grades (Table 1).

Chemotherapy predisposes patients with cancer to infections both by suppressing the production of neutrophils and by cytotoxic effects on the cells that line the alimentary tract. Neutrophils are the first line of defense against infection as the first cellular component of the inflammatory response and a key component of innate immunity. Neutropenia blunts the inflammatory response to nascent infections, allowing bacterial multiplication and invasion. Because neutropenia reduces the signs and symptoms of infection, patients with neutro-
penia often may present with fever as the only sign of infection. In this setting, patients with fever and neutropenia, or febrile neutropenia (FN), must be treated aggressively, typically with intravenous antibiotics and hospitalization, because of the risk of death from rapidly spreading infection.

The availability of hematopoietic growth factors and improvements in antibiotic therapy have changed greatly how clinicians approach the management of neutropenia, yet this complication remains a central concern in the delivery of cancer chemotherapy. This review summarizes the clinical consequences of chemotherapy-induced neutropenia (CIN) and describes current efforts to predict which patients are likely to experience neutropenic complications—delays and reductions in chemotherapy doses, FN, bacterial and fungal infections, and septic deaths.

Epidemiology of CIN and Risk of Neutropenic Complications

All patients who are treated with chemotherapy are at risk for the development of neutropenic complications, but it is difficult for clinicians to predict which patients or populations of patients clearly are at greater risk. Identified risk factors for neutropenia can be classified as patient-specific or regimen-specific.

Patient-specific risk factors

Because chemotherapy regimens are standardized by cancer type, patient-specific risk factors are particularly important in any given treatment setting. Patient-specific risk factors are type of cancer and disease stage, measures of pretreatment health, comorbid conditions, performance status, and age. With respect to disease type, it is clear that patients with hematologic malignancies are at greater risk for neutropenia than patients with solid tumors because of the underlying disease process as well as the intensity of the treatment that is required.

In a review of 18 published risk models that were developed to assess neutropenic risk, Lyman et al. described 2 types of models—those that predict severe neutropenia or FN or reduced dose intensity (Type 1) and those that predict bacteremia or other consequences of FN (Type 2).4 The risk factors that were validated in at least 2 models of either type were age, performance status, dose intensity, and serum lactate dehydrogenase (LDH) level for Type 1 models and age, leukemia or lymphoma, high temperature, and low blood pressure on admission for Type 2 models. Authors of another review found many of the same risk factors, including age and performance status.5

Laboratory abnormalities that indicate either comorbid conditions or disease extent may predict neutropenic complications. For example, retrospective studies have found predictive value in pretreatment leukocyte counts.6 In 1 prospective study of patients with aggressive non-Hodgkin lymphoma (NHL) who were treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), it also was found that a serum albumin concentration ≥ 3.5 g/dL, an LDH level greater than normal, and bone marrow involvement of the lymphoma all were significant predictors of life-threatening neutropenia (absolute neutrophil count [ANC] ≤ 0.5 × 10^9/L) or FN (ANC ≤ 0.5 × 10^9/L and body temperature ≥ 38.3 °C).7

The role of age in the susceptibility to neutropenic complications has been explored extensively. Initial attempts to document older age (> 65 years or > 70 years) as a risk factor were confounded by the exclusion of elderly patients from clinical trials as well as inclusion criteria that admitted only the most otherwise healthy elderly patients in those trials in which older age was not itself an exclusion criterion.8 In contrast, 7 of the 9 studies examined in a review of risk factors for severe neutropenia or FN demonstrated a significant effect of age on risk.9 This included a retrospective practice pattern study, which showed that older patients with NHL had more hospitalizations for FN and were given a lower relative dose intensity of

![FIGURE 1. Incidence of serious infection, by nadir absolute neutrophil count (ANC) and duration of neutropenia. Adapted from Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med. 1966;64:328–340.](image)

<table>
<thead>
<tr>
<th>Grades of Neutropenia*</th>
<th>Absolute neutrophil count (× 10^9/L)</th>
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<tr>
<td>0</td>
<td>Within normal limits</td>
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<tr>
<td>1</td>
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<td>2</td>
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*According to the National Cancer Institute Common Toxicity Criteria, version 2.0.3

TABLE 1

Grades of Neutropenia*
chemotherapy.9,10 In addition, a prospective study in women who were treated with doxorubicin and cyclophosphamide (AC) as adjuvant chemotherapy for breast carcinoma showed that, in women age > 70 years, there was a greater incidence, duration, and severity of neutropenia and also a trend toward deeper ANC nadirs with greater age.11 Furthermore, studies of risk factors for the toxicity of chemotherapy in older patients are underway. In a pilot trial in patients age ≥ 70 years who were treated with chemotherapy for solid tumors or nonleukemic hematologic malignancies, pretreatment parameters (such as increased diastolic blood pressure, bone marrow invasion, and above-normal LDH levels) were associated with greater toxicity.12

Age itself is a general risk factor for the development of severe neutropenia or FN, and it also may be associated with other patient characteristics that affect that risk. In some studies, it has been found that poor performance status (e.g., World Health Organization Grade > 1), as a measure of frailty, is a significant risk factor.5 Thus, a patient’s physiologic age, rather than chronologic age, may be a more accurate predictor of the neutropenic risk. One approach to determining a patient’s physiologic age is to use a comprehensive geriatric assessment, but this has not been adopted widely in oncology practice.13 Conversely, dose reductions in chemotherapy due to the risk of myelosuppression in older patients that are based on age alone are not appropriate, because otherwise healthy older patients may obtain equal benefit from chemotherapy if they are treated as aggressively as younger patients.8 The National Comprehensive Cancer Network, instead, recommends giving patients age ≥ 70 years prophylactic hematopoietic growth factors to improve the therapeutic index of myelosuppressive chemotherapy, such as CHOP, in this population (Table 2).14 In addition, the clinical evidence supports recognizing the elderly as one of the special populations for which the guidelines of the American Society of Clinical Oncology (ASCO) suggest considering primary prophylaxis with growth factors in conjunction with myelosuppressive chemotherapy.15,16

Another patient-specific risk factor for later neutropenic complications is the patient’s early hematologic response to chemotherapy.3 This has the advantage of being a functional assessment of the effect of treatment on the patient’s bone marrow. The first cycles of treatment can show which patients are at risk, after which dose modifications or prophylactic growth factors are often used, thus reducing the risk in later cycles. Studies have shown the predictive value of the first-cycle nadir in leukocyte counts17,18 and decreases in hemoglobin levels18 for predicting neutropenic complications in later cycles. This conditional approach to determining which patients are at greater risk may be useful with regimens with which the risk in the early cycles is low. With many regimens, however, most of the neutropenic complications may occur in the early cycles (see below). For this reason, unconditional strategies based on pretreatment risk factors would be preferable for determining which patients are at greater risk, because they would lead to the use of supportive measures before most complications would occur, not after they had occurred.

The use of growth factors early in chemotherapy also affects the risk of neutropenic complications both in the initial cycle and in subsequent cycles of therapy. Grade 4 neutropenia occurred during the first cycle in ∼ 80% of patients with advanced breast carcinoma who were treated with docetaxel and doxorubicin in 2 clinical trials and declined to ∼ 40% by Cycle 4.19,20 Those patients were given either pegfilgrastim or daily injections of filgrastim, and it appears that the early administration of these growth factors affected the risk of neutropenia in later cycles, perhaps due to a priming effect on myeloid precursors.21 This pattern of reduced severity of neutropenia in the later cycles also was seen in pivotal trials of filgrastim in the U.S. and Europe, in which the duration of Grade 4 neutropenia was reduced from 3 days in Cycle 1 to 1 day in the later cycles.22,23 In contrast, in the placebo arms of these randomized studies in patients with lung carcinoma, the duration of Grade 4 neutropenia was 6 days across all cycles.

Regimen-specific risk factors
The chemotherapy regimen is one of the primary determinants of the risk of neutropenia, and some regimens are more myelotoxic than others. For example, combined cyclophosphamide, methotrexate, and 5-fluorouracil is less toxic than AC or combined cyclophosphamide, doxorubicin, and 5-fluorouracil and, consequently, often is preferred in elderly patients with breast carcinoma.24 To determine more accu-

### TABLE 2
**National Comprehensive Cancer Network Guidelines to Minimize Toxicity of Chemotherapy in Elderly Patients (≥ 70 Years)**

| Use hematopoietic growth factors in patients treated with combination chemotherapy with dose intensity equivalent to that of CHOP |
| Maintain hemoglobin level ≥ 120 g/L with erythropoietin |
| Consider adjusting doses of renally excreted drugs according to patient’s glomerular filtration rate |

CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone.

* * *
rately the risks associated with commonly used chemotherapy regimens, we recently surveyed the literature for the rates of neutropenia that were reported in randomized clinical trials of chemotherapy.\(^{25}\) We limited our survey to trials in patients with early-stage breast carcinoma and NHL, because these malignancies can be treated with curative intent with appropriate doses of chemotherapy. We found that the rates of myelosuppression and associated complications were reported infrequently. Furthermore, when reported, the rates for the same and similar regimens varied greatly, making it difficult to determine the actual risk.\(^{25}\) In the absence of clearly defined, regimen-specific risks, assessing the patient-specific risk factors in each patient may have greater value in determining in which patients supportive intervention would be appropriate.

The risk of neutropenia also has been related to the phase of therapy, with the perhaps counterintuitive, but well supported, conclusion that the greatest risk is in the earliest cycles. In 1 study in older patients with aggressive NHL who were treated with CHOP, 63% of the toxic deaths (mostly neutropenia-related) occurred in the first cycle of the 6-cycle to 8-cycle regimens (Fig. 2).\(^{26}\) A recent practice pattern study also showed that 65% of the hospitalizations for FN occurred in the first 2 cycles of chemotherapy for intermediate-grade NHL.\(^{27}\) In addition, in patients with advanced breast carcinoma who were treated with docetaxel and doxorubicin in 2 clinical trials, approximately 75% of the episodes of FN during the course of chemotherapy occurred in the first cycle.\(^{28}\)

Again, with a secondary prophylaxis strategy of wait-

Consequences of FN

The relation between the neutrophil count and the risk of infection has been known for more than 30 years.\(^{1}\) In addition, for nearly as long, it has been known that the prompt administration of empiric antibiotics, before laboratory confirmation of infection, is crucial in patients with FN, because infection can progress rapidly in these patients.\(^{29}\) Indeed, there is a 50% likelihood of an established or occult infection in patients with FN, and 20% of febrile patients with severe neutropenia (ANC < \(0.5 \times 10^9/L\)) are bacteremic,\(^{30}\) but the initial phase of infection often is not apparent clinically because of the lack of an inflammatory response. The sites of infection most often are in the alimentary tract, the lungs, and the skin, where invasive procedures provide entry for pathogens.\(^{30,31}\)

The most common organisms that infect patients with cancer and neutropenia in general, as well as the most common causes of bacteremia, are gram-negative rods, such as Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa, and aerobic, gram-positive cocci, such as Staphylococcus and Streptococcus species and Enterococcus.\(^{30,31}\) There has been a shift in the most common infectious agents since the widespread use of effective empiric antibiotics, from highly lethal, gram-negative bacilli to more indolent, gram-positive bacterial and fungal pathogens.\(^{32}\)

The Infectious Diseases Society of America (IDSA) has published guidelines for the treatment of neutropenic patients with cancer who become febrile.\(^{31}\) For the majority of patients with FN, hospitalization with intravenous antibiotics remains the standard of care. Some low-risk patients may be managed with oral antibiotics on an outpatient basis,\(^{33–36}\) but strict adherence to a standard of care and close follow-up are needed in this population. The antibiotics must be chosen carefully, taking into consideration the institution’s patterns of infection and antibiotic susceptibility as well as patient-specific factors, such as drug allergies, and the potential for toxicities, such as renal toxicity from drug interactions or excessive serum levels of the drugs. Moreover, hospitalized patients are exposed to additional pathogens and are at risk for nosocomial infections. Hospitalization with FN continues to be associated with significant mortality (8% of more than 40,000 nontransplantation adult patients with cancer in a recent analysis of 1995–2000 discharge data from the University HealthSystems Consortium\(^{37}\)) as well as possible detrimental effects on...
patients' clinical outcomes because of the discontinuation of chemotherapy or substantial delays or reductions in its delivery. Indeed, a recent analysis that linked data from the Surveillance, Epidemiology, and End Result Program of the National Cancer Institute to data from a practice pattern survey in patients with aggressive NHL found a significant association between the occurrence of FN, reduction in the number of cycles of CHOP delivered, and lower 5-year overall survival.

In addition to its clinical impact, FN has economic consequences that are related to hospitalization and time lost from work. Indeed, 2 recent economic analyses have reported mean lengths of stay in hospitalizations for FN of approximately 10 days, with mean total costs of > $20,000. In addition, a study that examined the indirect, nonhospital costs of hospitalizations for FN estimated these at approximately $5000 per hospitalization, with the majority of this amount accounted for by lost wages. Finally, FN directly affects patients' quality of life. The hospital environment, separation from family members; the fear of infection, failure of cancer therapy, and death; and invasive procedures in the hospital all contribute to a substantial reduction in the well being of patients.

Consequences of Afebrile Neutropenia
The presence of Grade 4 neutropenia after chemotherapy and the absence of fever or other signs of infection should alert the clinician to the patient’s risk for developing fever and infection. It is recognized widely that profound neutropenia (ANC < 0.1 x 10^9/L) places a patient at very high risk for serious infectious complications. Prophylactic antibiotics may be prescribed in this setting, but the frequency of this practice is not known. Some oncologists maintain that such use of prophylactic antibiotics is warranted by the serious risk of infection, but infectious disease specialists generally warn against the use of empiric antibiotics, fearing the promotion of antibiotic-resistant bacterial and fungal strains. The 2002 guidelines of the IDSA for the prophylactic use of antimicrobial agents in afebrile neutropenic patients state that concern about the problem of emerging drug-resistant bacteria and fungi due to extensive antibiotic use, plus the fact that such prophylaxis has not been shown to consistently reduce mortality rates, leads to the recommendation of avoiding routine prophylaxis with these drugs in neutropenic patients, with the exception of use of trimethoprim-sulfamethoxazole for patients at risk for *Pneumocystis carinii* pneumonia.

Another response to neutropenia is the therapeutic use of colony-stimulating factor (CSF), i.e., as treatment after the patient has become neutropenic. The extent of this practice was shown in a retrospective survey of community oncology practice patterns that found a wide range in the number of days after chemotherapy that the use of CSF was initiated. In more than two-thirds of patients who were treated with CSF (27% of all patients), the therapy was initiated 5 or more days after the chemotherapy, and it was started in 32% of patients on Days 10–14, the expected time of the ANC nadir. CSF treatment for afebrile neutropenia clearly is not as effective in preventing neutropenic complications as CSF prophylaxis before neutropenia develops. In a randomized, controlled trial, Hartman and colleagues found that treating established neutropenia with CSF failed to provide the benefits achieved with prophylactic CSF.

Chemotherapy dose modifications—delays of the next cycle and/or dose reductions—are another common consequence of neutropenia and are implemented due to a slow recovery of the bone marrow after a previous course of chemotherapy. Recent practice pattern studies have shown the extent to which community oncologists delay and reduce the doses of the chemotherapy. In 1 study, there were neutropenia-related dose modifications in 28% of patients with early-stage breast cancer (more than once in 61% of these patients), and < 85% of the reference chemotherapy dose intensity was delivered in 30% of patients. In another, even larger survey of practice patterns in more than 20,000 patients, also in the setting of adjuvant chemotherapy for breast carcinoma, the average relative dose intensity was < 85% in more than half (58%) of patients. Dose delays and reductions were even more likely in elderly patients (age ≥ 65 years), with two-thirds (67%) of those patients receiving an average relative dose intensity of < 85%.

Dose delays and reductions also may be instigated automatically in certain settings, such as in elderly patients, because of concerns about a greater risk of toxicity. In light of the well-documented lower survival in some patients who are treated with less than the full doses of the chemotherapy, other options should be considered before reducing dose intensity. The recently reported results of a large randomized trial demonstrating improved survival with dose-dense (14-day) adjuvant regimens versus the standard 21-day regimens in patients with early-stage breast carcinoma provide further support for the hypothesis that delivered dose intensity is an important determinant of outcome. Finally, it is interesting to note that a higher incidence of myelosuppression, possibly correlated with greater dose intensity, was associated with greater survival in patients with early-stage breast
CARCINOMA who were treated with adjuvant chemotherapy (Fig. 3).51

The extent to which the doses of chemotherapy were modified in major randomized clinical trials also was explored in the aforementioned analysis of the literature on chemotherapy in patients with early-stage breast carcinoma and NHL.52 Data on the received dose intensity were reported in various ways, and approximately 40% of the studies did not report complete information concerning the delivered dose intensity.52 The majority of the studies described the protocols by which the doses could be modified, primarily in response to hematologic toxicity, but a significant portion of those studies did not report what the actual delivered dose intensity was as a result of these dose modifications. The true myelotoxic potential of a regimen cannot be determined from a report without data on both the incidence of neutropenic complications and the delivered dose intensity that was associated with those complications.

Diminished quality of life is another possible consequence of febrile neutropenia, and it is being explored in current research. Recent inquiries into the impact of neutropenia on the quality of life of patients with cancer have found that neutropenia affects patients before infection becomes apparent. In the development and validation of a neutropenia-specific quality-of-life instrument, 2 subscales became apparent, fatigue (distinct from that associated with anemia) and worry, which indicates that neutropenia affects specific domains of clinical and emotional well being.53 Furthermore, data from a large community setting showed a significant association between the depth of the ANC nadir and the decline in quality-of-life measures.54,55 In addition, there are numerous anecdotal reports that patients simply do not feel as well when their ANC is low. To our knowledge to date, there are no conclusive data showing that neutropenia impairs the quality of life of patients with cancer; however, additional studies in this area are needed. Quality of life has become a larger issue in oncology practice as cancer therapy evolves toward the management of chronic disease and as patient advocacy groups have begun to emphasize decision-making approaches that consider more than just well established clinical and economic outcomes.41

In addition to the direct effects of neutropenia on the risk of infection and quality of life, there is evidence that neutropenia is associated with exacerbations of other adverse effects of chemotherapy. A retrospective analysis of data from a study in patients with advanced breast carcinoma found that the incidence and the timing of nonneutropenic adverse events (e.g., abdominal pain, anorexia, fatigue, and emesis) were associated significantly with the incidence and timing of FN primarily occurring during Days 5–10 of the chemotherapy cycle.56 Whether the occurrence of neutropenia predicts the occurrence of other adverse events or whether neutropenia itself has a causal role in these events is not clear. However, in the current study, the greater incidence, severity, and duration of these common adverse events in patients with FN were independent of factors that increased the risk of FN.

The True Cost of Neutropenia

Significant costs are incurred when FN develops in a patient treated with chemotherapy, as mentioned above. These costs include both direct medical costs and indirect costs that are borne by the patient and his or her family. Economic analyses have estimated the different types of aggregate costs that are incurred in hospitalization for FN, and these can be weighed against the costs of the use of prophylactic CSFs. An early cost-minimization analysis calculated that, when the risk of FN was about 40%, the cost of universal prophylactic granulocyte-CSF was equalled by the reduction in the costs of hospitalization for FN.57 This threshold remains within the 2000 ASCO guidelines for the use of CSFs.15 More recent economic analyses suggest that this threshold value should be reevaluated. In 1 such economic analysis, the daily institutional costs in 1105 patients with cancer treated with chemotherapy who were admitted in 1994 and 1995 to the H. Lee Moffitt Cancer Center with FN were estimated.58 The patients were classified into a group who

![Figure 3. Actuarial survival in patients with breast carcinoma who were treated with cyclophosphamide, methotrexate, and 5-fluourouracil, by the presence or absence of Grade 3 or 4 myelosuppression. Adapted from Mayers C, Panzarella T, Tannock IF. Analysis of the prognostic effects of inclusion in a clinical trial and of myelosuppression on survival after adjuvant chemotherapy for breast carcinoma. Cancer. 2001;91:2246-2257.](image-url)
had a primary diagnosis of FN and hospital stays that averaged 8 days and a group that had either a primary or a secondary diagnosis of FN with other comorbidities and hospital stays that averaged 16 days. The average daily costs were similar in the 2 groups ($1675 and $1892), although the resulting total cost was greater for the second group with longer stays. These cost findings have been confirmed in another recent analysis of data from the 1995–2000 discharge summaries of the 115-member University HealthSystems Consortium on more than 55,000 hospitalizations for FN.37 With these updated and more inclusive data on costs, the threshold at which the use of prophylactic CSF becomes cost-neutral is a 23% risk for FN (Fig. 4).58,59 Moreover, the use of a treatment model with an outpatient option for low-risk patients had little effect on the cost-minimization threshold risk, because low-risk patients already have a minor impact on costs, which are dominated by the higher risk patients with comorbidities and long hospital stays.60

Another economic analysis of adjuvant chemotherapy for patients with early-stage breast carcinoma used a conditional risk model based on the first-cycle ANC nadir and drop in hemoglobin level to determine whether prophylactic CSF would be used in the subsequent cycles.18 If CSFs were used in the 50% of patients with the highest risk of FN, then the estimated cost per life-year saved was about $34,000 for a patient age 55 years. This estimate is based on assumptions about the effect of receiving full-dose chemotherapy on overall survival, and it declines as smaller percentages of the highest risk patients are given CSF. The cost per life-year saved with the 50% cut-off value is within the range of costs for other common medical conditions (Fig. 5).59,61

The aforementioned cost estimates include both direct (e.g., pharmacy) and indirect (e.g., nursing) medical costs but not nonmedical costs that patients incur, such as time lost from work and transportation costs. These costs have been estimated in women with gynecologic malignancies,40 and other surveys are planned or are underway. A true accounting of these out-of-pocket costs, in addition to updates of the medical costs, would help in determining when to use prophylactic CSF by adding a societal perspective to the debate. Focusing on only part of the costs, such as the direct medical expenses, may lead to cost shifting and fails to consider the actual financial impact on all affected parties.

Models for Predicting Risks in Individual Patients
It has been shown that prophylactic CSF reduces the duration of severe neutropenia and, thus, the risk of FN,19,20–23,62 but its use in all patients is not considered cost-effective. Ideally, these drugs would be targeted to patients who are at greater risk of neutropenic complications and, thus, would be more likely to benefit from them. A risk-prediction model would include an inventory of patient characteristics that have been associated with the risk of neutropenic complications in a given disease and treatment setting. Several studies have found a variety of risk factors in many clinical settings, as described above. Compiling these factors into a comprehensive risk model would make it possible for clinicians to estimate better the likelihood of neutropenic complications in individual patients and, thus, use appropriate prophylactic measures.

Risk models, as discussed above, can be based on unconditional factors, such as pretreatment measures, or on conditional factors, such as the patient’s hematologic response in the first cycle of chemotherapy. Oncologists often informally use the conditional model, in which CSF is used to treat patients who have had an episode of FN. Unfortunately, this can result in subjecting many patients to complications that could have been prevented. Unconditional models have the advantage of identifying those patients who are likely to have neutropenic complications before they are exposed to chemotherapy and its myelosuppressive effects.

With many predictors of neutropenic complications now identified, the task remains to test their validity and practicality for clinical use. An ideal risk model could be constructed from a prospective registry of patients treated with chemotherapy in community and academic settings, in which data on a variety of clinical measures could be collected along with
pretreatment and midcycle ANC values. A prospective registry for this purpose was established in 2001, and its initial findings are expected to be available in 2004.52,63

Conclusions

Despite the fact that neutropenia is the major dose-limiting toxicity of cancer chemotherapy, the epidemiology of CIN and its clinical and economic consequences only recently have begun to be elucidated. With additional research into factors that reliably predict neutropenic complications, researchers may be able to develop a predictive model that clinicians can incorporate easily into their everyday practice. The goal of these efforts is to accurately assess a patient’s risk for the development of neutropenic complications during the course of chemotherapy, so that appropriate prophylactic measures can be implemented before the first cycle of treatment in those patients who are at highest risk and so that such measures can be avoided in patients at lowest risk. This goal likely will be achieved in the near future, ushering in a new era in the cost-effective use of hematopoietic growth factors.

REFERENCES


