How We Treat Febrile Neutropenia in Patients Receiving Cancer Chemotherapy

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Fever in the setting of neutropenia should be considered a medical emergency requiring immediate evaluation and administration of empiric broad-spectrum antibiotics.¹ Early studies demonstrated that patients with febrile neutropenia not promptly treated often experience a rapidly fatal outcome, most notably because of Gram-negative bacteremia.² Recent studies of unselected patients with cancer with febrile neutropenia have reported rates of mortality of 5% to 20%, increasing in direct proportion to the number of major infectious complications and comorbid medical conditions (Fig 1).^{3,4} In fact, mortality in excess of 50% despite prompt antibiotic treatment has been reported in neutropenic patients presenting with septic shock or pneumonia and documented bacteremia.⁴⁻¹² Although improved supportive care has reduced the mortality associated with febrile neutropenia, it remains a major cause of morbidity, mortality, and cost among patients with cancer and may limit the delivery of full-dose chemotherapy on schedule.⁴ The risk of febrile neutropenia increases in direct proportion to the severity and duration of neutropenia and occurs most frequently early in a course of chemotherapy.¹³ Early neutropenic events often prompt chemotherapy dose reductions or delays or the addition of prophylactic myeloid growth factors or antibiotics in subsequent treatment cycles.^{14,15} Optimal management of patients with cancer at risk for febrile neutropenia includes immediate evaluation, prompt initiation of broad-spectrum antibiotics, and careful monitoring in those with documented febrile neutropenia as well as the appropriate use of myeloid growth factor prophylaxis in patients at increased risk, consisting of primary prophylaxis starting in cycle 1 when risk is > 20% and an equivalent but less myelosuppressive regimen is not available or secondary prophylaxis in cycle after a febrile neutropenia event.^{1,16,17}

Clinical and Laboratory Evaluation

Patient evaluation should include a complete history and physical examination, with particular attention directed to the oropharynx/periodontium, sites of catheters and recent procedures, the perineum/perirectal area, nail beds, nares, and external auditory canals. Laboratory evaluation should include a complete blood cell count with differential, basic chemistries and liver function tests, and cultures from all potential sites, along with at least two sets of blood cultures from peripheral

Figure 1. Risk of mortality among patients with cancer hospitalized with febrile neutropenia based on the reported number of major associated comorbidities and infectious complications, including Gram-negative or Gram-positive sepsis, invasive aspergillosis or candidiasis, pneumonia, hypotension, pulmonary embolism, or underlying diseases of the heart, lung, kidney, liver, or CNS. Data adapted.⁴

veins or one set each from a peripheral vein and a central venous catheter. Although a specific organism will not be found in half of patients with fever and neutropenia, a presumptive diagnosis of infection is important because of the risk of withholding antimicrobial therapy. Chest radiographs are not mandatory but should be obtained when clinical evidence of a respiratory infection is present. We recommend a computed tomography scan of the chest to detect signs of fungal infection in high-risk patients with unexplained fever who have not responded to 3 to 5 days of antibacterial therapy.¹⁸

Initial Antibiotic Therapy for Febrile Neutropenia

Currently, Gram-positive organisms are the predominant bacterial pathogens in this setting, with coagulase-negative staphylococci, *Staphylococcus aureus*, *Enterococcus spp.*, and viridans group streptococci being isolated most often.^{11,19} Among Gram-negative bacilli, *Escherichia coli*, *Klebsiella spp.*, and *Pseudomonas aeruginosa* remain the predominant species, although other *Enterobacteriaceae*, *Stenotrophomonas maltophilia*, and *Acinetobacter spp.* are isolated frequently.^{20,21} Approxi-

Requirements for a Successful Program of Outpatient Therapy for Low-Risk* Neutropenic Patients With Fever

- Dedicated team of health care providers (physicians, nurses, pharmacists, infusion therapists, midlevel providers) familiar with risk-based therapy
- Adequate institutional infrastructure
- Availability of real-time local epidemiologic and susceptibility/resistance data
- Adequate monitoring and follow-up (eg, febrile neutropenia clinic)
- Motivated, compliant patients and families and other caregivers (ie, careful patient selection)
- Adequate transportation and communication for patients, and proximity (eg, 30-mile radius) to the cancer treatment center
- Access 24 hours a day to management team (eg, hotline, emergency departments, pharmacy, infusion, other support services)

*Low-risk patient: ambulatory with good performance status, no serious comorbidity, and anticipated short duration of severe neutropenia or a Multinational Association of Supportive Care in Cancer risk index score of ≥ 21 .²⁸

mately 10% to 15% of bacteremias are polymicrobial, with Gram-negative bacilli being isolated from more than 80% of these infections.^{22,23} Resistance to common antimicrobial agents is being encountered increasingly at most centers, in part because of heavy usage of these agents.²⁴ Of particular concern, more than 50% of *Staphylococcus aureus* isolates are methicillin-resistant *Staphylococcus aureus*, and vancomycin resistance among enterococci constitutes nearly 30% of enterococcal isolates nationwide. Additionally, reduced susceptibility or resistance to penicillin is being reported increasingly with viridans group streptococci and in *Streptococcus pneumoniae* isolates.^{25,26} Invasive fungal infections are most often seen in patients with prolonged neutropenia and after stem-cell transplantation.²⁷

Empiric, broad-spectrum antibiotic therapy should be administered promptly to all patients with febrile neutropenia.¹ Patient risk should be quickly assessed to determine the number and spectrum of the antibiotic regimen (monotherapy or combination therapy), route of administration (parenteral or oral), and location of treatment (hospital *v* outpatient).^{28,29} Low-risk patients may be defined as ambulatory patients with good performance status and no serious comorbidity and anticipated short duration of severe neutropenia or those with an index score of 21 or more using the predictive model developed and validated by the Multinational Association for Supportive Care in Cancer (Table 1). The development of reasonably accurate risk prediction rules and the availability of suitable antimicrobial agents, ambulatory centers, and evidence of safety and efficacy have made the treatment of low-risk patients with febrile

Table 1. MASCC Scoring Index Identifying Low-Risk Febrile Neutropenic Patients

Characteristic	Score
Burden of illness	
No or mild symptoms	5
Moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection	4
No dehydration	3
Outpatient at onset of fever	3
Age < 60 years	2

NOTE. Score range, 0-26; risk score ≥ 21 indicates low-risk patient for medical complications and mortality.²⁸

Abbreviation: MASCC, Multinational Association of Supportive Care in Cancer.

neutropenia in the ambulatory setting feasible.^{30,31} Such an approach requires appropriate infrastructure and a multidisciplinary team of health care providers. Patients managed in the ambulatory setting should be tracked for readmission, important complications, or mortality. Many clinicians prefer an initial 24- to 48-hour period of hospitalization for evaluation and initiation of empiric broad-spectrum antibiotics followed by outpatient treatment for the duration of the neutropenic episode.^{32,33}

Although there is little to distinguish the many empiric regimens that have been studied in randomized controlled trials, patients at higher risk should be hospitalized immediately to receive parenteral antibiotic therapy.¹ Monotherapy with an antipseudomonal beta-lactam, such as the extended spectrum cephalosporins or a carbapenem, is adequate for uncomplicated episodes. Combination regimens with a beta-lactam and either an aminoglycoside or a fluoroquinolone should be considered in the treatment of complicated infections, including those with pneumonia or neutropenic enterocolitis or in the setting of hypotension or shock. The myeloid growth factors should not be used routinely in the treatment of established febrile neutropenia, although they may be considered in patients at increased risk for serious complications including mortality.^{16,34}

Patients who defervesce rapidly without identification of a specific organism should be continued on antibiotics through the period of neutrophil recovery.¹ When a specific organism has been identified, patients should be treated for 7 to 14 days. Vancomycin should be considered with catheter-related infection, Gram-positive organisms on blood culture, hypotension, mucosal damage, or colonization with penicillin-resistant pneumococci or methicillin-resistant *Staphylococcus aureus*.¹ For neutropenic patients with persistent fever after 3 to 5 days, empiric antifungal therapy may be considered.¹

Prevention of Febrile Neutropenia

Strategies aimed at reducing the risk and consequences of febrile neutropenia should include appropriate antimicrobial stewardship, which significantly limits the emergence of resistant

Risk-Based Treatment of Febrile Neutropenic Patients: Common Regimens for Empiric Antibiotic Therapy

Regimens Used in Low-Risk Patients

Oral Regimens

- Ciprofloxacin + amoxicillin/clavulanate
- Ciprofloxacin + clindamycin or azithromycin
- Moxifloxacin or levofloxacin

Parenteral Regimens

- Ceftriaxone ± amikacin
- Aztreonam + clindamycin or fluoroquinolone
- Ceftazidime (or other cephalosporins)

Regimens Used in High-Risk Patients

Monotherapy

- Extended-spectrum cephalosporins (cefepime, ceftazidime)
- Carbapenems (imipenem, meropenem)
- Other agents (piperacillin/tazobactam)

Combination Regimens

- Aminoglycoside + extended-spectrum cephalosporins
- Aminoglycoside + carbapenem or piperacillin/tazobactam
- Vancomycin (or linezolid) + extended-spectrum cephalosporin, or carbapenem, or piperacillin/tazobactam, or aztreonam
- Vancomycin + fluoroquinolone or aztreonam (beta-lactam allergic patients)

microorganisms while preserving the utility of available antimicrobial agents.^{35,36} Prophylactic antibiotics have demonstrated some efficacy in reducing the risk of febrile episodes in neutropenic patients with cancer; however, they have been associated with additional toxicity and the emergence of antibiotic-resistant bacteria.^{1,37} Although potentially efficacious in high-risk patients and in those who develop serious neutropenic complications despite hematopoietic growth factor support, the Infectious Disease Society of America and ASCO recommend against routine antibacterial prophylaxis.^{1,16}

The myeloid growth factors administered prophylactically after cancer chemotherapy but before the onset of neutropenia have been shown to reduce the risk of febrile neutropenia and documented infection.³⁸ A meta-analysis of randomized controlled trials of granulocyte colony-stimulating factor has also demonstrated a significant reduction in infection-related and early all-cause mortality while improving delivery of chemotherapy dose intensity.³⁹ Current guidelines recommend primary prophylaxis with a myeloid growth factor in patients with

cancer receiving chemotherapy associated with a 20% or greater risk of febrile neutropenia as well as in those with certain high-risk factors.^{16,17,40}

Conclusion

Myelosuppression and its complications, including febrile neutropenia, continue to represent major dose-limiting toxicities associated with systemic cancer chemotherapy resulting in considerable morbidity, mortality, and costs. The management of febrile neutropenia requires immediate evaluation, risk assessment, and treatment with empiric broad-spectrum antibiotics. Efforts to reduce the risk of febrile neutropenia should be based on appropriate antimicrobial stewardship and the prophylactic use of myeloid growth factors where indicated.

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