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Review Article

Febrile Neutropenia in Thoracic Malignancies

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Abstract

Febrile neutropenia (FN) is a critical medical condition characterized by fever resulting from infectious or non-infectious etiologies. This condition is accompanied by a massive decline in blood neutrophil counts, rendering patients highly susceptible to life-threatening infections. The incidence of FN varies depending on the type of malignancy and the use of chemotherapy regimens; patients with leukemia or lymphoma are at a significantly elevated risk. The pathophysiology of FN involves chemotherapy-induced myelosuppression, leading to reduced neutrophil production and decreased immune response to infection. The etiology of FN is often associated with infection from gram-negative and gram-positive and, less frequently, fungal and viral infections. Diagnostically, the Multinational Association for Supportive Care in Cancer (MASCC) score and the Clinical Index of Stable Febrile Neutropenia (CISNE) are utilized for risk stratification and to determine appropriate management strategies. Management of FN involves the early administration of antibiotics and hospitalization based on the patient's risk profile. Preventive measures include the use of prophylactic antibiotics and myeloid growth factors (MGFs) in high-risk patients to reduce infection risks and improve clinical outcomes.

Keywords: Chemotherapy, Febrile Neutropenia, MASCC/CISNE Score, Myeloid Growth Factor (MGF), Neutropenia

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Introduction

Febrile neutropenia (FN) is a medical oncologic emergency that frequently occurs in patients with compromised immune systems. This condition is commonly associated with individuals undergoing cytotoxic chemotherapy for cancer treatment. If not managed appropriately, FN may progress to multi-organ damage and clinical deterioration. It is characterized by the presence of fever, which can arise from infectious or non-infectious causes, accompanied by a reduction in blood neutrophil count below the normal threshold. Neutrophils are a part of white blood cells that play a critical role in the body's defense against infection. A marked decline in neutrophil levels places patients at a high risk of developing severe and potentially life-threatening infections.[1]

Febrile neutropenia is the most frequent condition that occurs in patients with cancer, including those with lung cancer. This condition occurs particularly in individuals receiving cytotoxic chemotherapy. The incidence of FN varies according to the type of malignancy and the chemotherapy protocol used. Patients with hematologic malignancies such as leukemia and lymphoma generally have a higher risk than those with most other cancers. Clinically, FN is highly significant because it often requires hospitalization and urgent medical management and may lead to dose reductions, delays, or modifications of the ongoing cancer treatment regimen. This literature review discusses febrile neutropenia with a focus on its pathophysiology, etiology, diagnosis, management, prognosis, and preventive strategies. By examining these aspects in greater detail, the review aims to support better clinical decision-making and ultimately improve outcomes in patients who develop this condition.[1]

Definition and Epidemiology

Neutropenia is a condition when the absolute neutrophil count falls below 1,500/µL in humans older than one year.[2] Neutropenia is classified into four categories based on the absolute neutrophil count, which are mild, moderate, severe, and agranulocytosis. Mild neutropenia has an absolute neutrophil count of 1,000–1,499/µL, moderate neutropenia 500–999/µL, severe neutropenia 200–499/µL, and

agranulocytosis has a count below 200/μL. Febrile neutropenia is a condition of fever that is characterized by an oral temperature above 38.3°C in a single measurement or 38.0°C in two measurements with a 2-hour interval, accompanied by a decrease in absolute neutrophil count below 500/μL or below 1,000/μL that is predicted to decrease below 500/μL within 48 hours.[2]

The incidence of FN in lung cancer patients reaches 38%. This incidence is influenced by the type of chemotherapy drugs used by the patient and the performance status of the patient.[3] A retrospective study found that 58.3% of advanced-stage non-small cell lung cancer (NSCLC) patients undergoing platinum-based chemotherapy regimens experienced neutropenia, and 8.3% of them experienced FN.[4] In study by Rodrigues et al., the incidence of FN in lung cancer patients receiving carboplatin/etoposide therapy was 26.2%, carboplatin/pemetrexed 23.8%, carboplatin/vinorelbine 14.3%, and carboplatin/gemcitabine 14.3%.[5]

In a study involving germ cell cancer patients and mediastinal tumors, FN occurred in approximately 34.7% of patients who did not receive granulocyte-colony stimulating factor (G-CSF) prophylaxis; however, the incidence decreased to 11% in those who received G-CSF prophylaxis.[6] In patients with small cell lung cancer (SCLC), FN is observed in around 20.4% of patients. This incidence could increase to 54.2% in SCLC patients who use proton pump inhibitors (PPIs) or potassium-competitive acid blockers (PCABs) and have a body mass index (BMI) below 22.5 kg/m².[7]

Pathophysiology

Neutrophils are white blood cells important in the patient's defense against bacterial and fungal infections. Neutrophils are produced in the bone marrow through hematopoiesis, with hematopoietic stem cells differentiating into mature neutrophils under the regulation of growth factors such as G-CSF. Neutrophils have a segmented nucleus and specific granules containing antimicrobial enzymes. The primary function of neutrophils is phagocytosis, which involves engulfing and digesting pathogens, while chemotaxis is the movement toward infection sites in response to chemical signals. Additionally, neutrophils can form extracellular traps (NETs) to trap and kill pathogens. They have a short lifespan, lasting approximately 6 hours to several days, and after completing their function, undergo apoptosis and are eliminated by macrophages.[2]

Neutrophils are the first immune cells to migrate to sites of infection during acute inflammatory responses. They release cytokines and chemokines to draw in more immune cells and help the immune response work together. They also interact with macrophages, dendritic cells, and lymphocytes to strengthen the immune response. Chemotherapy drugs such as platinum compounds and etoposide work by destroying rapidly dividing cells, including cancer cells and hematopoietic cells in the bone marrow. This leads to decreased production of white blood cells, particularly neutrophils, which are a major component in fighting infection. In neutropenic patients, infections can spread rapidly, causing delayed inflammatory responses and fever occurring when the infection has become severe.[8,9]

Etiology

In patients with thoracic malignancies, FN is commonly caused by bacteria, viruses, and fungi. The most common infection sites are the gastrointestinal tract, lungs, and skin. The most common organisms causing infection and bacteremia are gram-negative rod bacteria, such as *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa*. This is followed by gram-positive aerobic cocci bacteria, such as *Streptococcus sp.*, *Staphylococcus sp*., and *Enterococcus*. These gram-positive cocci bacteria are usually found in patients with prolonged central venous catheter use.[10]

Anaerobic microorganisms and polymicrobial infections rarely cause FN. Anaerobic microorganisms and polymicrobial infections can cause FN in special situations, for example, abscesses, enteritis, and other causes. Recently, there has been an increase in strains resistant to extended-spectrum beta-lactamase (ESBL) or carbapenemase. The likelihood of antimicrobial resistance is influenced by prior bacterial colonization, invasive procedures, previous antibiotic use, prior hospitalizations, chronic comorbid conditions, and local resistance patterns.[10]

Invasive fungal infections (IFI) rarely cause FN in patients with thoracic malignancies (<8%). Fungi most commonly causing infection in this condition include *Candida spp*., *Aspergillus spp*., and *Pneumocystis jirovecii*. Candida and Aspergillus are the primary pathogens associated with IFI. Risk factors for the incidents of IFI include a history of prior antibiotic use, a history of more than one cycle of chemotherapy, a history of high-dose corticosteroids (dose equivalent to or exceeding 20 mg/day use of prednisone for 4 weeks or longer), extensive mucositis, a history of central venous catheter use, and neutropenia for more than 7 days; which are responsible for most cases of candidemia, with an increase in infections caused by fluconazole-resistant species (such as *Candida glabrata* and *Candida krusei*).[11]

Seasonal respiratory viruses are commonly transmitted through contact with infected individuals, whereas reactivation of latent viruses or related pathogens, which is frequent in acute leukemia or bone marrow transplant settings, only rarely leads to FN in patients with thoracic malignancies.[10] Some respiratory viral infections include rhinovirus, respiratory syncytial virus (RSV), and coronavirus, including SARS-CoV-2. Research shows that rhinovirus and RSV are the most common causes among viral infections that cause FN in patients with thoracic malignancies.[11]

Assessment and Classification

In the diagnosis and classification of FN, several assessment tools can be used. The Multinational Association

for Supportive Care in Cancer (MASCC) scoring system can be combined with the Clinical Index of Stable Febrile Neutropenia (CISNE). The MASCC scoring system can be used widely to identify low-risk FN patients who may be managed safely in the outpatient setting. However, several studies indicate that its use may be associated with potential risks, particularly when it guides early hospital discharge decisions. Recent evidence suggests that combining MASCC with the CISNE score yields better accuracy in predicting poor outcomes, with CISNE offering higher specificity for identifying truly low-risk patients, although its sensitivity is lower than that of MASCC. Furthermore, incorporating procalcitonin as a biomarker can enhance the precision of mortality prediction in patients managed outside the hospital environment.[12]

The MASCC score is a clinical assessment tool used to estimate the risk of serious complications in patients with febrile neutropenia (FN). In cases of chemotherapy-induced neutropenia, this tool helps clinicians identify low-risk patients who can be safely managed in an outpatient setting. The MASCC score includes several parameters, such as the severity of the underlying illness, overall performance status, history of chronic lung disease or fungal infection, the presence of hypotension or dehydration, outpatient versus inpatient status at the onset of fever, and age. In general, a MASCC score higher than 21 indicates a low risk of severe complications and allows patients to be considered for outpatient care, whereas a score below 21 reflects a higher risk and the need for closer monitoring or inpatient management. Multiple studies have shown that the MASCC score has relatively high sensitivity for predicting critical complications, enabling it useful for ruling out low-risk patients, although its specificity may be less than optimal in certain clinical scenarios. This limitation is particularly evident in patients with severe infections such as sepsis caused by gram-negative bacteria, in whom the risk of rapid clinical deterioration and mortality remains high despite risk stratification.[12]

Table 1. MASCC Scoring System[8]

Characteristic	Score
Hypotension (systolic ≥90 mmHg)	No : 5 points Yes : 0 points
Active Chronic Obstructive Pulmonary Disease	No : 4 points Yes : 0 points
Dehydration requiring fluid resuscitation	No : 3 points Yes : 0 points
Clinical status	Mild : 5 points Moderate : 3 points Severe : 0 points
Hematologic malignancy or solid tumor without history of fungal infection	No : 5 points Yes : 0 points
Onset of fever	Outpatient : 3 points Inpatient : 0 points
Mild or moderate clinical status (no significant comorbid disease)	3 points
Age of the patient	< 60 years old : 2 points > 60 years old : 0 points

Table 2. CISNE Scoring System[8]

Characteristic	Score
ECOG performance status ≥2	2
Chronic Obstructive Pulmonary Disease	1
Neutrophil level <200/mm³	1
Chronic heart disease	1
Sepsis-induced hyperglycemia	2
Mucositis grade by National Cancer Institute criteria >2	1

In low-risk patients, a more specific assessment tool is available to assess whether hospitalization is necessary or outpatient management is appropriate. This tool is the Clinical Index of Stable Febrile Neutropenia (CISNE). The CISNE score may be particularly useful in the emergency department to help determine whether a patient can truly be managed as an outpatient or still requires inpatient care. One of the components of this scoring system is the Eastern Cooperative Oncology Group (ECOG) performance status, which evaluates the patient's functional condition and serves as a

surrogate for their ability to tolerate the treatment for severe illness.[12]

Febrile neutropenia can be classified based on two assessment tools: MASCC and CISNE. The MASCC is used to assess the risk of serious complications in the patients with febrile neutropenia. Patients with a score greater than 21 are considered low-risk, while a score less than 21 is considered high-risk. The CISNE, on the other hand, is more specific for assessing patients with stable febrile neutropenia, helping to distinguish between stable patients with high risk and low risk, who may not require hospitalization.[12]

Management

The primary goal of FN management is to prevent the occurrence of serious infection in patients who are susceptible to infection. This management focuses on prevention and early treatment of infection before it develops into more severe conditions such as sepsis. Quick and aggressive management is important because FN patients have a high risk of developing serious infections that can progress to sepsis or even septic shock.[13] Management begins with immediate antibiotic administration and consideration of hospitalization based on the patient's risk profile. Patients are divided into two groups: high-risk and low-risk. High-risk patients typically have severe neutropenia that is expected to last more than 7 days, a CISNE score ≥3, a MASCC score <21, or experience uncontrolled comorbidities such as liver or kidney insufficiency. These patients may also have undergone intensive therapy in the past two months, such as alemtuzumab.[14]

Treatment for low-risk patients generally can be done on an outpatient basis with empirical oral therapy using a fluoroquinolone such as ciprofloxacin, combined with amoxicillin/clavulanate, with close monitoring for at least 72 hours. For high-risk patients, treatment in the hospital with intravenous antibiotic therapy given within 1 hour of triage is required, such as cefepime or piperacillin/tazobactam. These patients need to be monitored for more than 4 hours before a decision is made for hospitalization or discharge. Blood culture examination is also recommended to detect infection, especially in patients with a central line. To prevent infection, prophylactic antibiotics can be used in high-risk patients.[14]

Vancomycin is not recommended as initial therapy; however, it should be considered if there is suspicion of infection caused by catheter use, skin or soft tissue infection, pneumonia, or hemodynamic disturbance. If the patient does not respond to treatment, antibiotic coverage should be expanded to handle resistant species, such as methicillin-resistant *Staphylococcus aureus* (MRSA) which can be treated with vancomycin, linezolid, or daptomycin. For vancomycin-resistant *enterococci* (VRE) infections, linezolid or daptomycin is recommended, while organisms producing extended-spectrum beta-lactamase (ESBL) can be managed with carbapenems. In cases of Klebsiella pneumoniae, carbapenems, polymyxins, colistin, or tigecycline may be treatment options.[15]

Empirical antifungal therapy is also recommended for high-risk patients who experience persistent fever after 4 to 7 days of broad-spectrum antibiotic use, especially if there is suspicion of fungal infection. Echinocandin antifungals are recommended as first-line empirical antifungal therapy in FN patients. Echinocandins, such as caspofungin, micafungin, and anidulafungin, are effective against fungal infections, particularly those caused by *Candida* and *Aspergillus*. The advantages of echinocandins are their broad antifungal spectrum and lower toxicity compared to some other antifungal classes, such as amphotericin B.[15] Antibiotics can be continued until the patient's neutrophil count reaches ≥500 cells/mm³ or the infection is declared cured. If the patient remains neutropenic after treatment, oral fluoroquinolone prophylaxis can be continued until all signs and symptoms of infection are resolved and the bone marrow recovers.[15]

In addition to antibiotics, myeloid growth factor (MGF) can be used as part of the management for FN patients. However, the use of MGF in FN management remains controversial. Results from a meta-analysis of 13 studies that evaluated MGF together with antibiotics in patients showed a reduction in the duration of intravenous antibiotic use and hospital stay duration but no change in overall survival.[16] The National Comprehensive Cancer Network (NCCN) recommends continuing MGF in patients who have already received daily MGF treatment and considering the addition of MGF with antibiotics only in individuals with risk factors for complications related to infection. Indications for MGF administration include sepsis syndrome, an absolute neutrophil count less than 100 cells/mm³, pneumonia, invasive fungal infection, or patients who have previously experienced FN. If not included in these indications, the addition of MGF is not standard care in FN management.[17]

Prevention

Infection prevention measures in cancer patients are very important, with hand washing being the most important non-pharmacological measure. Other preventive measures include the use of targeted antibacterial, antiviral, and antifungal prophylaxis, as well as stimulation of neutrophil production with MGFs.[14] The decision to start antimicrobial prophylaxis treatment is based on the patient's infection risk, which increases if the patient is expected to experience severe neutropenia (defined as an absolute neutrophil count of ≤100 cells/mm³ or less for more than seven days) or neutropenia lasting more than 10 days.[14]

The likelihood of developing severe neutropenia should be assessed in relation to the underlying malignancy and the specific chemotherapeutic agents administered. Hematologic cancers typically lead to more prolonged neutropenia because both the disease itself and the myelosuppressive regimens used directly impair bone marrow function. Patients undergoing bone marrow transplantation require more

specialized antimicrobial prophylaxis, whereas those with solid tumors may develop neutropenia if there is marrow infiltration or if they receive highly myelosuppressive chemotherapy. Once prophylaxis has been started, these antibiotics are usually continued until neutrophil counts have recovered and may be reintroduced later if clinically indicated.[14]

The use of antibacterial prophylaxis treatment has significantly reduced infection-related mortality in neutropenic patients and is recommended for high-risk patients. Meta-analysis data from 52 trials involving neutropenic patients with hematologic malignancies demonstrated that fluoroquinolones (FQs) are effective in preventing bacterial infections without significantly increasing the emergence of resistant strains. National guidelines recommend levofloxacin as the preferred FQ, and higher doses (500–750 mg) provide broader antimicrobial coverage than ciprofloxacin or moxifloxacin, including activity against Pseudomonas, other gram-negative bacilli, and several gram-positive organisms such as streptococci. For patients unable to receive FQs, trimethoprim–sulfamethoxazole (TMP/SMX) or a third-generation cephalosporin may be used as alternative prophylactic agents.[14]

Antiviral prophylaxis with acyclovir is recommended for herpes simplex virus–seropositive patients who are at risk of developing neutropenia because of the potential for viral reactivation. Patients who have previously required treatment for HSV or other viral infections during earlier chemotherapy cycles should also receive antiviral prophylaxis during subsequent therapies. Individuals undergoing hematopoietic stem cell transplantation (HSCT) have distinct prophylactic requirements because prolonged treatment-related immunosuppression markedly increases the risk of varicella zoster virus reactivation. In this setting, acyclovir is often prescribed at 800 mg orally twice daily (rather than 400 mg) and continued for up to one year after transplantation or until immunosuppressive therapy has been discontinued.[14]

Fungal prophylaxis is also recommended for patients at high risk of profound neutropenia, with the choice of agent tailored to whether Candida or Aspergillus coverage is required. Fluconazole effectively reduces Candida-related fungal infections, although other triazoles or echinocandins may be used as alternatives. Patients with acute myeloid leukemia or myelodysplastic syndrome receiving intensive chemotherapy are at particularly high risk for invasive Aspergillus infection, and posaconazole has been shown to prevent more invasive fungal infections and to improve overall survival compared with fluconazole or itraconazole in this group of patients. In most other patient groups, routine primary prophylaxis against Aspergillus is not advised unless there is a history of prior infection.[16]

The MGF is a substance that stimulates the growth and differentiation of myeloid cells in the bone marrow, which are precursor cells that develop into various types of blood cells such as neutrophils, eosinophils, basophils, and monocytes. MGFs, such as granulocyte colony-stimulating factor (G-CSF) and macrophage colony-stimulating factor (M-CSF), are used in clinical practice to accelerate the recovery of white blood cell counts in patients experiencing neutropenia. The G-CSF is primarily used in the treatment of neutropenia because of its effectiveness in selectively promoting neutrophil production. Conversely, M-CSF more specifically targets macrophages compared to neutrophils, playing a role in modifying immune and inflammatory responses, rather than directly combating neutropenia.[14]

The G-CSF prevents the risk of FN by enhancing the patient's immune system, increasing neutrophil production to counteract the bone marrow suppression effects of chemotherapy. Some chemotherapy regimens are believed to cause severe neutropenia, and the use of G-CSF may be recommended in these regimens. Generally, if the risk of FN is 20% or higher with a chemotherapy regimen, G-CSF should be used.[14] Risk of FN between 10% and 20% is considered moderate risk, and G-CSF use is determined by the healthcare provider's preference based on individual patient risk factors, such as age, comorbid conditions, and prior chemotherapy.[14] The mechanism of action of G-CSF is to make neutrophils attached to blood vessel walls become mobilized and circulate into the bloodstream and accelerate the maturation of human hematopoietic stem and progenitor cells (HSPCs) into neutrophils.[18]

The G-CSF is typically given 24 to 72 hours after chemotherapy is completed. Administration of G-CSF after this period is designed to support neutrophil recovery, which is affected by the cytotoxic effects of chemotherapy. This time interval is important because if G-CSF is given too early (before 24 hours), chemotherapy can still have a negative impact on blood cell production in the bone marrow. Conversely, if given too late, the risk of neutropenia and complications such as infection can increase. The NCCN guidelines recommend G-CSF administration primarily in patients receiving chemotherapy with high risk (>20%) of experiencing febrile neutropenia, or in the moderate-risk group (10–20%) if there are additional risk factors such as advanced age or comorbidities.[17]

The dose of G-CSF administration varies depending on the type of G-CSF used. For filgrastim, the recommended dose is 5 μg/kg/day given via subcutaneous or intravenous injection, usually starting 24–72 hours after chemotherapy and continuing daily until neutrophil count reaches a safe level. For pegfilgrastim, which is a long-acting formulation, the recommended dose is 6 mg given as a single subcutaneous injection, usually 24 hours after chemotherapy, with one administration per chemotherapy cycle. Pegfilgrastim does not need to be given daily like filgrastim because of its longer duration.[17]

Administration of G-CSF (Granulocyte-Colony Stimulating Factor) is generally well tolerated but can cause some side effects. The most common side effect is bone pain,

particularly in bone marrow-rich bones such as the spine, pelvis, and long bones, due to increased bone marrow activity in producing neutrophils. Additionally, patients may experience muscle or joint pain, headache, fatigue, injection site reactions such as redness or swelling, mild fever, nausea, or gastrointestinal disturbances. In rarer cases, G-CSF can cause serious side effects such as spleen enlargement (splenomegaly), which in some cases can develop into splenic rupture, a life-threatening condition. Additionally, there is a possibility of developing acute respiratory distress syndrome (ARDS) or severe allergic reactions in some patients.[17]

Evaluation of neutrophil count after G-CSF administration is performed periodically depending on patient response and clinical protocol. Generally, neutrophil evaluation is performed 5–7 days after G-CSF administration, with the aim of ensuring that the increase in neutrophil count reaches a safe level (>1,000 neutrophils/μL) and preventing complications related to neutropenia. In patients receiving daily G-CSF such as filgrastim, daily or every-few-days monitoring during therapy may be necessary. If pegfilgrastim (long-acting G-CSF) is used, neutrophil evaluation is performed at time points consistent with its longer duration of action. This evaluation is important for adjusting the dose and duration of G-CSF administration and for avoiding the risk of leukocytosis. Routine monitoring also ensures that G-CSF provides an optimal protective effect against neutropenia without causing additional complications.[17]

Conclusion

Febrile neutropenia is a serious complication that frequently occurs in patients undergoing cytotoxic chemotherapy and suffering from cancer, with a significant impact on morbidity and mortality rates. The use of MASCC and CISNE risk criteria allows healthcare professionals to assess patients' risk for complications from infection. Patients are classified as high risk or low risk, which then determines the choice of initial therapy, such as oral fluoroquinolone antibiotics for outpatient treatment. In high-risk patients, broad-spectrum intravenous antibiotic therapy as quickly as possible, such as cefepime, ceftazidime, carbapenems, or piperacillin/tazobactam, can be administered.

Based on current guidelines and research on FN management, empirical treatment can be adjusted according to clinical need. It is very important to know whether a patient has high risk or a history of FN so that preventive measures can be implemented. The use of G-CSF in FN management remains under debate. The G-CSF can be used in FN management with high infection risk, which will reduce the length of hospital stay in patients and accelerate neutrophil recovery. The use of G-CSF in FN prevention is used in cancer patients with moderate and high infection risks. A good understanding of FN and its management in immunosuppressed patients is key to improving treatment outcomes.

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