Literature Review

Management of Febrile Neutropenia in Lung Cancer

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Abstract

Febrile neutropenia (FN) is defined as an oral temperature of >38.3° C or two consecutive measures >38°C within 2 hours accompanied by an absolute neutrophil count (ANC) of 500/L or a predicted decrease below 500/L in individuals undergoing systemic chemotherapy for cancer. FN is one of the oncological emergencies that can influence cancer patients' outcomes since it can increase morbidity, treatment delays, decrease survival, and expand costs. The incidence of FN is 3.7-28% in lung cancer patients. Mortality associated with FN episodes is 15%. FN risk factors include chemotherapy regimen, age, comorbidities, mucositis, performance status, and previous FN history. Validated predicted instruments such as The Multinational Association for Supportive Care in Cancer (MASCC) or The Clinical Index of Stable Febrile Neutropenia (CISNE) score could assist in the risk assessment of FN and determine advanced management. Effective therapy of FN requires investigation of diagnosis as soon as possible and acknowledging the potential source of infection. The prophylactic granulocyte colony-stimulating factors (G-CSF) and anti-microbial successfully reduced mortality due to FN.

Keywords: antibiotics, febrile neutropenia, G-CSF, lung cancer

INTRODUCTION

Globally, lung cancer is the leading cause of cancer-related mortality. Global cancer statistics (Globocan) predicted 2.2 million new cases of lung cancer (11.4% of all cancer cases) and 1.79 million cancer-related fatalities (18.0% of all cancer-related deaths) in 2020, both of which were higher than in 2018 (1,76 million deaths and 2,09 million new cases).[1]

According to Globocan 2020 data, lung cancer fatalities in Indonesia rose to 30,843 (13.2% of all cancer deaths), with new cases reaching 34,783 (8.8% of total cancer cases). It made lung cancer the most frequent cancer and the main cause of cancer deaths in both genders.[2] Non-small cell lung cancer is the most common histologic form of lung cancer (85% of all cases) (NSCLC).[3]

The standard chemotherapy management for NSCLC is platinum-based. The suggested neoadjuvant chemotherapy in stage II (A/B) and stage IIIA NSCLC is doublet platinum chemotherapy. In advanced NSCLC, chemotherapy combination radiotherapy or chemotherapy

alone; however, the current first-line standard management is based on the outcomes of molecular testing. For instance, in stage IV NSCLC for tumors with EGFR mutation-positive, first-line therapy is EGFR tyrosine kinase inhibitors, and anaplastic lymphoma kinase (ALK) inhibitors are the first-line management suggested for ALK-rearranged NSCLC patients.[4,5]

The 5-year survival rate for NSCLC patients is dismal, ranging between 10 and 20%. Platinum-induced myelosuppression is a side effect of chemotherapeutic induction in NSCLC.[4] Certain chemotherapy drugs (e.g., carboplatin/docetaxel, cisplatin/etoposide) have been linked to an increased incidence of chemotherapy-induced neutropenia (CIN) or febrile neutropenia (FN).[6] The previous research reported that 10-20% of NSCLC patients treated with docetaxel and ramucirumab develop FN.[7]

According to additional studies, FN occurs in approximately 26% of docetaxel-based chemotherapy cases. FN is the most common cause of treatment-related morbidity in small cell lung cancer (SCLC) patients, with previous research analyzing a 6.8-9.5% prevalence of FN-related morbidity in hospitalized patients.[8]

There is a direct correlation between the degree of neutropenia and the dosage of chemotherapy. The chemotherapy regimen, age, comorbidities, history of FN, absence of prophylactic anti-microbials or granulocyte colony-stimulating factors (G-CSF), the status of performance, mucositis, and cardiovascular disorder are several individual risk factors that have been identified in FN.[8]

FN is a medical oncology emergency since it can raise morbidity, delay therapy, decrease survival rate, and increase expense, all of which can impact treatment success.[9] To avoid FN as soon as possible, there must be sufficient concern. This literature review will elaborate on FN as a major lung cancer consequence.

FEBRILE NEUTROPENIA IN LUNG CANCER

Definition

In cancer patients, the incidental fever with CIN is life-threatening and may need empiric broad-spectrum antimicrobial treatment. Even though the infection contamination is suspected to be the source of fever, it is troublesome to decide the pathogenic cause in most cases. Klastersky named this condition in 1990 FN, defined by:[6,10]

1. Oral temperature >38.3°C or >38°C within 2 hours in two sequent measurements.
2. Neutrophil count/ absolute neutrophil count (ANC) <500/µl or <1,000/µl with a presumed to reduce to <500/µl within 48 hours.

The ANC is measured by multiplying the WBC (white blood cell) count by the percentage of segments and bands.

Incidence

The incidence of FN reached 31% in lung cancer patients, according to Moreira-Pinto et al.[11] The prevalence may vary

based on the antineoplastic regimen used. The incidence of FN may decrease due to the therapeutic impact of G-CSF therapy.[12]

The retrospective study revealed an incidence of 58.3% for neutropenia and 8.3% for FN in advanced NSCLC patients undergoing platinum-based chemotherapy doublets.[13] Fujiwara et al research showed the incidence of FN was 20% in lung cancer patients in Japan who had never received chemotherapy while receiving etoposide and platinum in combination.[8]

Another study revealed that the incidence of FN in lung cancer patients after doublet platinum treatment ranged from 3 to 14%.[14] According to past studies, mortality risk is at least 15% lower for individuals without FN than for patients with FN.[15] Previous studies have identified that FN is responsible for a 6.8–9.5% of death among in-hospital patients.[8]

Risk Factors

Although faulty, the scoring methodology can aid in recommending clinical scoring indicators for advanced care (e.g., hospital versus outpatient, parenteral versus oral) and initial empiric antimicrobial treatment.[10,16] Validated scoring systems used to predict the defy of medical complexity in FN consist of:

1. Talcott Score. Talcott et al created a clinical prediction score that categorized patients into four risk categories. For instance, only 5% of outpatients with FN, well-managed cancer, and minor comorbidities are likely to experience severe consequences. This classification is prospectively verified in research undertaken at two chemotherapy-accepting centers in the United States.[10]
2. Multinational Association for Supportive Care in Cancer (MASCC). Table 1 demonstrates that a score of 21 points or more hints at a low risk of complications.[10]

Table 1. MASCC index risk[10]

Characteristics	Score
A burden of illness*; absence or mild symptoms	5
A burden of illness; absence or moderate symptoms	3
A burden of illness; absence or severe symptoms	0
No low blood pressure (systolic BP > 90 mmHg)	5
Absence of chronic obstructive pulmonary disease (COPD)	4
Solid tumor/lymphoma with no history of infection of fungal	4
The dehydration is none	3
Outpatient status (at the onset of fever)	3
Age <60 years	2

Note: *Burden of illness is a subjective characteristic based on symptom severity determined by the attending physician at presentation.

3. The Clinical Index of Stable Febrile Neutropenia (CISNE). The CISNE divides patients into three risk categories: low (0 points), intermediate (1 to 2 points), and high (>3 points) (shown in Table 2).[10]

Table 2. CISNE score[10]

Characteristics	Score
Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥2	2
Stress-induced hyperglycemia	2
COPD	1
Chronic Cardiovascular Disease	1
Mucositis National Cancer Institute (NCI), grade ≥2	1
Monocyte <200 per µL	1

A retrospective analysis study by Fujiwara et al determines a male gender and the previous radiotherapy as independent risk components for FN in patients treated with Cisplatin-Etoposide.[8] The characteristics of patients with a low and high risk for serious complications in FN are presented in Table 3, respectively.

Pathogenesis

Factors contributing to the pathophysiology of FN include chemotherapy's direct effects on the mucosal barrier and immune system and buffers in host defense linked to underlying malignancy.[9,17]

Chemotherapy will disrupt blood cell formation, causing neutropenia; other than that, chemotherapy also causes injury to the gastrointestinal (GI) mucosa, which induces mucosal barrier damage that actuates infection contamination. Using catheter indwelling will also increase access to tissues that can initiate bacterial colonization (Figure 1).[9,18] Most scenes of FN are related to microorganisms from the endogenous gastrointestinal flora that invade the circulatory system,[17] and cancer-associated immunosuppression is considered to be an essential pathogenesis factor of FN.[9]

Diagnostic Investigation

The initial assessment and investigation of FN are also essential to require a history of chemotherapy, previous prophylactic antibiotics, steroids, recent surgical procedures, and a history of allergy.[19,20]

Table 3. Characteristics of low and high risk for severe complications in FN[9]

Risk	Characteristics
Patients with any of the following are willfully at **low risk** for thought-full complications amid an FN scene	a. Outpatient when fever occurs b. Not associated with acute comorbid disease c. Anticipate a short period of severe neutropenia (≤100 cells/ml for <7 days) d. Performance Status is good (ECOG 0-1) e. Absence of hepatic or kidney disorder f. MASCC risk index score ≥ 21 or CISNE <3
Patients with any of the consecutive characteristics are contemplated to be at **high risk** for deliberate complications during an FN scene	a. Patients accepting adequate myelosuppressive cytotoxic treatment to cause extreme neutropenia (ANC <500 cells/ml) for >7 days b. MASCC risk index score <21 c. CISNE score ≥3 (in patients with solid tumors) d. Presence of uncontrolled active comorbidities: 1) Indicators of sepsis or septic shock (e.g., hemodynamic instability, new-onset mental status changes, respiratory dysfunction, oliguria) 2) Mucositis of the mouth or gastrointestinal system causes severe diarrhea or impairs swallowing. 3) Gastrointestinal manifestations, along with nausea and vomiting, abdominal pain, or diarrhea 4) Intravascular catheter infections, especially tunnel catheter infections 5) Current lung infiltrates or hypoxemia 6) History of chronic lung disease 7) Current complex infection e. Use of Alemtuzumab or CAR-T cells in the last two months f. Uncontrolled or progressive cancer g. Mucositis Grade 3-4 There is data of hepatic impairment that aminotransferase level > five times normal value or renal impairment that creatinine clearance <30 mL/min

Initial assessment and investigation of FN include:[19,20]

a. Attendance of indwelling IV catheters.
b. Respiratory system, gastrointestinal system, skin, perineal/ urogenital area, oropharynx, central nervous system symptoms or signs.
c. Awareness of previous positive microbiological outcomes by reviewing clinical data.
d. Routine inspections:
    1) Complete blood count, coagulation factors, C-reactive protein (CRP);
    2) Blood cultures (minimum two times), including cultures from indwelling IV catheters;
    3) Urinalysis and culture*, Sputum microscopy and culture*, Stool microscopy and culture* (Note: *Urinalysis, sputum, and stool cultures are onliest if a focus of infection in the area is suspected);
    4) Skin lesions (aspiration/biopsy/ swab);
    5) Chest X-ray.
e. Other examinations (profound/ prolonger neutropenia/ following allografts), High-resolution chest CT (if fever >72 hours with antibiotics), bronchoalveolar lavage.

Treatment

Several chemotherapeutic drugs pose a greater risk for CIN or FN. It may result in dose reduction and chemotherapy delay, reducing treatment success.[8,9] Therefore, CIN/FN prophylaxis must guarantee that cytotoxic treatment is administered on schedule and at the correct dose.[6,9] Antimicrobials and G-CSF have been used effectively to prevent chemotherapy-associated FN. Matsui et al observed that prophylactic long-acting G-CSF lowered the occurrence of FN in advanced NSCLC patients receiving docetaxel monotherapy.[21]

Effective management of FN requires immediate diagnosis and acknowledgment of potential infections. Daily symptom monitoring is urgent to teach in outpatients. Recognize FN earlier and creating a time-dependent calculation for establishing the diagnosis quickly and medicating cancer patients with FN and suspected sepsis is vital (Figure 2).[6,9,22]

Antibiotic Therapy

Antibiotics ought to be given as soon as conceivable. Prior studies recommend that patients with FN start empiric broad-spectrum antimicrobial treatment as soon as a blood culture is obtained. Empirical antibiotics can be considered based on the pathogenic organisms frequently found in FN. Gram-negative, such as *E. coli*, *P. aeruginosa,* or gram-positive such as *S. pneumonia* or *S. aureus*.[6,9,11]

According to the international guideline, FN patients suggest empirical antibiotics treatment within 60 minutes of onset (Figure 2). They are starting empiric antibacterial treatment as soon as possible to avoid developing sepsis and death. Early regimen selection should consider the patient history, allergy history, clinical symptoms and signs, recent use of antimicrobial agents, culture information, and local hospital bacterial patterns.[6,9,11,22]

Considering the risk of a resistant organism is the underlying factor of empirical therapy options and targeted therapies after the pathogenic bacteria have been identified.[6,9,11,22]

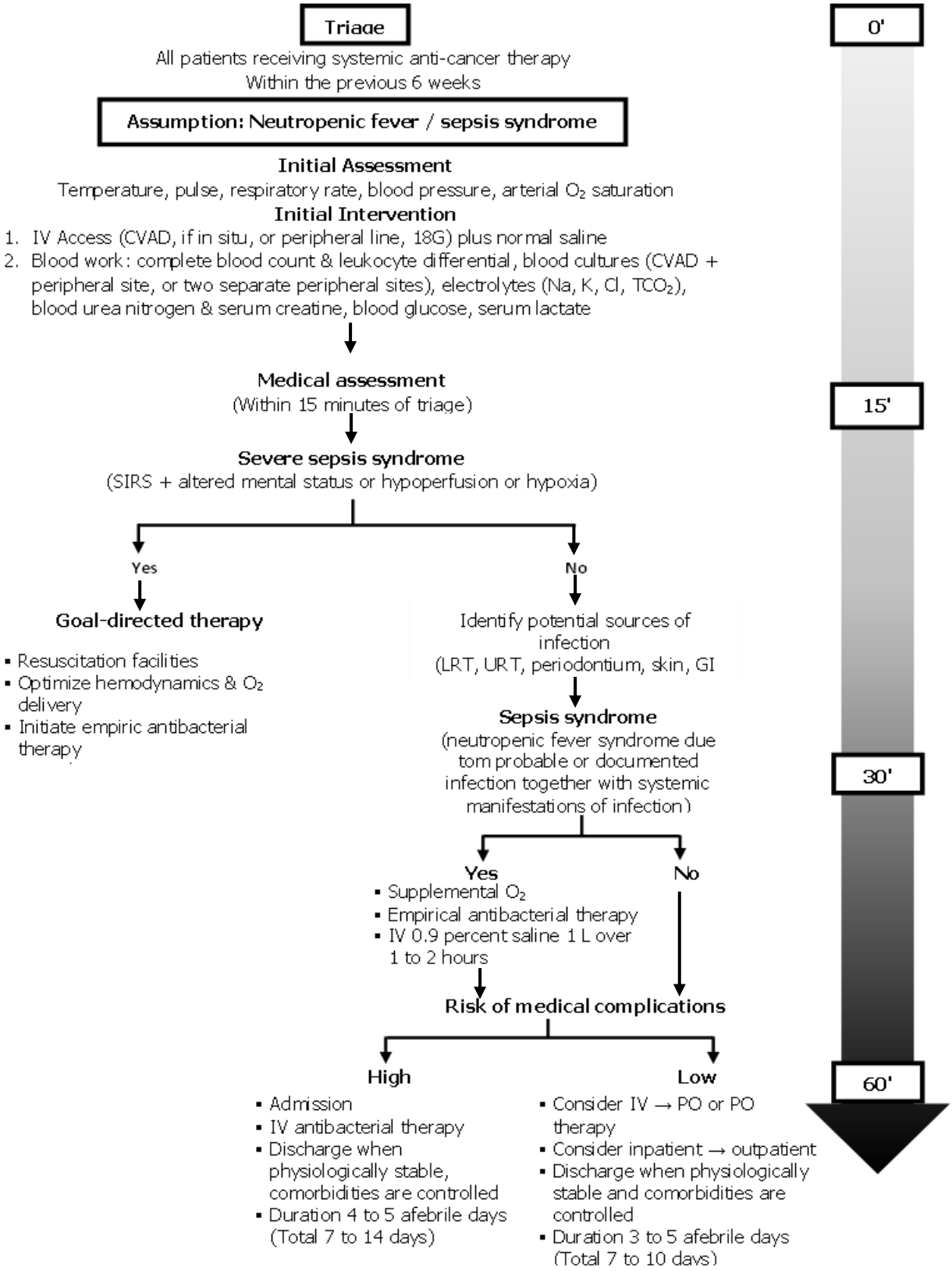

Figure 2. Initial assessment and management of cancer patients with FN and suspected sepsis based on a time-dependent algorithm[22]

Prior to obtaining bacterial culture results, empirical antibiotic treatment is based on the consideration of the most virulent and common pathogens that might cause significant disease or death. Based on the risk of infection and the clinical presentation, using a beta-lactam having antibacterial action against *P. aeruginosa* is recommended in monotherapy or in combination with another regimen.[6,23]

To inhibit the expansion of bacterial infections as a complication of neutropenia, prophylactic with antimicrobials is necessary. However, its usefulness in CIN is still controversial. According to Escrihuela et al, individuals at high risk for FN problems should consider hospitalization and beginning empirical antibiotic therapy (CISNE score 3).[23]

Antimicrobial treatment in neutropenic patients lowered the number of deaths, fever episodes, and bacterial infections. According to Lucas et al meta-analysis of 52 trials, including patients with neutropenia and predominantly hematologic malignancies, Quinolones are helpful in preventing bacterial infections without inducing resistance.[9]

The percentage of positive microbiological findings with conventional blood cultures is determined using antimicrobials as preventatives. Overall, in ±19% of FN patients, bacteremia can be identified.[11] Antibiotic-resistant bacteria, such as extended-spectrum-lactamase (ESBL), methicillin-resistant Staphylococcus aureus (MRSA), and vancomycin-resistant enterococci (VRE), are becoming more prevalent. Infections with Candida strains resistant to fluconazole (such as Candida krusei and Candida glabrata) are also rising. Antifungal prophylaxis with oral triazoles or parenteral echinocandins is recommended for individuals at risk for severe and extended neutropenia. For solid tumors patients, prevention with antifungals is not routinely given.[6,9]

MASCC or CISNE score as a validated instrument could be used to evaluate the possibility of complications in FN patients, and the recommendation is as follows:[9,10]

1. The risk of complications was low in FN patients (Table 3). Oral antibiotics could be given in this category, and if a good follow-up could be done, it could be outpatient. Parenteral regimens also could be given in some low-risk outpatients. Antibiotic choices are Ciprofloxacin + Amoxicillin/Clavulanate or Moxifloxacin, or Levofloxacin. The combination of quinolones with amoxicillin-clavulanic acid is not superior to single-agent quinolones. However, the increase in gram-positive infections in FN makes the former strategy preferable. Several reviews have supported the safety of switching to oral medication from intravenous therapy early in patients who have not had a fever for at least 48 hours.[6,9,24]
2. The risk of complications was high in FN patients (Table 3). Patients in this category must be hospitalized and not be delayed in administering broad-spectrum antimicrobial therapy. Patients must be observed to evaluate hemodynamic stability (pre-shock).

Antipseudomonal beta-lactams, such as cefepime, imipenem/cilastatin, meropenem, carbapenem, and piperacillin-tazobactam, are the intravenous antimicrobials of choice for hospitalized patients at high risk. However, antimicrobial medicines utilized in patients with solid tumors are scarcely documented. A meta-analysis assessing the efficacy of single-agent versus combination therapy revealed equal efficacy. Meropenem is one of the most commonly utilized antimicrobial medications in FN., while carbapenem is an alternate antibacterial treatment.[6,9] Numerous studies have indicated that carbapenem is one of the initial treatments for FN in both adults and children and is more effective in reducing all-cause mortality than anti-pseudomonas penicillin and fourth-generation cephalosporins.[25] However, Tang et al, found no difference between carbapenems and beta-lactam monotherapy or combination therapy in their investigation.[26] Intravenous combination anti-microbials are considered in case antimicrobial resistance is suspected.[9]

Granulocyte colony-stimulating factors (G-CSF)

The granulocyte colony-stimulating factor (G-CSF) administration as prophylaxis is recommended by The American Society of Clinical Oncology (ASCO) guidelines when the risk of FN is ≥20%.[8] G-CSF stimulates white blood cells (WBC), a biological growth factor promoting the proliferation, differentiation, and activation of neutrophils in the bone marrow. The efficacy of standard G-CSF agents (Filgastrim) and pegylated agents (Pegfilgastrim) as FN prophylaxis has proven to lower the risk, severity, length of FN episodes, and the troubling effects of chemotherapy.[6,9]

Several meta-analyses show that G-CSF as primary prophylaxis can lower the risk of FN by a minimum of 50% in solid tumors.[7] The administration of G-CSF and a granulocyte-macrophage colony-stimulating figure (GM-CSF) as primary prophylaxis in patients with a 20% or more risk of developing CIN/ FN is suggested by most international guidelines.[6,9]

As an example, those receiving high-risk chemotherapy regimens and risk factors that may intensify all patient-associated chance of CIN/FN, such as age >65 years, comorbid, history of chemotherapy, cancer type, chemotherapy regiment, the intensity of planned dose, the onset of leukopenia, hepatic and kidney disorder). Studies showed that patients with established FN who received MGFs in addition to antibiotics had a shorter time on IV antibiotics and a shorter hospital stay but no change in overall survival.[6,9]

At 24-72 hours after the last day of chemotherapy, filgrastim is delivered subcutaneously (sc) at a dosage of 5 g/kg/day until steady post-nadir ANC recovery. Pegfilgrastim 100 g/kg (individual) and a total dose of 6 mg (a common practice) are equally effective. There are no acceptable data for reducing the standard number of days and dose of

G-CSF, and The European Medicine Agency (EMA)/United States Food and Drug Administration (FDA) has approved using biosimilars.[27]

Therapeutic Response

The assessment of therapy response from clinical symptoms and ANC, as below:[28]

a. Oral antibiotics should be recommended if the patient has no fever and an ANC $\geq 0.5\times10^9$/l within 48 hours, with minimal risk and no focus infection.
b. The patient is at high risk without the cause of infection and receives a combination antimicrobial treatment. The aminoglycoside can be discontinued.
c. When the cause of infection is found, antibiotic administration is continued according to a specific therapy.
d. The patient is still febrile but clinically stable after 48 hours; continue early antibiotic therapy.
e. If the patient is clinically unstable, replace or expand antimicrobial treatment according to clinical considerations. Some centers add glycopeptide or replace the agents with imipenem, meropenem, and glycopeptides. Uncommon infections should be considered, especially in cases of elevated CRP. Imaging studies of the thorax and upper abdomen should rule out fungal infection or abscess. When fever persists for more than 4-6 days, empiric antifungal treatment may be required.
f. Asymptomatic patient with the ANC is $\geq 0.5\times10^9$/l, has no fever for 48 hours, and the blood culture is negative. Discontinue antibiotics.
g. Patients do not experience complications with the ANC is $\leq 0.5\times10^9$/l and no fever for 5-7 days; discontinue antibiotics, except in certain high-risk cases. After high-dose chemotherapy, antibiotics are usually extended for ten days or until the ANC is 0.5×10^9.
h. Even though neutrophil has improved, the patient with persistent fever should be assessed by a clinical microbiologist, and antifungal therapies are considered.

Prognosis

Mortality associated with the FN episode was 15%, with 53.8% being culture positive, creating a poor prognosis of FN. The existence of focus infection (e.g., pneumonia, abscess, cellulitis) also worsens outcomes. Moreira-Pinto et al found that one predictive factor of increased mortality in FN patients was ANC $<100/\mu L$.[11]

The investigation by Kauffmann-Guerrero et al, in 39 SCLC patients in Germany, reported that patients with FN showed significantly shorter PFS than those without FN. Chemotherapy interruption, delay, or dose reduction made these conditions, and therefore, the degree of remission in the patient was reduced. In the FN versus non-FN group, patients with at least one postponed chemotherapy administration are 75% and 35%,

respectively. In FN patients, the immune response to tumor cells may be impaired; those with an inadequate immune response may be more susceptible to FN and slightly to form an antitumor immune response.[29]

CONCLUSION

Febrile neutropenia (FN) continues to be a major problem for chemotherapy-treated lung cancer patients, leading to poor quality of life and even death. Risk variables are identified, including patient characteristics (age, performance status), underlying disorders (staging, comorbidities), and chemotherapy regimen. Assessing the risk of FN complications using proven prediction instruments, such as the MASCC score, is recommended. The management of FN with antimicrobials and G-CSF has been successful in lowering FN-related mortality.

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