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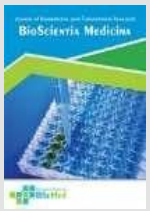

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Update Management of Chemotherapy-Induced Neutropenia: A Narrative Literature Review

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A B S T R A C T

One of the most frequent and significant complicated side effects of myelosuppressive drugs is neutropenia. Neutropenia is not only associated with high morbidity but also mortality. Generally, the onset of neutropenia occurs within 3-7 days after the administration of anticancer agents. Approximately 5-30% of patients will develop febrile neutropenia. The highest incidence occurs during the first cycle of chemotherapy. This literature review aimed to describe chemotherapy-induced neutropenia and its prevention and management. Administration of granulocyte colony-stimulating factor as prophylaxis can prevent neutropenia-induced anticancer drugs. The use of granulocyte colony-stimulating factor (G-CSF) as therapeutic is contradictive, and some guidelines recommend not to use the G-CSF for therapeutic purposes. Up to 70% of mortality among these populations was associated with gram-negative sepsis, therefor empirical antibiotics, and antifungals are the keys to the management of neutropenia. In conclusion, prevention and appropriate management of neutropenia are extremely important in the treatment of patients with cancer.

1. Introduction

Neutrophils play an important role in the innate immune system as a defense mechanism against pathogens. They act directly by attacking bacteria or fungal hyphae and indirectly by producing cytokines that will exert inflammatory responses at the infected site. Both quantitative and qualitative neutrophil deficits will lead to a high risk of severe infections, especially those caused by bacteria and fungi. Chemotherapy drugs can affect the bone marrow, which is responsible for producing white blood cells, including neutrophils. Neutrophils are a type of white blood cell that helps the body fight infections. When the number of neutrophils in the blood is low, it is called neutropenia.[1-3]

Neutropenia can increase the risk of infections as the body's ability to fight off infections is weakened. Patients undergoing chemotherapy may be at a higher risk of developing infections due to neutropenia. Cytotoxic anticancer agents act on actively proliferating cells, including bone marrow myeloproliferative cells resulting in neutropenia. The grading and duration of neutropenia are directly correlated with the risk of infection. Patients with neutropenia often manifest mild to severe local or systemic infection as a result of the inability to

respond to the inflammatory response.[4,5] This literature review aimed to describe chemotherapy-induced neutropenia and its prevention and management.

Chemotherapy-induced neutropenia (CIN)

The onset of neutropenia generally occurs within 3-7 days after the administration of anticancer agents. Approximately 5 – 30% of patients undergoing chemotherapy will develop febrile neutropenia. The highest incidence occurs during the first cycle of chemotherapy. Gram-negative bacterias, particularly *Enterobacteriaceae (Escherichia coli, Klebsiella, Enterobacter*) and *Pseudomonas aeruginosa*, are the most common pathogens causing infection in neutropenic cancer patients. These pathogens caused high morbidity and mortality (up to 70%) associated with gram-negative sepsis. According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0, neutropenia is categorized into four degrees based on the absolute neutrophil count (ANC): grade 1 if ANC <1.500/μL, grade 2 if ANC 1.000 – 1.500/μL, grade 3 if ANC 500 – 1.000/μL, and grade 4 (severe neutropenia) if ANC <500/μL. Neutropenia with ANC <100/μL is termed profound neutropenia. Protracted neutropenia is severe neutropenia that lasts ≥7 days. Febrile neutropenia is severe neutropenia (ANC <500/μL, or expected to fall <500/μL for the next 48 hours) accompanied by an increase of oral temperature ≥38.3°C (101°F), or ≥38,0°C (100,4°F) in lasts 1 hour.[6,7,11]

Risk factor and risk stratification

The risk factors for neutropenia in cancer patients are divided into three categories; treatment-related, patient-related, and cancer-related neutropenia. Treatment-related risk factors include chemotherapy regimen, dose, history of radiotherapy exposure, especially in bone marrow area, and history of neutropenia with previous cycle complications. Patient-related risk factors included age ≥ 65 years, low state performance (ECOG ≥2), poor nutritional status, anemia (hemoglobin level <12 g/dl), baseline ANC <1.500 cells/mm^3, baseline serum albumin ≤ 3,5 g/dl, prolonged febrile neutropenia, sepsis or pneumonia, fungal infection, hypotension, presence of an open wound, and presence ≥ 1 comorbid (cardiovascular disease, chronic obstructive pulmonary disease, liver impairment, diabetes). Cancer-related risk factors consisted of cancer type (hematologic cancer has a higher risk than solid cancer), bone marrow involvement, advanced disease, and not in remission status (refractory or progressive disease).[8,10,12]

Based on the anticancer regimen, neutropenia risk is categorized as low risk (incidence of neutropenia less than 10%), intermediate risk (10-20%), and high risk (≥20%). The high-risk regimen includes dose-dense anthracycline cyclophosphamide (AC) followed by a taxane (T); docetaxel and cyclophosphamide (TC); fluorouracil, leucovorin, oxaliplatin, irinotecan (FOLFOXIRI); cyclophosphamide, vincristine, anthracycline (VDC); bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP); brentuximab vedotin and doxorubicin, vinblastine, dacarbazine (AVD); topotecan; mesna, doxorubicin, ifosfamide, dacarbazine (MAID); etoposide, ifosfamide, cisplatin (VIP). The intermediate risk regimen includes gemcitabine/docetaxel; fluorouracil, leucovorin, oxaliplatin (FOLFOX); gemcitabine, dexamethasone, cisplatin/carboplatin (GDP); cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP); bendamustine; cisplatin/paclitaxel or vinorelbine; cabazitaxel or docetaxel; etoposide/carboplatin; bleomycin, etoposide, cisplatin (BEP). The low-risk regimen includes fluorouracil, doxorubicin, cyclophosphamide (FAC), cyclophosphamide, methotrexate, and fluorouracil (CMF). The chemotherapy regimen risk determines whether the patient needs granulocyte-colony stimulating factor (G-CSF) with or without antimicrobial prophylaxis. Those neutropenia risks of anticancer regimen are

useful for the clinician in administrating granulocyte-colony stimulating factor (G-CSF) prophylaxis.[13]

Another important thing in managing a patient with febrile neutropenia is risk stratification. The risk stratification for neutropenic patients is assessed by clinical judgment and scoring system; Multinational Association of Supportive Care in Cancer (MASCC) and the Clinical Index of Stable Febrile Neutropenia (CISNE). On MASCC, risk stratification becomes a low risk when a score of ≥21 and a high risk for a score <21 (Table 1). CISNE risk category is divided into low risk if the score is 0, intermediate risk if the score is 1 – 2, and high risk if the score is ≥3 (Table 2).[13]

Table 1. Multinational Association of Supportive Care in Cancer (MASCC) scoring system.[12,13]

Categories		Score
Burden of illness	No or mild symptoms Moderate symptoms Severe	5 3 0
Hypotension (systolic BP >90 mmHg)	No	5
Active COPD	No	4
Type of cancer	Solid tumor or lymphoma with no previous fungal infection	4
Dehydration requiring IV fluids	No	3
Status at the onset of fever	Outpatient Inpatient	3 0
Age	<60 years ≥60 years	2 0

BP: Blood Pressure; COPD: Chronic Obstructive Pulmonary Disease.

Table 2. CISNE risk stratification.[14]

Category	Score
ECOG performance status ≥2 (capable of all self-care, out of bed >50%)	2
Stress-induced hyperglycemia	2
COPD on therapy	1
Cardiovascular disease history	1
NCI mucositis ≥2	1
Monocytes <200/μL	1

Notes: ECOG: Eastern cooperative oncology group; COPD: Chronic obstructive pulmonary disease; NCI: National Cancer Institute.

Management of neutropenia in undergoing chemotherapy patients

The initial management of neutropenia in the cancer population includes assessing the risk of neutropenia according to the anticancer given as mentioned above, identifying the presence of indwelling intravenous catheters for pathogens culture, assessing the presence of focal infection (skin, respiratory system, oropharynx, digestive system, perineal area, and nervous system), examining routine laboratory tests (complete peripheral blood count, liver function test, renal function test, electrolytes (Na, K, Ca), haemostatic test include INR PT, aPTT, and D-dimer, CRP, urinalysis, sputum/oropharynx/nasopharynx swab culture, urine culture, routine faeces, tissue culture (if there is skin or soft tissue lesion), and chest imaging as indicated), followed by analysing medical record to look antibiotics and microbiology with/without granulocyte-colony stimulating factor (G-CSF) administration history.[4,15,16]

Generally, the management of neutropenic fever is differentiated from inpatient and outpatient care. The risk stratification tools described above are important to determine whether the patient is a candidate for hospitalization or outpatient care. These stratification

tools are also used as an initial assessment of neutropenic fever. The low-risk group (MASCC score ≥21, solid tumor, anticipated neutropenia more than 7 days, and no hemodynamic instability) are considered outpatient management and assessed for the CISNE tool. Patients for whom CISNE scores ≥3 should be treated as inpatient management, but if CISNE scores 1-2 may continue outpatient. The high-risk group whose MASCC score is <21, hematologic malignancy, or anticipated neutropenia ≥7 days are candidates for inpatient management (Figure 1).[4]

The etiologic of fever in patients receiving chemotherapy in the last six weeks should be assumed to be bacterial. Initial management includes taking pre-treatment blood collection within the first 15 minutes and administration of empirical antibiotics within the first hour. In health care centers that specifically have integrated oncology care, all neutropenic fever patients receive the first dose of empirical antibiotics intravenously according to the regional germ pattern and are observed for 24 hours in the clinic. The choice of empirical antibiotics is divided into intravenous antibiotics (cefepime, piperacillin, tazobactam, meropenem) and oral antibiotics (fluoroquinolones plus amoxicillin-clavulanate or plus clindamycin for those whose allergy to penicillin, levaquin, moxifloxacin). Vancomycin is only given if there is a catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability.[12,13]

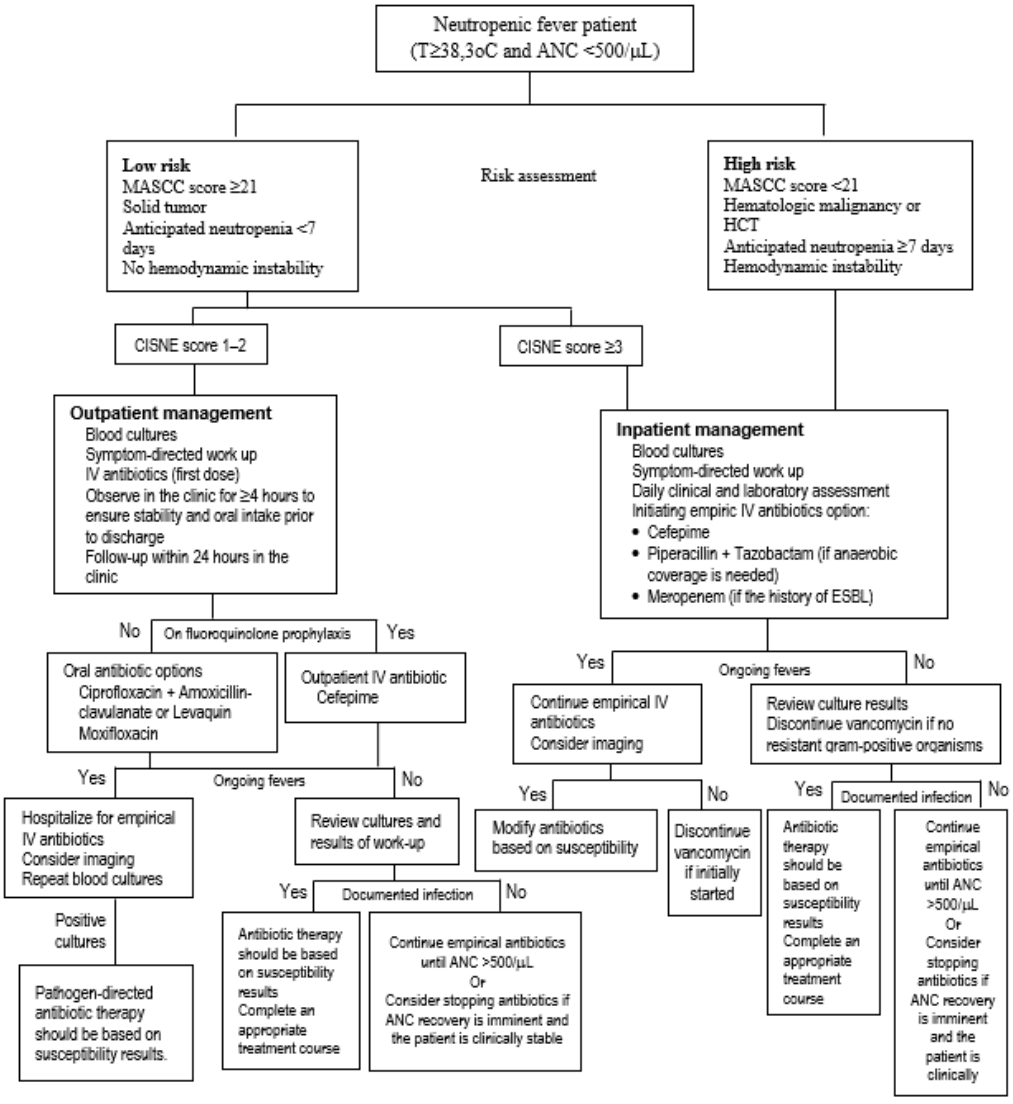

Figure 1. Management of neutropenic fever.[11]

The type of antimicrobial prophylaxis in cancer patients receiving chemotherapy include antibacterial, antifungal, and antiviral. Infectious Diseases Society of America (IDSA) recommends fluoroquinolone as antibacterial prophylaxis and oral triazole or parenteral echinocandin as antifungal prophylaxis during the period of expected neutropenia for patients at high risk of febrile neutropenia. A mold-active triazole is recommended if there is a risk of invasive aspergillosis is more than 6%, such as in patients with acute myeloid leukemia (AML)/ myelodysplasia syndrome (MDS) or during treatment of graft versus host disease (GVHD). For herpes simplex virus (HSV)-seropositive patients who are undergoing hematopoietic stem cell transplant (HSCT) or leukemia induction therapy, antiviral prophylaxis with nucleoside analogue is recommended. So that for patients at substantial risk of reactivation of hepatitis B virus (HBV) infection, treatment with a nucleoside reverse transcription inhibitors (entecavir or tenofovir) is recommended.[12,13,17]

Granulocyte-colony stimulating factor (G-CSF) in cancer

Granulocyte-colony stimulating factor (G-CSF) is a type of growth factor that helps our bone marrow to produce granulopoiesis products called neutrophils. This growth factor is not only naturally produced in the body but also can be given as a drug injection. Generally, the use of G-CSF in cancer patients is divided into primary prophylaxis, secondary prophylaxis, and therapeutic use. Primary prophylaxis is the administration of G-CSF since the first cycle of myelosuppressive chemotherapy high-risk category (>20%) or intermediate risk (10 – 20%) with the presence of one or more patient-related risk factors. This primary prophylaxis aims to prevent potential complications of neutropenia. The patient risk factors include prior chemotherapy or radiation, persistent neutropenia, bone marrow involvement by tumour including leukaemia, recent surgery and/or open wounds, liver dysfunction (bilirubin >2), renal dysfunction (CrCL <50), age >65 years at receiving full chemotherapy intensity. Patients who are treated with low-risk intensity neutropenic anticancer are not recommended to accept G-CSF injection.[10,18]

Secondary prophylaxis is the administration of G-CSF during subsequent chemotherapy cycles after an episode of febrile neutropenia that developed in the previous cycle. It aims to accelerate neutropenic recovery and avoid delays in chemotherapy. Giving G-CSF as secondary prophylaxis is preferred if the goal of chemotherapy is curative. If the goal is a palliative treatment, dose reduction of anticancer therapy is preferred.[10,18] The therapeutic use of G-CSF is only considered if neutropenic fever coincidence with the presence of one or more risk factors: age >65 years old, ANC <100/μL, hypotension, and multiple organ failure (MOF), pneumonia, invasive fungal infection, the need for hospitalization, or previous neutropenia.[10,19]

The currently available G-CSF agents include filgrastim/lenograstim at a dose of 5 μg/kgBW subcutaneously, administered in 24 – 72 hours after chemotherapy until ANC >1.000/μL. Other is pegylated-filgrastim (pegfilgrastim) at a dose of 6 mg or 100 μg/kgBW subcutaneously as a single dose. Giving G-CSF is contraindicated 48 hours before or at the same time as chemotherapy because the stimulation effect is considered not to be maximal because it will be inhibited by myelosuppressive cytotoxic agents.[7,18]

2. Conclusion

The principal management of neutropenic patients is preventive and therapeutic. Preventive management includes the use of G-CSF with or without antimicrobial prophylaxis for patients receiving intermediate to high-risk anticancer regimens. Antimicrobial is the key to managing neutropenic fever. G-CSF as therapeutic is only allowed if indicated.

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