

Editorial

Febrile Neutropenia: Prevention and Initial Management

Tontanai Numbenjapon

Division of Hematology, Department of Medicine, Phramongkutklao Hospital

Introduction

The definition of febrile neutropenia (FN) is an unidentified source of single episode of fever $> 38.3^{\circ}\text{C}$ or persistence of fever $> 38.0^{\circ}\text{C}$ over a one-hour period in conjunction with an absolute neutrophil count (ANC) less than $0.5 \times 10^9/\text{L}$ or an ANC which is expected to decrease to $0.5 \times 10^9/\text{L}$ during the next 48 hours.¹ Approximately 1% of patients with cancer receiving cytotoxic chemotherapy experience FN. The morbidity rate and mortality rate of FN is 20-30% and 10%, respectively. FN is not only a life-threatening complication of cancer chemotherapy, but also leading to unwanted dose reductions of chemotherapy and treatment delays which may compromise treatment outcomes.

Prevention and treatment of febrile neutropenia

The intensity of different chemotherapy regimens can directly influence the incidence of FN and can be classified into 3 groups consisting of low-risk (< 10%), intermediate-risk (10-20%) and high-risk (> 20%) regimens.

In general, primary granulocyte-colony stimulating factor (G-CSF) prophylaxis of FN is strongly recommended in patients treated with high-risk chemotherapy regimens.² Other additional risk factors which may be used to determine the chance of having FN are old age, advanced disease, history of prior FN, mucositis, poor performance status and cardiovascular disease.² These additional risk factors should be guided in deciding whether an intermediate-risk chemotherapy regimen-treated patients should receive primary G-CSF prophylaxis to decrease the potential risk of FN or not.²

Multinational Association of Supportive Care in Cancer (MASCC) risk index score is scored by burden of FN based on presence of no, mild or moderate symptoms;

Table 1 Multinational Association of Supportive Care in Cancer (MASCC) risk index³

Characteristics	Score
Burden of illness: no or mild symptoms	5
Burden of illness: moderate symptoms	3
Burden of illness: severe symptoms	0
No hypotension (systolic BP $> 90 \text{ mmHg}$)	5
No chronic obstructive pulmonary disease	4
Solid tumour/lymphoma with no previous fungal infection	4
No dehydration	3
Outpatient status (at onset of fever)	3
Age < 60 years	2

absence of hypotension; no chronic obstructive pulmonary disease; solid tumor or hematologic malignancy without previous fungal infection; no dehydration requiring parenteral fluids; outpatient status and age < 60 years as shown in Table 1.³ Based on MASCC risk index score, febrile neutropenic patients are classified into low-risk (MASCC risk index score ≥ 21) and high-risk (MASCC risk index score < 21) category.³

Low-risk patients have a chance of mortality of 5% while high-risk ones may have mortality rates as high as 40%.³

Evidence-based guidelines for the management of patients with FN have been developed by the IDSA, ESMO and NCCN in 2011, 2016 and 2017, respectively.^{1,4,5} Any given patient with FN should be undergone an initial risk assessment for serious complications of infection, including morbidity and mortality, to guide an appropriate treatment (Figure 1).^{1,4,5}

Low-risk febrile neutropenic patients are initially treated with oral empirical antibiotics, such as fluoroquinolones, and possibly as outpatient setting (Figure 1).^{1,4,5}

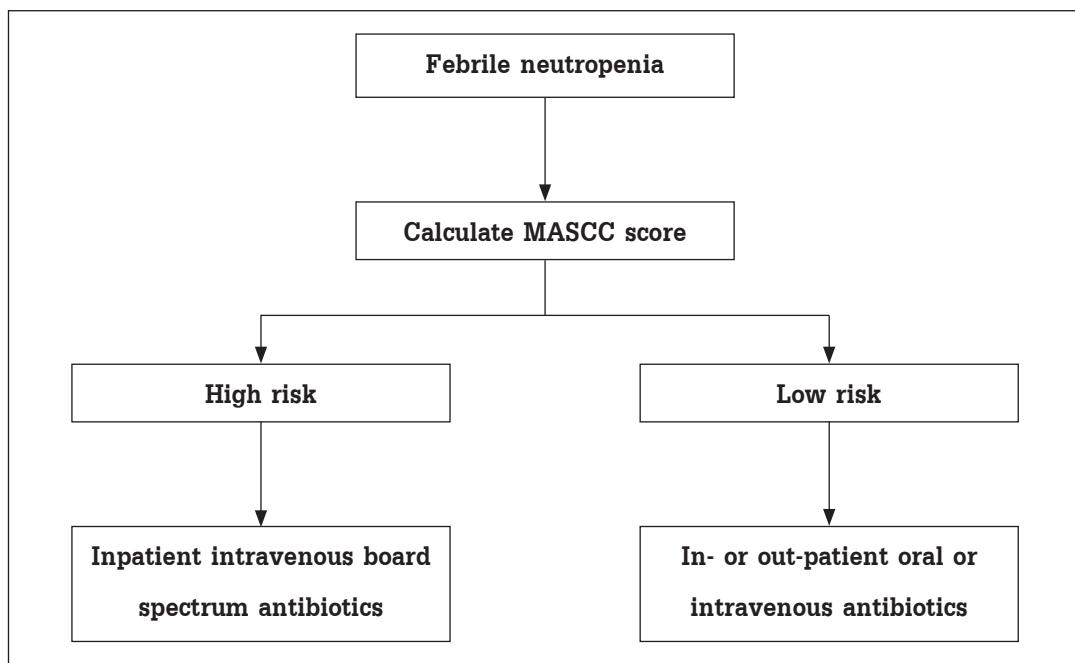


Figure 1 Initial management of febrile neutropenia

High-risk febrile neutropenic patients should be administered into the hospital and promptly initiated with intravenous empirical single-agent antibacterial therapy including antipseudomonal beta-lactam, carbapenem and piperacillin-tazobactam depending on local epidemiological bacterial isolation and resistance patterns (Figure 1).¹ However, most of Thai patients with FN regardless of risk stratification are treated in hospital. Kerdsin S, et al. has retrospectively evaluated the efficacy of empirical antimicrobial therapy for acute myeloid leukemia (AML) patients with FN. A total of 70 AML patients with 260 episodes of FN were enrolled into the study. This study did not classify patients according to the risk stratifications as mentioned before. All three commonly used empirical antibiotics including ceftazidime plus amikacin/ciprofloxacin, piperacillin/tazobactam and imipenem/meropenem had comparable efficacy to treat FN.

An addition of empirical antifungal agent to initial empirical antibiotics is not recommended for routine practice in all febrile neutropenic patients. However, empiric antifungal therapy is indicated in patient who has persistent fever of unidentified etiology following 4 to 7 days of proper antimicrobial therapy and is expected

to have overall duration of neutropenia > 7 days.¹

Fluoroquinolone prophylaxis is recommended only for patients with FN at high risk of complications.^{2,6,7} However, Thai hematologists do not widely prescribe antibacterial prophylaxis for their high-risk patients.

Antifungal prophylaxis with fluconazole, itraconazole, voriconazole, posaconazole, micafungin or caspofungin is recommended for patients with high-risk FN, such as patients with acute leukemia during induction therapy and ones with allogeneic stem cell transplantation, in whom the risks of invasive fungal infection (IFI) are high.¹

The limited use of fluconazole prophylaxis is an increasing number of fluconazole-resistant invasive candidiasis and lack of activity against most molds while the limited use of itraconazole prophylaxis is potential drug interactions, a narrow spectrum of antifungal activity and its more toxicity as compared with fluconazole. Tusanpituk T, et al, has recently conducted a retrospective study comparing the benefit of antifungal prophylaxis between oral itraconazole and fluconazole among patients with AML receiving induction chemotherapy. There were 80 AML patients with 281 cycles of chemotherapy enrolled into the study. The prevalence of IFI was 14.9% and the most common pathogen was invasive aspergillosis

(90%). In agreement of a previous meta-analysis, oral itraconazole demonstrated a better efficacy than that of fluconazole for prevention of IFI during neutropenic episodes of AML treatment.⁸ However, the authors did not compare the side effects between these two antifungal agents.

Conclusion

Since chemotherapy-induced FN may lead to overwhelming infectious complications and significant morbidity and mortality, risk assessment of an occurrence of FN and strategy to prevent FN is crucial. Intensity of different chemotherapy regimens influencing the incidence of FN plays a key role in determining whether primary G-CSF prophylaxis should be initiated or not. Prompt initiating antibacterial therapy is recommended for this group of patients. It is recommended to perform a risk assessment prior to determine whether the route of antibiotics should be oral or intravenous and outpatient or inpatient setting.

Reference

1. Freifeld AG, Bow EJ, Sepkowitz KA, et al. *Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis.* 2011;52:e56-93.doi:10.1093/cid/cir073.
2. Aapro MS, Bohlius J, Cameron DA, et al. *2010 Update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer.* 2011;47:8-32.
3. Klastersky J, Paesmans M, Rubenstein EB, et al. *The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol.* 2000;18:3038-51.
4. Klastersky J, de Naurois J, Rolston K, et al. *ESMO Guidelines Committee. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. Ann Oncol.* 2016;27(suppl 5):v111-v8.
5. NCCN Clinical Practice Guidelines in Oncology. *Prevention and treatment of cancer-related infections, version 1. 2018. National Cancer Comprehensive Network website. www.nccn.org/professionals/physician_gls/PDF/infections.pdf. Published December 1, 2017. Accessed May 13, 2018.*
6. Smith TJ, Khatcheressian J, Lyman GH, et al. *2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol.* 2006;24:3187-205.
7. Gafner-Gvili A, Fraser A, Paul M, Leibovici L. *Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med.* 2005;142:979-95.
8. Vardakas KZ, Michalopoulos A, Falagas ME. *Fluconazole versus itraconazole for antifungal prophylaxis in neutropenic patients with haematological malignancies: a meta-analysis of randomized-controlled trials. Br J Haematol.* 2005;131:22-8.

