

Chapter 31

FEBRILE NEUTROPENIA IN CANCER PATIENTS

İrem BİLGETEKİN¹

Myelosuppression associated with chemotherapy, and neutropenia is a serious side effect that can be life threatening. The most serious consequence of neutropenia is febrile neutropenia, which leads to morbidity and mortality and requires admission to hospital and broad spectrum antibiotic treatment. In febrile neutropenia (FEN), neutropenia is a major risk factor for various types of infection. Initiating antibiotic treatment without delay is of crucial importance. The choice of antibiotics varies, depending on clinical picture, previous culture results, antibiogram and especially antibiotic resistance. In this chapter, definition of febrile neutropenia, evaluation of patient with febrile neutropenia, determination of risk score, the use of colony stimulating factor and treatment of febrile neutropenia will be addressed.

FEBRILE NEUTROPENIA

Febrile Neutropenia is defined as a body temperature over 38.3°C at a single oral measurement or its being over 38 °C for one hour and an absolute neutrophil count (ANC) under 500 cells/mL or expectation that ANC will fall under 500 cells/mL within 48 hours (1). Neutropenia induced by chemotherapy leads to morbidity and mortality and the modification of chemotherapy dose in cancer patients (2). FEN may occur at the rate of about 10-50% in solid tumors and over 80% in hematological tumors (3).

Agent may be isolated only in 40-50% of neutropenic patients. Bacteremia occurs in 10%-30% of cases (4). Therefore, rapid institution of antibiotic treatment is important. The source of infection is usually intestinal system, lung and skin (5). In neutropenic patients, agents are often bacteria and fungi and viral and parasitic agents, which occur less frequently, arise with enhancement of myelosuppression (6).

Gram negative bacteria, particularly Enterobacteriaceae (including *Escherichia coli*, *Klebsiella* species, and *Enterobacter* species) and *Pseudomonas aeruginosa*

¹ Medical Doctor, University of Health Sciences, Dr A. Y. Ankara Oncology Education and Research Hospital, Department of Medical Oncology, Ankara-TURKEY e-mail: irembilgetekin@gmail.com

MONITORIZATION AND TREATMENT PROCESS

When patient is afebrile and the leucocyte count is >500 neutrophils/mm³ at 48 hours, oral antibiotic treatment may be started in low risk patient. In high risk patient, if the causative agent has not been detected and combined treatment is used, monotherapy with carbapenem or antipseudomonal penicillin is recommended.

If the patient is still febrile at 48 hours, clinical condition is evaluated. If clinical condition is stable, empiric treatment used at onset is continued. If it is unstable, treatment spectrum is extended (6).

In conclusion; Febrile neutropenia is an oncological emergency condition that requires immediate detection and treatment. In its treatment, the initiation of empiric antibiotic treatment may significantly decrease morbidity and mortality.

REFERENCES

1. Freifeld AG, Bow EJ, Sepkowitz KA, et al: 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* 52:e56-e93, 2011
2. Crawford J, Ozer H, Stoller R, et al: Reduction by granulocyte colony stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *N Eng J Med* 325:164-170, 1991.
3. Bodey, G.; Buckley, M.; Sathe, Y.S.; Freireich, E.J. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann. Intern. Med.* 1966, 64, 328. [CrossRef] [PubMed]
4. Baden LR, Swaminathan S, Angarone M, et al: Prevention and treatment of cancer-related infections, version 2.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 14:882-913, 2016
5. Freifeld, A.; Bow, E.J.; Sepkowitz, K.A.; Boeckh, M.J.; Ito, J.I.; Mullen, C.A.; Raad, I.I.; Rolston, K.V.; Young, J.A.; Wingard, J.R. 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–e93. [CrossRef] [PubMed]
6. M. Alonso J. Corral Febrile Neutropaenia in Cancer Patients: esmo handbook of oncological emergencies (2016) part:21(208-218)
7. Schimpff SC: Gram-negative bacteremia. *Support Care Cancer* 1:5-18, 1993
8. Andrea J. Zimmer, MD and Alison G. Freifeld, MD Optimal Management of Neutropenic Fever in Patients With Cancer *Journal of Oncology Practice* 2018, 15:19-24
9. J.Klastersky, J.deNaurois, K.Rolston, B.Rapoport, G.Maschmeyer, M.Aapro, J.Herrstedt Management of febrile neutropaenia: ESMO Clinical Practice Guidelines *Annals of Oncology* 2016, 27 v111-v118.
10. Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R, 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.
11. NCCN Clinical Practice Guidelines in Oncology, Myeloid Growth Factors version 2.2018 NCCN.org

12. Vogel CL, Wojtukiewicz MZ, Carroll RR, et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double blind, placebo –controlled phase 3 study *J Clin Oncol* 2005; 23: 1178-1184. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15718314>.
13. Lyman GH, Kuderer NM. The economics of the colony-stimulating factors in the prevention and treatment of febrile neutropenia. *Crit Rev Oncol Hematol* 2004; 50: 129-146. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15157662>
14. Ozer H, Armitage JO, Bennett CL et al. :2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. American Society of Clinical Oncology Growth Factors Expert Panel. *J. Clin. Oncol.* (2000) 18(20):3558-3585.
15. Amgen: Neulasta (pegfilgrastim). Package Insert (2002).
16. Lyman GH, Kuderer NM, Crawford J, Dale D: Economic impact of pegfilgrastim use based on the risk of febrile neutropenia (FN) in NHL patients with CHOP. *Proc. Am. Soc. Clin. Oncol.* (2003) 22:593.
17. Feld R. Bloodstream infections in cancer patients with febrile neutropenia. *Int J Antimicrob Agents* 2008; 32 (Suppl. 1): S30–S33.
18. Montassier E, Batard E, Gastinne T et al. Recent changes in bacteremia in patients with cancer: a systematic review of epidemiology and antibiotic resistance. *Eur J Clin Microbiol Infect Dis* 2013; 32: 841–850.
19. Rolston KV, Bodey GP. Comment on: empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2006; 58: 478; author reply: 479–480.
20. Averbuch D, Orasch C, Cordonnier C, et al: European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: Summary of the 2011 4th European Conference on Infections in Leukemia. *Haematologica* 98:1826-1835, 2013.
21. Raad I, Kassar R, Ghannam D et al. Management of the catheter in documented catheter-related coagulase-negative staphylococcal bacteremia: remove or retain? *Clin Infect Dis* 2009; 49: 1187–1194.
22. Theel ES, Doern CD: b-D-glucan testing is important for diagnosis of invasive fungal infections. *J Clin Microbiol* 51:3478-3483, 2013.
23. Glenny AM, Fernandez Mauleffinch LM, Pavitt S, Walsh T. Interventions for the prevention and treatment of herpes simplex virus in patients being treated for cancer. *Cochrane Database Syst Rev* 2009; (1): CD006706.

ABBREVIATIONS:

ANC: Absolute neutrophil count

CMV: Cytomegalovirus

CT: Computerized tomography

FEN: Febrile neutropenia

G-CSF: Granulocyte stimulant factor

HRCT: High resolution computerized tomography

MASCC: Multinational Association for Supportive Care in Cancer

MGF: Myeloid growth factor

NCCN: The National Comprehensive Cancer Network