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Research

C-reactive Protein Guided Empirical Antibiotic Therapy Versus Standardized Neutropenic Fever Approach in Patients Undergoing High-dose Chemotherapy Followed by Autologous Stem Cell Transplantation

Yüksek Doz Kemoterapi Sonrası Otolog Kök Hücre Nakli Yapılan Hastalarda C-reaktif Protein Rehberliğinde Ampirik Antibiyotik Tedavisi ile Standart Nötropenik Ateş Yaklaşımının Karşılaştırılması

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ABSTRACT

Objective: To evaluate the outcomes of C-reactive protein (CRP) guided empirical antibiotic therapy versus standardized neutropenic fever approach in patients undergoing autologous stem cell transplantation.

Methods: Group 1 (n=133) comprised patients who were administered triple combination antibiotic treatment when their plasma CRP levels doubled. Group 2 (n=117) composed of patients who received guideline-based triple combination antibiotic treatment only when fever was detected during neutropenia.

Results: The median duration of neutropenia was 7 days in group 1 (3-18) and group 2 (4-21). The median length of hospital stay was 20 days for group 1 and 18 days for group 2, with similar durations. Fever was encountered in 64.7% of patients within group 1. The median duration of antibiotic therapy until discharge was 9 days in group 1 and 10 days in group 2, with no significant difference observed (p=0.212). One patient in group 1 died, and two patients in group 2 died due to sepsis. In patients who were diagnosed with lymphoma, the median value of the duration of antibiotic therapy until discharge was 10 days in group 1 and 14 days in group 2 (p<0.05).

Conclusion: Our findings demonstrate that empirical antibiotic initiation in this patient group was not beneficial in terms of duration of hospital stay, engraftment periods, duration of antibiotic treatment, and mortality rates. While the strategy was non-inferior to the standardized approach, further research is required for risk stratification and implementation, especially in frail patients with specific diagnoses and comorbidities.

Keywords: Neutropenic fever, empirical antibiotic treatment, C-reactive protein, hematopoietic stem cell transplantation

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ÖZ

Amaç: Otolog kök hücre nakli yapılan hastalarda C-reaktif protein (CRP) rehberliğinde ampirik antibiyotik tedavisi ile standart nötropenik ateş yaklaşımının sonuçlarını karşılaştırmalı olarak değerlendirmektir.

Gereç ve Yöntem: Grup 1 (n=133), nötropeniye girdikten sonra plazma CRP seviyeleri önceki iki güne kıyasla iki katına çıktığında üçlü kombinasyon antibiyotik tedavisi uygulanan hastalardan oluşuyordu. Grup 2 (n=117) ise nötropenik dönem esnasında ateş tespit edildiğinde kılavuzlara uygun şekilde üçlü kombinasyon antibiyotik tedavisi uygulanan hastalardan oluşuyordu.

Bulgular: Medyan nötropeni süresi her iki grupta 7 gün saptanmıştır (grup 1: 3-18, grup 2: 4-21). Medyan hastanede yatış süresi grup 1 için 20 gün ve grup 2 için 18 gün olup, süreler benzerdir. Grup 1'e hastaların %64,7'sinde ateş gözlemlenmiştir. Medyan antibiyitoik tedavi süresi grup 1'de 9 gün, grup 2'de 10 gün olup, anlamlı bir fark saptanmamıştır (p=0,212). Grup 1'de bir hasta, grup 2'de ise iki hasta sepsis nedeniyle kaybedilmiştir. Lenfoma tanısı alan hastalar ayrıca incelenmiş ve toplam antibiyotik tedavi süresinin medyan değeri grup 1'de 10 gün, grup 2'de ise 14 gün olarak bulunmuştur (p<0,05).

Sonuç: Çalışmamız, bu hasta grubunda standart nötropenik ateş yaklaşımına kıyasla CRP artışına göre ampirik antibiyotik başlanmasının hastanede yatış süresi, engraftman süreleri, antibiyotik tedavi süresi ve mortalite oranları açısından daha faydalı olmadığını göstermektedir. Bu strateji standart yaklaşımdan daha kötü olmamakla birlikte, özellikle belirli tanılara ve komorbiditelere sahip hastalarda uygun risk belirlenmesi ve uygulanabilmesi için daha fazla geniş kapsamlı çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Nötropenik ateş, ampirik antibiyotik tedavisi, C-reaktif protein, hematopoetik kök hücre nakli

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT), the procedure of administering hematopoietic stem cells to quickly restore bone marrow function following high-dose chemotherapy, has been widely used for treating hematological diseases. Although its use has increased patient survival, the risk of infection is an important cause of morbidity and mortality among those undergoing this therapeutic approach. Modifications in HSCT management and better supportive care have resulted in improvements in prevention and successful treatment of infections. The modifications mentioned may be listed as the incorporation of new anti-microbial agents, increased knowledge of immune reconstitution, and development of less toxic conditioning regimens. Despite these advances, infection is the primary cause of death in 8% to 15% of autologous HSCT patients and 17% to 20% of allogeneic HSCT recipients (1).

Following disease relapse, infection is the second most frequent cause of death after autologous HSCT. Patients have the highest risk of infection during the neutropenia period for up to 30 days after bone marrow grafting (2,3). Patients who have undergone autologous HSCT are at the highest risk of infection during the neutropenia period and for up to 30 days after bone marrow grafting. The prolonged neutropenia period and the breach of the mucocutaneous barrier are the main risks for the developing infections (2,4).

Anti-bacterial, anti-viral, and anti-fungal prophylaxis has become a standard measure for protecting HSCT patients against serious infections. The effort to minimize infection-related complications and deaths continues, so the guidelines for prevention and treatment of infections in the HSCT setting are being constantly updated (5). The main focus of the current guidelines is prevention of infections, adequate timing and selection of the anti-infective therapy according to the patients' clinical condition. In common practice, an anti-infective therapy is usually commenced following a febrile episode in neutropenia. Virtually all HSCT patients are under anti-infective prophylaxis at the time of their first febrile episode. Usually, the prodromal period of the infection is short and may remain unnoticed due to symptoms overlapping with the conditioning regimen. The most common initial symptom of the infection in patients is high fever, sometimes accompanied by systemic inflammatory response syndrome features. The guidelines postulate urgent commencement of broad spectrum antibiotics after obtaining adequate culture samples and supportive care as an initial approach for HSCT patients with neutropenic fever (2). The vast majority of the patients benefit from this and fully recover after neutrophil engraftment, but some patients still develop septic shock and die before neutrophil recovery despite seemingly appropriate treatment.

C-reactive protein (CRP) is a valuable and commonly used marker for inflammation, particularly infection severity. To predict the risk of fatal infections in neutropenic HSCT patients, some researchers have studied the impact of the CRP levels on infection-related mortality of the allogeneic and autologous HSCT patients (6). In a recent review, Massaro and colleagues researched the value of different biomarkers as predictors for infection and mortality in febrile neutropenic HSCT patients (7). In some of the major studies included in the review, elevation of CRP levels was associated with increased risk of death from infection and was well correlated with bloodstream infections (7,8). CRP levels commonly rise shortly after the level of IL-6 is elevated. This usually occurs before the body temperature starts to increase; thus, a CRP surge can be the first sign

of an ongoing infectious process. Given the importance and the usefulness of CRP as an early predictor of serious infections, we hypothesized that early empirical anti-bacterial therapy based on the increasing CRP levels, before the febrile response, may reduce the incidence and duration of neutropenic fever in autologous HSCT patients.

METHODS

Patient Selection

In this single-center observational retrospective study, 250 patients who underwent autologous HSCT due to lymphoma or multiple myeloma were enrolled. Age, gender, remission status, number of previous chemotherapies, Hematopoietic Cell Transplantation-Comorbidity index score, and baseline CRP levels were recorded upon admission. Those who had clinical evidence of any infection, decreased renal function, cardiac event within the past three months, and unexplained high CRP levels were excluded from the study. Since the requirements for autologous HSCT necessitate at least partially controlled primary malignancy, patients with active lymphoma and myeloma were not included in the study. Primary prophylaxis with valacyclovir 500 mg/d starting on day-7, levofloxacin 500 mg/d on day-5 and fluconazole 100 mg/d starting after the transplant day was given to all patients until neutrophil engraftment (>500/mm^3). In some patients who had neutropenic fever under primary prophylaxis, levofloxacin was changed to amikacin, and a few patients required broad spectrum anti-fungal therapy with caspofungin or liposomal amphotericin B instead of fluconazole.

A total of 133 patients who underwent autologous HSCT between 2016 and 2018 were enrolled to receive triple combination antibiotic treatment with piperacillin/tazobactam, amikacin, and teicoplanin when their plasma CRP levels doubled compared to the CRP levels on the previous two days after neutropenia had commenced. This group who started antibiotic treatment according to CRP trend was named group 1. In the neutropenic patients whose CRP levels did not increase significantly and who had febrile episodes, the same triple combination antibiotic therapy was commenced at the time of fever. Samples for aerobic and anaerobic blood culture, urine culture, and sputum culture were obtained in advance from all patients according to their symptoms who received triple antibiotic therapy. The patients who remained afebrile during the neutropenia period and had maintained normal CRP levels continued with the primary prophylaxis until neutrophil engraftment.

Apyrexial patients with a rapid increase in CRP levels preceding neutropenia were followed without changing the primary prophylaxis, as long as their neutrophils remained above 500/mm^3. Those patients were administered triple antibiotic treatment after they entered neutropenia even in the absence of fever. Before the neutropenic period, development of a febrile condition without an evident infection locus and without concurrent CRP increase was not an indication for empirical antibiotic therapy.

After a neutropenic patient was administered triple antibiotic therapy based on CRP levels, further antibiotic modification was performed according to the culture and antibiotic susceptibility results, or if there was breakthrough fever with no clinical response to the ongoing treatment. Antibiotics were discontinued if the patient had a neutrophil count greater than 1000/mm^3, and remained clinically stable and afebrile for at least 48 hours.

A total of 117 patients who underwent autologous HSCT between 2012 and 2015 were administered empirical triple combination antibiotic therapy at the time of first episode of neutropenic fever, regardless of the CRP levels, in accordance with the latest Infectious Diseases Society of America guideline (9). Treatment was modified based on the results of the culture and antibiotic susceptibility testing and if there was no initial clinical response to the primary anti-infective treatment. This group was named group 2, and both groups received the same conditioning regimens and primary prophylaxis.

Stem Cell Harvesting

Patients diagnosed with myeloma underwent stem cell mobilization with filgrastim 10 mcg/kg for 5 days, with the exception of patients who had insufficient peripheral CD34+ cells on day 4 of mobilization. The mentioned patients were mobilized 3 weeks later, with plerixafor and filgrastim.

Stem cell harvesting was performed after second line salvage chemotherapy followed by filgrastim in patients who were diagnosed with lymphoma.

Conditioning Regimens

Melphalan 200 mg/m^2 on day-2 was administered as a conditioning regimen before autologous HSCT in patients diagnosed with multiple myeloma. Dose reduction to 140 mg/m^2 was performed in patients who had creatinine clearance below 50 mL/min.

Patients diagnosed with Hodgkin's disease and non-Hodgkin lymphoma received the BEAM protocol (BCNU 300 mg/m^2, on day-7; etoposide 200 mg/m^2, and ARA-C 200 mg/m^2/bid, between day-6 and -3; MLN 140 mg/m^2, on day-2) as

a conditioning regimen. Stem cell infusion was performed on day 0 following premedication for infusion reactions with acetaminophen, diphenhydramine, and prednisolone.

This study was approved by Acıbadem University Ethics Committee (approval no: 2024-9/361, date: 30.05.2024) and written informed consent was obtained from each patient.

The clinical and laboratory data obtained from these patients were recorded and compared statistically. The primary end points of this study were to investigate whether there was a positive effect of initiating empirical antibiotic therapy based on the surge of CRP levels, on the death rate due to infection, the number of febrile neutropenic days, and hospitalization duration in patients undergoing autologous transplant. The secondary endpoint was to investigate whether shorter antibiotic treatment periods and fewer breakthrough febrile episodes, with fewer changes in the anti-infective regimen, could be achieved in group 1 compared to the patients who were given empirical antibiotics based on the classical indications for treatment of neutropenic fever.

Statistical Analysis

The statistical analysis was performed with SPSS version 26.0 (IBM Corp., released 2019, IBM SPSS Statistics for Macintosh, Version 26.0) and a value of $p<0.05$ was considered statistically significant. The normality of the variables was assessed using the Shapiro-Wilk test.

RESULTS

A total of 250 patients were included; 133 patients were in group 1, who were given empirical antibiotic treatment following a threefold increase in their CRP levels (Table 1). Group 2, which included patients who received a guideline-based standardized approach, consisted of 117 patients. The median age of the patients in group 1 was 55 (range: 18-76), while it was 58 (range: 21-73) in group 2, and there was no significant difference between the two groups ($p=0.632$). The median length of hospital stay was 20 days in group 1, while it was 18 days in group 2. Median duration of neutropenia was 7 days in group 1 (3-18) and group 2 (4-21). In group 1, fever was encountered in 90 out of 133 patients (64.7%). The mean number of days with fever was 3.14 in group 1 and 1.01 in group 2, and a significant difference was detected ($p<0.05$). Median day of neutrophil engraftment was 11 in group 1 and 9 in group 2, and a clinically significant difference was not observed. As consecutive CRP testing was not performed on patients in group 2, a baseline CRP level was only available for group 1 and it was calculated as 0.47 (normal value <0.5 mg/dL). The median day of the detection of a threefold increase in CRP was 5±1.71 days in group 1. The median CRP level at discharge was 2.02±1.86 in group 1. Median day of platelet engraftment was 13 in group 1 and 11 in group 2, and a significant difference was not detected.

The median value of the total duration of antibiotic treatment until discharge was 9 days in group 1 and 10 days in group 2, and a significant difference was not detected ($p=0.212$). The type of antibiotic treatment was escalated in a total of 70 (52.6%) patients within group 1, compared to 27 (23%) patients within group 2.

Anti-fungal treatment was administered to 22 (19%) patients in group 1 while 4 patients received anti-fungals in group 2 (0.3%) ($p=0.001$). Anti-viral treatment was not required in any patient. One patient in group 1 died, while two patients died due to sepsis in group 2, despite ICU admission.

Multiple myeloma was the most frequent diagnosis with a total of 162 patients, with the two groups combined. The patients who were diagnosed with multiple myeloma were further investigated, and the median length of hospital stay was 18 days in group 1 (n=84) while it was 16 days in group 2 (n=78) ($p<0.05$). Median duration of neutropenia was 6 days in group 1 (4-13) and group 2 (4-18). The mean number of days with fever was 2.62 in group 1 and 0.54 in group 2, which was statistically significant ($p<0.05$). The median day

Table 1. Patient characteristics and end points analysis

	Group 1 (n=133)	Group 2 (n=117)	p-value
Age, median (min-max)	55 (18-76)	58 (21-73)	0.632
Length of hospital stay, median days (min-max)	20 (13-47)	18 (12-66)	**0.0001**
Duration of neutropenia, median days (min-max)	7 (3-18)	2 (4-21)	0.059
Number of days with fever, mean	3.14	1.01	**0.0001**
Neutrophil engraftment, median days	11	9	**0.0001**
Platelet engraftment, median days	13	11	**0.0001**
Duration of antibiotic treatment, median days	9	10	0.212
Anti-fungal treatment administered n (%)	22 (19)	2 (0.3)	**0.0001**

min: Minimum, max: Maximum

of neutrophil engraftment was 11 in group 1 and 8 in group 2 ($p<0.05$).

A total of 88 patients were diagnosed with lymphoma. Out of these, 44 patients were in group 1, while 39 patients were in group 2. The subset of patients who were diagnosed with lymphoma was analyzed, and the median length of hospital stay was calculated as 22 days for both groups. The median duration of neutropenia was 8 days in group 1 (3-18) and 10 days in group 2 (6-21). The mean number of days with fever was 4.05 in group 1 and 1.95 in group 2 ($p<0.05$). Median day of neutrophil engraftment was 10 in group 1 and 12 in group 2 ($p<0.05$). The median value of the total duration of antibiotic treatment until discharge was 10 days in group 1 and 14 days in group 2 ($p<0.05$).

Blood culture was obtained from 116 patients within group 1, and a positive blood culture was detected in 16 (13.8%) (Table 2). Culture studies were performed on all of the 117 patients within group 2, and 39 (33.2%) patients had a positive blood culture. If remission was not achieved within 48 hours, a second blood culture was performed. A second culture was required for 50 patients among group 1, and positive culture results were obtained from 5 patients. In group 2, 116 patients required second blood cultures and positive results were detected in 12 patients. If satisfactory clinical or biochemical response was not achieved after the second culture, a third blood culture was performed. A third culture was performed in 13 patients in group 1. One patient's blood culture was positive. A third blood culture was not required for 120 patients in group 1. In group 2, a third blood culture was performed on 114 patients, and 5 patients had positive results. The median days for the total duration of indwelling catheters was 20.1 in group 1 and 16.1 in group 2.

Among the 16 patients who had positive first blood cultures, 19 microorganisms were detected with the culture studies, in group 1. Within this patient population, *Staphylococcus epidermidis* was detected in 11 (57%) patients and *Staphylococcus hominis* was detected in 4 (21%) patients. Among the reaiming 4 cultures, each of the microsoganisms *Streptococcus viridans, Staphylococcus aureus,* extended-spectrum beta-lactamase producing *Escherichia coli* and *Globicatella sanguinis* was detected once (0.5%).

Within group 2, microorganisms were identified from all 39 first blood cultures. Within this patient population, *Staphylococcus epidermidis* was detected in 14 (35%) patients, *Escherichia coli* was detected in 9 (23%), *Staphylococcus aureus* was identified in 5 (12%) patients, and *Staphylococcus hominis* was identified in 4 (20%) patients. The bacterial isolates identified were *Clostridium difficile* in 3 (7%) patients and *Staphylococcus haemolyticus* in 2 (5%) patients. *Klebsiella pneumoniae* and *Candida species* was detected once (0.2%).

DISCUSSION

Prompt management of febrile neutropenia is especially critical for patients with hematological malignancies due to their higher risk of mortality from severe infections (10). In harmony with guideline-directed medical therapy, the onset of fever has been the cornerstone of broad-spectrum antibiotic treatment initiation. Despite early initiation of antibiotic treatment after detection of fever, mortality rates range from 10% to 30% in this patient population, and patients with comorbidities have the highest risk (11,12). As the capacity to generate an inflammatory response is hindered, some patients may not demonstrate signs and symptoms of infection, especially in the early days, resulting in a delay in treatment. We aimed to investigate the outcomes of an alternative approach that used preemptive antibiotic treatment in the setting of CRP doubling before the development of fever, and to compare the outcomes of the cohort that was treated with a standardized approach.

One of the prominent differences between two groups was that fever was not detected in 47 patients within group 1 (35.3 %). Among the 47 patients who were afebrile throughout their hospital stay, 34 were diagnosed with multiple myeloma while 13 were diagnosed with lymphoma. As antibiotic treatment was empirically started, sepsis, septic shock, or other manifestations of invasive infection may have been prevented. It is well-established data that neutropenic fever is encountered in more than 80% of

Table 2. Blood culture outcomes

	Group 1 (n= 133)	Group 2 (n= 117)
Blood culture obtained (%)	116 (87.2)	117 (100)
No of patients with positive first blood culture (%)	16 (13.8)	39 (33.2)
Second blood culture obtained (%)	50 (37.6)	116 (99.1)
No of patients with positive second blood culture (%)	5 (10)	12 (10.3)
Third blood culture obtained (%)	13 (9.8)	114 (97.4)
No of patients with positive third blood culture (%)	1 (7.7)	5 (4.4)

patients with hematologic malignancy (9). In our study, as only 65.7% of the patients developed fever within group 1, severe infection risk may have been reduced in a substantial number of patients. This risk reduction was more prominent in patients who were diagnosed with multiple myeloma since most of the afebrile patients had this diagnosis. This finding may be associated with the fact that the duration of neutropenia is generally lower in myeloma patients compared to patients diagnosed with lymphoma (13).

In a study where the outcomes of empirical and preemptive anti-fungal treatment during neutropenic fever were compared in patients with hematologic malignancies, the mortality rates were 97.1% and 94.6% respectively (p=0.305) (14). Even though there was not a significant difference between mortality rates, invasive fungal infection was detected 9.2% in the preemptive group, while it was 2.2% in the empirical treatment group. Similar to our study, Yuan et al. (14), postulated that empirical treatment in this vulnerable patient population may be effective in the prevention of invasive infections.

The median durations of antibiotic treatment were similar for both groups, were 9 days and 10 days for group 1 and group 2, respectively. Therefore, in terms of treatment duration, we concluded that the empirical approach was not favorable compared to the standardized approach. However, when we further analyzed these data for lymphoma patients, the median durations of antibiotic treatment were 10 days for group 1, while it was 14 days for group 2 ($p<0.05$). As most of the patients who were diagnosed with lymphoma were more frail due to a history of recurrent chemotherapy, and as most of these patients were not in complete remission; this patient population is more vulnerable to infections due to issues like longer neutropenia periods. Consequently, for a subset of patients with lymphoma from our study, this empirical strategy may be beneficial to alleviate the severe burden of infection.

Additionally, while 70 patients required antibiotic treatment escalation within group 1, only 27 patients required escalation within group 2. In our study, the early initiation of antibiotic treatment was associated with treatment escalation. Anti-fungal treatment was administered to 19% and 0.3% of the patients in groups 1 and 2, respectively. Overall, our study demonstrated that broader spectrum antibiotic treatment, along with higher rates of anti-fungal treatment, were used when the empirical approach was implemented.

The median length of hospital stay and the duration of neutropenia were similar in both groups. The median days of neutrophil engraftment and platelet engraftment were also similar between both groups. Mortality rates were 0.75 and 1.7 for groups 1 and 2, respectively, and a clinically significant difference was not detected. A positive blood culture result was obtained in 13.8% of the patients in group 1, while 33.2% of the patients in group 2 had positive culture results.

Study Limitations

This study has several limitations. Besides the small sample size and the lack of random sampling, a retrospective analysis was performed, which may have resulted in bias.

CONCLUSION

Our data demonstrate that empirical antibiotic initiation within this patient population was not favorable in terms of duration of hospital stay, engraftment periods, duration of antibiotic treatment, and mortality. This strategy may be considered for patients with certain diagnoses and comorbidities, taking into account the frailty of patients. This study showed that the empirical treatment strategy was non-inferior to the standardized approach. More research is needed to perform proper risk stratification and implementation in the future.

ETHICS

Ethics Committee Approval: This study was approved by Acıbadem University Ethics Committee (approval no: 2024-9/361, date: 30.05.2024).

Informed Consent: Written informed consent was obtained from each patient.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: A.U., C.Ü., N.R.C., H.G., T.Y., B.K., S.S.K., Concept: A.U., C.Ü., Y.O., B.K., S.S.K., Design: A.U., C.Ü., B.K., S.S.K., Data Collection or Processing: Y.G., Y.O., N.R.C., H.G., Analysis or Interpretation: A.U., Y.G., C.Ü., Y.O., T.Y., S.S.K., Literature Search: Y.G., N.R.C., T.Y., Writing: A.U., Y.G.

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REFERENCES

1. CIBMTR Summary Slides [Internet]. Available from: https://cibmtr.org/CIBMTR/Resources/Summary-Slides-Reports
2. Dykewicz CA; Centers for Disease Control and Prevention (U.S.); Infectious Diseases Society of America; American Society of Blood and Marrow Transplantation. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis. 2001;33:139-44.

3. Mendes ET, Dulley F, Basso M, Batista MV, Coracin F, Guimarães T, et al. Healthcare-associated infection in hematopoietic stem cell transplantation patients: risk factors and impact on outcome. Int J Infect Dis. 2012;16:424-8.
4. Mackall C, Fry T, Gress R, Peggs K, Storek J, Toubert A, et al. Background to hematopoietic cell transplantation, including post transplant immune recovery. Bone Marrow Transplant. 2009;44:457-62.
5. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15:1143-238.
6. Ortega M, Rovira M, Almela M, de la Bellacasa JP, Carreras E, Mensa J. Measurement of C-reactive protein in adults with febrile neutropenia after hematopoietic cell transplantation. Bone Marrow Transplant. 2004;33:741-4.
7. Massaro K, Costa SF. Role of biomarkers as predictors of infection and death in neutropenic febrile patients after hematopoietic stem cell transplantation. Mediterr J Hematol Infect Dis. 2015;7:e2015059.
8. Prat C, Sancho JM, Dominguez J, Xicoy B, Gimenez M, Ferra C, et al. Evaluation of procalcitonin, neopterin, C-reactive protein, IL-6 and IL-8 as a diagnostic marker of infection in patients with febrile neutropenia. Leuk Lymphoma. 2008;49:1752-61.
9. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, 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. 2011;52:56-93.
10. Shmuely H, Monely L, Shvidel L. All-cause mortality and its predictors in Haemato-oncology patients with febrile neutropenia. J Clin Med. 2023;12:5635.
11. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer. 2006;106:2258-66.
12. Weerasubpong B, Makruasi N, Linasmita P, Rattanamongkolgul S. Factors associated with survival outcomes of febrile neutropenia in hematologic malignancy patients. J Med Assoc Thai. 2016;99(Suppl 8):S53-62.
13. Ria R, Reale A, Moschetta M, Dammacco F, Vacca A. Neutropenia and G-CSF in lymphoproliferative diseases. Hematology. 2013;18:131-7.
14. Yuan W, Ren J, Guo X, Guo X, Cai S. Preemptive antifungal therapy for febrile neutropenic hematological malignancy patients in China. Med Sci Monit. 2016;22:4226-32.