Original Article

Prognostıc Factors and Changing Paradigms in Febrile Neutropenia Episodes

Febril Nötropeni Ataklarında Prognostik Faktörler ve Değişen Paradigmalar

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ABSTRACT

Introduction: The epidemiology of pathogens responsible for febrile neutropenia (FEN) has changed and so did the diagnostic tools in the field of infectious diseases. This study examined the changing paradigms and prognostic factors in FEN episodes.

Materials and methods: This was a prospective and observational study of 145 adult patients aged 18 and older with solid tumor and hematological malignancies and who received FEN treatment at our cancer center between April 2020 and April 2021; 176 FEN episodes developed in patients and were examined.

Results: Hematological malignancy was present in 70.3% (n=102) of the 145 patients. Microbiologically-confirmed infections were seen in 46% of FEN episodes. The most common focus of infection was lower respiratory tract infections with 27.1%. In 66.2% (n=45) of FEN episodes, only gram-negative microorganisms grew while only gram-positive microorganisms grew in 19.1% (n=13). Bacteremia was significantly higher in patients with hematological malignancies versus patients with solid organ tumors (p<0.001). Deep neutropenia on day zero was associated with bacteremia (p<0.001), but the relationship between prolonged neutropenia and bacteremia could not be demonstrated (p=0.34). FEN-related mortality was 9.7% (n=17). The risk of mortality in FEN was 10.25-fold higher in patients with pneumonia and 6.05-fold higher in patients with prolonged neutropenia.

Discussion: We determined that the frequency of pneumonia increased in the FEN clinic due to the effects of newly introduced chemotherapeutics. Gram-negative microorganisms were more common in the causative profile unlike the previous decade. Pneumonia and prolonged neutropenia increase mortality. Comprehensive multicenter studies will allow for the development of new management algorithms for changing paradigms.

Keywords: Febrile neutropenia, Hematological Malignancies, Mortality, Solid Tumor

ÖZET

Giriş: Enfeksiyon hastalıklarının klinik ve laboratuvar tanısındaki gelişmeler ve yıllar içinde değişen etken spektrumu kanser tedavisi süresince Febril nötropeni (FEN) ataklarının güncel takibini gerekli hale getirmiştir. Bu çalışmada FEN ataklarında değişen paradigmaların ve prognostik faktörlerin araştırılması amaçlanmıştır

Gereç ve yöntemler: Prospektif, gözlemsel yürütülen bu çalışmaya, Nisan 2020-Nisan 2021 tarihleri arasında kanser merkezimizde FEN nedeniyle yatarak tedavi gören 18 yaş ve üzeri solid tümörü ve hematolojik malignitesi olan 145 erişkin hasta alındı ve hastalarda gelişen 176 FEN atağı incelendi.

Bulgular: Çalışmaya dâhil edilen 145 hastanın %70.3'ünde (n=102) hematolojik malignite mevcuttu FEN ataklarının %46'sında mikrobiyolojik olarak kanıtlanmış enfeksiyon saptandı ve en sık enfeksiyon odağının %27.1 ile alt solunum yolu enfeksiyonları olduğu görüldü. FEN ataklarının %66.2'sinde (n=45) sadece gram negatif, %19.1'inde (n=13) sadece gram pozitif mikroorganizma üredi. Hematolojik maligniteli hastalarda solid organ tümörlü hastalara göre bakteriyemi istatistiksel olarak anlamlı olacak şekilde daha yüksekti (p<0.001). Sıfırıncı günde derin nötropeni olması bakteriyemi ile ilişkili

First Received: 01.04.2023, Accepted: 07.06.2023 doi: 10.5505/aot.2023.79990

bulunurken (p<0.001), uzamış nötropeninin bakteriyemi ile ilişkisi gösterilemedi (p=0.34). FEN'e bağlı mortalite %9.7 (n=17) oranında görüldü. FEN'de mortalite riski, pnömonisi bulunan hastalarda 10.25 kat ve uzamış nötropenisi olan hastalarda 6.05 kat daha fazlaydı.
Tartışma: FEN ataklarının klinik ve laboratuvar bulgularının araştırıldığı bu çalışmada yeni kullanıma giren kemoterapötiklerin etkisiyle FEN kliniğinde pnömoni sıklığının arttığı ve etken profilinde geçtiğimiz dekattan farklı olarak gram negatif mikroorganizmaların daha çok olduğu saptanmıştır. Ayrıca pnomoni ve uzamış nötropeni varlığının mortaliyeti arttırdığı görülmüştür. Kapsamlı multicenter çalışmalar, değişen paradigmalara yönelik yeni yönetim algoritmalarının oluşturulmasına olanak sağlayacaktır.

Anahtar kelimeler: Febril Nötropeni, Hematolojik maligniteler, Mortalite, solid tümör

Introduction

The development of multi-drug chemotherapy protocols and the use of higher doses in cancer treatment has increased treatment success, the resulting immunosuppression (especially neutropenia) predispose patients to severe infections. Infections occurring in the neutropenic period can cause rapid mortality due to the insufficiency of defense cells. Infection signs that are vague in the neutropenic patient group cause clinical complexity in the FEN period and delay the start of treatment. The most important approach reduces mortality in these patients and initiates empirical antibiotic therapy as soon as possible after taking the necessary samples for culture [1,2]. Therefore, it has become a priority to quickly interpret clinical and laboratory findings and proceed to the treatment phase without losing time.

The patient's primary disease, the chemotherapy protocol, the factors detected in the previous FEN attack, and the level and duration of neutropenia should all be considered during the empirical treatment decision. In addition, each clinic's causative profile is a crucial factor that should be considered when choosing an empirical antibiotic [3,4]. Therefore, surveillance data that includes causative microorganisms and antibiotic susceptibility play an important role in developing an effective empirical treatment protocol [5,6].

This study aimed to determine the clinical characteristics of FEN episodes, laboratory parameters, agents growing in culture, and growth rates to identify the causes of infection and review compatible treatment plans. We further aimed to determine the factors impacting mortality and prognosis in patients with solid tumor and hematological malignancies who were followed up prospectively for one year at the our cancer center.

Material and Methods

Patients

This study included 145 adult inpatients with solid tumors and hematological malignancies aged 18 and older and treated for FEN between April 2020 and April 2021 at the our cancer center; 176 FEN episodes developed in these patients and were examined prospectively. No intervention was made in the follow-up and treatment of the patients enrolled here. Permission was obtained from the Clinical Research Ethics Committee prior to the study (Decision no:2020-03/581).

In accordance with the Infectious Diseases Society of America (IDSA) and National Comprehensive Cancer Network (NCCN) clinical guidelines, the episodes of patients who had a fever of ≥38.3°C determined with one oral measurement or a fever of ≥38.0°C for more than one hour, those who had an absolute neutrophile count of ≤500 cells/mm^3 or 500-1000 cells/mm^3 and expected to decrease to below 500 cells/mm^3 within 24-48 hours were included as FEN. People with more than one isolate during the same episodes were not included in the study. The study's criterion was that each FEN patient included in the study recovered completely from the previous neutropenia attack. If there was a period longer than four weeks between the two episodes in the same patient, then the

second attack was also considered a new neutropenic attack.

Data collection

All patients eligible for the study were followed up in the wards with daily visits, and their data were recorded in the patient data form after obtaining signed informed consent form. Laboratory data and microbiological data were recorded daily from the hospital automation system. Peripheral blood cultures, urine cultures, and catheter blood cultures, if any, were taken simultaneously from all patients included in the study prior to treatment. Peripheral blood culture was obtained as two blood samples from peripheral veins in patients without a catheter. There was at least half an hour between the two blood samples. Other cultures such as sputum and stool cultures were taken from the sites considered to be the focus of infection based on the clinical symptoms and findings. The samples taken for culture were examined using traditional microbiological methods. Isolated agents were identified using conventional methods and the automated VITEK 2 (bioMerieux, France) system. If a known pathogenic microorganism grew in at least one blood culture, then the blood culture was deemed positive. Two or more growths in the blood culture of coagulase-negative staphylococci were considered positive. According to the standards of the European Committee on Antimicrobial Susceptibility Testing (EUCAST), the disc diffusion method or an automated system were used to determine the antibiotic susceptibility of these grown agents.

In the hematology and medical oncology clinics of our center, empirical antibiotic therapy was started by the doctor in charge of the ward or an infectious diseases specialist after considering the microorganism profile from the previous year and their antibiotic susceptibility. The patients were evaluated with clinical findings, physical examination findings, laboratory results, and micro-biological results at daily visits; daily changes were also recorded. Infectious diseases in FEN patients who were followed up were defined as primary bloodstream infection, catheter-related bloodstream infection, urinary tract infection, pneumonia, soft tissue infection, and gastrointestinal tract infection in accordance with the Centers for Disease Control and Prevention (CDC) definitions. Other patients in whom no focus could be detected with clinical, laboratory, microbiological, and radiological findings were evaluated as fever of unknown origin (FUO).

Statistical Method

Data were analyzed with the SPSS software (version 22.0. Armonk, NY: IBM Corp.). The conformity to normal distribution of the data was examined using visual (histogram and probability graphs) and analytical methods (Kolmogrorov-Smirnov/Shapiro-Wilk tests). The arithmetic mean, standard deviation, median, minimum and maximum values were used for evaluation of numerical data while frequency distributions and percentages were used to summarize categorical data. A Chi-squared ($\chi 2$) test was used to compare categorical data. The relationship between non-normally distributed numerical data and categorical data was evaluated with the Mann-Whitney U test. The Kruskal-Wallis test was used to evaluate three or more groups with numerical data. A posthoc Mann-Whitney U-test and Bonferroni correction were performed for pairwise comparisons between groups with significant Kruskal-Wallis test results. Logistic regression analysis was used to examine potential risk factors and independent predictors of treatment outcomes in FEN patients. The Hosmer-Lemeshow test was used to determine the goodness of fit of the model. A p-value of <0.05 was considered statistically significant.

Results

Sociodemographic Characteristics of Patients

We found 176 FEN episodes in 145 adult inpatients. Of the 145 patients included in the study, 52.4% (n=76) were female. The mean age of the patients was 47.16±15.50 years ranging from 18 to 80 years old; 70.3% (n=102) of the patients had hematological

Table 1: Baseline Characteristics of Patients

	n	%
Mean age	47.16 (±15.50)	
Gender		
Female	76	52.4
Male	69	47.6
Malignancy Type		
Solid Organ Tumor	43	29.7
Hematological Malignancy	102	70.3
Comorbidities		
Diabetes Mellitus (DM)	16	11.0
Hypertension	28	19.3
Coronary Artery Disease	5	3.4
Other (Chronic kidney disease, COPD)	25	17.2

malignancies, while 29.7% (n=43) had a solid organ tumor. The characteristics and comorbidities of the patients are presented in Table 1.

Characteristics of the FEN Episodes

Of the 176 FEN episodes, 112(63.6%) were developed during hospitalization, while 64 (36.4%) began outside the hospital. Among the nosocomial FEN episodes, 108 (96%) occurred in patients with haematological malignancies and 84 (75%) were associated with prolonged neutropenia. Bacteremia was significantly more frequent in patients who had FEN episodes during hospital stay ($p<0.001$). The most common focus of infection in FEN episodes was pneumonia. This was followed by catheter infection (22.6%) and primary bloodstream infection (20.3%) (Table 2). The total mucositis rate was 17.0% (n=30). Diarrhea was seen in 19.9% (n=35) of the FEN episodes.

Considering neutropenic fever syndromes both clinically and microbiologically, 46% (n=81) of the FEN episodes were micro-biologically-proven infections (44.8% diagnosed with culture, 1.2% with PCR test); 29.5% (n=52) had clinically identified focus of infection. The FEN focus could not be detected in 24.5% (n=43) of the patients, and thus they were evaluated as FUO. The median duration of treatment in FEN episodes was 14 days (min: 2.00-max: 47.00) and 13 days (min:2.00 - max: 50.00) days, respectively, for microbiological and clinically-documented infections. This was significantly longer than

Table 2. Distribution of Infection Foci

Focus	n	%
Lung Infection	36	27.1
Catheter Infection	30	22.6
Primary Bloodstream Infection	27	20.3
Gastrointestinal System Infection	18	13.5
Soft Tissue Infection	17	12.8
Urinary Tract Infection	5	3.8

the treatment duration of patients with unexplained fever. The total FEN time and total neutropenia times were shorter in the group of patients with unexplained fever ($p<0.001$). The mean duration of FEN was 7 (min:1-max:141) days in patients with hematological malignancies, and 2 days (min:1-max:14) in patients with solid organ malignancies ($p<0.01$). Additionally, 96.2% (n=51) of patients with prolonged neutropenia (neutropenia lasting longer than 10 days) (n=53) had hematological malignancies.

Laboratory and Radiological Characteristics of Patients

The mean leukocyte count at the onset of FEN attack was 595.7 $x10^3$ cells/uL, the mean neutrophil count was 129.6 $x10^3$ cells/uL, and the mean CRP was 121.21 mg/L. The effects of leukocyte count, CRP, and procalcitonin level at the time of diagnosis on mortality and duration of neutropenia was not shown ($p>0.05$). Here, 64.8% (n=114) of the patients had deep neutropenia on day zero, and the mean duration of deep neutropenia in these patients was 8.15±13.34 days (min: 1.00 - max: 112.00). The laboratory findings of the patients during FEN are presented in Table 3. Computed tomography (CT) was performed in 64.8% (n=114) of the patients. The CT of 53.5% (n=61) of the patient did not reveal any findings of infection, while pneumonia findings were detected in 46.5% (n=53) of the patients.

Microbiological Characteristics of FEN Episodes

Culture samples were positive in 53.4% (n=94) of FEN episodes. Growth was observed in peripheral blood culture in 38.6% (n=68), catheter culture in 36.4% (n=64), urine culture in 9.1% (n=16), and sputum culture in 5.1% (n=9). Simultaneous growth

Table 3. Laboratory Values of Patients in the Neutropenic Fever Period

Value	Mean±SD	Median (Min-Max)
WBC (n=176)	595.79±771.53	340.00 (00.00-6180.00)
Neutrophil (n=176)	129.60±160.95	70.00 (0.00-500.00)
Lymphocyte (n=176)	476.16±2154.44	160.00 (00.00-27900.00)
Platelet (n=176)	57,256.00±74,344.96	26,000.00 (9.60-523,000.00)
Hemoglobin (n=176)	8.70±1.84	8.30 (5.00-14.30)
MPV (n=176)	9.98±2.35	10.00 (0.00-14.30)
AST (n=159)	29.14±35.99	17.80 (5.70-221.00)
ALT (n=161)	33.47±47.53	19.20 (3.00-412.00)
Creatinine (n=165)	0.85±0.90	0.66 (0.19-6.80)
CRP (n=164)	121.21±89.14	106.01 (0.24-517.00)
Procalcitonin (n=132)	6.34±21.99	0.39 (0.01-75.00)
Glucose (n = 131)	126.99±76.53	111.00 (67.00-888.00)

Abbreviations: WBC= White Blood Cell, MPV=Mean Platelet Volume, AST=Aspartate Aminotransferase, ALT=Alanine Transaminase, CRP=C-Reactive Protein

Table 4. Microorganisms in Blood Culture

Microorganism	**n**	**%**
Gram Negative Bacteria		
E. coli	28	41.2
K. pneumoniae	8	11.8
P. aeruginosa	7	10.3
Enterobacter cloacae	3	4.4
Achromobacter xylosoxidans	1	1.5
Aeromonas sobria	1	1.5
Gram Positive Bacteria		
Coagulase negative staphylococci	12	17.6
Enterococcus spp.	2	2.9
Streptococcus gordonii	2	2.9
Staphylococcus aureus	1	1.5
Other		
Candida spp.	3	4.4

Table 5: Comparison of Treatment Results and Characteristics of Patients

	Recovered		Ex			
	n	%	n	%	χ^2	*p*
Combined Treatment	115	72.8	16	94.1**	3.711	0.041
Comorbidities	46	29.1	4	23.5	0.235*	0.433
Hematological Malignancy	115	72.8	15	88.2	1.918*	0.135
Attack Developed at the Hospital	99	62.7	12	70.6	0.416	0.519
G-CSF prophylaxis	52	32.9	3	17.6	1.659	0.198
Antibiotic prophylaxis	112	70.9	15	88.2	2.321*	0.103
Mucositis Presence	27	17.1	3	17.6	0.003*	0.587
Pneumonia	30	19.0	13	76.5	27.364*	<0.001
Antifungal Therapy	27	17.1	10	58.8	16.035*	<0.001
Second Line Treatment	13	8.2	14	82.4	64.632*	<0.001
Final Focus Detected	116	73.4	16	94.1**	3.548*	0.046
Culture Positivity	81	51.3	13	76.5**	3.922	0.048
Prolonged Neutropenia	41	25.9	12	66.7	12.730	<0.001

Fisher's exact chi-square test was used.** Represents the group from which the difference originates

Table 6. Logistic regression model developed to predict treatment outcomes

Variables		B	Standard error	*p*	Exp (β)
Pneumonia presence	Yes (Ref)	2.328	0.638	0.000	10.25
Prolonged Neutropenia	Yes (Ref)	1.800	0.643	0.005	6.05
Hematological Malignancy	Yes (Ref)	1.363	1.352	0.313	3.910
G-CSF Prophylaxis	Yes (Ref)	0.143	0.928	0.878	1.154
Antifungal Therapy	Yes (Ref)	0.197	0.936	0.834	1.217
Final Focus Detected	Yes (Ref)	0.401	1.315	0.760	1.493
Blood Culture Positivity	Yes (Ref)	1.067	0.846	0.207	2.908

Ref= Reference Assessed by binary logistic regression analysis. Hosmer-Lemeshow test: 0.590 Nagelkerke R Square: 0.425

was observed in peripheral blood and catheter blood cultures in 27.27% (n=48) of the episodes. The most frequently isolated micro-organisms in blood cultures were E. coli and coagulase-negative staphylococci. Of fatal cases, 50% had P. aeruginose and 33% had Klebsiella pneumoniae (K. pneumoniae) (Table 4) in blood culture.

Bacteremia was detected in 47.7% (n=84) of the episodes. Bacteremia was significantly higher in patients with hematological malignancies compared to patients with solid organ tumors ($p<0.001$). While deep neutropenia on day zero was found to be associated with bacteremia ($p<0.001$), the relationship between prolonged neutropenia and bacteremia could not be demonstrated ($p=0.34$). A model was developed with the type of malignancy, the initial antibiotic treatment regimen (monotherapy or combination therapy), and the presence of deep neutropenia on the first day to predict the development of bacteremia in patients with FEN. The logistic regression model explained 28.9% of the bacteremia risk (Nagelkerke R Square= 0.289). According to the model, the risk of developing bacteremia in patients with hematological malignancies was 8.33-fold higher than the risk of developing bacteremia in patients with solid organ tumors. The risk of developing bacteremia was 2.77-fold higher in patients receiving combined therapy than in patients receiving monotherapy. Patients with deep neutropenia on the first day were 2.45-fold more likely to develop bacteremia than those without.

Treatment Characteristics

Monotherapy was started as an initial treatment in 68.7% (n=121) of 176 FEN episodes. Cefaperazone- sulbactam was used most frequently. Here, 76.3% of the patients who were started on combination therapy were given β-lactam/β-lactamase inhibitors. It was determined that 51.1% (n=90) of the patients who received the initial treatment had a treatment change. Growth in blood culture was detected in 61.8% of the patients whose treatment was changed, and patients with a growth in their blood culture required more treatment changes after isolation ($p<0.05$). Due to clinical course and/or culture results treatment success was achieved in 75.5% of the patients who underwent a treatment change but 24.4% of them underwent another treatment change

Factors Affecting Survival Outcomes and Mortality

It was observed that 18.2% (n=32) of the patients developed hypoxia during the given treatments, and 9.7% (n=17) of the patients were intubated. Another 12.5% (n=22) of the patients were treated in the intensive care unit for an average of 3.77±2.28 days (min: 1.00 - max: 10.00). It was determined that 89.8% (n=158) of the patients were discharged with full recovery, 9.7% (n=17) of the patients died due to infection, and 0.6% (n=1) died due to other causes. Table 5 compares the patient characteristics associated with mortality.

A model including pneumonia and prolonged neutropenia was developed to predict treatment success in FEN patients (Table 6). The logistic regression model can predict 42.5% of treatment success (death or discharge with cure) (Nagelkerke R Square= 0.425). Table 6 shows that the mortality risk of patients with pneumonia in the FEN period was 10.25-fold higher than that of those

without pneumonia. Patients with prolonged neutropenia during the FEN period had a 6.05-fold higher risk of dying after treatment than those without prolonged neutropenia.

Discussion

Our study prospectively examined FEN patients in our hematology, oncology, and bone marrow transplant (BMT) centers: 9.7% (n=17) of the patients died due to FEN. The mortality rates related to FEN vary according to the literature. Ghosh et al. studied hematological patients and found that mortality due to FEN was 19.5% [7]. Another study's mortality rate was 11.2% in 232 patients—56.6% of whom had hematological malignancies [8]. Hatamabadi et al. examined FEN episodes in patients with mostly solid organ tumors (97.8%), and the mortality rate was 5.3% [9]. These differences may be due to several factors such as malignancy types, chemotherapy regimens given, accompanying comorbid diseases, different microorganisms grown in the culture depending on flora of centers and demographic characteristics of the population.

The mean age of the patients in the study was 57, and 52.4% were female. Most patients had hematological malignancies, and one-third of them had comorbidities such as DM, hypertension, and coronary artery disease. Gender, type of malignancy and presence of additional diseases were not associated with mortality. The absence of differences between gender and mortality in the study by Hatamabadi et al. supports our study [9]. However, unlike our study, there are also publications in the literature suggesting that additional diseases affect mortality negatively [10,11]. While the rate of patients over 65 years of age in our study was 15%, it was 28.5% in the studies of Kuderer et al [10]. The entire population of Hosmer et al.'s study consists of elderly people [11]. Therefore, the reason for this difference with the literature can be because comorbidities are more common in the elderly population, and the elderly population in these studies is higher than in our study.

The use of granulocyte colony stimulating factor (G-CSF) in patients receiving chemotherapy leads to a decrease in the normalization of neutrophil counts and the duration of hospitalization but has no effect on mortality [12,13]. Renner et al. found evidence for the decrease of all-cause mortality during chemotherapy with prophylactic G-CSF administration, but this relationship was less reliable. In this study, there was no relationship between the use of G-CSF and the mortality associated with infection after the development of FEN [13]. We found that 31.8% of the patients were receiving primary G-CSF prophylaxis: No relationship between the use of primary G-CSF and mortality could be demonstrated, which is consistent with the literature.

The long duration of neutropenia during episodes not only facilitates the development of complications due to the long-term insufficiency of the immune system, but also leads to a dose reduction in subsequent chemotherapy and thus to the disruption of effective cancer treatment. The mean duration of neutropenia was 12 days in the study of Demirel et al., and 15 days in Mert et al [14,15]. The mean duration of neutropenia was shorter than in those studies. Özden et al. observed a short duration of neutropenia (mean 3.3 days) in their study similar to our study [16]. While no statistically significant difference was found in this study in the mean neutropenia duration between patients with hematological malignancies and patients with solid organ tumors, the neutropenia duration was significantly longer in patients with hematological malignancies in our study. Neutropenia duration is one of the factors that is directly associated with mortality [17,18]. We found that a prolonged neutropenia duration (longer than 10 days of neutropenia) was significantly associated with mortality ($p<0.001$). Ceken et al. reported that the duration of neutropenia was also a risk factor for mortality [19].

Leukocyte count, CRP, and procalcitonin had no effect on mortality or duration of neutropenia. On the other hand, there are

many publications in the literature reporting that CRP and procalcitonin are effective in predicting the course of FEN and mortality. A Turkish study by Sahin et al. showed that CRP was an important prognostic parameter in FEN episodes [20]. Another study conducted in hematological malignancies revealed that the procalcitonin measured on hour 24 and the CRP measured on hour 48 were helpful in detecting fungal infections. On the other hand a study found that CRP could be a better marker than procalcitonin in determining disease-related fever [21].

The focus of infection could not be detected by clinical, microbiological, and radiological methods in 24.5% of the episodes. Demirel et al. reported that the rate of clinically-proven infection was 36% [15]. Maybe the main reason why more clinically and microbiologically proven fever foci and fewer unknown fevers were seen in our study is that we have finest diagnostic tools now like procalcitonin, quicker CT scan, ultrasound, cultures etc.

The most common infection focus detected was pneumonia at 27.1%. In studies conducted on hematological and oncological patients, the rate of pneumonia was 12.3% and 18.6% [9,22]. Our study was conducted during the COVID-19 pandemic, and imaging studies were performed more frequently during episodes. Thorax CT was performed in 64.8% of the patients, and pneumonia was found in 46.5% of the images. Therefore, patients in our series may have been diagnosed with pneumonia more frequently.

An uprising of gram-positive infections was reported after the 2000s [23,24,25]. Gram negative infections are much more commonly reported lately [26,27]. This is consistent with our findings. It is known that the presence of mucositis is an important risk factor for the predominance of gram-positive micro-organisms [28,29]. Safia et al. found that the incidence of mucositis was 50% [30]. Similarly, the rate of mucositis was 36% in a multicenter Spanish study conducted by Aguilar-Guisada [31]. In our study, mucositis was present in 17% of FEN episodes. Reducing the incidence of mucositis with appropriate oral care in our center may have reduced the incidence of FEN episodes caused by gram-positive bacteria.

Bacteremia was significantly more frequent in patients with hematological malignancies than in patients with solid organ tumors. Patients with hematological malignancies are usually treated with high-dose cytotoxic chemo-therapy regimens: Thus, the length of hospitalization is longer, and immuno-suppression is deeper, which causes a high risk of bacteremia [32]. In support of this, the rate of bacteremia in our study was higher in patients with deep neutropenia at day zero versus those without. A Turkish study examined 164 FEN cases, and found that the rate of bacteremia was higher in the group with deep neutropenia at the beginning33. Although it is known that prolonged neutropenia increases the risk of bacteremia, no relationship between prolonged neutropenia and bacteremia was found in our study [34].

One of the most important factors reducing mortality in FEN is the rapid initiation of empirical antibiotic therapy [35]. Mono-therapy was started as the initial treatment in 68.7% of the episodes. A review of the literature identified studies showing that monotherapy has similar efficacy to combination therapy and is even more advantageous because it has fewer side effects [36,37,38]. We found that the mortality rate in the group in which combination therapy was initiated was higher than that in the monotherapy group. The need for glycopeptide group antibiotics in the clinical evaluation at the beginning of the treatment suggests that the clinical situation in these patients is severe. The cause of mortality depends on the severity of the patient's FEN attack rather than the inadequacy of the combination therapy.

Invasive fungal infections (IFI) are important causes of morbidity and mortality in febrile neutropenic patients and other immuno-compromised populations after intensive chemotherapy [39]. Candidemia was

observed in three FEN episodes (1.7%) in our study. Goldberg et al. showed in a systematic review that empirical treatment did not significantly reduce mortality but reduced IFIs [40]. In our study, antifungal treatment was started in 21% (n=37) of the patients. Mortality was statistically higher in the group that received antifungal therapy than in those who did not. This proves that the mortality of invasive fungal infection is high even with appropriate treatment protocols.

Limitations

Our study has several limitations. First, the empirical treatment change rates were high in episodes. The reasons for these treatment changes in patients could not be investigated. Second, we could not reported data regarding susceptibility patterns and colonization. Third, we could not report etiological data for pneumonia which was the major cause of death in the study. Furthermore, the single-center limited the study population. Multicenter studies can offer more detailed results.

Conclusion

We prospectively examined the clinical and laboratory findings of FEN episodes in patients with hematological and solid malignancies and found that the frequency of pneumonia increased in FEN. The mortality associated with pneumonia was high, and gram-negative microorganisms were more common in the causative profile. The increasing rates of resistance in gram-negative microorganisms worldwide have brought this agent profile change to an alarming level. For better management of the process in FEN episodes, centers should know their own causative pathogen profiles and antibiotic susceptibilities and develop treatment algorithms accordingly.

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Doi: 10.5505/aot.2023.79990

