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Single-center and reverse evaluation of febrile neutropenic attacks of patients followed with acute myeloid leukemia diagnosis

Akut myeloid lösemi tanısı ile takip edilen hastaların febril nötropenik ataklarının tek merkezli ve geriye dönük değerlendirilmesi

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ABSTRACT

Aim: Since fever may be the only symptom in patients with hematological malignancy, fever in neutropenic patients is considered to be related to infection until proven otherwise. The standard approach is the rapid evaluation of febrile neutropenic (FEN) episodes and initiation of appropriate antibiotic treatment. In this study, it was aimed to examine the duration of FEN, infection categories, symptoms and examination findings, isolated microorganisms and mortality rates of the patients we followed up in our clinic due to acute myeloid leukemia.

Materials and Methods*:* We examined 155 adult patients with AML who were treated at the Adult Hematology Clinic. In our study, we retrospectively evaluated 337 chemotherapy-related FEN episodes in terms of infection categories, offending pathogenic microorganisms and mortality rates.

Results: 43.92% (n=148) of the patients had pathological examination findings accompanying the fever. FEN attacks in 249 patients had clinically and/or microbiologically proven foci of infection. The most frequent infection site was the lungs (41.5%). The most frequently isolated microorganisms were found to be *coagulase negative staphylococcus* (37.30%) and E.coli (36.21%). 32.94% of the patients (n=111) were recorded as smokers. When the relationship between smoking and lung infection was investigated, it was determined that the incidence of lung infection was higher in smokers (p= 0.007). In 91 (27%) of those who had a FEN attack in our hospital resulted in death. It was the lung infection that mostly correlated with the mortality (40.71%).

Conclusion: Each clinic can determine empirical antibiotic treatment policies by investigating infectious agents. It can manage the FEN episode process more accurately by providing the necessary infection control measures.

Keywords: Febrile neutropenic attacks, acute myeloid leukemia, neutropenia.

ÖZ

Amaç: *Hematolojik maligniteye sahip hastalarda tek semptom ateş olabildiği için nötropenik hastalarda ateş aksi ispat edilene kadar enfeksiyon ile ilişkili kabul edilir. Febril nötropenik (FEN) ataklarının acil olarak değerlendirilip uygun antibiyotik tedavisinin hızlıca başlanması standart yaklaşımdır. Bu çalışmada akut myeloid lösemi (AML) nedeniyle kliniğimizde takip ettiğimiz hastaların FEN süreleri, enfeksiyon kategorileri, semptom ve muayene bulguları, izole edilen mikroorganizmalar ve mortalite oranlarının incelenmesi amaçlanmıştır.*

Gereç ve Yöntem: *Araştırmamıza erişkin hematoloji kliniğinde yatarak tedavi gören 155 erişkin AML tanılı hasta alındı. Kemoterapiye bağlı gelişen 337 FEN atağı; enfeksiyon kategorileri, izole edilen patojen mikroorganizmalar, mortalite oranları açısından geriye dönük olarak değerlendirildi.*

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Bulgular: *Hastaların %43,92'sinde (n= 148) ateşe eşlik eden patolojik muayene bulgusuna rastlanmıştır. 249 hastadaki FEN ataklarında klinik ve/veya mikrobiyolojik olarak kanıtlanmış enfeksiyon odakları vardı. En sık saptanan enfeksiyon odağının akciğer olduğu görülmüştür (%41,5). İzole edilen mikroorganizmaların en sık %37,30 ile koagülaz negatif stafilokok (KNS) ve %36,21 ile E. coli olduğu görülmüştür. Hastaların %32,94'ü (n=111) sigara kullandığı kaydedilmiştir. Sigara kullanma ile akciğer enfeksiyonu arasındaki ilişki incelendiğinde, sigara içenlerde akciğer enfeksiyonu görülme sıklığının fazla olduğu belirlendi(p=0,007). FEN ataklarının %27'sinin (n= 91) mortal seyrettiği görülmüştür. Mortaliteyle en fazla ilişkili olan %40,71 ile akciğer enfeksiyonuydu.*

Sonuç: *Her klinik, enfeksiyon etkenlerini araştırarak, ampirik antibiyotik tedavi politikalarını belirleyebilir. Gerekli enfeksiyon kontrol önlemlerini sağlayarak FEN epizod sürecini daha doğru yönetebilir.*

Anahtar Sözcükler: *Febril nötropenik atak, akut myeloid lösemi, nötropeni.*

INTRODUCTION

While it is aimed to increase the survival time with intensive chemotherapy protocols applied in acute myeloid leukemia (AML) patients, hospital stays due to the disease and chemotherapy are prolonged and bone marrow toxicity may develop. These patients are at increased risk of developing serious infections, especially in the neutropenic period. Patients receiving chemotherapy or having neutropenia may not have the expected classical symptoms and signs of infection due to decreased inflammatory response. Since fever may be the only symptom in these patients, it should be considered to be related to infection until proven otherwise and urgent intervention should be performed. Rapid evaluation of the patient and initiation of empirical antibiotic therapy as soon as possible is of vital importance. The primary disease of the patient, the chemotherapy protocol he/she received, the factors detected in the previous febrile neutropenia (FEN) attack, the level and duration of neutropenia are important in the selection of empirical antibiotics. Additionally, the causative profile of each clinic is also important in the selection of empirical antibiotics. For this purpose, FEN periods, infection categories, symptoms and examination findings, isolated microorganisms and mortality rates of the patients we followed up in our clinic for AML were all examined.

MATERIALS and METHODS

This study included 155 adult AML patients who were hospitalized in the Adult Hematology Clinic of Ege University Medical Faculty Hospital between January 2012 and January 2016. AML was diagnosed by clinical, complete blood count, peripheral smear, bone marrow aspiration and/or bone marrow biopsy, histochemical staining, flow cytometry and/or cytogenetic evaluation according to French-American-British and World Health Organization criteria. 337 FEN attacks that developed during the hospitalization of these patients were retrospectively examined. A single measurement of 38.3°C and above or a temperature measurement of 38.0–38.2°C for 1 hour without any environmental factors was considered fever. Neutropenia was considered when the neutrophil level was below 500/mm³ or when the neutrophil level was between 500–1000/mm³ and was expected to fall below 500/mm³ within 24–48 hours. Blood culture positivity was defined as the growth of a known pathogenic microorganism in at least one blood culture. It was determined that blood cultures were studied using an automated system (BACTEC). Patient data were obtained from the electronic file system of Ege University Faculty of Medicine Hospital. Age, gender, diagnosis, additional diseases, smoking habit, presence of urinary catheter and central venous catheter, major symptoms and findings accompanying fever, detected primary infection focus, abnormal radiological findings, culture results, and survival status were reviewed and recorded from the patient files. Local ethics committee approval was obtained before starting the study.

SPSS.23.0 statistical package program was used. Measurement variables are presented either mean ± standard deviation (SD) or categorical variables as numbers and percentages (%). Intergroup comparison of qualitative variables was done with chi-square analysis, and performed quantitative variables was done with Mann-Whitney U test. $P < 0.05$ was considered statistically significant. The ethics committee approval was received for this study.

RESULTS

In our study, 337 FEN attacks developed in 155 adult patients who were hospitalized in the Ege University Medical Faculty Hospital were examined. While 36.73% (n=57) of the patients were women, 63.22% (n= 98) were men. The mean age was 51.56 (SD±14.82). While the average number of FEN attacks for men was 2.98, it was 2.93 for women. No statistically significant difference was found between genders and FEN attack numbers (p=0.867).

Culture (kx) positivity was detected in 54.90% (n=185) of FEN attacks. Of the patients with positive cultures, peripheral blood cultures were detected in 57.30% (n=106), catheter-catheter tip positivity in 45.41% (n=84), and urine positivity in 26.49% (n=49). During the 337 FEN period, blood kx positivity was found to be 31.4% (n = 106).

Nothing was isolated in 45.10% of the patients. 48.66% of the isolates were bacteria, 2.67% were fungi and 3.57% were both bacteria and fungi. 62.16% of the isolated bacteria were gram negative, 54.05% were gram positive and 1.08% were anaerobic. It was also observed that both gram positive and gram-negative bacteria were isolated in the same patient. (Table-1).

While 32.94% (n= 111) of the patients were smoking, 67.06% (n= 226) were non-smokers. When the relationship between the presence of lung infection according to smoking status was investigated, 144 of the non-smoking patients did not have lung infection, while lung infection was observed in 82 patients. While lung infection was seen in 47.74% of smokers, it was seen in 25.66% of non-smokers. According to the analysis, it was found that the frequency of lung infections was significantly higher in smokers (p= 0.007). In our hospital, 27% (n= 91) of FEN attacks resulted in exitus (ex). While looking at the relationship between the detected area of infection and mortality, mostly the patients with pulmonary infection died (40.71%), then patients with gastrointestinal (GIS) (32.30%), genitourinary (GUS) (26%), and lastly the catheter infections (5.30%). In some patients, more than one focus of infection was detected in the same febrile neutropenia attack. The results regarding the distribution of infection foci and relationship between area and mortality are shown in Table-2 and Table-3.

Table-1. Agents isolated.

Agent Isolated	N (number)	Percent (%)
CNS	69	37.30
E. coli	67	36.21
Enterococci	32	17.30
Klebsiella	23	12.43
Acinetobacter	16	8.65
ESBL+ E. coli	12	6.49
Pseudomonas	11	5.95
VRE	10	5.40
Candida	7	3.78
Enterobacter	7	3.78
Stenotrophomonas	7	3.78
Aspergillus	6	3.24
Aeromonas	4	2.16
Streptococci	4	2.16
CRE	4	2.16
Proteus	3	1.62
Staphylococcus aureus	**3**	1.62
Corynebacterium	2	1.08

Abbreviations*: CNS:* *Coagulase-negative staphylococci****, ESBL:*** *Extended spectrum beta lactamases****, VRE:*** *Vancomycin resistant enterococcus spp.****, CRE:*** *Carbapenem resistant erobacteriaceae.*

Table-2. Distribution of infection foci.

		N (number)	Percent (%)
Detected Focus of Infection	**Present**	249	73.89
	Absent	88	26.11
Lung Infection		140	56.22
Catheter Infection		82	32.93
Gastrointestinal System Infection		65	26.10
Genitourinary Tract Infection		50	20.08
Soft Tissue Infection		28	11.24
Sinus Infection		13	5.22

Table-3. The relationship between infection area and mortality.

Infection Groups	**Mortality**		
	Ex: N (number)	**Ex: Percent (%)**	**Lives: N(number)**
Lung infection	57	40.71	83
Catheter Infection	21	25.30	62
Gastrointestinal System Infection	21	32.30	44
Genitourinary Tract Infection	13	26	37
Soft Tissue Infection	7	25	21
Sinus Infection	3	23.07	10

DISCUSSION

In neutropenic attacks, the only sign of infection may sometimes be bacteremia, and identifying the causative agents is crucial for managing the patient. Bacteremia rates ranging from 10-25% to 45.9% have been reported in various studies (1, 2). In our study, the rate of bacteremia was found to be 31.4%.

The causative agents of febrile neutropenic attacks shifted from gram-negative bacteria to gram-positive bacteria before the 2000s; however, there has been a resurgence of gram-negative bacteria today (3, 4). Currently, antibiotic-resistant gram-negative strains are emerging (3, 4). In our study, 62.16% of the causative agents of febrile neutropenic attacks were gram-negative and 54.05% were gram-positive bacteria. It was also observed that both gram positive and gram-negative agents were detected in the same patient. Coagulase-negative staphylococci (CNS) were the most common cause among gram-positives, while E. coli was the most common among gram-negatives.

Considering the distribution of infection foci, in a study by Gupta A. et al. examining 382 febrile episodes in 95 AML patients, lung infection was reported at 46%, gastrointestinal system infection at 33%, and soft tissue infection at 22% (5). In our study, clinical and/or microbiologically proven focus of infection was found in 73.89% (n= 249) of the patients. Lung infection was present in 56.22% (n=140), and catheter infection in 32.93% (n=82) of these patients. The frequency of lung infections in our clinic was found to be above the average stated in the literature (Table-2).

As is well-known, smoking is an important risk factor for developing chronic obstructive pulmonary disease (COPD) and can also worsen lung function in patients with lung infections. Studies on community-acquired pneumonia have shown that 72% of pneumonia cases requiring intensive care hospitalization had a history of smoking (6). Similarly, smoking has been identified as a risk factor for the need for intensive care in viral pneumonias (7). A review published in 2017 stated that cigarette exposure is a recognized risk factor for both acute and chronic respiratory diseases. In our study, the

frequency of lung infections was also found to be higher in smokers (p= 0.007).

In our study, we examined the relationship between the infection site and mortality. Accordingly, patients with pulmonary infections had the highest mortality rate at 40.71%, while gastrointestinal (GIS), genitourinary (GUS), and catheter-related infections had mortality rates of 32.3%, 26%, and 25.3%, respectively. When considering the distribution of infection sites in the literature, lung infections account for 46%, GIS infections for 33%, and soft tissue infections for 22% (5). In a study conducted in a hematology clinic, including 60 patients, it was observed that the most common reason for referral to the intensive care unit during a febrile neutropenic (FEN) episode was respiratory failure, with a rate of 38.5% (8). GIS infections also contribute significantly to mortality. Delphine et al. reported that acute abdomen developed in 171 (5.3%) of their 3222 cancer patients. Neutropenic enterocolitis was detected in 33% of patients who developed an acute abdomen, and 22% of these patients died (9).

While mortality rates in febrile neutropenic patients were 75% before the use of empirical antibiotic treatments, today, mortality has been reduced to 5-10% with advances in diagnosis, treatment options, and standardized approaches in FEN attacks (10). In our study, the mortality rate in febrile neutropenic patients was 27%, higher than the average reported in the literature.

Patients with the highest risk of developing neutropenia-associated infections are those with AML and those undergoing allogeneic bone marrow transplantation who are receiving high-dose chemotherapy and induction therapy. Although our results are generally consistent with the literature, the rates of lung infections, catheter-related infections, and mortality in our clinic were found to be higher than those reported in the literature (Table-3).

CONCLUSION

Multidrug-resistant organisms pose a major challenge in the management of neutropenic febrile patients with hematological malignancies, including AML. Future directions to improve outcomes require advances in biomarker research as well as innovative treatment approaches to facilitate diagnosis and disease monitoring (11). When FEN attacks of AML patients were examined retrospectively in our clinic, it was observed that the isolated microorganisms were gram-negative, and lung infections were the most common as the infection site. Today, mortality in FEN attacks is gradually decreasing; however, it is still an important cause. In conclusion; each clinic's determination of its own infectious agent profile may contribute to empirical antibiotic selection and better management of this process.

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