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Research Article

Etiologic, Microbiologic, Clinical and Outcome Characteristics of Febrile Neutropenia in Children with Malignancy

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ABSTRACT

Background: The purpose of this study is to examine the clinical, laboratory findings and treatments of pediatric patients who were followed up in our clinical institute for malignancy and those who had Febrile Neutropenia (FEN) attacks.

Materials and methods: 55 patients between the ages of 1-17 and 83 episodes of FEN who were followed up and treated for cancer in our Pediatric Hematology- Oncology clinic between January 2019 and June 2019 were examined cross-sectionally. Patients with Absolute Neutrophil Count (ANC) <500/mm^3 were included in the study. Febrile neutropenia was diagnosed in neutropenic patients with a single measurement of body temperature ≥ 38.3°C (101°F) or ≥ 38.0°C (100.4°F) for a period of 1 hour. The demographic information of the patients, laboratory and physical examination findings, FEN risk groups, the most recent chemotherapy protocols, fever and neutropenia durations, fever foci, culture reproduction, and treatments started were recorded in a standard form.

Results: Among 83 FEN attacks included in the study, 28 of the patients were female (34%) and 55 were male (66%). The median age was 5.5 (range 1.1-16.7) years. Sixty-six (80%) of the patients were being followed up for leukemia and 17 (20%) for solid tumors. The average number of attacks per patient was 1.4 (1-4) attacks. According to the risk classification of febrile neutropenia, 80 attacks (96%) were classified as high risk and 3 attacks (4%) as low risk. Mean duration of fever was in patients with leukemia and in patients with solid tumors. Mean duration of neutropenia was significantly higher versus 1.9 ± 1.3 days to 1.9 ± 1.1 days in patients with leukemia than those treated for solid tumors ($p<0.05$). The most common microorganism was Coagulase negative staphylococcus. Galactomannan was positive in one patient and Enterobacter growth was detected in the blood culture.

Conclusion: Febrile neutropenia is among the important causes of mortality in cancer patients. Most of the attacks in our study were high-risk FEN attacks. The reason for this may be duration of active chemotherapy, prolonged neutropenia periods, remission status of cancer, and delays related to hospitalization of patients. Fever focus is often not detected in FEN attacks; the most common fever focus in our study was mucositis. The most common gram-positive microorganisms were found in the blood culture of our patients. This study is important in terms of creating up-to-date algorithms in the treatment and management in FEN patients. However, the results to be obtained by conducting studies with more patients will be more beneficial in this senses.

Keywords: Febrile neutropenia; Children; Cancer

INTRODUCTION

The presence of fever with neutropenia in cancer patients is defined as febrile neutropenia. Disruption of natural barriers with chemotherapeutic drugs as well as duration and depth of neutropenia predispose to infection. Fever in neutropenic patients receiving chemotherapy may indicate the presence of serious infection. Therefore, it is very important to start empirical anti-biotherapy before the agent is proven in the laboratory [1].

The first thing to do in patients with febrile neutropenia should be determining the risk group and initiating empirical anti-biotherapy.

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According to the risk classification, it is decided that patients should receive hospitalization or outpatient treatment. Patients with chemotherapy-related neutropenia and fever are treated in the hospital until their fever is controlled, blood culture results are negative and the absolute neutrophil count exceeds 500 μL [2]. The places where infections are most common in patients with febrile neutropenia are the intestinal system, lungs, skin and soft tissue. In only 10%-30% of the cases, the agent can be documented microbiologically. While gram-negative factors were common in the past, nowadays the reproduction frequency of gram-positive factors has increased.

In this study, 55 patients and 83 febrile neutropenia attacks who were followed up and treated for cancer in the Pediatric Hematology-Oncology clinic between January 2019 and June 2019 were examined cross sectionally. The duration of fever and neutropenia of the patients, the chemotherapy protocols and phases they received during the FEN attack, the infection foci detected, the growth rate in the cultures taken, the microorganisms grown, the culture antibiogram results, the examination of the treatments applied and all the data and results obtained in the future studies to be conducted in our clinic and It was intended to be used in algorithms to be created.

MATERIALS AND METHODS

Patients

In this study, 55 patients between the ages of 1-17 and 83 febrile neutropenia attacks who were followed up and treated for malignancy in the Pediatric Hematology-Oncology clinic of our University Hospital between January 2019 and June 2019 were examined cross-sectionally. Patients without malignancy were excluded from the study. Patients under 1 year of age with a diagnosis of malignancy were not included in the study. Ethics committee approval was obtained before the study.

Definitions

Patients with an absolute neutrophil count of <500/mm³ or between 500-1000/mm³ and expected to fall below 500/mm³ within 24-48 hours were considered neutropenic [3,4]. Fever measurement was done with a Galena brand non-contact infrared thermometer from a distance of 5-8 cm from the dry forehead. It is known that skin temperature measurement is 0.5 C lower than intraoral measurement. Accordingly, the diagnosis of febrile neutropenia was made in neutropenic patients when a single body temperature measurement measured from the forehead was 38°C (101 F) or 37.7 C (100.4 F) for a period of 1 hour.

Infections in neutropenic patients the definitions recommended by the "International Immunocompromised Host Society" were used:

1. Fever of unknown cause: It is a febrile neutropenia that has not been clinically and microbiologically proven.
2. Clinically proven infection: Infection with clinical signs; microbiological factor may or may not be detected.
3. Microbiologically proven infection: It is an infection detected microbiologically in blood culture and/or other tests [5].

Method

Age, gender, diagnosis, the time between the last chemotherapy and chemotherapy and fever, complaints, physical examination findings, blood count at diagnosis, C-Reactive Protein (CRP), procalcitonin (PCT) values, imaging methods, applied Receiving anti biotherapy, Granulocyte Colony Stimulating Factor (G-CSF) or granulocyte infusion was recorded on a standard form (Febrile Neutropenia Study form). The patients were divided into high and low risk febrile neutropenia groups according to febrile neutropenia risk classification.

Laboratory findings

During febrile attacks, blood culture, CRP, PCT, complete blood count, and routine biochemical test results were evaluated. Venous blood samples were drawn from both arms of all patients for antibiotic susceptibility tests. In patients with catheters, culture material was obtained from catheter tips as well as venous blood samples. The blood culture was performed using BD BACTEC pediatric blood culture bottles. For complete blood count, at least 1 cc blood sample taken into an EDTA tube was studied with the "Sysmex" device in the laboratory. For CRP, at least 1 cc serum sample was taken into a straight tube and studied on the "Roche Diagnostics Cobat Integra 800" device.

CRP level of 5 mg/lt and above was accepted as a positive test result. One cc serum sample taken for the measurement of procalcitonin was studied on the same day with the "Roche Cobas" brand kit. Procalcitonin levels above 0.5 ng/ml were considered as a positive test result. Urine culture was obtained from patients with complaints of dysuria, pollakiuria, or suprapubic sensitivity, or those who had no focus of infection while fever persisted. Materials for stool culture and microscopic examination for adenovirus, rotavirus, and stool from patients with diarrhea were sent for analysis. In patients with prolonged fever despite appropriate antibacterial therapy, pulmonary CT was performed and GM level was measured considering fungal infection. For the galactomannan test, at least 0.5 cc serum sample taken in a gel tube was studied in the external center laboratory with a "Biorad" brand kit. Galactomannan level above 0.5 Optical Density (OD) was considered as a positive test result.

Imaging

Posteroanterior chest X-ray was performed in patients who were thought to have lung infection as a focus of fever. Thoracic ultra sonographic examination was performed in patients with pleural effusion on X-ray. In patients with prolonged fever despite appropriate antibacterial therapy, lung CT was performed with a pre-diagnosis of fungal infection. Patients were examined using Siemens CT devices. All CT examinations were performed with the patient holding his/her breath in the supine position with arms above the head, (if the patients were cooperative)

Statistics

Mean, standard deviation, median, minimum, maximum, frequency and ratio values were used in the descriptive statistics of the data. The distribution of variables was evaluated with the Kolmogorov-Simirnov test. Patients with normal distribution

were compared with Student's t test and those with non-normal distribution with Mann-Whitney U test. Chi-square test was used in the analysis of qualitative independent data, and Fisher test was used when chi-square test conditions were not met. The level of statistical significance was set at $p<0.05$. Analyses were performed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY:IBM Corp program.

RESULTS

In our study, 55 patients and 83 febrile neutropenia attacks that were followed up and treated with cancer diagnosis in Pediatric Hematology-Oncology Clinic between January 2019 and June 2019 were examined cross-sectionally. Approximately 25-30 new leukemia patients and 20 solid tumors were diagnosed and followed up in our hospital annually. One attack in 37 of 55, 2 attacks in 10, 3 attacks in 6, and 4 attacks in 2 patients were examined. Each patient experienced an average of 1.4 (range 1-4) attacks. The Demographic data for patients have shown in Table 1. The patients with leukemia were in the high (n=18:27%), moderate (n=35:53%), and standard (n=7:11%) risk groups. Six patients (9%) were being treated for recurrent leukemia. The median time interval between the diagnosis of cancer and the FEN attack was 12.4 (3.4-155.6) months. Leukemia patients presenting with febrile neutropenia received induction (n=27:41%), consolidation (n=23:35%), intensification (n=1:2%), and reinduction (n=6:9%) therapy. Three patients (5%) presented with FEN attack during maintenance treatment. According to the risk classification of febrile neutropenia, 80 attacks (96%) were classified as high risk, 3 attacks (4%) as low risk.

The median duration of fever during febrile neutropenia of the patients was found to be 1 (1-7) days. Fever continued for 1 day in 41, 2 days in 20, 3 days in 11, and more than 3 days in 11 attacks. Mean duration of fever was 1.9 ± 1.3 days in patients with leukemia and 1.9 ± 1.1 days in patients with solid tumors. There was no statistically significant difference as for duration of fever between the groups with and without leukemia ($p>0.05$). The patients had fever on the median 2nd (0-33) day of neutropenia, and that they were totally neutropenic for a mean 11.6 ± 9.7 days. The median duration of total neutropenia was 10 (3-46) days in patients with leukemia, and the median duration of neutropenia was 5 (2-10) days in the group with solid tumors. Total duration of neutropenia was statistically significantly higher in the leukemia group than in the solid tumor group ($p<0.05$). When the FEN attack was evaluated on the day after receiving chemotherapy, fever developed within the median 5 (1-17) days after chemotherapy in the leukemia group, and a median 6 (1-10) days after chemotherapy in the solid tumor group.

Some important laboratory test results of the patients presenting with febrile neutropenic attacks were as follows: mean hemoglobin level : 9.4 ± 1.8 g/dl; mean hematocrit level : 26.0 ± 5.3%; median white blood cell count: 510 (30-11650)/mm^3; neutrophil count: 30 (0-530)/mm^3; platelet counts: 43 (1-364) × 10^3/mm^3; CRP l: 41 (0.2-269) mg/lt; procalcitonin : 0.5 (0-156) ng/ml. There was no significant difference between the groups with and without leukemia as for hemoglobin, hematocrit, CRP and procalcitonin values, and also white blood cell, neutrophil, and platelet counts ($p>0.05$) (Table 2).

Table 1: Demographic information of the patients.

Characteristics	
Gender, n (%)	83 (100)
Male	55 (66)
Female	28 (34)
Median age (min.-max.)	5.5 (1.1-16.7) years
Diagnosis, n (%)	83 (100)
Leukemia	66 (80)
ALL	52
AML	13
Mixed phenotype leukemia	1
Solid	17 (20)
Burkitt lymphoma	7
Rhabdomyosarcoma	4
Hepatoblastoma	2
Hodgkin lymphoma	1
Adenocorticoid tumor	1
Wilms tumor	1
Neuroblastoma	1

Table 2: Comparison of laboratory values in febrile neutropenia episodes of patients with leukemia and solid tumors. Data are expressed as mean ± SD or median (range).

	Leukemia n=66	Solid tumors n=17	p
Hemoglobin (g/dL)	9.5 ± 1.8	9.1 ± 1.5	0.479
Hematocrit (%)	26.3 ± 5.5	25.2 ± 4.5	0.494
White blood cell (mm^3)	475 (30-11650)	690 (40-8010)	0.897
Neutrophil (mm^3)	20 (0-530)	70 (0-440)	0.307
Platelet (× $10^3 mm^3$)	49 (1-364)	35 (10-192)	0.453
CRP (mg/L)	41.5 (0.2-269	33 (0.4-218)	0.304
Procalcitonin (ng/ml)	0.55 (0-156)	0.8 (0.1-1.5)	0.895

While no complaints other than fever were detected during 21 (25%) attacks, in 62 (75%) attacks complaints other than fever were indicated. The most common complaint was mouth sores (28%). Eighteen patients (22%) had cough and 12 patients (15%) had diarrhea. Any focus of fever was not detected in 19 attacks (23%). The most common focus of fever was mucositis (29%). The detection rate of foci of fever of the patients in the group with and without leukemia did not differ significantly ($p>0.05$). Mucositis was the most common physical examination finding (30%). Physical examination findings were not found in 33 (40%) attacks (Table 3).

In 19 (23%) of febrile neutropenia attacks, bacterial growth was detected in the blood culture obtained from the peripheral vein. Nine (47%) Gram-positive and 10 (53%) Gram-negative microorganisms were detected. The most common causative agent was Coagulase- negative staphylococcus. Distribution of Gram-positive and Gram-negative microorganisms in blood culture in the group with and without leukemia did not differ significantly ($p>0.05$) (Table 4).

Urine cultures obtained in nineteen (23%) attacks were sent for analysis. No growth was detected in 15 (79%) of the urine cultures sent. Distribution of bacterial growths in central catheter cultures in febrile neutropenia attacks are displayed in Table 5. Central

Table 3: Distribution of complaints, foci of fever and physical examination findings in patients with leukemia and solid tumors during attacks of febrile neutropenia.

Characteristics	Leukemia n (%)	Solid tumors n (%)	p
Complaints			
No	16 (24.2)	5 (29.4)	0.662
Yes	50 (75.8)	12 (70.6)	
Mouth sore	17 (25.8)	6 (35.3)	0.433
Coughing	13 (19.7)	5 (29.4)	0.386
Diarrhea	12 (18.2)	0	0.057
Abdominal pain	8 (12.1)	0	0.197
Vomiting	7 (10.6)	1 (5.9)	1
Constitutional	4 (6.1)	0	0.577
Shortness of breath	2 (3)	0	1
Pain on anal region	1 (1.5)	0	1
Throat sore	1 (1.5)	0	1
Skin rashes	1 (1.5)	1 (5.9)	0.37
Joint pain	1 (1.5)	0	1
Painful urination	1 (1.5)	1 (5.9)	0.37
Foci of fever			
No	15 (22.7)	4 (23.5)	0.944
Yes	51 (77.3)	13 (76.5)	
Mucositis	18 (27.3)	6 (35.3)	0.515
ACE	14 (21.2)	0	0.037
Pneumonia	13 (19.7)	2 (11.8)	0.448
URTI	6 (9.1)	4 (23.5)	0.103
Cellulitis	1 (1.5)	1 (5.9)	0.37
Chicken pox	1 (1.5)	0	1
Typhlitis	1 (1.5)	0	1
Physical examination			
Unremarkable	25 (37.9)	8 (47.1)	0.49
Remarkable	41 (62.1)	9 (52.9)	
Mucositis	19 (28.8)	6 (35.3)	0.602
RS	17 (25.8)	2 (11.8)	0.221
GIS	9 (13.6)	1 (5.9)	0.381
Skin	2 (3)	2 (11.8)	0.184
CVS	0	1 (5.9)	0.205

Note: URTI: Upper Respiratory Tract Infection, AGE: Acute Gastroenteritis, UTI: Urinary Tract Infection, RS: Respiratory System, GIS: Gastrointestinal System, CVS: Cardiovascular System.

venous catheters were present in 20 attacks (24%). Gram- positive microorganisms were grown in 4 (20%) catheterized patients, while no growth was detected in 14 (70%) of these patients. Sampling for culture was not performed from two patients (10%).There was growth of Candida albicans in one, Gram-positive microorganism in one, and Gram-negative microorganism in another culture media. One (5%) of the urine cultures was reported as contamination (Table 6).

Galactomannan levels of 11 patients were evaluated. Galactomannan was detected in one patient but not detected in ten patients. The patient with galactomannan-positivity was diagnosed with ALL and presented with a FEN attack while on induction therapy. The patient was at high risk according to the FEN risk classification. Total duration of fever was 3 days. Focus of fever was mucositis. Meropenem and amikacin antibiotherapy and caspafungin antifungal treatment were initiated. Growth of Enterobacter spp. was detected in the blood culture. Control galactomannan level was negative.

Findings supporting the fungal infection were detected in the lung tomography of two patients. Both patients received the diagnosis of AML in the moderate risk group. One patient was receiving intensification phase of chemotherapy and the other the consolidation phase. Lung CT was performed in patients with focal pneumonia due to the lack of treatment response. Galactomannan levels of both patients were negative. One patient had growth of Coagulase-negative staphylococci in blood culture. As antibiotiherapy one patient was started with cefepime and amikacin, and the other one with meropenem and amikacin. Caspofungin was initiated as an antifungal agent.

Table 4: Comparison of blood culture growths in febrile neutropenia episodes of patients with leukemia and solid tumors.

Blood	Leukemia n (%)	Solid tumors n (%)
Growth of microarganisms		
No	51 (77.3)	13 (76.5)
Yes	15 (22.7)	4 (23.5)
Gram-positive microorganisms		
Coagulase-negative staphylococci	5 (33.3)	1 (25)
S. Aureus	1 (6.6)	0
S.mitis	1 (6.6)	0
S.sanguis	1 (6.6)	0
Gram-negative microorganisms		
Klebsiella spp.		0
Acinetobacter baumannii	1 (6.6)	0
Agrobacterium radiobacter	1 (6.6)	0
E.coli	1 (6.6)	2 (50)
Enterobacter cloacae	1 (6.6)	0
Pseudomonas aeroginosa	1 (6.6)	0
Pseudomonas aryzihabitans	0	1 (25)

Table 5: Distribution of bacterial growths in central catheter cultures in febrile neutropenia attacks.

Central catheter culture	n (%)
Bacterial Growth	
No	14 (70)
Yes	4 (20)
Coagulase–negative staphylococci	3 (75)
S. Aureus	1 (25)

Table 6: Distribution of bacterial growths in urine cultures obtained during febrile neutropenia attacks.

Urine culture	n (%)
Bacterial growth	
No	15 (78.9%)
Yes	3 (15.7%)
Candida albicans	1
Corynebacterium jeikeium	1
Klebsiella pneumoniae	1

Single antibiotic therapy was started for the management of 16 (19%) febrile neutropenia attacks. Dual antibiotic therapy was initiated on 67 of them (81%). Cefepime was started in 15 patients (94%), and ciprofloxacin in 1 patient (6%). It was observed that the patient who was started on ciprofloxacin had a known allergy to meropenem and cefepime, and had a FEN attack while receiving azithromycin treatment due to pneumonia, so the patient was switched to ciprofloxacin treatment. A combination of cefepime and amikacin was initiated in 28 patients (42%) who were started on dual antibiotherapy. The most common combined antibiotherapy consisted of cefepime and amikacin. The second most commonly used combined therapies consisted of cefoperazone/sulbactam and amikacin (19%), meropenem and teicoplanin (18%) (Table 7).

The distribution of antibiotic use in the group with and without leukemia did not differ significantly (p>0.05) (Table 8).

Antifungal treatment was initiated for the management of 34 attacks (41%) considering possible fungal infection. Antifungal treatment was started on the median 2nd (0-8) day after onset of fever. The most commonly used antifungal agent was caspofungin (59%). Fluconazole was started in 11 (32%), voriconazole in 2 (6%), and liposomal amphotericin B in 9 patients (27%) (Table 9).

Antifungal treatment was initiated in 30 (46%) of the patients diagnosed with leukemia and 4 (24%) of the patients with a diagnosis of solid tumor. The rate of antifungal use did not differ significantly between the groups with and without leukemia (p>0.05). G-CSF was applied for the management of 39 (47%) attacks. The median duration of application was 5 (1-11) days in those who received G-CSF. Granulocyte infusion was applied for the management of 21 (25%) attacks. Median duration of its application was 2 (1-5) days. The number of days of G-CSF and granulocyte administration in the leukemia group was similar to that of the solid group (p>0.05).

Three (4%) patients were lost during the FEN attack. Two of the patients who died were diagnosed with ALL and aged 2.5 and 4 years, respectively. The third one aged 7.5 years, and diagnosed with adrenocortical tumor. A patient treated for ALL was taken to the intensive care unit due to sepsis on the 27th day of chemotherapy. Necrotizing pancreatitis developed in the patient. Growth of E.coli was detected in the blood culture. The other ALL patient was taken to the intensive care unit on the 20th day of induction treatment due to pneumonia and severe respiratory distress. Meropenem and teicoplanin antibiotherapy and liposomal amphotericin B antifungal treatment was initiated. There was no bacterial growth in the blood culture of the patient. The patient, who was followed up due to adrenocortical tumor, could not be operated, and came with FEN attack after the first chemotherapy. In two patients who died, presence of any microbiological infection was not confirmed.

Table 7: Distribution of antibiotherapies in febrile neutropenia attacks.

Antibiotic	
Single antibiotic treatment n (%)	16 (19.3)
Cefepime	15 (93.7)
Ciprofloxacin	1 (6.3)
Combination antibiotherapy n (%)	67 (80.7)
Cefepime+Amikacin	28 (41.8)
Cefaperazone/Sulbactam+Amikacin	13 (19.4)
Meropenem+Teicoplanin	12 (17.9)
Meropenem+Amikacin	9 (13.4)
Cefepime+Teicoplanin	3 (4.5)
Ceftazidime+Teicoplanin	1 (1.5)
Cefepime+Metronidazole	1 (1.5)

Table 8: Comparison of antibiotic treatments used in febrile neutropenia attacks in patients with leukemia and solid tumors.

Antibiotic	Leukemia n (%)	Solid tumor n (%)	p
Single antibiotherapy	13 (19.7)	3 (17.6)	1.000
Combination antibiotherapy	53 (80.3)	14 (82.4)	

Table 9: The frequency and distribution of antifungal treatment applied during febrile neutropenia attacks.

Antifungal treatment	
No n (%)	49 (59)
Yes	34 (41)
Caspofungin	20 (58.8)
Fluconazole	11 (32.4)
Liposomal Amphotericin B	9 (26.5)
Voriconazole	2 (5.9)

DISCUSSION

Survival rate in children with cancer has increased due to improved treatment options in recent years. However, some side effects related to treatment may develop. The most common side effect due to intensive chemotherapy in children with cancer is febrile neutropenia. Delay in treatment can lead to an increase in morbidity and mortality. The risk of developing infection in patients receiving chemotherapy is closely related to the duration and depth of neutropenia. The lower the neutrophil count, the higher the risk of developing infection. In addition, as the duration of neutropenia increases, the incidence rates of fungal and bacterial infections infections increase as well [6].

In our study, 55 patients and 83 febrile neutropenia attacks were examined cross-sectionally. Patients with moderate and severe neutropenia were included in the study. 76% of the attacks had deep neutropenia. The median neutrophil level was 30 (0-530)/mm^3. Patients had fever on the median 2nd day of neutropenia, and they were total neutropenic for an average of 11.6 days. Total duration of neutropenia was statistically significantly higher in the leukemia group than in the solid tumor group. In Alexander, et al. study the presence of hypotension, tachypnea, hypoxia, emergence of new infiltration on chest X-ray, mental status changes, severe mucositis, vomiting or abdominal pain, focal infection, and other clinical indications requiring hospitalization placed the patient in the high risk group. In the presence of these findings, the patient is at high risk of developing serious medical complications [7].

The presence of every uncontrolled adverse condition (relapse, treatment refractory cases, during induction therapy), high- risk ALL and AML, consolidation or late intensification treatment, ANC <100/mm^3 after high dose cytarabine treatment if expected neutropenia duration ≥ 7 days, toxic appearance (hypotension, shock, tachypnea, hypoxia, neurological changes), evidence of

infection (pneumonia, cellulitis, abdominal pain and diarrhea, neurological changes), known MRSA colonization, previous bacteremia/sepsis history, development of mucositis after chemotherapy were included in the high risk group in our study. According to these criteria, 96% of the attacks in our study were high-risk.

Bone marrow suppression is different according to chemotherapy protocols. Since bone marrow suppression is higher in ALL and AML induction treatments, the risk of febrile neutropenia are higher [8].

There are some studies showing that the risk of febrile neutropenia increases during the induction period [8,9]. Yılmaz et al. reported that febrile neutropenia attacks were experienced most frequently during consolidation treatment in pediatric leukemia patients [10]. In our study, the most common febrile neutropenia attack in leukemia patients developed during induction therapy (41%). Second most frequently FEN attack was observed during consolidation treatment (35%). The difference between studies may stem from multifactorial reasons including the difference in the chemotherapy protocols applied,, the type of solid or leukemia malignancy and the number of patients enrolled to these studies.

Mostly investigated and well known infection marker in cancer studies is CRP. However, there are some limitations in clinical practice. CRP rises within 24-48 hours and may be affected by the underlying malignancy and tissue damage [11-13]. Since procalcitonin level starts to rise within 3-4 hours and reaches the highest level in 8-24 hours it is more advantageous than CRP [14,15]. Secmeer and et al. suggested that CRP and PCT levels in patients with febrile neutropenia attack were significantly higher than in non-febrile patients [16]. In our study, high CRP and PCT levels were detected in FEN patients with attack. The CRP, and PCT levels were found to be 41 (0.2-269) mg/lt, and 0.5 (0-156) ng/ml, respectively. In a study conducted, it was found that 41%, and 48% of the patients with microbiologically proven infections had CRP, and PCT positivity's, respectively [17]. In our study, high CRP and PCT levels were found in 9 (40%) of 22 attacks experienced by patients with microbiologically proven infections.

In many neutropenic patients, especially those taking steroids, the systemic inflammatory response is weakened, so the focus of infection may not be clearly identified. Most of the time, fever focus cannot be detected in FEN attacks in patients receiving chemotherapy [18]. Regular Kar et al. reported that the frequency of clinically defined infections was found to be 40.5%. Among these, the most common focal mucositis has been identified [19]. Özdemir, et al. reported that the frequency of clinically proven infections was found to be 35%, and the most common focus among them was mucositis, with a frequency of 32% [20]. Clinically proven infection rate was found to be 77% in our study.

Mucositis is a common complication of cancer treatment. Mucositis risk is increased in hematological malignancies compared to solid tumors. Otmani et al. 60% of the patients with hematological malignancy developed oral mucositis, while 48% of the patients with solid tumors developed mucositis [21]. In our study, the frequency of developing mucositis was not different between patients diagnosed with leukemia and solid tumors. Although the laboratory conditions are very good in 60-70% of the cases with febrile neutropenia, the causative microorganism cannot be demonstrated [22,23]. Microbiologically proven infection rate in many studies ranges between 17-29% [24-27]. In some studies; the frequency of microbiologically proven infections varies between 16-36% [19,28,29]. In our study, microbiologically proven infection was found during 22 (27%) of 83 attacks. The factors responsible for the infection differ according to the hospitals. While Gram-negative bacteria were the most common factors in febrile neutropenia attacks in the previous years, nowadays Gram-positive microorganisms are frequently observed [30]. In studies conducted in our country, the detection rate of Gram-positive agents were reported as 69%, 64% and 70% [20,29,31].

The cause of the increase in Gram-positive agents was the development of mucositis as a result of the use of chemotherapeutic agents such as cytosine arabinoside, deep and prolonged neutropenia attacks, long-term inserted intravenous catheters, protective treatment with fluoroquinolone and cotrimoxazole, use of antacid and histamine receptor blockers [32,33]. Demirkaya et al. found most frequently Coagulase-negative staphylococci during febrile neutropenia attacks in their study [34]. In our study, bacterial growth was detected in 23% of blood cultures taken from the peripheral veins, while 47% of them were Gram-positive and 53% of them Gram- negative microorganisms. Gram-positive microorganism was grown in 20% of the cultures taken from the central catheter. No reproduction was detected in 70% of these cases. Growth of Gram negative microorganisms was not observed in the blood culture taken from the central catheter. When we consider as a whole, in blood culture media of 55% of the patients demonstrating bacterial reproduction Gram-positive agents were grown.

Most frequently Coagulase-negative staphylococci were detected. Hann et al. reported that the growth rate of active microbial agents in the blood was lower in patients treated for solid tumors compared to leukemia patients [35]. Delebarre, et al., the growth rate of Gram-negative agents during FEN attacks was found to be higher in patients receiving leukemia treatment compared to those treated for solid tumors [36]. In our study, no significant difference was found in the growth rate of Gram-negative and Gram-positive agents during FEN attacks between patients with leukemia and those with solid tumors.

Urinary tract infections are common in children. The importance of Urinary Tract Infections (UTIs) in febrile neutropenic patients has not been clearly determined [22]. Özdemir, et al. UTI was found in 4% of patients during febrile neutropenia [37]. The most frequently isolated microorganism is E.coli [38]. In our study, urine culture was sent during 23% of the attacks. Bacterial growth occurred in 3 (79%) of the urine cultures sent. Candida albicans, Corynebacterium jeikeium, and Klebsiella pneumoniae were isolated separately from each one of them. The focus of fever was UTI in 4% of the attacks. The frequency of foci of fever detected was similar to the literature.

All high-risk patients with febrile neutropenia attack should receive inpatient treatment. A broad spectrum antibiotic effective against Gram-positive and Gram-negative agents, including Pseudomonas aeruginosa should be initiated empirically and in no time. This approach has decreased the infection-related mortality rates in FEN attacks in patients with cancer. Antibiotics that can be used in monotherapy can be antipseudomonal beta lactams, 4th generation

cephalosporins or an antibiotic in the carbapenem group [39]. It is recommended that a second antibacterial effective against Gram-negative microorganism or glycopeptide group antibiotherapy be initiated for patients with suspected resistant infection, who are clinically unstable and treated in centers with a high rate of resistant microorganisms. In one study, no difference was found between monotherapy with 4th generation cephalosporin and combined therapy containing aminoglycoside in terms of efficacy and safety [40].

Antipseudomonal penicillin and aminoglycoside; antipseudomonal cephalosporin and aminoglycoside; carbapenem and aminoglycoside are the most commonly used antibiotics in combination therapies. Combination therapy has advantages such as synergistic effect and prevention of resistance development, but the increase in side effects such as nephrotoxicity and ototoxicity due to aminoglycosides is especially seen in cisplatin, cyclosporine, and amphotericin B users [41]. Kebudi, et al. showed that the effectiveness of cefepime and ceftazidime monotherapies is comparable [42]. Kamonrattana, et al. detected no significant difference between piperacillin/tazobactam monotherapy and ceftazidime/amikacin combination therapy, as for treatment response, duration of fever,neutropenia, and antibiotic use [43].

Ponraj, et al., compared cefepime monotherapy with cefoperazone/sulbactam and amikacin combination treatment and they suggested no difference between the two groups in terms of efficacy and safety [44]. In our study, for 19%, and 81% of the FEN attacks treatment with single and dual antibiotherapy were initiated, respectively. Cefepime was used most frequently as single antibiotherapy (93%). Cefepime and amikacin were used most frequently as dual antibiotherapy (42%). In Marín M, et al. study, empirically combined antibiotherapy was found to be more appropriate than single antibiotherapy in patients with hematological malignancies. In the same study, combination antibiotic treatment was found to be more effective than single antibiotic treatment in patients with solid tumors [45]. In our study, no significant difference was found between the initiation of single and combined therapy.

Since invasive fungal infection cannot be excluded in patients who do not respond to empirical antibiotic therapy and have refractory fever, empirical antifungal therapy is recommended. Caspofungin and liposomal amphotericin B are antifungals recommended for empirical therapy [39]. In a study by Güneł et al. antifungal treatment was given to 20% of the patients experiencing FEN attacks and fluconazole was used most frequently as antifungal treatment (47%) [28]. in a study conducted, it was revealed that the effectiveness of caspofungin and liposomal amphotericin B were similar [46]. In our study, antifungal treatment was started for the management of 41% of the attacks. Mostly used antifungal agent was caspofungin (%58).

While the mortality rate due to febrile neutropenia was over 90% in the 1960s, it has now fallen below 5% as new studies and guidelines are implemented [47]. In a study conducted in previous years, the mortality rate during the FEN attack was determined to be 3%, and race, age group, age of diagnosis, type of cancer and developing complications were found to be associated with the mortality rate [48]. In Demirkaya et al. study, the mortality rate in FEN attack was found to be 1 percent. Bacteremia was found in one of the deceased patients, and no focus of infection was found in the other two [34]. In our study, 3 patients (4%) who were examined due to FEN attacks died. Two of the patients were being treated for ALL and one for adrenocortical tumor. Growth of E.coli was detected in the blood culture of one of them. In the other two patients, presence of any microbiological infection was not confirmed.

CONCLUSION

The limitations of the study can be expressed as the small number of cases, the short follow-up period, the inability to standardize culturing methods, the simultaneous evaluation of solid tumors and leukemias, and the inability to separate leukemias according to their risk groups. This study is the first study on FEN in the Pediatric Hematology and Oncology Clinic of our hospital. We think that this study will be important in terms of creating up-to-date algorithms in the treatment and management of FEN. In literature; the results of new studies in which the number of patients is higher and subgroups are determined will be more beneficial in the diagnosis and treatment of FEN.

DECLARATION

Ethics approval and consent have been taken from Health Sciences University Ethical Committee.

CONSENT FOR PUBLICATION

Have been taken from the patients' parents. Patient's parents gave informed written consent for their personal or clinical details along with any identifying images to be published in this study.

AVAILABILITY OF DATA AND MATERIAL STATEMENT

Not applicable

CONFLICT OF INTEREST STATEMENT

None declared

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AUTHORS' CONTRIBUTIONS

Author Huseyin Avni Solgun, Zeynep Gunal Turk have contributed in design and data collection of manuscript. Author Huseyin Avni Solgun, Zeynep Gunal Turk Cengiz Bayram and Ali Aycicek have checked and approved the final manuscript file.

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