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Original Article

Evaluation of febrile neutropenic attacks of pediatric hematology-oncology patients

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Abstract

Aim: Febrile neutropenia is an important cause of mortality and morbidity in hematology-oncology patients undergoing chemotherapy. The objective of this study was to evaluate febrile neutropenic episodes in children with malignancy.

Material and Methods: Sixty-eight children who received chemotherapy for malignancy between 2010 and 2015 were retrospectively reviewed. The demographic characteristics, laboratory data, infection foci, and frequency of microorganisms grown in culture were examined. Also, the frequency of febrile neutropenic attacks was investigated according to the chemotherapy periods.

Results: Of the total 200 episodes, 81 (40.5%) were clinically documented, and 73 (36.5%) were microbiologically documented infections. Fever of unknown origin was observed in 46 (23%) episodes. The most frequently clinically documented focus were mucositis (33.4%) and pneumonia (24.7%). Blood culture was positive in 55 (75.3%) episodes of microbiologically documented infections. The most commonly isolated microorganisms in blood culture were Gram-negative bacteria (47.2%). C-reactive protein levels in microbiologically documented infections were higher than in clinically documented infections, and fever of unknown origin ($p<0.05$, for both). The most common underlying malignancy was acute lymphoblastic leukemia (73.5%). The highest proportions (34.6%) of febrile neutropenic episodes were observed during the reinduction period for these children. Nine (13.2%) children died of neutropenic sepsis.

Conclusions: Febrile neutropenia continues to be an important cause of mortality in pediatric patients with malignancy. C-reactive protein levels may be an indicator for predicting bacterial infection in children with febrile neutropenia without apparent focus. The most frequently isolated agents in our center were Gram-negative microorganisms. Determining the microbial flora of each center may be beneficial to improving survival rates.

Keywords: Children, febrile neutropenia, malignancy

Introduction

One of the most important complications of chemotherapy is febrile neutropenia and it is an important factor in terms of mortality. In the past, the mortality rate related with febrile neutropenia in pediatric patients was above 90%, whereas the current mortality rates have been reported to be reduced. In developed countries, the mortality rate ranges between 0.7% and 3.9% (1, 2). The reduction in mortality rates has been explained by the improvement of nursing conditions, positive developments in supportive therapies, and use of strong antibiotics and antifungal agents (3).

In febrile neutropenia, variance has been observed in the distribution of infectious agents over time. Gram-negative agents were observed more frequently at the beginning of the 1970s, but Gram-positive agents have been observed more frequently since the beginning of the 1990s (4). However, an increase in the frequency of Gram-negative agents has been reported in recent years (5-8). The initiation of appropriate antibiotherapy in the early stage decreases morbidity and mortality. Therefore, identifying the frequencies of causative microorganisms is important in terms of reducing mortality. It has been reported that approches including specification of the periods during which fe-

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brile neutropenia episodes occur more frequently and empirical antibiotic use in chemotherapy protocols contribute markedly to reductions in mortality (3).

In this study, the foci of infection in febrile neutropenia episodes, changes in blood counts and acute- phase reactants by foci of infection, and the frequency of causative microorganisms were investigated in children with malignancy receiving chemotherapy, and the frequencies of febrile neutropenia were examined according to protocol periods.

Material and Methods

Sixty-eight pediatric patients aged between 1 and 18 years who were being followed up with a diagnosis of malignancy (acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML), lymphoma and solid tumor) between January 2010 and December 2015 were included in the study. The file data were examined retrospectively. An axillary body temperature measured once above 38°C or continuance of the axillary body temperature above 37.5°C for longer than one hour in patients who had an absolute neutrophil count (ANC) of <500/mm³ or who were expected to have an ANC below 500-1000/mm³ in 48 hours was considered as ahving febrile neutropenia (FEN) (9, 10). Febrile neutropenia attacks were classified as clinically documented febrile neutropenia attacks (CDFEN), microbiologically documented infections (MDI), and fever of unknown origin (FUO). Clinically documented infection (CDI) was defined as infection that was clinically specified, but for which a microbiologic pathogen could not be demonstrated. MDI was defined as cases of infection where blood culture was positive, but no clinical focus could be specified or blood culture was positive/negative, but the microbiologic agent was specified in the clinical focus (10). Isolated fever that developed without clinical or microbiologic findings of infection was defined as FUO (10). Growths of coagulase-negative staphylococcus, *Micrococcus* species and *Corynebacterium* species belonging to skin flora in a single culture were considered contamination. Growth of the same microorganism in two cultures obtainded at different times was considered significant (11). Growth of ≥100,000 bacterial colonies or ≥1000 fungal colonies in urine culture was considered significant (12).

The patients were grouped by infection foci. It was examined if there was difference between the groups in terms of white blood cell (WBC) count, absolute neutrophil count (ANC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. Patients with ALL received chemotherapeutic agents in accordance with the ALL Intercontinental Berlin Frankfurt Münster (IC BFM) 2009 protocol. Patients with AML received chemotherapeutical agents according to the AML BFM 2004 and AML BFM 2013 protocols. Patients with lymphoma received chemotherapeutic agents as per the non-Hodgkin lymphoma (NHL) BFM 95 protocol. Patients with solid tumors received different chemotherapy protocols in accordance with the type of tumor. The numbers of febrile neutropenia attacks that occured during induction, consolidation, intensification, and maintenance treatment periods were examined in patients with ALL.

Ethics committee approval was obtained for the study on 01.04.2017 from Eskişehir Osmangazi University Clinical Researches Ethics Committee (number: 80558721/G-05).

Statistical analysis

Statistical analyses were performed using statistical package software (SPSS 21, Chicago, IL, USA). The qualitative characteristics of the patients are shown as numbers (n) and frequencies (%) in the tables. The Kolmogorov-Smirnov test was used to evaluate the distribution of numeric variables. Median and inter-quartile range (IQR) (25p-75p) were used in descriptive statistics and in inter-group comparisons for variables that did not comply with normal distribution. Inter-group comparisons were performed using the Kruskall-Wallis test. A p value of <0.05 was considered significant. For the CRP variable, for which a significant difference was found between the groups in the Kruskal-Wallis test, paired comparisons were performed using the Mann-Whitney U test and the results were subsequently evaluated using Bonferroni correction. A p value of <0.016 was considered significant.

Results

Two hundred febrile neutropenia attacks of 68 pediatric patients were evaluated. Fifty (73.5%) of the patients had ALL, eight (11.8%) had AML, seven (10.3%) had NHL, one (1.5%) had Hodgkin lymphoma, one (1.5%)

had neuroblastoma, and one (1.5%) had Wilms tumor. Thirty-three (48%) of the patients were female and 35 (52%) were male. The median age was 3.4 years (range, 5.7-11.9 years) and the median number of febrile neutropenia attacks per patient was 2 (range, 2-4). Twelve (17.6%) of the patients had a central venous catheters. The median time of fever was three (range, 3-6) days, the median ESR was 57 mm/h (range, 3-131 mm/h), and the median CRP level was 2.03 mg/dL (range, 0.03-22 mg/dL). CDI was shown in 81 (40.5%) of the febrile neutropenia attacks and MDI was shown in 73 (36.5%). A focus of infection could not be shown in 46 (23%) of the attacks. The clinical characteristics and laboratory test results are shown in Table 1.

The most common CDI included mucositis (33.4%) and pneumonia (24.7%). A microorganism was isolated in blood culture in 55 (75.3%) of MDI attacks and in urine culture in 17 (23.3%). A positive viral serology result was found in one patient. In this patient, parotitis and diffuse eruption in the whole body developed during induction treatment. Parvovirus immunoglobulin (Ig)-M antibody was found as positive. The foci of infection found in febrile neutropenia attacks are shown in Table 2.

In blood cultures, Gram-negative agents were isolated in 26 (47.2%) of 55 attacks in which a microorganism was isolated, Gram-positive agents were isolated in 21 (38.2%), and fungal agents were isolated in five (9.1%). Polymicrobial growth occured in three (5.5%) of the attacks. The most commonly isolated Gram-negative microorganism was *Klebsiella* species (30.8%) and the most commonly isolated Gram-positive microorganism was *Staphylococcus* species (85.7%). The most commonly isolated fungal agent was *Candida* species (80%). A microorganism was isolated in urine culture in 17 (23.3%) of the microbiologically documented attacks. The most commonly isolated microorganism in urine culture was *E. coli*. The distribution of the agent microorganisms in MDIs is shown in Table 3. Nine (13.2%) patients died; 3 patients had infant leukemia and one had Down syndrome and ALL. Two patients died of fungal sepsis and 7 died of Gram-negative bacterial sepsis.

The patients were grouped by foci of infection, and WBC counts, ANCs, ERSs, and CRP levels were compared. There was no difference between the three groups in terms of WBC count, ANC, and ESR ($p>0.05$ for all). A significant difference was found between the three groups in terms of CRP levels ($p<0.05$) (Table 4). Mann-Whitney U test results were evaluated by per-

Table 1. Clinical characteristics and laboratory measurements of the patients

Sex: n (%)	Female: 33 (48%)
	Male: 35 (52%)
Malignancy type: n (%)	ALL: 50 (73.5%)
	AML: 8 (11.8%)
	Lymphoma: 8 (11.8%)
	Solid tumor: 2 (2.9%)
Number of patients with catheter: n (%)	12 (17.6%)
Age (years)	3.41 (5.75-11.9)[a]
Number of FEN per patient	2 (2-4)[a]
Time of fever (days)	3 (3-6)[a]
White blood cell count (/mm^3)	700 (400-1200)[a]
Absolute neutrophil count (/mm^3)	100 (0-300)[a]
Erythrocyte sedimentation rate (mm/h)	57 (23-86)[a]
C-reactive protein level (mg/dL)	2.03 (0.03-6)[a]
Clinically documented FEN (n/%)	81(40.5%)
Microbiologically documented FEN (n/%)	73(36.5%)
Fever of unknown origin (n/%)	46 (23%)

[a]median (25-75% range); ALL: Acute lymphoblastic leukemia; AML: Acute myeloblastic leukemia; FEN: Febrile neutropenic attack; n: number of patients; %: frequency

Table 2. Distribution and frequency of foci of infection

Focus of infection	Number (n)	Frequency (%)
Clinically documented infection	81	40.5
Mucositis	27	33.4
Pneumonia	20	24.7
Soft tissue	10	12.3
Tonsillitis/sinusitis	8	9.9
Gastroenteritis	7	8.6
Anal abscess/wound	3	3.7
Zona	3	3.7
Herpes labialis	2	2.5
Dental abscess	1	1.2
Microbiologically documented infection	73	36.5
Blood culture	55	75.3
Urine culture	17	23,3
Serology	1[a]	1,4
Fever of unknown origin	46	23

[a]Paravovirus IgM positivity

Table 3. Distribution of agent microorganisms in microbiologically documented infections

Blood culture	**55 (75.3%)**	**Urine culture**	**17 (23.3%)**
Gram negative agents	**26 (47.2%)**	*E. Coli*	*12*
K.penumoniae	*6*	*Klebsiella spp*	*2*
Klebsiella spp.	*2*	*E.cloacae*	*2*
A. baumannii	*5*	*C.albicans*	*1*
S. maltophilia	*4*	*Viral serology*	*1 (1.4%)*
E.cloacae	*4*	*Parvovirus*	*1*
E. coli	*3*		
P.aeruginosa	*2*		
Gram positive agents	**21 (38.2%)**		
Staphylococcus spp.	*9*		
KNS	*8*		
E. faecium	*2*		
MRSA	*1*		
S. pneumoniae	*1*		
Polymicrobial	**3 (5.5%)**		
Streptocockus spp+C.parapsilosis	*1*		
CNS+Weeksolla Wirosa	*1*		
E.cloacae+K.pneumoniae	*1*		
Fungal agents	**5 (9.1%)**		
Candiada spp.	*4*		
G.capitatum	*1*		

A.baumannii: Acinetobacter baumannii; C.albicans: Candida albicans; C.parapsilosis: Candida parapsilosis; E.cloacae: Enterobacter cloacae; E.coli: Escherichia coli; E.faecium: Enterococcus faecium; G.capitatum:Geotrichum capitatum; K. pneumoniae: Klebsiella pneumoniae;CNS: Coagulase negative satphylococcus aureus; MRSA: Methicillin resistant satphylococcus aureus; P. aeruginosa: Pseudomonas aeruginosa; S. maltophilia: Stenotrophomonas maltophilia; S. pneumoniae: Streptococcus pneumoniae

Table 4. Comparison of withe blood cell counts, absolute neutrophil counts, erythrocyte sedimentation rates, and C-reactive protein levels by foci of infection

	CDI	**MDI**	**FUO**	**p[a]**
White blood cell count	800 (400-1 300)	700 (400-1 100)	800 (500-1 200)	>0.05
ACN	100 (0-400)	100 (0-250)	200 (0-500)	>0.05
Erythrocyte sedimentation rate	53 (17-86)	61 (29-90)	55 (25-73)	>0.05
CRP level	2.02 (0.3-5.31)	3.46 (0.45-8.345)	0.98 (0.3-4.5)	<0.05

[a]Kruskall-Wallis test; CRP: C-reactive protein; CDI: Clinically documented infection; ANC: Absolute neutrophil count; MDI: Microbiologically documented infection; FUO: Fever of unknown origin

forming Bonferroni correction in order to determine between which groups this difference occured. It was found that the CRP value was higher in MDIs compared with CDIs and cases of unkown focus of infection (p=0.014, p=0.09).

Twenty (15%) of 133 attacks that occured in patients with ALL developed in the induction period, 33 (24.8%) developed in the early intensification period, 29 (21.8%) developed in the consolidation period, 46 (34.6%) developed in the reinduction period, and five (3.8%) developed in the maintenance period. The FEN attack frequency by chemotherapy periods is shown in Figure 1.

Discussion

Febrile neutropenia is a life-threatening problem that occurs as a result of underlying malignant disease and immune deficiency developing during its treatment. It should be kept in mind that a serious infection manifest with minimal symptoms, especially in

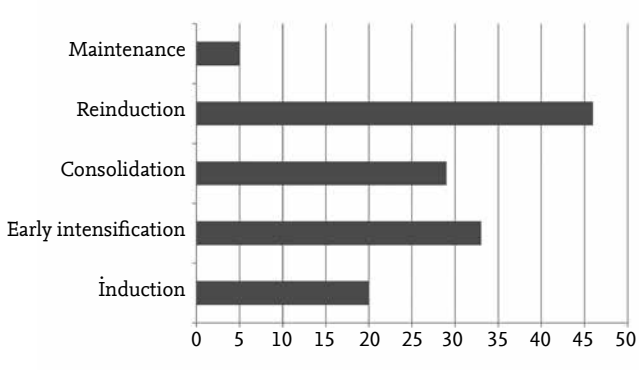

Figure 1. The frequencies of febrile neutropenia by chemotherapy periods

neutropenic patients receiving steroid treatment, because an inflammatory response cannot be obtained. In these patients, the only sign of infection may be fever, or neutropenic patients may be infected in the absence of fever and the body temperature may have a subfebrile course (13). Therefore, early diagnosis of febrile neutropenia and initiation of appropriate treatment in the early stage are life-saving in neutropenic patients receiving chemotherapy. Currently, the origin of fever cannot be demonstrated in 15-79% of FEN attacks despite the use of advanced laboratory techniques (14-16). The frequency of MDIs ranges between 17% and 28.7% (17-20). In studies conducted in our country, the frequency of fever of unknown origin ranged between 15% and 50%, the frequency of MDIs ranged between 28% and 35%, and the rate of blood culture positivity ranged between 12% and 32.4% (21-23). In our study, the frequency was found as 23% for fever of unknown origin, 36.5% for MDIs, and 27.5% for blood culture positivity in all attacks. These data were similar to the data of our country (Table 3).

The frequencies of microorganisms leading to febrile neutropenia show variance over time. Differences may be observed from country to country and even from region to region in the same country. In a prospective study conducted in our country in 2004 in which 829 febrile neutropenia attacks were evaluated in 24 centers, it was reported that an MDI was found in 32% of the attacks, bacteriemia was found in 21%, and Gram-positive agents were isolated more frequently (24). In other studies conducted in our country, the frequency of Gram-positive agents was reported as 69% by Baysallar et al. (22), 63.8% by Özdemir et al. (23), and 70% by Akçay et al. (25). Gram-positive and negative agents were reported to be isolated with an equal frequency in one study (26). In the study conducted by Tezcan et al. (27), it was shown that Gram-positive microorganisms were isolated more frequently between 1996 and 2004, but the frequency of Gram-negative microorganisms tended to increase between 2000 and 2004. In a study from Turkey in which 18 years' experience was conveyed, it was reported that the frequency of Gram-negative microorganisms was 52% and bacteriemia was present in 41% of these (28).

In studies conducted worldwide in recent years, it has been reported that the frequency of Gram- negative microorganisms is increasing (5-8). The most common Gram-negative agents reported in the literature include *E. coli* and *Klebsiella* species and the most common Gram-positive agents are *Staphylococcus* species (22, 25, 29). In our study, Gram-negative microorganisms were also observed more frequently in MDIs (the frequency was found as 47.2%). The most common microorganisms were *Klebsiella* species (30.8%) among Gram-negative agents, and *Staphylococcus* species among Gram-positive agents (85.7%). It has been proposed that the increase in extended spectrum beta-lactamase-producing Enterobacteriaceae and *P. aeruginosa* and *A. baumannii* with multiple drug resistance as a result of widespread use of flouroquinolone prophylaxis might be related with the increase in Gram-negative agents (5). In addition, differences in the microbial flora in hospitals and communities may be a factor that affects the frequency of agent microorganisms. The frequency of fungal infections also shows variance by centers. The frequency of fungal infections was reported as 5.2% by Tezcan et al. (27), 6.4% by Kebudi et al. (24), 24.7% by Aslan et al. (30), and 9% by Viscoli et al. (31). In our study, the frequency of fungal infections was found as 10%. The most commonly isolated fungal agent was *Candida* species (Table 3). In the literature, the most common foci of infection include oral mucositis, soft tissue infection, pneumonia, and gastroenteritis (29, 32). Similarly, the most common foci of infection in our study included mucosits, pneumonia, and soft tissue infections (Table 2). The frequency of urinary tract infection in two hundred febrile neutropenia attacks was found as 8.5%, which was similar to the rates found in the literature (23, 25).

CRP, which is an acute-phase reactant, has been used as an indicator of inflammation for many years. Its serum level starts to increase 4-6 hours after the beginning of inflammation. The serum level is parallel to the degree of tissue damage (33). In studies in which CRP levels were evaluated by focus of infection in febrile neutropenia, Fleischhack et al. (34) found that CRP levels were significantly higher in subjects with Gram-negative bacteremia compared with the FUO group, and similar to the subjects with CDIs. Chaudhary et al. (35) found that CRP values on the first day of febrile neutropenia did not show a difference between groups, but were significantly higher on the third day in MDIs compared with the other groups. Tezcan et al. (27) could show no difference between MDIs and microbiologically unconfirmed infections in terms of CRP levels. In our study, the CRP value was significantly higher in MDIs compared with FUO and CDIs (Table 4). This result suggested that CRP could assist in predicting patients with bacterial infection.

In some studies, it has been reported that FEN attacks develop most commonly in the induction period (36, 37). In a study conducted in Turkey, it was reported that febrile neutropenia attacks developed most commonly during the consolidation treatment in patients with pediatric leukemia treated with the BFM protocol (29). In the study conducted by Lee et al. (38), it was reported that febrile neutropenia most commonly developed after the consolidation period. In our study, febrile neutropenia attacks developed most commonly in the reinduction period. The difference between studies may be related with the combination and doses of drugs used in chemotherapy protocols.

Febrile neutropenia still continues to be an important problem in children with malignancy. According to our results, the reinduction period seems to be a risky period in terms of infection in children treated with the BFM protocol. Gram-negative microorganisms were observed more commonly in our center. If each center specifies its own microbial flora, this would be directive in antibiotic selection.

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Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

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