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Original Article

Febrile neutropenia in children with acute lymphoblastic leukemia: single center experience

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Abstract

Aim: An important life-threatening complication of intensive chemotherapy administered in children with leukemia is febrile neutropenia. The objective of this study was to evaluate the clinical features and consequences of febrile neutropenia attacks in children who were treated for acute lymphoblastic leukemia.

Material and Methods: Nighty-six children who received chemotherapy for acute lymphoblastic leukemia in our center between January 1995 and December 2010 were included in the study. The data related to demographic characteristics, treatment features, relapse and febrile neutropenia incidences, risk factors, culture results and prognosis were retrospectively evaluated from the patients' files.

Results: A total of two hundred-ninety nine febrile neutropenia attacks observed in the patients during initial treatment and relapse treatment were evaluated. When the incidence of febrile neutropenia was evaluated by years, it was observed that the patients treated after year 2000 had statistically significantly more febrile neutopenia attacks compared to the patients treated before year 2000. When the incidences of febrile neutropenia during initial treatment and during relapse treatment were compared, it was observed that more febrile neutropenia attacks occured during relapse treatment. Fifty-nine percent of all febrile neutropenia attacks were fever of unknown origin. Eighty microorganisms grew in cultures during febrile neutropenia throughout treatment in 75 patients; 86% were bacterial infections (50% gram positive and 50% gram negative), 8% were viral infections and 6% were fungal infections. *Coagulase negative staphylococcus* (n=17) was the most frequent gram positive pathogen; *E. Coli* (n=17) was the most commonly grown gram negative pathogen.

Conclusions: In this study, it was found that an increase in the incidence of febrile neutropenia occured in years. Increments in treatment intensities increase the incidence of febrile neutropenia while improving survival. Evaluation of febrile neutropenia results by hematology-oncology units in years will be directive in early and successful treatment. (Turk Pediatri Ars 2016; 51: 79-86)

Keywords: Acute lymphoblastic leukemia, child, febrile neutropenia

Introduction

The disease-free survival rates have increased markedly in children with cancer with advances in cancer treatment, intensification of chemotherapy protocols and stem cell transplant therapies. A life-threatening and significant complication of intensive chemotherapy in children with cancer is febrile neutropenia. Treatment of febrile neutropenia which is an oncological emergency with early and efficient therapy decreases morbidity and mortality significantly (1). Differences between countries, regions and centers may be observed in terms of the microorganisms which are involved in the etiology of febrile neutropenia (2).

In this study; the clinical features, risk factors and prognosis of febrile neutropenia attacks were retrospectively evaluated in children with acute lymphoblastic leukemia (ALL), who were treated with chemotherapy at initial disease and relapse between January 1995 and December 2010 at Cerrahpaşa School of Medicine (CTF) Hospital. Results of this study may be directive at appropriate initiation of therapies which have vital importance in febrile neutropenia attacks.

Material and Methods

Ninety-six children (1-18 years old) with a diagnosis of ALL who were treated with chemotherapy between Janu-

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ary 1995 and December 20010 at CTF Division of Pediatric Hematology-Oncology and whose files were complete, were included in this study. Children younger than one year old were excluded, because they were treated with a different protocol (infant ALL protocol). The demographic data, treatment risk groups, treatment features, presence of relapse, frequency of febrile neutropenia, causative microorganisms of febrile neutropenia attacks, invasive fungal infections, culture results and disease prognosis were evaluated retrospectively from patients' files.

Leukemia treatment

In our center, BFM (Berlin Frankfurt Münster) protocol was initiated in treatment of ALL in 1989 for the first time. The BFM protocol which was used initially was the modified ALL-BFM 81 protocol. In August 1990, administration of the modified ALL-BFM 90 protocol was initiated. In January 2000, the ALL-BFM 95 protocol was changed and the Turkish ALL-BFM 2000 (TRALL-BFM 2000) protocol was started to be used. Afterwards, unmodified ALL-BFM 95 protocol was used between 2004 and 2010.

Patients with acute lymphoblastic leukemia were classified in three groups as standard, medium and high risk groups according to the BFM protocol (3). The classification was based on the leukocyte count, age, absolute blast count in the peripheral blood on day 8, bone marrow response on day 33 and high risk chromosomal changes. Molecular genetic studies could be performed after the year 1996.

Standard Risk Group (SRG) should include all the following criteria.

Initial leukocyte count <20 000 /mm^3 and
Age ≥1 year or <6 years and
Absolute blast count in the peripheral blood on day 8 after 7 days of prednisolone treatment <1 000/mm^3 and
No T-cell immunology and
Complete remission on day 33 and
Absence of t (9;22) and t (4;11).

Medium Risk Group (MRG) should include at least one of the following criteria.

Leukocyte count ≥20 000/mm^3 or
Age <1 year or ≥6 years or
T-cell immunology positive
In addition, all the following conditions should be present.
Absolute blast count in the peripheral blood on day 8<1 000/mm^3 and
Complete remission on day 33 and
Absence of t (9;22) and t (4;11)

High Risk Group (HRG) should include at least one of the following criteria.

Absolute blast count in the peripheral blood on day 8 >1 000/mm^3 or
No complete remission on day 33 or
One of the translocations is present (t (9;22) or t (4;11)).

Febrile neutropenia

In this study, febrile neutropenia was defined as an axillary temperature measured as >38°C for once or as >37.5°C for at least one hour in patients who had an absolute neutrophil count (ANC) of <500/mm^3 or who had an ANC between 500 and 1 000/mm^3 and whose ANC was expected to decrease below 500/mm^3 in 24-48 hours (4).

Invasive fungal infections were classified in three groups as "suspicious", "probable" and "proven" according to the criteria regulated in 2008 (5). Proven infection was considered demonstration of fungus in tissue by biopsy or needle aspiration. Some clinical and microbiological criteria were used to define probable and suspicious infection. These criteria included host factors, clinical signs and symptoms related to the disease and diagnostic tests including culture, direct examination and antigen tests. Positive serological tests in addition to specific imaging findings indicate "probable" infection. In order to define a probable fungal infection, one host factor, one clinical factor and one mycological factor should be present. Patients who have no mycological factor, but who have host and clinical factors are classified as suspicious fungal infection (5). This classification was used also in this study.

Antimicrobial and prophylactic treatment

All patients were given trimethoprim-sulphametoxasole and acyclovir as prophylactic treatment from the beginning of treatment. Empiric antibiotics used in patients with febrile neutropenia in our clinic showed changes in years. From the time when the BFM protocols went into use until 1999; piperacillin, cefazolin and netilmicin or cefaperasone/sulbactam, netilmicin or imipenem/cilastatincombinations were used in association alternately in treatment of febrile neutropenia. Ceftazidim-amikacin was preferred between 1999 and 2001, piperacillin-tazobactam was preferred between 2001 and 2003, cefaperasone/sulbactam-amikacin was preferred between 2004 and 2008 and ceftazidim-amikacin combination or imipenem was preferred after year 2008 by evaluating the infectious agents and susceptibilities at that time.

Statistical analysis

The numeric variables obtained in the study were expressed as mean±standard deviation, if they showed a normal distribution. If they did not show a normal dis-

tribution, they were expressed as median values. The categorical variables were expressed as percentages. In comparison of the mean values between groups, Mann-Whitney U test was used for two groups and Kruskal-Wallis test was used for more than two groups. The difference between the categorical variables was evaluated using the chi-square test. SPSS (Statistical Package for Social Sciences) for Windows 15 program was used for statistical analysis in the study. A p value of <0.05 was considered significant.

Ethics approval was obtained from Istanbul University, Cerrahpaşa School of Medicine Ethics Committee for the study (03.08.2010-23400).

Results

Patients

Ninety-six ALL patients aged between 1 and 18 years (mean age=5.9±3.7 years) were included in the study. The demographic features of the patients are summarized in Table 1. When the patients were evaluated in three date ranges according to the protocol used, it was observed that 13 patients were treated with modified ALL-BFM 90, 13 patients were treated with TRALL-BFM 2000 protocol and 70 patients were treated with unmodified ALL-BFM 95 protocol after year 2004. Sixty-one patients received radiotherapy for central nervous system prophylaxis. Treatment responses and prognosis of the patients are shown in Table 2.

Febrile neutropenia

A total of 245 febrile neutropenia attacks were observed during initial treatment (mean 2.5±1.58 per patient (range=0-8)). Eight patients completed their treatment without febrile neutropenia. All of these patients were in the SRG or MRG treatment groups. When the frequency of febrile neutropenia was examined by gender, it was found that the mean frequency of febrile neutropenia attacks was 2.2±1.52 in male patients and 2.7 ±1.62 in female patients. There was no difference between the female and male patients in terms of the frequency of febrile neutropenia (p=0.1). When the frequency of febrile neutropenia was examined by risk groups, statistically insignificantly more febrile neutropania attacks were found in the HRG patients compared to the SRG and MRG patients (p=0.066) (Table 3). When the febrile neutropenia frequency was examined by year ranges of treatment, statistically significantly more febrile neutropania attacks were observed in patients who were treated after year 2 000 compared to the ones treated before year 2000 (p≤0.05) (Table 4).

Fifty four febrile neutropenia attacks occurred during relapse treatment in 15 patients with relapse. The mean number of febrile neutropenia attacks was found as 3.6±1.88 (range: 1-8) in these patients. When the number of febrile neutropenia attacks at treatment of relapse and at initial treatment were compared, it was found that statistically significantly more febrile neutropania attacks occurred during treatment of relapse (p≤0.05).

The cause of 50% of all febrile neutropenia attacks (n=177/299) was fever of unknown origin. The focus of

Table 1. Demographic features of the patients

Gender	**n (%)**
Male	50 (52.1)
Female	46 (47.9)
Age	**n (%)**
1-6 years	62 (64.5)
>6 years	34 (35.5)
Risk group	**n (%)**
SRG	32 (33.3)
MRG	56 (58.3)
HRG	8 (8.3)

SRG: Standard risk group; MRG: Medium risk group; HRG: High risk group

Table 2. Treatment responses and prognosis of the patients

Steroid response	**n (%)**
Present	91 (94.8%)
Absent	5 (5.2)
Bone marrow examination on the 33rd day n (%)	
M1 (<5% blast)	95 (98.9)
M2 (5-25% blast)	1 (1.0)
M3 (>25% blast)	0 (0.0)
Prognosis	**n (%)**
Complete response	81 (84.4)
Recurrence	15 (15.6)
Bone marrow	9 (9.4)
Testicle	3 (3.1)
CNS	1 (1.0)
Bone marrow and testicle	1 (1.0)
Bone marrow and CNS	1 (1.0)
Second reccurence	2 (2.0)
Mortality	9 (9.4)
Fungal infection	4 (4.2)
Febrile neutropenia	2 (2.0)
Leukemia	2 (2.0)
Secondary tumor (brain tumor)	1 (1.0)

CNS: central nervous system

Table 3. Frequency of febrile neutropenia and fungal infection by risk groups

	SRG (n=32)	MRG (n=56)	HRG (n=8)	p
Febrile neutropenia (mean±SD)	2.5±1.43	2.2±1.43	4.0±2.39	0.066*
Fungal infection (n,%)	4; 12.5%	6; 10.7%	2; 25%	0.52**

SGR: standard risk group; MRG: medium risk group; HRG: high risk group
*SRG and MRG patients were compared with HRG patients using Kruskal-Wallis test.
**SRG and MRG patients were compared with HRG patients using chi-square test.

Table 4. Frequency of febrile neutropenia and fungal infection according to treatment years

	1990-2000 (n=13)	2000-2010 (n=83)	p
Febrile neutropenia (mean±SD)	1.1±1.06	2.6±1.56	<0.05*
Fungal infection (n, %)	2; 15.4 %	10; 12.0 %	0.73**

*Mann-Whitney U test
**Chi-square test

infection was defined clinically in 66 attacks (22%) (excluding bacteremia); pulmonary infection was found in 25 patients (38%), gastrointestinal infection in 19 patients (29%), urinary tract infection in 12 patients (18%), otolaryngological or dental infection in 6 patients (9%), dermatological and soft tissue infection in three patients (4.5%) and meningitis in one patient (1.5%). Among patients with pulmonary infection; five had fungal pneumonia, one had atypical pneumonia and one had viral bronchiolitis. When the gastrointestinal system infections were examined, it was found that 10 patients had acute gastroenteritis, three had fungal infection in the liver and spleen, two had typhilitis, one had splenic abscess, one had Candida esophagitis, one had appendicitis and one had gallbladder infection. Eighty culture growths occurred during febrile neutropenia in 75 patients throughout treatment. Eighty-six percent (n=69) of the microbiologically defined infections were bacterial infections, 8% (n=6) were viral infections and 6% (n=5) were fungal infections. Sixty percent of the positive growths occurred in blood, 16% occurred in urine, 7% occurred in port catheters, 5% occurred in sputum, 4% occurred in tissue (biopsy) and 3% occurred in stool. The causative infectious agents are shown in Table 5.

Fungal infections

Fungal infection was diagnosed at initial treatment in eight (8.3%) of 96 patients. When the fungal infections were evaluated by states of evidence, it was found that four were proven fungal infections, two were probable fungal infections and two were suspicious fungal infections. Fungal infection occurred in the lung in one patient; both in the liver and spleen in one patient; in paranasal sinus in one patient; in the lung, liver and spleen in one patient; in the lung and palate in one patient; in the blood in one patient; in the lung, liver and esophagus in one patient and in the lung, paranasal sinus and esophagus in one patient. *Candida albicans* was cultured in three patients and Aspergillus and Mucor were cultured in one patient (subgroup typing could not be made). Single therapy was used in two patients and combination therapy was used in six patients for antifungal treatment. Granulocyte colony stimulating factor (G-CSF) treatment was given to four patients. Fungal infection was diagnosed in four (26.6%) of 15 patients with ALL relapse. All were suspicious infections according to the degree of evidence. None of the patients who had fungal infection during initial treatment expired. All four patients who had invasive fungal infection during treatment of relapse died and ALL did not improve in any of these patients.

When the frequencies of fungal infections were examined by risk groups; the frequency of invasive fungal infections was higher in HRG patients, but the difference was not statistically significant (Table 3). When the frequencies of fungal infections were examined by date range of treatment, 83% (n=10) of all fungal infections (n=12) occurred after year 2004, but no significant difference was found when 10-year date ranges were compared (Table 4). When the causes of death were evaluated, it was found that the most common causes of death were fungal infections and febrile neutropenia (Table 2).

Discussion

Treatment success rates have reached up to 80% with advances achieved in treatment of ALL which is the most common pediatric cancer. Although major improvement have occurred in supportive treatment, the most important cause of death in leukemia is still febrile neutropenia. It is known that patients who receive higher doses of chemotherapy and who have undergone stem cell transplantation are especially risky (3-5). In this study, we found that febrile neutropenia attacks were observed more frequently in high risk patients compared to medium and standard risk patients, but the difference was not

Table 5. Infectious agents grown in the culturs

Agent	n
Bacteriae	69
Gram positive	35
Staphylococci:	23
Coagulase(-) staphylococci	17
MRSA	4
MSSA	2
Streptococci:	10
α–hemolytic streptococus	4
S.pneumoniae	2
S. mitis	1
Other	3
Enterococci	1
Corynebacterium fermentas	1
Gram negative:	34
Escherichia coli:	17
ESBL (-)	14
ESBL (+)	3
Klebsiella spp.	6
ESBL (-)	4
ESBL (+)	2
Stenotrophonomas maltophilia	2
Flavobacterium	2
Enterobacter cloacae	1
Aeromonas	1
Haemophilus influenza	1
Haemophilus parainfluenza	1
Providencia	1
Alcaligenes xylosoxidans	1
Salmonella	1
Viruses	6
H1N1 influenza virus	2
RSV	1
Rota virus	1
Herpes virus	1
Adenovirus	1
Fungi	5
Candida albicans	3
Aspergillus spp.	1
Mucor spp.	1

ESBL: extended -spectrum beta-lactamase; MRSA: methicillin-resistant (Staphylococcus aereus); MSSA: methicillin susceptible (Staphylococcus aereus); RSV: respiratory syncitial virus

statistically significant. This finding may be attributed to unequal distribution of the patients in the groups. Again in this study, we showed an increase in febrile neutropenia attacks in years. This increase was more prominent after year 2004. We thought that intensification of treatment protocols especially in the last 10 years might have a role in the increase in febrile neutropenia attacks. Many different factors including increased number of patients, altered hospital flora, structural changes in wards and patient care may have an impact on the frequency of febrile neutropenia, but these factors were not investigated in this study (6). In addition, it is known that the risk of febrile neutropenia is higher in children with cancer who have relapse and who have advanced disease despite treatment. In our study, the frequency of febrile neutropenia was increased in patients with relapse which was an expected finding and this finding was compatible with the literature (6-9).

In children receiving treatment for ALL, the mortality related to bacterial infections has decreased with appropriate use of wide spectrum antibacterial agents and with empirical treatment, but an increase in opportunistic fungal infections has emerged (10-12). According to autopsy findings, invasive fungal infections are present in 50% of cases of hematological malignancies (10, 11). In patients with febrile neutropenia, fungi are important microorganisms not only because of their increased frequency, but also due to limited treatment options, altered resistance patterns, increased diversity of fungi and the fact that they lead to severe infections with limited treatment options (12-15). In recent years, the reasons for increased frequency of fungal infections in cancer patients include advances in mycological diagnostic methods, applications of intensive chemotherapeutics and steroids, long-term neutropenia and use of wide spectrum antibiotics and venous catheters (16-18). Fungal infection was observed during initial treatment in eight (8.3%) patients in our study. The frequency of invasive fungal infection was found as 26.6% during treatment of relapse. When the patients were evaluated by risk groups, fungal infection was found in 10-12% of SRG and MRG and 25% of HRG patients. No statistically significant difference was found between risk groups in terms of fungal infections, but this result may be due to insufficient number of patients per group. When the frequency of fungal infections was examined by date range of treatment, 83% of all fungal infections occurred after year 2004 when treatment intensities have increased, but no difference was found between 10-year frequencies when date ranges were compared. In the study conducted by Hammond et al. (19), invasive fungal infections were evaluated retrospectively in adult leukemia patients. In their study, it was shown that the risk of fungal infection was higher in patients who were not in complete remission. Again in this study, it was shown that the frequency

of fungal infections increased with prolonged neutropenia periods. When 12 patients who had fungal infections were evaluated in our study, we found that leukemia did not improve in four of these patients and the neutrophil count was below 500/mm3 in all. The low frequency of proven fungal infections suggests that there is still need for new diagnostic methods for specifying fungal infections in these patients.

It is known that the mortality rate related to fungal infections is high in neutropenic patients. In high risk neutropenic patients, the mortality rate related with systemic candidiasis has been reported to be 50% and to invasive aspergillosis as high as 80-100% (20). The most important factor which has been shown to affect survival is neutropenia in invasive fungal infections (21, 22). The most important reason for lack of improvement of neutropenia is absence of response of accompanying malignancy to treatment. In the study conducted by Nivoix et al. (22), it was reported that progression of accompanying malignancy had more impact on mortality related to invasive fungal infection than prolonged neutropenia period alone. In this study, it was observed that none of the patients who had fungal infection during initial treatment expired, but all patients who had fungal infection during relapse treatment died. Acute lymphoblastic leukemia was not in remission in none of these patients.

The causative agent can not be demonstrated in 60-70% of cases of febrile neutropenia attacks even with best laboratory conditions (23, 24). Similarly, the cause of 59% of febrile neutropenia attacks was fever of unknown origin in our study. Most frequent causative agents were gram negative rods in the years when the concept of febrile neutropenia was introduced. In time, the frequency of gram positive infections increased. Oral mucositis due to chemotherapeutic drugs including cytosine arabinoside, deep and prolonged neutropenia attacks, long-term indwelling intravenous catheters, prophylactic treatment with flouroquinolone and cotrimoxasole and use of antiacids and histamine blockers have been blamed as the causes of this increased frequency (25, 26). Viridians streptococci which are isolated frequently following mucositis are among the most important causative agents. In our study, gram positive and gram negative agents were cultured with similar frequencies. *Coagulase negative staphylococci* and *E. coli* were the most common bacterial organisms isolated.

Bacterial and fungal infections constitute the majority of causative infections in febrile neutropenia, but the importance of viral infections has been better understood with the increase in improved diagnostic tests (27). In a study conducted at St. Jude Hospital in USA, viral agents were responsible for 34% of microbiologically proven infections in 337 febrile neutropenia attacks evaluated, but no patient expired due to viral infection (27). In our study, only 8% of the microbiologically proven infections were caused by viral agents. This low rate was associated with insufficient diagnostic tests and with the fact that these tests are not always available. H1N1 infections constituted two of six cases and these cases were diagnosed during the H1N1 epidemic when the viral agents which could lead to fever and respiratory tract complaints were screened in each patient with these complaints. H1N1 infection was diagnosed in 10 hematology-oncology patients in our clinic during the H1N1 epidemic which occurred between 2009 and 2010 (28). Only five of these patients were neutropenic. None of the patients expired due to H1N1 infection, but chemotherapy was delayed and the hospitalization period was prolonged in four patients.

Urinary tract infections (UTI) are observed commonly in children. The importance of UTI in febrile neutropenia has not been fully elucidated (24). In a recent study, the frequency of UTI was reported as 8.6% in children with febrile neutropenia (29). In our study, UTI was diagnosed in 12 (4%) of 299 febrile neutropenia attacks.

In conclusion, febrile neutropenia continues to be a significant oncologic emergency in children. In our study, we showed that febrile neutropenia and especially fungal infections were the most common cause of mortality in ALL patients. The frequency of febrile neutropenia increased in years with the increase in the intensity of treatment. Febrile neutropenia developed more commonly in patients with high risk and thus received more intensive treatment and patients who were not in remission. Among the infections which could be demonstrated microbiologically, bacterial infections were the most common. Hematology-oncology centers should evaluate their results and especially the changes in causative agents in time for early and efficient treatment of febrile neutropenia.

Ethics Committee Approval: Ethics committee approval was received for this study from İstanbul University School of Medicine Ethic Committee.

Informed Consent: Informed consent was not obtained due to retrospective nature of this study.

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