BRIEF REPORT

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Identifying Risk Factors and Improving Preventive Strategies for Febrile Neutropenia in Children with Leukemia Receiving Ciprofloxacin Prophylaxis

Siprofloksasin Profilaksisi Alan Lösemili Çocuklarda Febril Nötropeni için Risk Faktörlerinin Belirlenmesi ve Önleyici Stratejilerin Geliştirilmesi

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Abstract

The purpose of this study was to identify risk factors and improve preventive strategies for febrile neutropenia (FEN) in children with leukemia who were receiving ciprofloxacin prophylaxis. The study included 100 children with leukemia [n=80 with acute lymphoblastic leukemia and n=20 with acute myeloblastic leukemia (AML)]. Patients were divided into two groups based on whether they had three or fewer FEN episodes (Group 1) or more than three FEN episodes (Group 2). Group 1 contained 63 (63%) of the 100 patients, while Group 2 contained 37 (37%). Older age (≥7 years), leukemia type, prolonged neutropenia (>10 days), and the presence of neutropenia and hypogammaglobulinemia at diagnosis were all risk factors for having more than three FEN episodes. Our findings suggest that, in addition to ciprofloxacin prophylaxis, identifying risk factors and improving preventive strategies could help reduce FEN episodes in children with leukemia.

Keywords: Febrile neutropenia, Children, Leukemia, Risk factor, Prophylaxis

Öz

Bu çalışmanın amacı, siprofloksasin profilaksisi alan lösemili çocuklarda febril nötropeni (FEN) için risk faktörlerini belirlemek ve önleyici stratejileri geliştirmektir. Çalışmaya lösemili 100 çocuk dahil edildi (akut lenfoblastik lösemi n=80 ve akut myeloid lösemi (AML) n=20). Hastalar üç ve üçten az FEN atağı (Grup 1) veya üçten fazla FEN atağı (Grup 2) geçirmelerine göre 2 gruba ayrıldı. Yüz hastanın 63'ünü (%63) Grup 1, kalan 37'sini (%37) Grup 2 oluşturdu. İleri yaş (≥7 yaş), lösemi tipi, uzamış nötropeni (>10 gün), tanı anında nötropeni ve hipogamaglobulinemi varlığı üçten fazla FEN atağı için anlamlı risk faktörleriydi. Bulgularımız, siprofloksasin profilaksisine ek olarak, lösemili çocuklarda risk faktörlerinin belirlenmesinin ve önleyici stratejilerin geliştirilmesinin FEN atağını azaltmaya yardımcı olabileceğine işaret etmektedir.

Anahtar Sözcükler: Febril nötropeni, Çocuklar, Lösemi, Risk faktör, Profilaksi

Introduction

Routine antibiotic prophylaxis in children with acute leukemia was described as a weak recommendation in the most recent guidelines for the management of febrile neutropenia (FEN) [1]. However, randomized controlled pediatric studies have demonstrated that quinolone prophylaxis dramatically reduces bacteremia and mortality in children with acute leukemia [2,3,4]. Recent studies have focused on identifying risk factors and other supportive management for FEN in pediatric leukemia [5,6,7,8].

The objective of this research was to identify risk factors and improve preventive strategies for FEN episodes in children with acute leukemia receiving ciprofloxacin prophylaxis.

Materials and Methods

The medical records of 100 patients aged 1 to 18 years with acute lymphoblastic leukemia (ALL) (n=80) or acute myeloblastic leukemia (AML) (n=20) between 1998 and 2018 were retrospectively reviewed. The BFM-95 protocol for ALL and the MRC-12 protocol for AML were used for risk classification and treatment [9,10]. Immunoglobulin levels and neutrophil counts

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were monitored periodically throughout the chemotherapy protocol. This study was approved by the relevant institutional ethics committee.

In the hematology department, children receiving intensive chemotherapy were isolated in private rooms with en suite facilities. Between 1998 and 2011, there was no air filtering system, although two special rooms with high-pressure air circulation technology were available after 2011. Ciprofloxacin prophylaxis at two daily doses of 20 mg/kg was administered at the start of each chemotherapy cycle for AML until neutrophil recovery and only during severe neutropenia [absolute neutrophil count (ANC) of <500/µL] for ALL. FEN was defined as a single oral or axillary area temperature of >38.5 °C or a fever of >38.0 °C maintained for 1 hour in addition to neutropenia defined as ANC of 500/µL or ANC likely to decrease to 500/µL within 48 hours after chemotherapy [11]. Patients were stratified into two study groups based on the number of FEN episodes, and patients in Group 1 had three or fewer episodes while those in Group 2 had more than three episodes. Data were analyzed using SPSS 15.0.

Results

This study included 20 patients with AML and 80 patients with ALL, with median ages of 5 (1-17) years and 7 (1-16) years, respectively. There were no statistically significant differences among the patient groups according to age, sex, or leukemia risk types (p>0.05). While 63% of the patients were categorized in Group 1, 37% of the patients were in Group 2. Our research identified multiple risk factors that could predict more than three FEN episodes. Patients over the age of 7, AML diagnosis, neutropenia and hypogammaglobinemia at initial diagnosis, and prolonged neutropenia lasting more than 10 days were all found to be significant risk factors (p<0.05) (Table 1). Patients with AML had an approximately twofold risk of more than three FEN attacks, while those with hypogammaglobinemia at the time of diagnosis had a fourfold risk. The risk of FEN attacks with the remaining significant identified risk factors ranged from 1.3- to 1.5-fold. The changes in mean immunoglobulin levels and neutrophil counts of these patients with ALL and AML at diagnosis and throughout chemotherapy are shown in Figure 1. Immunoglobulin levels and neutrophil counts were significantly lower in patients who had more than three FEN attacks during chemotherapy in Group 2 compared to patients who had fewer than three FEN attacks in Group 1 (p<0.05). The occurrence of more than three FEN episodes was significantly more common among patients treated before 2011 (75%) than patients treated after 2011 (25%) (p<0.05). The rate of infection-related mortality was significantly higher in Group 2 (16%) than in Group 1 (4%) (p<0.05).

Discussion

Our research has revealed that the occurrence of more than three FEN episodes was observed among 37% of children with leukemia who received ciprofloxacin prophylaxis. We identified multiple risk factors in our patient groups. Disease type was one of these risk factors. The occurrence of more than three FEN attacks was more common among patients with AML, which is consistent with the European Conference on Infections in Leukaemia guidelines [12]. In addition to the patients' disease

Table 1. Risk factors for febrile neutropenic episodes in children with acute leukemia.

Variables	Group 1 n=63	Group 2 n=37	p	Odds ratio (95% CI)
Age at diagnosis				
<7 years	45 (72%)	19 (52%)	0.03	1.4 (1.0-2.1)
≥7 years	18 (28%)	18 (48%)		
Leukemia type				
ALL	56 (88%)	24 (64%)	0.005	2.1 (1.0-3.6)
AML	7 (12%)	13 (36%)		
Neutropenia at diagnosis				
Yes	11 (17%)	14 (38%)	0.02	1.5 (1.0-2.3)
No	52 (83%)	23 (62%)		
Hypogammaglobulinemia at diagnosis				
Yes	8 (12%)	14 (38%)	0.004	4.1 (1.5-11.3)
No	55 (88%)	23 (62%)		
Prolonged neutropenia (more than 10 days)				
Yes	28 (44%)	24 (64%)	0.03	1.3 (1.0-1.9)
No	35 (56%)	13 (36%)		

ALL: Acute lymphoblastic leukemia, AML: acute myeloblastic leukemia, CI: confidence interval.

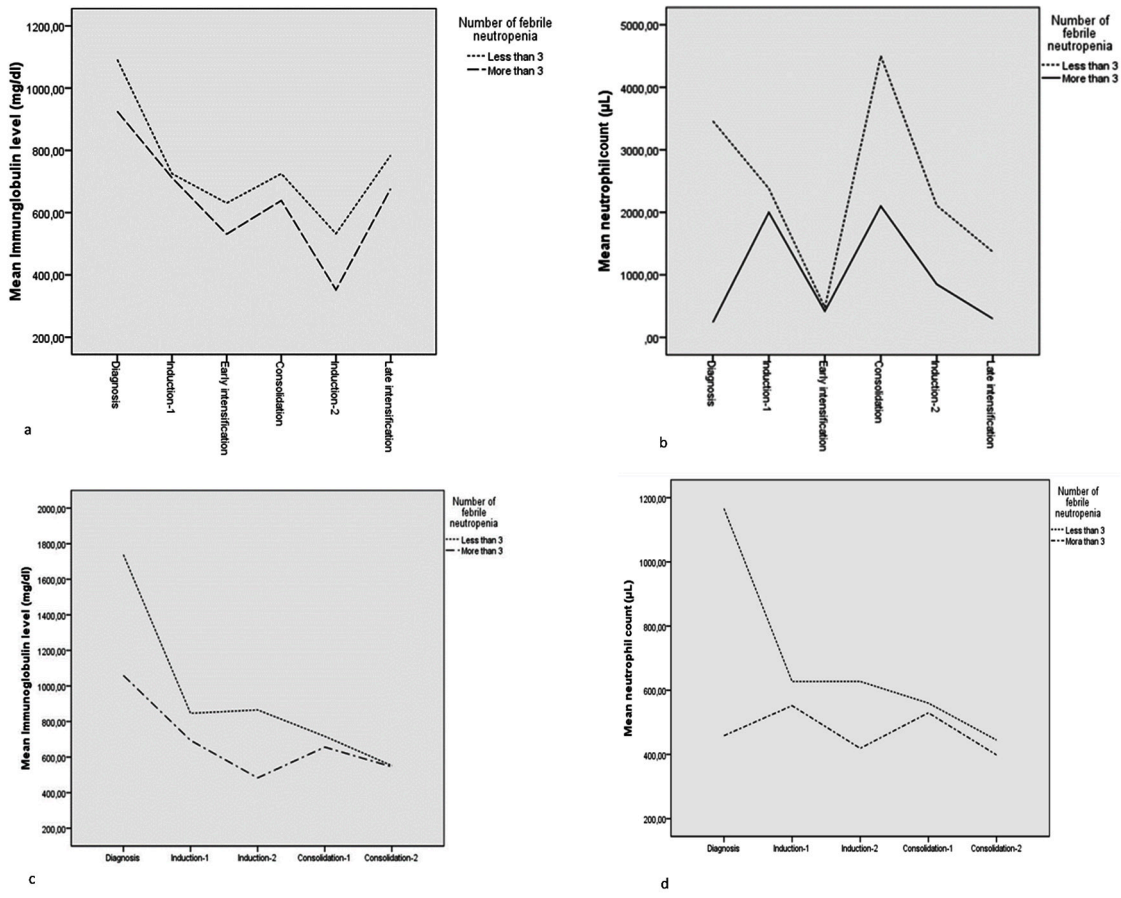

Figure 1. Changes in mean immunoglobulin level (a) and mean neutrophil count (b) during the chemotherapy protocol for acute lymphoblastic leukemia and changes in mean immunoglobulin level (c) and mean neutrophil count (d) during the acute myeloblastic leukemia chemotherapy protocol based on number of febrile neutropenic episodes.

types, the high rate of FEN episodes was also linked to insufficient clinical settings in our center. After private rooms with separate HEPA filters were built in our center in 2011, the rate of more than three FEN attacks occurring per patient decreased from 75% to 25%. This finding highlights the importance of isolating and outfitting patient care rooms to prevent infection.

To reduce the frequency of FEN attacks, it is critical to understand patient risk factors in addition to oncology unit design. Based on a review of the literature, induction chemotherapy, prolonged and severe neutropenia (>7 days), high temperature (>39 °C), elevated acute-phase reactants, hypotension, and the presence of a central venous catheter were considered as high-risk factors for FEN in patients with acute leukemia in previous studies [5,6,7,8,12,13,14,15]. Similarly, in a previous study that included the data of some of our patients, having more than three FEN episodes with neutropenia lasting more than 10 days and being older than 7 years were shown to be important risk factors [5]. In parallel with these findings, the present study has shown that the rate of prolonged neutropenia lasting more than 10 days was significantly higher in patients of Group 2 compared to Group 1. Furthermore, we previously documented a significantly increased rate of bacterial infections and FEN episodes during induction and early intensification phases of a leukemia chemotherapy protocol [16]. A comprehensive study also indicated that more than three febrile episodes required intensive therapy and had unfavorable outcomes in pediatric oncology patients using multivariate analysis [17]. Consistent with this finding, despite ciprofloxacin prophylaxis, the rate of infection-related mortality was significantly higher among patients with more than three FEN episodes in our study. We also previously reported the prevalence of bacterial infections and ciprofloxacin resistance in our leukemia protocol [16]. As a result, identifying high-risk patients and clinical conditions is critical for preventing unnecessary prophylactic antibacterial use. Hypogammaglobinemia and neutropenia at the initial diagnosis were identified as additional risk factors for more than three FEN attacks in our study. Decreases in immunoglobulin levels and neutrophil counts during the chemotherapy protocol were also linked to more FEN attacks in our study, which is consistent with a few previous reports [5,6,7,8,15,17]. Furthermore, we found that patients who had neutropenia and hypogammaglobinemia at the time of their initial acute leukemia diagnosis had a 1.5-fold to 4.1-fold

higher likelihood of having more than three FEN attacks. Our study's main limitation was the small sample size.

Our findings suggest that leukemia specialists should be aware of the increased risk of FEN episodes in children with hypogammaglobulinemia and neutropenia at the time of diagnosis. Furthermore, potential beneficial and preventive strategies for reducing FEN episodes include improving isolated clinical settings, giving granulocyte-colony stimulating factors to leukemia patients to quickly reverse severe neutropenia if complete remission has been obtained, intermittently monitoring immunoglobulin levels, and administering immunoglobulin when low levels are detected.

Ethics

Ethics Committee Approval: Gazi University's Ethics Committee approved the study.

Informed Consent: All patients and their parents provided informed consent.

Authorship Contributions

Concept- Z.K., N.A.; Design- Z.K., N.A; Data Collection or Processing- Z.K, N.A, S.K., U.K; Analysis or Interpretation- Z.K., N.A; Literature Search- Z.K., N.A; Writing- Z.K., N.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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