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Comparison of augmented Berlin-Frankfurt-Münster (BFM) and BFM 2000 treatment protocols in children diagnosed with high-risk acute lymphoblastic leukemia

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ABSTRACT

Objectives: The main purpose of this study is comparing the augmented Berlin-Frankfurt-Münster (BFM) and BFM 2000 treatment protocols applied to pediatric patients diagnosed with high-risk acute lymphoblastic leukemia (ALL) in our clinic in different years in terms of relapse incidence and survival rates.

Methods: When evaluated all patients considering the Children's Oncology Group (COG) criteria, 53 of our patients who were in the medium or high risk group according to the BFM 2000 protocol and were in the high risk group received treatment with Augmented BFM protocol and 17 of them received the BFM 2000 protocol. Age, gender, bone pathology, physical examination, hepatomegaly, splenomegaly, lymphadenopathy, presence of bleeding, hemogram values, immunophenotype, 8th, 14th and 33rd day treatment response, presence of translocation, central nervous system (CNS), extramedullary involvement, risk group, presence of relapse, time to relapse, follow-up period and hospital stay until maintenance treatment were examined.

Results: Event-Free Survival (EFS) and Overall Survival (OS) values of patients were 83.6% and 90.1%, respectively. While EFS was 89.4% and OS was 90.6% in the group receiving the Augmented BFM treatment protocol, EFS was calculated as 71.7% and OS was 88.2% in those receiving the BFM-2000 treatment protocol. Accordingly, when the EFS values of those who received the Augmented BFM treatment protocol were compared with those who received BFM-2000, statistically significant values were found (P<0.01).

Conclusions: It was observed that the augmented BFM treatment protocol was more protective against relapses and shortened the duration of hospitalization compared to the BFM 2000 treatment protocol.

Keywords: Acute lymphoblastic leukemia, child, treatment protocol

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy and accounts for around 30-35% of all types of malignancies. The incidence of leukemia among all cancer cases in Türkiye has been reported to be 31.3%. ALL is most commonly diagnosed between the ages of 2 and 5 years and is more prevalent in males [1, 2]. The life expectancy for ALL, which used to be considered an incurable disease, has increased dramatically with the discovery of new drugs, the

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determination of the combinations in which these drugs can be used and the development of treatment protocols [3]. In the past two decades, expected 5-year Overall Survival (OS) rates in children with ALL have reached 90% in developed countries [3, 4, 5]. Moreover, relapse rates in particular have been significantly reduced. The improvement in outcomes over the last few decades can be attributed mainly to changes in the use of drug combinations and intensification of treatment for patients diagnosed with more difficult-to-treat disease [6]. The optimization of standard cytotoxic chemotherapy has resulted in significant improvements in Event-Free Survival (EFS) and OS outcomes, particularly in high-risk ALL patients, although it has not brought about a notable enhancement in EFS and OS rates in some ALL patients [7]. Numerous cancer study groups worldwide have contributed to the development of treatment protocols to increase the expected EFS and OS. In particular, the Children's Oncology Group (COG), which unites the Children's Cancer Group and the Pediatric Oncology Group, and the Berlin-Frankfurt-Munster (BFM) study group are pioneers in the development of these effective treatment protocols [8]. Up to date, various prognostic factors have been identified in ALL. Some prognostic factors vary according to treatment protocols; however, age, leukocyte count at the time of initial diagnosis, and response to treatment remain unchanged. With the development of diagnostic and treatment centers and advancing research, it has been realized that both clinical and laboratory findings are effective on prognosis, and thus, treatment by risk class has been brought to the agenda. Recent studies have also focused on defining new prognostic factors to intervene in patients with poor prognosis with new treatment protocols [9, 10]. The COG and the BFM study group treat ALL by stratifying it into risk groups. However, they do not use the same risk classification. This leads to some variations in the treatment protocols of the two groups. In the present study, all patients were divided into two groups: patients in the high-risk group according to COG criteria, and patients in the intermediate-risk or high-risk group according to the BFM study group criteria, but in the high-risk group according to COG criteria. The aim is to compare the effects of both treatment protocols on EFS and OS and the effects of prognostic factors on overall survival and event-free survival rates.

METHODS

Patients who were referred to our clinic with a prediagnosis of ALL or who were diagnosed with ALL upon examination were evaluated with bone marrow aspiration in the Department of Pediatrics, Division of Pediatric Hematology-Oncology, İstanbul University Istanbul Faculty of Medicine. Accordingly, the data of 70 patients diagnosed with ALL were retrospectively analyzed. The study included 53 patients who were classified in the high-risk ALL group according to COG criteria and treated with augmented-BFM treatment protocol, and 17 patients who were classified in the intermediate-risk or high-risk ALL group according to BFM study group criteria and in the high-risk ALL group according to COG criteria and treated with BFM 2000 treatment protocol. The following characteristics of all patients were analyzed: age and gender at presentation, presence of organomegaly on physical examination, complete blood count parameters, treatment responses to bone marrow aspiration on day 8, day 14, and day 33, FAB classification, immunophenotypes, presence of translocations, extramedullary involvement, risk group, presence of relapse, time of relapse, and duration of follow-up period and hospitalization. The patients receiving the two treatment protocols were compared according to the data obtained.

Bone marrow aspiration samples were evaluated under light microscopy. Typing was performed according to FAB criteria. Immune phenotyping was performed using the flow cytometry method at the Molecular Oncology and Hemopathology Research Center, İstanbul University Cerrahpaşa Faculty of Medicine. CD13, CD14, and CD33 were used as myeloid markers for immune phenotyping; CD19, CD20, CD22, CD24, and CD10 were used as lymphoid markers for the B cell line; CD3, CD5, and CD7 were used for the T cell line. The presence of CD34 above 10% and any data above 20% was considered positive. The presence of t(9;22), t(4;11), t(1;19), and t(12;21), translocations known to have positive and negative effects on prognosis, were investigated at the Genetic Department of İstanbul University Experimental Medicine Research Institute. The presence of mediastinal mass was evaluated by chest radiographs. Central nervous system (CNS) involvement was investigated by cytologic and biochemical evaluation of the cerebrospinal fluid sample. The high-risk criteria

used according to COG were 1<Age <10 and WBC ≥50,000/mm^3 or Age ≥10 and any WBC value, and testicular involvement. According to the BFM study group, for the intermediate risk group, criteria include a blast count in the peripheral blood of <1000/mm^3 on day 8, complete remission on day 33, negative t(9;22), and bcr/abl, absence of t(4;11) (MLL/AF4 recombination), and not meeting any high-risk criteria. For the high-risk group, criteria include a blast count in the peripheral blood of ≥1000/mm^3 on day 8, positive t(9;22) and/or bcr/abl, positive t(4;11), and MLL/AF4, and bone marrow classified as M2/M3 on day 33 (M2: blasts 5-25%, M3: blasts >25%).

Statistical Analysis

All statistical analyses were performed using SPSS 12.0 for Windows software package. Chi-Square and Fisher's exact Chi-Square tests were used for comparisons between groups. Student-T tests were used for response to treatment, relapse, and survival. Overall survival and event-free survival between the groups receiving the Augmented BFM protocol and BFM 2000 protocol were analyzed using Kaplan-Meier survival analysis. Long rank and Breslow tests were used to compare the overall survival and event-free survival rates of both groups. Factors that may cause relapse were analyzed using Cox-Regression analysis.

RESULTS

The combined evaluation of patients who received treatment according to the two treatment protocols resulted in an EFS of 83.6% and OS of 90.1%. EFS was 89.4% and OS was 90.6% in patients treated with the augmented BFM treatment protocol alone, while EFS

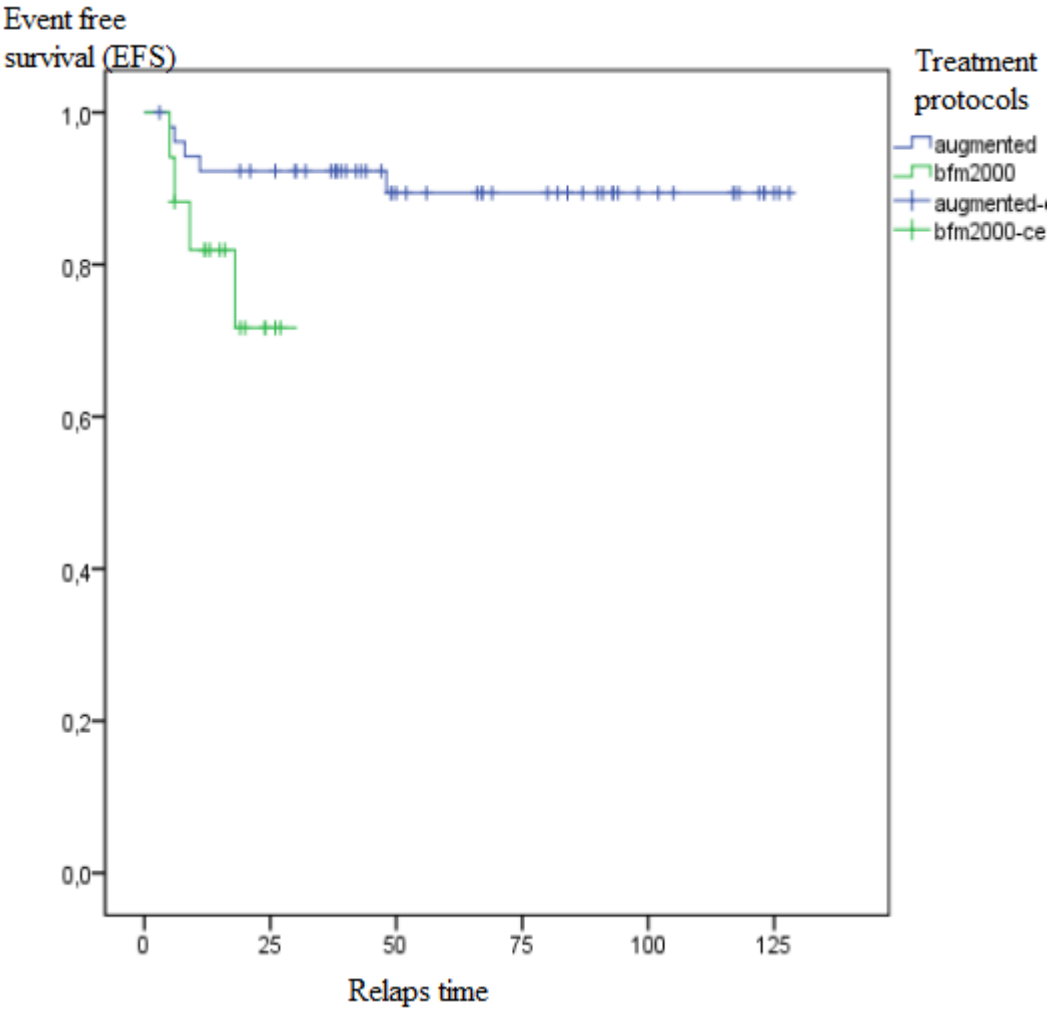

Fig. 1. Survival of patients according to event-free survival values.

was 71.7% and OS was 88.2% in patients treated with the BFM 2000 treatment protocol. The EFS values of the patients who received the augmented BFM treatment protocol were statistically significantly higher when compared to the patients who received the BFM 2000 treatment protocol (P<0.001). Patients treated according to the augmented BFM treatment protocol showed a lower rate of relapse. The augmented BFM treatment protocol was more protective against relapses than the BFM 2000 treatment protocol (Figs. 1 and 2).

Demographic data of the patients revealed that 47 (67.1%) of our 70 patients were male and 23 (32.9%) were female. The male/female ratio was 2/1. A total of 34 (48.6%) patients were 10 years and older, while 36 (51.4%) of the patients were between 1 and 9.99 years of age. Due to organ infiltration, 42 (60%) patients had hepatomegaly smaller than 2 cm and 25 (35.7%) patients had hepatomegaly larger than 2 cm at the time of admission. It was determined that 39 (55.7%) patients had splenomegaly smaller than 2 cm and 27 (38.6%) patients had splenomegaly larger than 2 cm. In the evaluation of complete blood counts, it was found that in 41 cases (58.6%), the hemoglobin (Hb) value was below 10 g/dL, while in 25 cases (35.7%), it was above 10 g/dL. the leukocyte count was less than 10,000/mm^3 in 21 cases (30%), between 10,000 and 50,000/mm^3 in 18 cases (25.7%), and above 50,000/mm^3 in 29 cases (41.4%). The platelet count was found to be below 20,000/mm^3 in 12 cases (17.1%), between 20-100,000/mm^3 in 30 cases (42.9%) and above 100,000/mm3 in 24 cases (34.3%). Bleeding was found in 12 patients with a platelet count below 100.000/mm^3 on admission. CNS involvement was found in 3 (4.3%) patients, mediastinal mass in 6 (8.6%) patients, and testicular involvement in 1 (1.4%) patient. One patient exhibited biphenotypic characteristics, while 44 patients (62.8%) exhibited B-cell characteristics and 16 patients (22.9%) exhibited T-cell characteristics. In the evaluation of the presence of translocation in bone marrow aspiration material, t(4;11) was determined in 4 (5.7%), t(9;22) in 6 (8.6%), and t(12;21) in 1 (1.4%) of the patients. When patients were compared based on the presence of

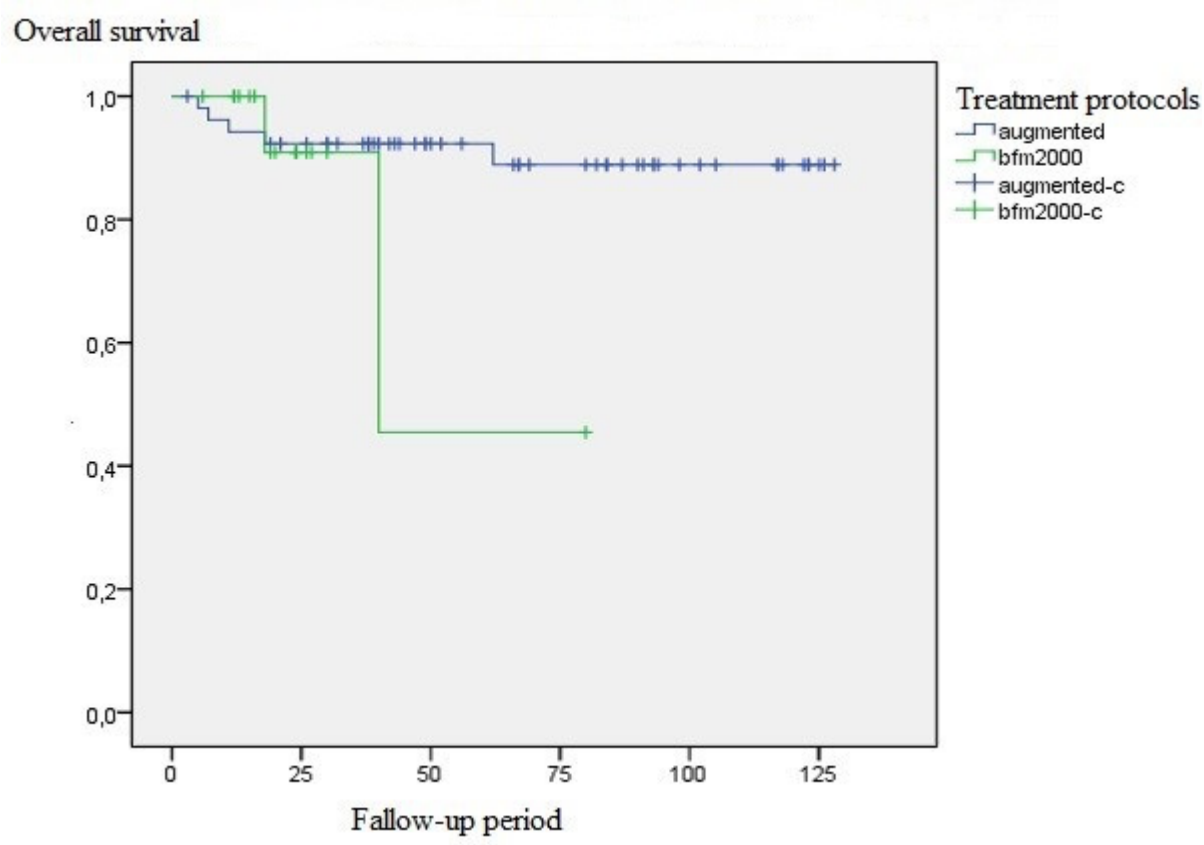

Fig. 2. Survival of patients according to overall survival values

Table 1. Comparison of the features of two treatment protocols groups

Features at diagnose	Augmented BFM treatment group			BFM 2000 treatment group			P value
	n	Event	EFS (%)	n	Event	EFS (%)	
Gender							
Male	35	4	86.6	12	4	74.7	0.398
Female	18	1	94.4	5	1	75	
Age							
1-9.9 year	30	1	96.6	6	3	41.7	0.446
≥10 year	23	4	80.3	11	1	81.8	
Hepatomegaly							
<2cm	32	1	100	10	3	80	**0.029**
≥2cm	19	4	77	6	2	55.6	
Splenomegaly							
<2cm	29	3	87.1	10	2	80	0.679
≥2cm	22	2	90.9	5	3	40	
Lenfadenopathy							
<2cm	45	5	87.1	11	3	80.8	0.921
≥2cm	7	0	100	4	2	37.5	
CNS involvement							
+	2	0		1	1		
-	51	5	88.9	1	1		
Mediastinal mass							
+	6	1	83.3				0.432
-	47	4	90	14	4	77.9	
Morphology							
L1	26	1	96.2	13	3	80.8	0.325
L2	24	3	87	2	0		
Hemoglobin							
<10 g/dL	33	3	89.9	8	3	56.3	0.755
≥10g/dL	17	2	87.5	8	2	87.5	
White blood count							
<50000/mm^3	27	3	87.7	12	3	83.3	0.709
≥50000/mm^3	25	2	91.7	4	2	50	
Platelets							
<100000/mm^3	32	3	90.6	10	4	83.3	0.858
≥100000/mm^3	18	2	85.6	6	1	64	
CALLA							
Positive	10	0					
Negative	34	5	84				
Translocations							
+	4	1	86.7	14	4	50	0.810
-	38	2	100	2	1	75	
8th day blast response							
Blast<1000	38		90.4	13		81.3	0.732
Blast>1000	4		9.6	3		18.7	
33rd day blast response							
Blast<5%	53		100	17		100	
Blast>5%	0			0			

CALLA=Common Acute Lymphoblastic Leukemia Antigen, CNS=Central Nernous System, EFS=Event-Free Survival

translocations, it was observed that relapse occurred in only one patient. Regarding the response to the treatment, relapse was detected in 5 of 53 patients (9.4%) treated according to the augmented BFM treatment protocol and in 5 of 17 patients (29.4%) who received the BFM 2000 treatment protocol. It is 5.6 times more common in patients receiving the BFM 2000 treatment protocol. (Table 1).

In both treatment groups, the mean duration of hospitalization during intensive chemotherapy before maintenance treatment was 4.4 months for the patients treated with the augmented BFM treatment protocol and 6.8 months for the patients treated with the BFM 2000 treatment protocol. The mean duration of hospitalization was statistically significantly shorter in those who received treatment according to the augmented BFM treatment protocol ($P<0.001$). The mean duration of hospitalization during the intensive chemotherapy period was 6.4 months in patients with relapse and 4.6 months in those without relapse before switching to maintenance treatment.

DISCUSSION

In the treatment of acute lymphoblastic leukemia, an almost complete cure can be achieved through chemotherapy, radiotherapy, bone marrow transplantation, targeted therapies and immunotherapy, and the establishment and development of leukemia centers. In the last 40 years, it has been observed that radiotherapy, intensified multiple chemotherapy, and the application of treatment options based on risk groups have significantly increased life expectancy. Five-year overall survival in children has increased to almost 80% [11]. Although hematopoietic stem cell transplants have contributed positively to survival, intensive chemotherapies given to improve overall survival in some ALL subtypes have failed to achieve the desired goal of survival. The researchers aim to improve treatment protocols in chemotherapy-resistant cases by better understanding the pathogenesis [12].

Numerous study groups have been established to date to achieve success in the treatment of pediatric cancers. However, over time, some of them came to the fore and incorporated other study groups into their group. Today, pioneering studies are carried out by the COG and the BFM Study Group, in which many European countries now participate. These two study groups have been developing treatment protocols by examining prognostic factors to ensure successful leukemia treatment for years. Although prognostic factors change over time, mainly the patient's age, leukocyte count on admission, and response to treatment remain unchanged. Almost all treatment protocols consider age and leukocyte count at diagnosis as the most common prognostic factors. It is known that a higher leukocyte count at the time of diagnosis indicates a poorer prognosis, and the leukocyte count at the time of diagnosis has been considered an unchanging prognostic factor for years [2]. The 5-year event-free survival was 79.4% in those who received treatment according to the treatment protocol of the BFM group. In a study conducted by the COG group in a large group of patients, the 5-year event-free survival rate was 81.2% in patients treated with the augmented BFM protocol. Patients are stratified into risk groups in all ALL chemotherapy protocols, and remission induction, consolidation, CNS eradication, and maintenance treatment schemes are applied with some modifications [12].

Of the 70 patients included in the study, 10 relapsed and the EFS was 86.3% in all patients regardless of the treatment protocol. Among these cases, 5 showed relapse while receiving treatment according to the augmented BFM protocol, and the other 5 showed relapse while receiving treatment according to the BFM 2000 protocol. The incidence of relapse in patients treated with the augmented BFM treatment protocol was found to be 9.4%. This was found to be consistent with the literature [13]. The incidence of relapse in patients treated according to the BFM 2000 treatment protocol was 29.4%. The blast count on day 8 was below 1000 may be considered to be a significant factor in the high incidence of relapse. The rate of patients who received augmented BFM with a blast count of less than 1000 on day 8 was 94.7%, while this rate was 84.6% in patients who received the BFM 2000 treatment protocol. Relapses were 5.6 times more common in patients treated according to the BFM 2000 treatment protocol compared to augmented BFM treatment.

The 5-year event-free survival rate in children diagnosed with ALL was around 50%, whereas today, with multiple chemotherapy, radiotherapy, and treatment according to the risk group, event-free survival

is achieved in 75-80% of patients for a much longer time [14]. In the present study, patients treated according to the augmented BFM treatment protocol had a median event-free survival of 116.7 months. This was determined as 56.2 months in patients who received treatment according to the BFM 2000 treatment protocol. However, the follow-up period of the patients who received the BFM 2000 treatment protocol was still shorter when compared to the other group. It can be concluded that the A-BFM treatment protocol is statistically significantly more protective against relapses than the BFM 2000 treatment protocol in high-risk ALL. However, researchers should take into account that the number of patients receiving treatment according to the BFM 2000 treatment protocol was limited. The literature suggests that the male/female ratio in ALL is usually in the range of 1.1-1.4/1 [15]. The prevalence of ALL in male children was 54-57% according to the study conducted in a large series of patients by the Pediatric Oncology Group, which evaluated numerous major studies to date, whereas the rate of male patients was 67.1% in the present study. Only high-risk ALL patients were included in this study. Multiple studies have shown that boys have a worse prognosis than girls receiving the same treatment [15]. The EFS was found to be 79.7% in boys and 91.1% in girls. However, in the present study, when all cases were evaluated together, the effect of gender on EFS was not found to be statistically significant. The literature shows that male gender is a poor prognostic factor. This inconsistency may be attributed to the fact that the study group included only patients diagnosed with high-risk ALL [16].

Hepatomegaly, splenomegaly, or lymphadenomegaly is observed in 30-40% of ALL due to infiltration of the liver, spleen, and lymph nodes. In the present study, hepatomegaly was present in 95.7% of cases and splenomegaly in 94.3% of cases. The high rate of organomegaly compared to the literature can be attributed to the fact that the study group consisted only of high-risk ALL patients. Hepatomegaly and splenomegaly increase the risk of relapse in ALL patients [17]. On physical examination, the EFS value was found to be 73.5% in cases with hepatomegaly larger than 2 cm and 90.7% in cases with hepatomegaly <2 cm. Hepatomegaly larger than 2 cm on physical examination has a statistically significant negative effect on EFS. Hepatomegaly was found in approximately half of the patients diagnosed with ALL and was found to be associated with a higher peripheral blast count in the periphery [18]. In contrast to hepatomegaly, splenomegaly had no effect on EFS.

Harousseau investigated the effect of hemoglobin level at diagnosis on prognosis in a series of 141 patients. It was found that the rate of complete remission was 63% in patients with Hb values above 8 gr/dl, 84% in patients with Hb values between 8-10 gr/dL, 70% in patients with Hb values between 10-12 gr/dL and 60% in patients with Hb values >12 gr/dL [19]. On the other hand, in a few studies, it was observed that the Hb level at the time of diagnosis was not effective on the duration of event-free survival [20]. In our study, EFS was 83.9% in patients with Hb <10 g/dL and 80.6% in patients with Hb ≥10 g/dL, and it was determined that hemoglobin values had no statistically significant effect on EFS.

In a study in which patients included in all leukemia groups were evaluated, the rate of patients with a white blood cell count >50.000/mm^3 was found to be 17% [20]. The effect of leukocyte count at the time of diagnosis on prognosis has been well-known for a long time. Many researchers have examined the relationship between leukocyte count at diagnosis and prognosis. In some patient groups, a leukocyte count of >50,000/mm^3 at the time of diagnosis was found to be a poor prognosis criterion, similar to that of large study groups developing childhood leukemia treatment protocols [21-23]. Since our study included patients with high-risk leukemia, 41.4% of the cases had a white blood cell count above 50,000/mm^3. In patients with a white blood cell count of more than 50.000/mm3, EFS was found to be 85.7%, while in patients with a white blood cell count < 50.000/mm^3, EFS was found to be 81.4%. However, the effect of leukocyte count on EFS was not statistically significant in our study. This variation can be attributed to the fact that the patients were in the high-risk group.

Zhang *et al*. [24] investigated the relationship between platelet count and prognosis and found that the prognosis was poor in patients with a platelet count <20.000/mm^3 at the time of initial diagnosis. In the present study, EFS was found to be 82.7% in patients with a platelet count of less than 100,000/mm^3 and 82.8% in patients with a platelet count of more than 100,000/mm3. Since the number of patients with a platelet count below 20,000/mm^3 was low, no compar-

ison could be made. However, it was observed that the frequency of bleeding decreased as the platelet count increased in our patient group.

Among the patients included in this study, 10 patients had relapse. The most prominent indicator of treatment failure in leukemia is the development of relapse. Approximately 15-25% of pediatric patients with ALL develop relapse. The majority of relapses occur in the bone marrow (80%), followed by the CNS (12-16%) and testis (8%) [25].

Limitations

The most important limitation of this study is the small size of the study group. In particular, the number of patients receiving the BFM 2000 treatment protocol is low. To increase the reliability of the study, data from a larger patient group and longer follow-up data need to be collected and analyzed.

CONCLUSION

In high-risk ALL patients who were followed up for more than 5 years in our clinic, the event-free survival rate was 83.6% and the overall survival rate was 90.1%. The EFS values of the different treatment protocols applied were 89.4% and 71.7% for the augmented BFM and BFM 2000 treatment protocols, respectively. The augmented BFM treatment protocol offers a better treatment option for high-risk ALL patients. However, it is essential to consider that the number of patients receiving treatment according to the BFM 2000 treatment protocol was low, and further comparisons with larger patient groups are required.

Authors' Contribution

Study Conception: SÖ, FLA; Study Design: SÖ, FLA, ZK; Supervision: SÖ, FLA, AÜ; Funding: N/A; Materials: SÖ, FLA, ZK, AÜ, ÖD; Data Collection and/or Processing: SÖ, FLA; Statistical Analysis and/or Data Interpretation: SÖ, FLA, AÜ; Literature Review: SÖ, FLA, ZK, AÜ, ÖD; Manuscript Preparation: SÖ and Critical Review: SÖ, FLA, ZK, AÜ, ÖD.

Ethical declaration

Since ethics committee approval is not mandatory for retrospective studies in the years this study was conducted, ethics committee approval was not obtained. The Dean of Istanbul University Faculty of Medicine, where the study was conducted and the article was prepared, was not notified and no negative feedback was received.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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