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RESEARCH

Improved outcomes in children with acute lymphoblastic leukemia treated with modified BFM protocols: a single-center experience

Modifiye BFM protokolleriyle tedavi edilen akut lenfoblastik lösemi tanılı çocuklarda başarılı sonuçlar: tek merkez sonuçları

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Abstract

Purpose: We compared the treatment protocols used for acute lymphoblastic leukemia (ALL) patients admitted to our clinic between January 1990 and September 2021.

Materials and Methods: Patient files were retrospectively reviewed. Data collection was finalized in June 2022. Patients were divided into three groups based on treatment protocols. Group I (n=234) received BFM-85, -90, or -95 protocols between 1990 and January 2001. Group II (n=139) received a modified BFM-95 protocol (TRALL-2000) between January 2001 and March 2007. Group III (n=199) received a center-modified TRALL-2000 protocol starting in 2007.

Results: Of the patients, 344 (60.1%) were boys and 228 (39.9%) were girls. The 10-year overall survival (OS) rates were 30%, 53%, and 73% for Groups I, II, and III, respectively. Event-free survival (EFS) rates were 27%, 40%, and 64%. In Group III, the 10-year OS was 92% for the standard-risk group (SRG), 71% for the medium-risk group (MRG), and 59% for the high-risk group (HRG); the corresponding EFS rates were 72%, 68%, and 49%. Among Group III patients, the 10-year OS was 64% for girls and 78% for boys. The OS for B-cell ALL was 71%, and for T-cell ALL, 78%.

Conclusion: OS and EFS rates in Group III were significantly higher than in earlier groups. Contrary to existing literature, T-cell ALL patients and male patients in Group III had superior outcomes compared to B-cell ALL patients and female patients.

Keywords: Acute lymphoblastic leukemia, childhood, chemotherapy, BFM protocols.

Öz

Amaç: Ocak 1990 ile Eylül 2021 tarihleri arasında kliniğimize başvuran ALL hastalarına uygulanan tedavi protokolleri karşılaştırıldı.

Gereç ve Yöntem: Hastaların dosyaları retrospektif olarak incelendi. Veriler Haziran 2022'e kadar alındı. Hastalar tedavi protokollerine göre 3 gruba ayrıldı. Grup I (n=234); Ocak 1990-Ocak 2001 tarihleri arasında BFM-85-90-95 kullanılan hastalardan, Grup II (n=139); Ocak 2001-Mart 2007 tarihleri arasında modifiye BFM-95 protokolü (TRALL-2000 adı verildi) kullanılan hastalardan, Grup III (n=199); 2007'den itibaren tarafımızca modifiye edilmiş bu TRALL-2000 protokolü kullanılan hastalardan oluşturuldu.

Bulgular: Hastaların 344'ü (%60,1) erkek, 228'i (%39,9) kız idi. Grup I'de 10 yıllık genel sağkalımın (GS) %30, grup II'de %53 ve grup III'te %73 olduğu ve olaysız sağkalımın (EFS) sırasıyla %27, %40 ve %64 olduğu bulundu. Ayrıca, Grup III hastalarını risklerine göre analiz ettiğimizde; standart risk grubundaki (SRG) hastalarda 10 yıllık GS %92, orta risk grubundaki (MRG) hastalarda %71 ve yüksek risk grubundaki (HRG) hastalarda %59 idi. 10 yıllık EFS sırasıyla %72, %68 ve %49 idi. Ayrıca, grup III'teki kız hastaların 10 yıllık GS'si %64, erkeklerde ise %78 olarak bulundu. Benzer şekilde, B hücreli ALL için 10 yıllık GS %71 ve T hücreli ALL için %78 olarak bulundu.

Sonuç: Grup III hastalarının GS ve EFS'si önceki protokolleri kullanan hastalara kıyasla anlamlı derecede yüksek idi. Ayrıca, literatürün aksine, grup III'teki T hücreli ALL hastalarının GS ve EFS oranları B hücreli ALL hastalarından daha iyi idi ve erkeklerdeki sağkalım kızlara göre daha uzun idi.

Anahtar kelimeler: Akut lenfoblastik lösemi, çocukluk çağı, kemoterapi, BFM protokolleri.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a hematologic malignancy characterized by the clonal proliferation of immature lymphoid cells. The incidence and outcomes of childhood ALL vary by socioeconomic status, geographic location, and racial factors[1-5].

In Turkey, the incidence of ALL is reported as 1.5 per 100000 children[6]. Remission can be achieved in approximately 80–90% of cases. Globally, treatment protocols originating from Europe (e.g., BFM) and the United States (e.g., COG, St. Jude) are commonly used[1]. Patients are stratified into low-, intermediate-, and high-risk groups for therapeutic purposes. Treatment protocols typically include induction, consolidation, and maintenance phases. For intermediate- and high-risk patients, reinduction-reconsolidation and central nervous system (CNS) prophylaxis phases are also added. Additionally, hematopoietic stem cell transplantation is an option for selected high-risk cases[1,7].

The treatment duration for childhood ALL is typically 2–3 years, with the most intensive phase occurring during the first 6–12 months. Although over 95% of patients achieve complete remission following induction, 1–3% may die during the first remission due to treatment-related complications[8,9].

In recent years, long-term survival rates have approached 90% as a result of childhood ALL treatment[10]. Despite positive developments, recurrence of the disease is seen in approximately 12-20%. The rate of leukemia relapse is high in infantile leukemia. Additionaly, relapses of leukemia occurring within the first 18 months of diagnosis have been shown to have a poor outcome[11,12].

This study aims to evaluate treatment outcomes of ALL patients managed at our institution in southern Turkey between January 1990 and September 2021, with particular focus on the impact of protocol modifications implemented by our center.

MATERIALS AND METHODS

Sample

A total of 635 patients aged between 1 month and 18 years diagnosed with ALL at the Division of Pediatric Oncology/Stem Cell Transplantation Unit, Cukurova University, Balcali Research Hospital between January 1990 and September 2021. The data were obtained retrospectively from pediatric oncology patient files and hospital computer records and follow-up continued until June 2022. As this was a retrospective study, patients with incomplete medical records, those who were referred to other healthcare centers during diagnosis or treatment, and those with ALL L3 subtype were excluded. Of the 635 patients diagnosed with ALL between January 1990 and September 2021, 9 patients diagnosed with ALL L3, 29 patients who were followed-up by another center after diagnosis and 25 patients lacking file information were excluded from the study. The remaining 572 patients with ALL were included in the study.

Procedure

Diagnosis of ALL was confirmed based on morphological, histo-cytochemical, and immunophenotypic findings. A diagnosis was made if >25% lymphoblasts were detected in bone marrow smears[13]. Immunophenotyping was performed using flow cytometry with CD2, CD3, CD19, CD7, CD10, CD20, CD13, CD22, CD33, CD34, HLA-DR, intracytoplasmic MPO, CD117, and anti-TdT. Subclassification of ALL was made according to FAB classification and immunophenotyping results, including pre-B-ALL, common ALL, B-ALL, and T-ALL. CD surface antigen expression above 20% was considered positive. A T-lineage was defined as CD2/CD3 positivity exceeding 20% in flow cytometry[14].

Overall survival (OS) was defined as the time from diagnosis to death or last follow-up for living patients. Event-free survival (EFS) was defined as the time from diagnosis to death or relapse, or last follow-up for patients without relapse.

Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Çukurova University Faculty of Medicine (Decision No. 136, dated September 1, 2014). Written and verbal informed consent was obtained from the legal guardians of all patients.

Chemotherapy protocols

BFM-based chemotherapy protocols were used throughout the study period. From January 1990, the clinic implemented BFM-85, BFM-90, and BFM-95 treatment regimens. Between January 2001 and

March 2007, a modified BFM-95 protocol (designated TRALL-2000) was employed.

Based on clinical and laboratory parameters and the response to corticosteroids, patients were stratified into three risk categories: standard risk group (SRG), medium risk group (MRG), and high risk group (HRG). The TRALL-2000 protocol consisted of remission induction (Protocol I), consolidation (Protocol M), reinduction (Protocol II), and maintenance phases. For HRG patients, the treatment included Protocol I (Phase 1), two cycles of HR1–3 blocks, Protocol II, and maintenance therapy. The total maintenance period was 2–3 years, beginning after Protocol II in SRG patients, and after prophylactic cranial radiotherapy in MRG and HRG patients (approximately two weeks later), once the patient was in hematologic and clinical remission. For boys, maintenance therapy was extended to three years.

Maintenance therapy included daily oral 6-mercaptopurine (50 mg/m²) and weekly oral methotrexate (20 mg/m²)[8,15-18]. Due to high relapse rates, especially among T-cell ALL patients during or after maintenance, our center introduced modifications to the TRALL-2000 protocol starting in March 2007.

To evaluate the impact of these modifications, patients were categorized into the following groups: Group I (n=234), treated with BFM-85/90/95 protocols from 1990 to January 2001; Group II (n=139), treated with the TRALL-2000 protocol from January 2001 to March 2007; and Group III (n=199), treated with a locally modified TRALL-2000 protocol beginning in 2007.

Protocol modification

In Group III, modifications were introduced to the maintenance phase for all risk categories (SRG, MRG, and HRG). Intravenous (IV) and bimonthly intrathecal (IT) medications were added to maintenance therapy to enhance treatment efficacy.

All T-cell ALL patients were classified as medium risk (MRG) and received modified maintenance therapy. Additionally, the methylprednisolone dose during Protocol I, Phase 1 was escalated to 10 mg/kg/day. This dose was maintained for one week, tapered to 2 mg/kg, and then further reduced starting from Day 29, and discontinued on Day 36.

Further protocol modifications were made in Protocol M. On Day 1, 500 mg/m² cyclophosphamide (with mesna) was administered intravenously, followed by 5 g/m² methotrexate as a 10-hour IV infusion on Day 2. To support high-dose methotrexate, folinic acid (leucovorin) was given at a dose of 50 mg/m² every 6 hours for a total of 10 doses.

Bone marrow aspiration was performed on Day 36 of Protocol I, Phase 1 to evaluate remission status, defined as <5% blasts. Unfortunately, minimal residual disease (MRD) could not be assessed due to laboratory limitations, and therefore bone marrow examination on Day 15 was not conducted.

Prophylactic cranial radiotherapy (12 Gy) was administered to MRG and HRG patients prior to maintenance. In patients with CNS involvement who were over 3 years of age, therapeutic radiotherapy was applied at a dose of 18 Gy.

Table 1. Treatment protocol chart

B-cell ALL	SRG	Protocol I (Phase 1 and Phase 2)	Protocol M	Protocol II (Phase 1 and Phase 2)	Maintenance I (6 months) ve II (18 months)
	MRG	Protocol I (Phase 1 and Phase 2)	Protocol M	Protocol II (Phase 1 and Phase 2)	Maintenance I (6 months) ve II (18 months)
	HRG	Protocol I (Phase 1)	2X(HR1-3) block		Maintenance I (6 months) ve II (18 months)
T-cell ALL	MRG	Protocol I (Phase 1 and Phase 2)	Protocol M	Protocol II (Phase 1 and Phase 2)	Maintenance I (months) ve II (18 months)

ALL: Acute lymphoblastic leukemia, SRG: standard risk group, MRG: medium risk group, HRG: high risk group.

Table 2. Treatment phases and drugs used

Risk Groups	**Protocol-I**	
	Phase-1	**Phase-2**
SRG	●**PRED** 60 mg/m²/d po/iv 1-33 days ●**VCR** 1.5 mg/m²/d iv 8., 15., 22., 29. days ●**DNR** 30 mg/m²/d iv 8., 15., 22., 29. days ●**ASP** 5000 ü/m²/d 12., 15., 18., 21., 24., 27., 30., 33. days ●**MTX IT** at age-adjusted dosage, 12., 33. days	●**CPM** 1000 mg/m²/d + Mesna iv 36. day ●**ARA-C** 75 mg/m²/d iv 38-41, 45-48, 53-56, 60-63. days ●**MP** 60 mg/m²/d po 36-64. days *** MTX IT** at age-adjusted dosage, 37.,44.,51.,58. days
MRG	● The same	● The same
MRG (T-ALL)	●MP (2-10 mg/kg/gün) iv, other drugs are the same	● The same
HRG		
	Protocol M	
SRG	●**MP** 25 mg/m²/d, po 1-58 days ●**MD MTX** 1 g/m2/36h + Leucovorin Ca 15 mg/m², IV, 48 h, 54 h after the start of MTX infusion ●**MTX IT,** at age-adjusted dosage, 1 h after the start of MTX infusion	
MRG	● The same	
MRG (T-ALL)	●**MP** 25 mg/m²/d, po 1-58 days ●**CPM** 500 mg/m²/d + Mesna iv 1. day ●**HD MTX** 5 g/m²/10h + Leucovorin Ca 50 mg/m² starts at 48th h, a total of 10 doses every 6 h ●**MTX IT**, at age-adjusted dosage, 1 h after the start of MTX infusion	

	HRG		
	HR1	**HR2**	**HR3**
HRG	●**DEXA** 20 mg/m²/d iv 1-5 days ●**MD MTX** 1g/m²/36h 1. Day Leucovorin Ca 15 mg/m², 48 h, 54 h after the start of MTX infusion ●**CPM** 200 mg/m²X2/d, iv 2-4 days, 5 dose + Mesna (100%) ●**ASP** 25000 ü/m²/d, 6. day ●**HD ARA-C** 2g/m²/3h x2, 5. day ●**MTX/ARA-C**/Pred IT (MAP) 1. day	●**DEXA** 20 mg/m2/d iv 1-5 days ●**MD MTX** 1g/m²/36h 1. day Leucovorin Ca 15 mg/m², 48 h, 54 h after the start of MTX infusion ●**IFO** 800 mg/m²X2/2-4.days, 5 dose + Mesna (100%) ●**ASP** 25000 ü/m²/d, 6. day ●**DNR** 30 mg/m²/d, /5. day ●**MTX/ARA-C/Pred IT (MAP)** 1. day	●**DEXA** 20 mg/m²/d iv 1-5 days ●**HD ARA-C** 2000 mg/m²/3h X4/ 1. day, (q 12 h) ●**VP-16** 100 mg/m2/1h X5/ 2.day, (q 12 h) ●**MTX/ARA-C**/Pred IT (MAP) 5. day ●**ASP** 25000 ü/m²/d, 6. day

ALL: Acute lymphoblastic leukemia, SRG: standard risk group, MRG: medium risk group, HRG: high risk group
PRED: Prednisolone, VCR: Vincristine, DNR: Daunorubicin, ASP: E. coli L-asparaginase, MTX IT: Intrathecal methotrexate, CPM: Cyclophosphamide, ARA-C: Cytarabine, MP**:** 6-Mercaptopurine, MD MTX: Medium dose methotrexate, HD MTX: High dose methotrexate, h: hour, DEXA: Dexamethasone, IFO: Ifosfamide, MAP: MTX/ARA-C/Pred IT.
Note: There are 6 cycles in HRG, and vincristine (1.5 mg/m² on days 1 and 6) was added in 2.HR1. HR2 and HR3 are implemented in the same way.

Table 3. Drugs used in Protocol II and Maintenance

Risk Groups	Protocol-II	
	Phase-1	**Phase-2**
SRG **MRG** **HRG** **MRG T-cell** **ALL**	●DEXA 10 mg/m²/d iv 1-29 days ●VCR 1.5 mg/m²/d iv 8., 15., 22., 29. days ●DNR 30 mg/m²/d iv 8., 15., 22., 29. days ●ASP 10000 ü/m²/d 8., 11., 15., 18. days ●MTX IT at age-adjusted dosage, 1., 18. days	●CPM 1000 mg/m²/d + Mesna iv 36. day ●ARA-C 75 mg/m²/d / iv 38-41, 45-48 days ●TG 60 mg/m²/d po 36-49 days (14 days) ● MTX IT at age-adjusted dosage, 38., 45. days
	Maintenance	
	I (6 months)	**II (18 months)**
SRG **MRG** **HRG** **MRG T-cell** **ALL**	●**MP** 50 mg/m²/d, po daily* ●**MTX** 20 mg/m²/d po weekly* ●**DEXA** 20 mg/m²/d po 1-5 days, every month ●**VCR** 1 mg/m²/d iv, 1. day, (1., 4. month) ●**ARA-C** 75 mg/m²/d / iv, 1. day, (1., 4. month) ●**DNR** 10 mg/m²/d iv, 1. day, (2., 5. month) ●**MTX** 250 mg/m²/d+Leucovorin Ca 15 mg/m², 1. day, (2., 5. month) ●**CPM** 500 mg/m²/d + Mesna iv, 1. day, (3., 6. month) ● **MTX/ARA-C/Pred IT (MAP)** 1. day, (1., 3., 5. month)	●**MP** 50 mg/m²/d, po daily* ●**MTX** 20 mg/m²/d po weekly* ●**DEXA** 20 mg/m²/d po 1-5 days, every 2 months ●**VCR** 1 mg/m²/d iv, 1. day, (7., 13., 19., 24. month) ●**ARA-C** 75 mg/m²/d / iv, 1. day, (7., 13., 19., 24. month) ●**DNR** 10 mg/m²/d iv, 1. day, (9., 15., 21. month) ●**MTX** 250 mg/m²/d+Leucovorin Ca 15 mg/m², 1. day, (9., 15., 21. month) ●**CPM** 500 mg/m²/d + Mesna iv, 1. day, (11., 17., 23. month) ● **MTX/ARA-C/Pred IT** (MAP) 1. day, (7., 9., 11., 13., 15., 17., 19., 21., 23. month)

ALL: Acute lymphoblastic leukemia, SRG: standard risk group, MRG: medium risk group, HRG: high risk groupDEXA: Dexamethasone, VCR: Vincristine, DNR: Daunorubicin, ASP: E. coli L-asparaginase, MTX IT: Intrathecal methotrexate, CPM: Cyclophosphamide, ARA-C: Cytarabine, TG: 6-Thioguanine, MP: 6-Mercaptopurine, MTX: methotrexate.
* In maintenance I treatment, oral treatments are interrupted 1 week before and 1 week after monthly IV treatment.

Statistical analysis

All statistical analyses were conducted using SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA). Categorical variables were analyzed using the chi-square test, and non-parametric variables were analyzed using the Mann–Whitney U test. Numerical and normally distributed variables were analyzed using the Student's t-test. Patients' OS and EFS outcomes were calculated using the Kaplan–Meier method, and these outcomes were compared using the log-rank test. A p-value of <0.05 was considered statistically significant for all analyses.

RESULTS

A total of 572 patients were included in the study between January 1990 and September 2021.

Of these, 344 (60.1%) were boys and 228 (39.9%) were girls, resulting in a male-to-female ratio of 1.51. The mean follow-up duration was 73.4 ± 75.9 months (range=1 day to 204 months).

Table 4 summarizes the clinical and laboratory characteristics of the patients at diagnosis. A leukocyte count >50000/mm³ was observed in 29.7% of cases. Based on flow cytometry, 29.2% of patients were diagnosed with T-cell ALL.

When Group III patients were compared with those in Groups I and II, statistically significant improvements were observed: higher remission rates, reduced relapse rates, and lower mortality. The number of patients who did not achieve remission or died before Day 36 was 12 (6.0%) in Group III, compared to 61 (16.4%) in Groups I and II combined (p=0.0001). In addition, both male and female patients in Group III exhibited better OS than those in Groups I and II across all age groups (see Tables 5 and 6).

Table 4. Clinical and laboratory characteristics of children with ALL at the time of diagnosis

Characteristics of the Patients		**n**	**%**
Gender	Male	344	60.1
	Female	228	39.9
Age	<2 years	75	13.1
	2-6 years	274	47.9
	7-10 years	115	20.1
	>10 years	108	18.9
Laboratory features			
Leukocyte count (mm^3)	<10000	160	28
	10000-50000	242	42.3
	>50000	170	29.7
Lymphoblast Origin	T-cell ALL	167	29.2
	B-cell ALL	249	43.5
	*Unknown	156	27.3

*Treated as B-cell ALL.

Table 5. Treatment protocols and results

Treatment protocol	**Group-I** n=234 %:40.9		**Group-II** n=139 %:24.3		**Group-III** n=199 %:34.8		**P***
36th day bone marrow							
Remission	186	79.5	129	92.8	187	94	**0.0001**
Partial Remission	5	2.1	-	-	1	0.5	
Non remission	4	1.7	3	2.2	2	1	
Death before day 36	39	16.7	10	7.2	9	4.5	
Relapse (-)	129	55.1	90	64.7	152	76.4	
(+)	105	44.9	49	35.3	47	23.6	**0.0001**
Relapse localization							
Systemic	63	26.9	32	23	21	10.6	**0.0001**
CNS	20	8.5	6	4.3	13	6.5	
CNS+ Systemic	22	9.4	9	6.5	11	5.5	
Testis+ Systemic	-	-	2	1.4	1	0.5	
CNS+ Systemic+Testis	-	-	-	-	1	0.5	
Risk groups							0.23
SRG	57	24.4	33	23.7	39	19.6	
MRG	77	32.9	76	54.7	114	57.3	
HRG	100	42.4	30	21.6	46	23.1	
Lymphoblast Origin							0.07
T-cell ALL	77	32.9	44	31.7	46	23.1	
B-cell ALL	58	24.8	57	41	134	67.3	
Unknown	99	42.3	38	27.3	19	9.5	
Latest status							
Live	68	29.1	64	42.4	130	65.3	**0.0001**
Dead	155	66.2	59	47.4	48	24.1	
Lost to follow-up	11	4.7	16	11.5	21	10.6	

Note:* Group III was compared with groups I and II.; ALL: Acute lymphoblastic leukemia, CNS: central nervous system, SRG: standard risk group, MRG: medium risk group, HRG: high risk group

Table 6. Evaluation of factors with Kaplan-Meier Test

Factors	Group I & Group II (n=373)				Group III (n=199)				
	n	3 years	5 years	10 years	n	3 years	5 years	10 years	Log Rank P*
Gender									
Male	215	46	32	32	129	78	78	78	**0.001**
Female	158	56	50	48	70	72	64	64	**0.028**
Age									
<2 years	40	40	34	34	35	68	68	68	**0.01**
2-6 years	192	50	44	40	82	80	78	78	**0.0001**
>6 years	141	44	38	38	82	76	71	71	**0.0001**
≥10 years	87	40	38	38	47	75	72	72	**0.0001**
<10 years	286	50	42	40	152	75	74	74	**0.0001**
Laboratory									
Leukocyte count (mm^3)									
<10000	102	44	38	38	58	74	74	74	**0.0001**
10000-50000	166	56	48	46	76	80	78	78	**0.0001**
>50000	105	38	29	28	65	70	76	76	**0.0001**
Lymphoblast Origin									
T-cell ALL	121	50	39	38	46	80	78	78	**0.0001**
B-cell ALL	115	46	40	40	134	74	71	71	**0.0001**
Unknown**	137	50	42	39	19	74	74	74	**0.013**
Relapse	154	36	18	15	47	46	36	36	**0.033**
Systemic	97	35	15	10	22	40	20	20	0.9
CNS	26	42	32	28	13	60	51	51	0.11
CNS+Systemic	31	40	18	6	12	42	42	42	0.18
Risk Groups									
SRG	90	60	52	42	41	92	92	92	**0.0001**
MRG	153	56	46	46	108	74	71	71	**0.0001**
HRG	130	36	29	28	50	62	59	59	**0.001**
Survival									
OS	373	45	42	38	199	76	73	73	**0.0001**
EFS	373	42	34	32	199	68	64	64	**0.0001**

Note:* Group III was compared with groups I and II. **Treated as B-cell ALL; ALL: Acute lymphoblastic leukemia, CNS: central nervous system, SRG: standard risk group, MRG: medium risk group, HRG: high risk group, OS: overall survival, EFS: event-free survival.

The 10-year OS rates were 30% for Group I, 53% for Group II, and 73% for Group III (Figure 1), while the corresponding 10-year EFS rates were 27%, 40%, and 64%, respectively. Statistically, OS was significantly higher in Group III compared to Groups I and II (p=0.0001). Similarly, EFS in Group III was significantly higher than in Group I (p=0.0001) and Group II (p=0.001).An analysis of patients in Group III according to risk stratification revealed that the 10-year OS was 92% for SRG, 71% for MRG, and 59% for HRG (Figure 2). Corresponding 10-year EFS rates were 72%, 68%, and 49%, respectively (p=0.005).

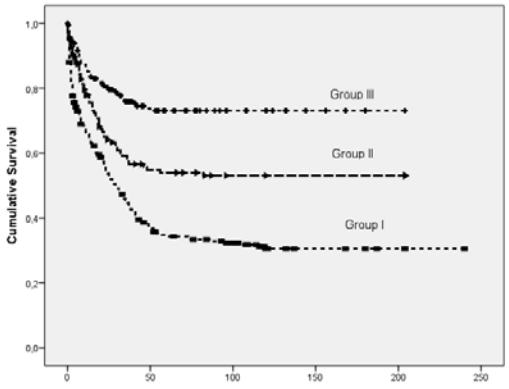

Figure 1. Overall survival of patients in the groups (months).

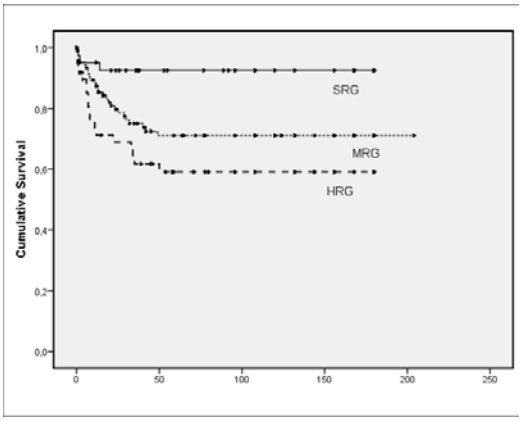

Figure 2. Overall survival of group III (months).

DISCUSSION

An elevation in leukocyte count (>10000/mm³) is observed in approximately half of patients with acute lymphoblastic leukemia (ALL), and nearly 20% present with a leukocyte count exceeding 50000/mm³ [1]. In our cohort, 29.7% of patients had leukocyte counts above 50000/mm³. Approximately 20% of childhood ALL cases are of T-cell origin, while 1–2% arise from mature B cells. The remaining cases, which are neither T- nor B-cell derived, typically exhibit CD10 positivity[1,19,20].

In our study, approximately one-third of the patients demonstrated CD2/CD3 positivity, a rate slightly higher than that reported in the literature. This finding may be attributed to the fact that our center frequently receives referrals for leukapheresis in children presenting with hyperleukocytosis. Another possible explanation could be regional geographic differences.

In 2010, Möricke et al. published the outcomes of BFM protocols implemented between 1981 and 2000. The patient numbers and protocols were as follows: BFM-81 (611 patients), BFM-83 (653 patients), BFM-86 (998 patients), BFM-90 (2178 patients), and BFM-95 (2169 patients). Mortality rates during first complete remission were 2.5%, 1.2%, 1.7%, 1.6%, and 2.1%, respectively. Corresponding relapse rates were 28.5%, 33.8%, 25.9%, 19.8%, and 16.9%. Isolated CNS relapse occurred in 5.0%, 2.6%, 1.8%, 1.0%, and 1.8% of cases, respectively. The 10-year OS rates were reported as 77.0%, 72.0%, 79.0%, 83.0%, and 85.0%, respectively[8].

A closer look at the BFM-95 data (n=2169) reveals a male-to-female ratio of 1.3. The 10-year OS was 83.6% for males and 87.2% for females. The incidence of T-cell ALL was 12.8%, with a 10-year OS of 76.4%, compared to 86.4% in non–T-cell ALL. Among risk groups, the 10-year OS rates were 94.6% for standard-risk group (SRG; n=758, 35.0%), 85.4% for medium-risk group (MRG; n=1157, 53.3%), and 56.3% for high-risk group (HRG; n=254, 11.7%). CNS involvement was identified in 3% of patients; among them, the 10-year OS was 64.1%, compared to 84.9% in CNS-negative patients[8].

In our study, the early mortality rate before achieving complete remission was 16.2% in 1990. Although this rate declined to 4.5% in later years, it remained relatively high. Relapse rates were also elevated, despite a reduction from 43.9% to 23.6%. CNS relapse declined from 16.7% to 6.0%.

While the 10-year OS and EFS rates in Group III (73% and 64%, respectively) were markedly higher compared to Groups I and II (38% and 34%, respectively), they remained below the rates reported in the literature. However, when patients in Group III were analyzed according to risk categories (SRG, MRG, HRG), our results were found to be comparable to published data.

Kamps et al. from the Netherlands reported the outcomes of BFM-based treatment in 467 pediatric patients with ALL treated between 1991 and 1996. The 5-year EFS rate for the entire cohort was 73%, while the EFS rates stratified by risk group were 85% for SRG, 73% for MRG, and 39% for HRG. The proportion of patients with T-cell ALL was 11.2%, and CNS involvement was observed in 5% of cases[21]. In another Dutch study, van Binsbergen et al.

reported a relapse rate of 12.1% among high-risk patients, with 5-year EFS and OS rates of 72.8% and 79.1%, respectively[22]. Although T-cell ALL and CNS relapse rates were higher in our cohort, the OS and EFS rates in Group III were comparable to these findings.

Stary et al. published the results of the ALL IC-BFM 2002 protocol, which was applied to pediatric ALL patients treated between 2002 and 2007. This study included 5060 children from 130 centers, predominantly in European countries. The reported 5-year EFS and OS rates were 74% and 82%, respectively. When analyzed by risk group, EFS and OS were 81% and 90% for SRG, 75% and 83% for MRG, and 55% and 62% for HRG[23]. The survival outcomes of patients in Group III at our center were found to be similar to these results.

Volejníková et al., from the Czech Republic, reported outcomes of patients treated with the ALL-BFM 90, ALL-BFM 95, and ALL IC-BFM 2002 protocols (n=97). The EFS rates were 75%, 83%, and 83%, and the OS rates were 84%, 92%, and 92%, respectively[24]. These results were slightly more favorable than those observed in our study.

Vora et al. published the outcomes of the UKALL-2003 protocol, which was implemented between October 2003 and June 2011 across 46 centers in the United Kingdom and Ireland, involving a total of 3126 pediatric patients with ALL. The incidence of T-cell ALL was reported as 12%. The number of patients who either died or failed to achieve remission prior to the scheduled assessment was 35 (1%). The 5-year EFS and OS rates were reported as 87.3% and 91.6%, respectively[25]. In our cohort, the proportion of T-cell ALL cases was considerably higher, while the remission rate was relatively lower, and the number of patients who failed to achieve remission or died before assessment was notably greater.

From Türkiye, Hazar et al. reported the outcomes of 142 pediatric ALL patients treated with the BFM-95 protocol between 1997 and 2007. The mean patient age was 4.3 years. The complete remission rate was 93.5%, the pre-remission mortality rate was 2.1%, and the rate of refractory disease was 0.7%. The 8-year OS and EFS rates were 72.0% and 63.2%, respectively. Stratified by risk groups, 8-year EFS rates were 78% for SRG, 60.5% for MRG, and 38.5% for HRG. The incidence of T-cell ALL was 16.2%, and relapse occurred in 20.4% of patients[26]. Güneş et al. analyzed 343 patients treated with the BFM-95 protocol and reported 5-year OS and EFS rates of 79.9% and 78.4%, respectively. Among patients with T-cell ALL, both OS and EFS rates were 66.7%. When evaluated by risk group, the 5-year OS rates were 97.7%, 82.3%, and 63.4% for SRG, MRG, and HRG, respectively, while the corresponding EFS rates were 95.5%, 82.7%, and 56.3%[27].

Compared to these national studies, our remission rate appears slightly lower, and the rate of patient deaths prior to remission is higher. Despite these limitations, the outcomes for patients treated under our Group III protocol demonstrated relative improvement, with a 10-year OS of 73%.

Patients with ALL have the poorest prognosis when diagnosed under one year of age. This group is commonly characterized by massive organomegaly, CNS involvement, elevated leukocyte counts, MLL gene rearrangements, and resistance to treatment[7,28]. While the prognosis is unfavorable in patients younger than one year, the 2–6-year age group is known to have the most favorable outcomes[1,29]. In our study, among patients treated with the Group III protocol, the 10-year OS rate was 78% for those aged 2–6 years, and 68% for those younger than 2 years.

In a study conducted by Testi et al. in Italy in 2019, adolescents (aged 10–17 years, n=1094) were compared to younger children (aged 1–9 years, n=3647) with ALL. The 5-year OS rates were 83.4% for adolescents and 92.7% for younger children, while the 5-year EFS rates were 74.6% and 84.4%, respectively. The differences in OS and EFS between the two age groups were statistically significant ($p<0.001$). When subdividing the adolescent group into 10–14 and 15–17 years of age, the 5-year EFS rates were 76.2% and 70.0%, and the 5-year OS probabilities were 84.9% and 78.8%, respectively. However, the differences between these two adolescent subgroups were not statistically significant[30].

In our cohort, there was no statistically significant difference in 10-year OS between patients younger than 10 years and those aged 10 years or older, with rates of 74% and 72%, respectively, among those treated under the Group III protocol.

Acute lymphoblastic leukemia has a higher incidence in boys. Moreover, several studies have demonstrated that the prognosis tends to be more favorable in girls[1]. In 2022, Gupta et al. investigated the impact of sex on treatment outcomes in ALL. Their study included 8202 patients with B-cell ALL (54.4% male)

and 1562 patients with T-cell ALL (74.3% male), all aged between 1 and 31 years and treated between 2004 and 2014. The 5-year EFS was 84.6% in boys and 91.3% in girls (p=0.009), while OS was 86.0% in boys and 92.5% in girls (p= 0.02)[31].

In our earlier cohorts, OS was higher in female patients. However, under the Group III treatment protocol, this trend reversed in favor of male patients, although the difference was not statistically significant (p=0.051). Following protocol modifications, we observed an improvement in survival among boys with ALL; in Group III, the 10-year OS was 64% in girls and 78% in boys.

ALL is typically classified into B-cell and T-cell subtypes[14]. T-cell ALL accounts for 10–15% of newly diagnosed cases, although this figure can vary by age, race, and ethnicity[1]. Studies have shown that patients of African descent have a higher incidence of T-cell ALL and other high-risk features[32]. T-cell ALL is generally associated with poorer prognosis compared to B-cell ALL. It predominantly affects older children and adolescents, is more common in males, and is frequently associated with elevated leukocyte counts, mediastinal masses, and CNS involvement[1]. Additionally, certain mutations specific to T-cell ALL have been linked to adverse prognostic outcomes[1,33,34].

A study from China reported 5-year EFS and OS rates of 62.5% and 62.7%, respectively, in pediatric T-cell ALL patients[35]. At diagnosis, CNS involvement is observed in approximately 10–15% of T-cell ALL cases and in fewer than 5% of B-cell ALL cases[23,25,36]. The poorer prognosis seen in T-cell ALL is attributed to high leukocyte counts, lymphadenopathy, hepatomegaly, splenomegaly, and overall higher tumor burden, which also increase the risk of CNS leukemia[1,37].

CNS leukemia is a critical complication and contributes significantly to disease recurrence. Due to the blood–brain barrier, systemic chemotherapeutic agents exhibit limited penetration into the CNS. Prophylactic intrathecal therapy plays a key role in reducing CNS relapse. This may involve single-agent methotrexate or triple therapy combining methotrexate, cytarabine, and hydrocortisone or prednisone[38,39]. High-dose methotrexate and prophylactic cranial radiotherapy are also effective in lowering the incidence of CNS relapse[8,40].

In our cohort, the proportion of T-cell ALL was higher than generally reported in the literature. This is likely due to our institution's role as a referral center, particularly for patients with hyperleukocytosis requiring leukapheresis. Geographic and possibly ethnic factors may also contribute to this increased incidence. Notably, following protocol modifications targeting T-cell ALL specifically, survival outcomes improved substantially. In fact, both OS and EFS in T-cell patients surpassed those of children with B-cell ALL in Group III.

In relapsed ALL, drug resistance occurs as a result of genetic structure differences and copy number changes in chromosomes[41,42] acquired genetic anomalies (EBF1 and IKZF1 deletions) and deletions in MSH6, NR3C1, and BTG1 genes[43]. Möricke et al. reported relapse rates at the most 33.8% and at the least 16.9% in the patient groups to whom BFM-81-95 treatment protocols were applied[8]. Stary et al. reported the rate of T-cell ALL as 12.7% in their study. It was reported that 16.4% (830 patients) of all patients developed relapse[23]. In our study, according to the treatment protocols, relapse was observed at a rate of 43.9% in group I, while this rate decreased to 23.6% in the group III patients. These results show that our relapse rates have decreased significantly (p=0.033).

Our future thoughts in childhood ALL treatment are as follows; morbidity and mortality are important problems during and after treatment of children with leukemia[44-46]. New drugs are being developed to reduce chemotherapy toxicity. These drugs have been produced that are currently used in childhood relapsed ALL, which will be used in ALL treatment protocols in the coming years[47].

There were some limitations in our study, the first of which is its single-center and retrospective design. As it is a retrospective study, data of all patients could not be reached. Immunophenotyping, genetic study, and minimal residual disease evaluation could not be performed in all patients. New targeted therapies could not be used in our study.

The outcomes observed in Group III demonstrate substantial improvements compared to earlier treatment protocols. The protocol modifications—including enhanced maintenance therapy, intensified CNS prophylaxis, and dose adjustments tailored to risk and immunophenotype—contributed to higher OS and EFS rates.

Furthermore, these improvements were most notable among historically disadvantaged subgroups such as

boys and patients with T-cell ALL. Contrary to previous findings in the literature, male patients and those with T-cell ALL achieved survival rates comparable to or better than their B-cell and female counterparts.

Our results suggest that protocol modifications can overcome some of the negative prognostic factors traditionally associated with T-cell lineage and male gender. In addition, both CNS relapse and overall relapse rates declined significantly in Group III.

While our findings are encouraging, prospective studies with larger sample sizes and MRD-based risk stratification are needed to validate the long-term effectiveness and reproducibility of our modified treatment approach.

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