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The Survival of Relapsed Childhood Leukemia: An 12-year Single-center Experience

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What is known on this subject?

In acute lymphoblastic leukemia, which is the most common type of cancer in childhood, despite a remission rate of up to 85-95%, recurrence and subsequent events are the most common and undesirable situation with a rate of 15-20%.

What this study adds?

To share the outcome of our recurrent cases among acute lymphoblastic leukemia patients who have been treated and followed for 12 years in our hospital, which is at the forefront of newly diagnosed cancer applications every year in our country.

ABSTRACT

Objective: Relapse is still the most important cause of death all over the world, and approximately 15-20% of children experience a recurrence of the disease.

Material and Methods: Among 474 patients who received their first treatment from December 2012 to March 2024 at pediatric hematology oncology clinic, 48 patients who relapsed were included in the study. Diagnosis of initial and relapse acute lymphoblastic leukemia was made by morphological and immunophenotypic evaluation of bone marrow and other samples, and the patients were treated with Berlin-Frankfurt-Munster protocols. The risk of recurrence, T-cell bone marrow relapse, very early relapse, early bone marrow relapse, recurrence after bone marrow transplantation, t(9;22) and t(1;19) positive were defined as "high-risk"; the others as "standard-risk".

Results: Thirty four (71%) of the cases were male, 32 (67%) were bone marrow 4 (8%) were isolated central nervous system (CNS), 5 (10%) were bone marrow + CNS, 7 (17%) were other sites, 27 (44%) were high-risk, and 8 (21%) allogeneic transplants were performed. The calculated 86-month overall survival rate is 51%. The event-free survival (EFS) is 62% at 96 months in standard-risk and 36% at 61 months in high-risk (p=0.037). It is 38% at 37 months after relapse. Furthermore, EFS 53% at 49 months for isolated bone marrow recurrence and 31% at 14 months for recurrence at other sites (p=0.481). Also, it is 25% at 14 months, which is considered very early according to the time of recurrence, 36% in the last 16 months, and 81% EFS at 73 months (p=0.02).

Conclusion: Although follow-up periods are relatively short, our overall and EFS is comparable to that of developed countries. The risk situation and the time of recurrence are the most important factors affecting the outcome. Contrary to expectations, isolated bone marrow recurrences had a better EFS rate, suggesting that the lack of statistical difference is because of the low number of isolated non-bone marrow recurrence cases.

Keywords: Acute lymphoblastic leukemia, child, event-free survival, pediatric hematology, recurrence, survival

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, accounting for 25-30% of all childhood cancers. As a result of advances in chemotherapy and supportive care, the 5-year survival rate for childhood ALL has increased from 10% to 86% in the last 50 years (1,2). However, the survival in resource-limited countries is significantly lower compared with high-income countries, with a long-term survival of only 35-80% (3). After two years of treatment that wears out the child and the family, the disease relapses in approximately 15-20% of children, and it is the leading cause of death worldwide from leukemia (4). The present study aimed to evaluate overall survival (OS) and event-free survival (EFS) in children with relapsed ALL.

Material and Methods

The study included 474 ALL patients who were diagnosed and treated at University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital, Pediatric Hematology Oncology Clinics between December 2012 and June 2020, and at University of Health Sciences Türkiye, Çam and Sakura City Hospital, Pediatric Hematology Oncology Clinics from 2020 to March 2024. Out of 474 patients, the data from 48 ALL patients who relapsed were retrospectively analysed. For newly diagnosed ALL patients ALL-Inter-Continental (IC) Berlin-Frankfurt-Munster (BFM) 2009 trial protocol was used until September 2022, and then ALL European European Standard Clinical Practice 2022 guidance document was used. Relapsed patients were treated according to childhood ALL 1st relapse guidance that was developed by ALL-IC Study Group in 2016, except for 4 patients (5). Diagnosis was made by morphologic and immunophenotypic examination of bone marrow and/or peripheral blood. The flow cytometry analysis for immunophenotyping was performed at İstanbul University Immunology Laboratory until 2018 due to unavailibilty of flow cytometry device, and started to be performed in our hospital since then. Starting from June 2020, an Excel-based software program was used for patients' clinical, laboratory, and follow-up data records. Relapse within 18 months after initial diagnosis is defined as very early relapse; as early relapse if it occurs ≥18 months after initial diagnosis or within <6 months after completion of initial treatment; and late relapse if it occurs ≥6 months after completion of initial treatment. Site of relapse was defined as: bone marrow, central nervous system (CNS), testicular, other sites, bone marrow + CNS, bone marrow + testicular, or bone marrow + other sites. Patients were stratified into "high-risk group" or "standard-risk group" based on immunophenotype, site, and time to relapse. Patients with certain genetic abnormalities, including t(9;22) and t(1;19), T-cell bone marrow relapse, any very early relapse, early bone marrow relapse, and relapse after hematopoietic stem cell transplantation (HSCT), are defined as "high-risk" while those not stratified as high-risk are defined as "standard-risk".

Statistical Analysis

Patient data were analysed retrospectively and evaluated with descriptive statistics. Kaplan-Meier and Cox regression survival analyses were performed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY.

Results

Thirty four (71%) patients were male and 14 (29%) were female; median age (interquartile range) at time of diagnosis and at the time of relapses were 6.9 (8.8) and 9 (7.6) years, respectively. The cell types were: 3 proB, 34 preB, and 8 T-cell ALL. The rate of T-cells at the first diagnosis was 17%. According to the time to relapse, 11 (23%) were very early relapse, 19 (40%) early relapse early, and 18 (37%) late relapse. Relapse site was bone marrow in 32 patients (67%); isolated CNS (iCNS) in 4 patients (8%), bone marrow + CNS in 5 patients (10%); and other sites in 9 patients (14%), two of patients with isolated retina involvement, one of whom also subsequently developed CNS relapse (Table 1). There were 27 patients (56%) in the standard-risk group and 21 patients (44%) in

Table 1. Relaps cites of cases

	Frequency	Percent
Bone marrow (BM)	32	66.7
Central nervous system (CNS)	4	8.3
Testis	1	2.1
Other cites	2	4.2
BM + CNS	5	10.4
BM + testis	2	4.2
BM + other cites	2	4.2
Total	48	100

Table 2. Distribution of cases according to risk status at initial diagnosis and relapse

		Relapse		
		Standard	High	Total
Initial diagnosis	Medium	15	12	27
	High	9	12	21
	Total	24	24	48

the high-risk group (Table 2). After the patients experienced relapse, the median follow-up period was 14 months (with an interquartile range of 28 months). Two patients (4%) who were at high-risk due to very early relapse could not achieve remission with induction and subsequent rescue treatments and died of the disease. Another two patients (4%) in the high-risk group, the response to induction therapy was poor, and bone marrow transplantation from a matched unrelated donor was possible for one of them and the other patient died from an infection. In one case in the standard-risk group with inadequate induction response, chemotherapy was continued because a matched donor could not be found, and the patient is currently being followed up in remission in the 15th month of maintenance. A patient with T-ALL who had a relapse at 54 months of follow-up, presented with left retinal involvement. He entered the intensive care unit, due to septic shock that occurred at the third week of induction treatment. He received supportive treatment in the intensive care unit for 1.5 months, and in the meantime, he completely lost his vision in both eyes. The treatment was terminated upon the request of the family; he has been followed in remission without chemotherapy for 20 months.

Ten patients (21%) received allogeneic HSCT; 7 were high-risk and 3 were standard-risk. Four received transplants from matched sibling donors, 1 from a family-matched donor, 4 from matched unrelated donors, and 1 from an HLA-9/10 compatible parent. One of the two patients was lost to follow-up without disease 7 months after transplantation, and the other was lost 1 year later. Three patients died due to disease despite two transplants each, and five patients are being followed up, disease-free, for a median of 15 months.

During the follow-up period, no event occurred in 46% of the cases. The most common events were a second relapse in 24% of the patients, and death due to ALL in 12.5% of the patients (Table 3). Two patients (4%) in their first relapse died during induction from septic shock (unknown source) before response evaluation could be obtained. One patient never achieved remission and was lost to follow-up 6 months later.

Table 3. Events after relapses

	Frequency	Percent
No event	22	45.8
Chemotherapy resistance	1	2.1
Second relapse	11	22.9
Permanent sequelae	3	6.3
Died disease free	4	8.3
Died with disease	7	14.6
Total	48	100

According to the risk status at the time of initial diagnosis, two of the 27 medium-risk patients had non-disease-free deaths and one disease-related death, while two of the 21 high-risk patients had non-disease-free deaths and six disease-related deaths. The rate of T-cells was 17% both at the initial diagnosis and at the time of recurrence. Two of the three permanent sequelae occurred in cases of T-cell relapse (blindness and osteomyelitis). While two of the seven leukemia deaths before remission were due to T-cells, none of the deaths in remission were due to T-cells.

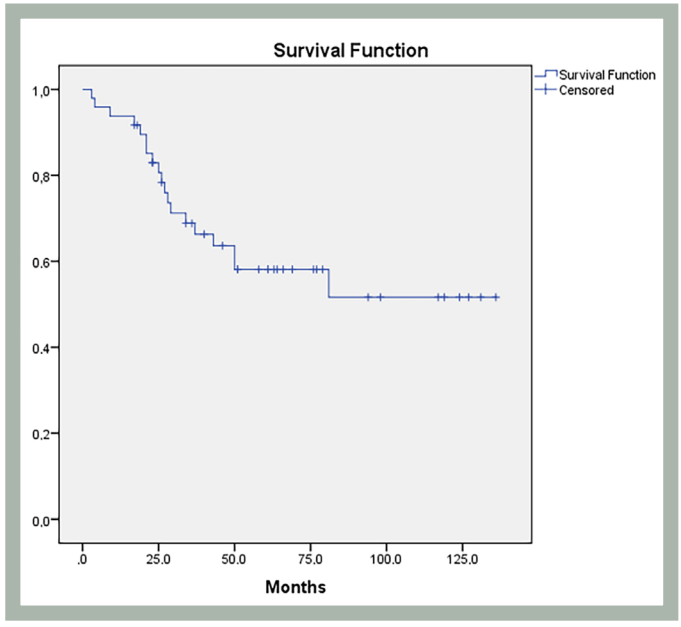

Figure 1. Kaplan-Meier curves of overall survival of all studied patients (n=48)

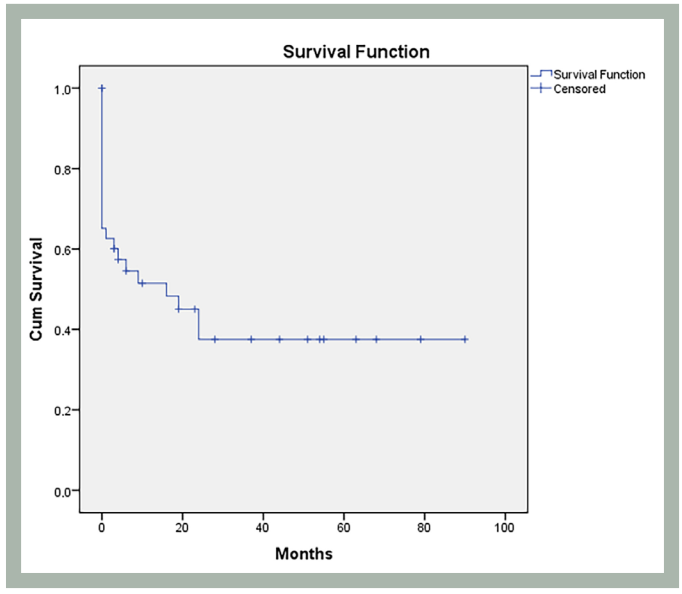

Figure 2. Kaplan-Meier curves of overall survival of all studied patients (n=48)

The estimated OS at 86 [95% confidence interval (CI): 70-104] months was 51% (Figure 1) and EFS at 37 (95% CI: 24-51) months was 38% (Figure 2). According to the risk stratification at the time of relapse, OS was 62% at 96 months (95% CI: 77-115), in the standard-risk group and was 36% at 67 months (95% CI: 42-92) in the high-risk group (p=0.037) (Figure 3). Depending on the site of relapse EFS was 53% at 49 (95% CI: 32-66) months for isolated bone marrow relapse and was 31% at 14 (95% CI: 3-25) months for isolated extramedullary or combined relapse (p=0.481) (Figure 4). According to the time to relapse EFS was 25% at 13 (95% CI: 0-31) months for very early relapse and was 81% at 73 (95% CI: 55-90) months for late relapse, respectively (p=0.02) (Figure 5).

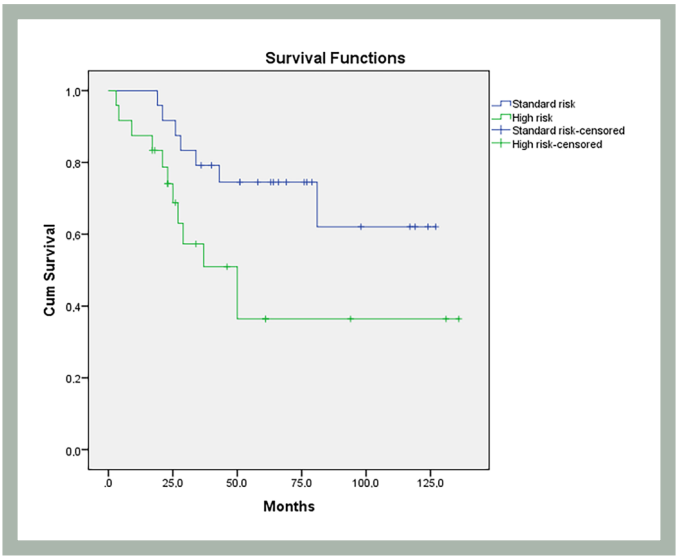

Figure 3. Kaplan-Meier curves of overall survival for standard-risk (n=27) and high-risk (n=21) groups

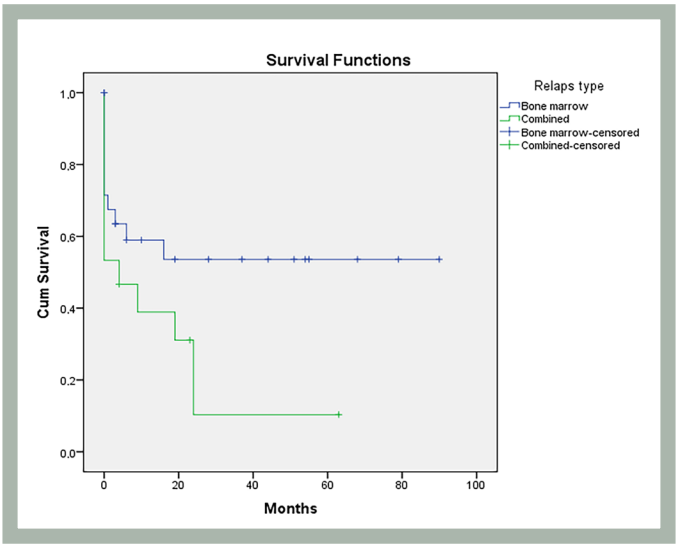

Figure 4. Kaplan-Meier curves of event-free survival for bone marrow (n=32), and combined (n=16) groups

Discussion

Despite the significant survival improvements in newly diagnosed childhood ALL, outcomes for relapsed patients remain poor (2), and only half of patients achieve long-term survival (6). The most important prognostic factors determining survival after relapse are the site of relapse, duration of first complete remission, and disease immunophenotype (7). According to the relapse site, 50-60% of relapses occur in the bone marrow, following relapse CNS in ~20%, isolated testicular relapse in ~5%, and a combination of bone marrow and extramedullary disease in the remainder (8). In our study, relapse rates were similar to those reported in the literature (7,9).

In general, in the treatment of patients at high-risk for the first recurrence of ALL, bone marrow transplantation is performed after several courses of chemotherapy, while in the standard-risk group, several courses of chemotherapy lasting up to 9 months, followed by low-dose chemotherapy, are given orally for up to 2 years (10). Although there have been some improvements in outcomes over the past few decades, only 50% of children with a first relapse of ALL survive long-term, and outcomes are much worse with second or subsequent relapses (11,12). In patients with relapse, chemotherapy-related mortality is approximately three times higher (10%) than in patients with primary treatment, and as with primary treatment, infections are the most common cause of death (9). Relapses that occur within 3 years of diagnosis and any recurrence of T-ALL are particularly difficult to recover from (11). Our results appear to be similar to those in the literature,

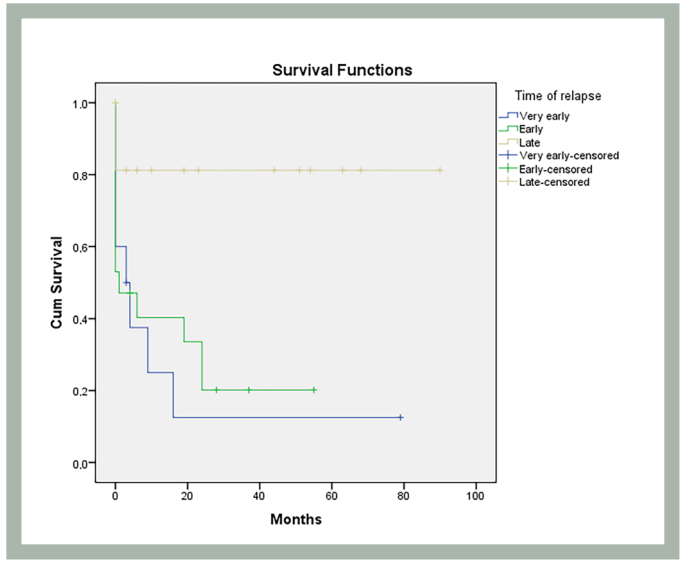

Figure 5. Kaplan-Meier curves of event free survival for very early (n=11), early (n=19), late (n=18) groups

showing a similarity of 54%. We believe that it is valuable not to be left behind as well.

Blinatumomab, a bispecific T-cell-binding antibody that connects CD3+ T-cells to CD19+ B-ALL cells, has become a part of current treatment protocols in high-risk relapsed pediatric ALL cases due to increased disease-free survival with 2 cycles of blinatumomab, lower toxicity, and superior minimal residual disease clearance (13). However, it could not be used in any of our cases. In a subsequent publication by the same researchers, it was stated that there was no statistically significant effect on EFS (14). Although other studies state that it contributes to the short-term effects, it is understood that time is needed to see its long-term effects (10).

In a study from the southeast region of Türkiye, the relapse rate of 93 pediatric ALL patients, who were in remission after induction chemotherapy, was 6.4%. Five patients (4.7%) had a bone marrow relapse, one patient (0.9%) had a retinal relapse, and five patients (4.7%) had a second occurrence of acute myeloid leukemia (15). In this study, the development of second AML was thought to be due to the epipodophyllotoxins that were used in the St. Jude Total XIII protocol during the first treatment (16). By contrast, no ALL patients developed second AML in the current study, despite the fact that the current study's patients' number was four times greater than the latter study, and a total of 500 mg/m^2 etoposide was used in 44% of patients who were stratified into the high-risk arm of the ALL BFM protocols.

In the Children's Cancer Group ALL trial and ALL relapse BFM 90 trial, 5-year OS and 10-year OS rates were 36.3%, and 36%, respectively (11,12). In the recent reports, 5-year OS for first relapse of childhood ALL is around 50% (9,17). Long-term survival was not lagging behind the reported results.

It is known that the presence of T-cell leukemia is one of the most important prognostic factors in general, and in some studies of T-cell leukemia cases, relapse rates of up to 30% have been reported (6,18). However, it is also noteworthy that in our cases, the T-cell rate remained unchanged at 17% both at the time of initial diagnosis and at the time of recurrence. The reason for the low recurrence rate of T-cell cases cannot be an immunophenotyping error. Because they can be easily distinguished from each other in flow cytometric analysis, cells of different types can be efficiently separated. Regional and racial differences remain.

Two of the three permanent sequelae occurred in cases of T-cell relapse. While 2 of the 7 leukemia deaths before remission were caused by T-cells, none of the deaths in remission were due to T-cells. In an analysis of Children's Oncology Group that included 9,585 pediatric ALL patients, patients with iCNS relapse comprised 20.9% of all relapses, and the 5-year OS rates for very early, early, and late iCNS relapse were 44%, 68%, and 78%, respectively (19). In the recent report by Children's Oncology Group, the 3-year EFS and OS rates were 41.4% and 51.7%, respectively, for very early iCNS relapse. The 3-year DFS/OS for transplanted patients was significantly better than those who received chemotherapy/radiotherapy alone among patients with very early iCNS relapse (20,21). In the current study, there were only 4 patients (8.3%) with iCNS relapse, and thus survival comparison could not be carried out. Despite a good prognosis in early and late iCNS relapses, very early iCNS relapses prognosis remains poor. Early initiation of HLA typing and selection of a donor should be performed as soon as possible to shorten the pretransplantation interval, if possible, HSCT from a compatible donor should be performed.

Relapse of childhood ALL presenting as ocular involvement is a rare event, and accounts for only 2.2% of ALL relapses. Although the most common site of involvement in isolated ocular relapse of ALL is the retina, it may involve all parts of one or both eyes with subretinal infiltration; or it may occur as bilateral exudative retinal detachment (22). It is noteworthy that two of our relapsed ALL patients presented with retinal involvement. In the literature, cases of retinal relapse have been treated with the ALL treatment protocol, and radiotherapy, and it has been stated that by this approach, the eye can be saved without surgical removal (23,24). It was remarkable that, in the present study, one patient diagnosed with T-cell ALL who presented with retina relapse received only 3-week induction chemotherapy and has been in remission for 20 months.

Study Limitations

The limitations of the present study were relatively short follow-up time and small number of patients.

Conclusion

Despite the relatively short follow-up period, OS and EFS rates for the the relapsed ALL patients were similar to those in the developed countries. Risk group stratification at the time of relapse (high-risk group vs. standard-risk group) and time to relapse were the most important factors affecting the outcome. Survival rate of patients with recurrences in the first 2.5 years after completion of initial treatment remains below 20%. However, patients with isolated bone marrow relapse had a better EFS, which might have been due to a low number of patients.

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Ethics

Ethics Committee Approval: University of Health Sciences Türkiye, Çam and Sakura City Hospital (approval number: 2022/03/82, date: 14/03/2022).

Informed Consent: All participants provided written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.A., S.T., O.Z.Ş., E.A., T.N.T., A.Ö.K., D.Y., G.K., Ö.H., S.E., Ö.Ö., E.P.U., C.B., Concept: A.A., Design: A.A., Data Collection or Processing: A.A., Analysis or Interpretation: A.A., Literature Search: A.A., Writing: A.A.

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

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