DOI: 10.4274/csmedj.galenos.2022.2022-1-4

ORIGINAL ARTICLE

49

Cam and Sakura Med J 2022;2(2):49-58

CSMJ

Overall and Event-free Survival in Children with Acute Lymphoblastic Leukemia and Evaluation of Treatment Related Acute Toxicity

Orhan Özdoğan[1], Ali Ayçiçek[2], Sibel Tekgündüz[2], Ezgi Paslı Uysalol[2], Müge Gökçe[3], Cengiz Bayram[2]

[1]Hacettepe University Faculty of Medicine, Department of Pediatric Neurology, Ankara, Turkey
[2]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Pediatric Hematology Oncology, İstanbul, Turkey
[3]Memorial Bahçelievler Hospital, Clinic of Pediatric Hematology Oncology, İstanbul, Turkey

What is known on this subject?

Although childhood cancers can be treated with chemotherapy today, deaths and recurrences caused by the disease itself and the drugs used are seen at certain rates.

What this study adds?

It is an important study because it has the first results of the Pediatric Hematology Oncology Clinic of Kanuni Sultan Suleyman Hospital, which has the highest bed capacity in its field in Istanbul at the time of the study.

ABSTRACT

Objective: The study aimed to evaluate the acute toxicity, overall survival (OS) and event-free survival (EFS) of children with acute lymphoblastic leukemia (ALL).

Material and Methods: This study included retrospective analysis of the medical records of 129 pediatric ALL patients aged 1 to 18 years old. Gender, risk group, central nervous system involvement at diagnosis, relapse and mortality status of patients, OS and EFS was evaluated. The Kaplan-Meier method was used to estimate survival rates. The survival difference of two groups was compared using the log-rank test.

Results: Eighty-six (66%) patients were boys and forty-three (33%) were girls. The mean age at diagnosis was 6.9±4.46 and 5.6±4.01 in male and female, respectively. Seventeen (13%) patients were classified as standard risk, 76 (58%) were intermediate risk, and 36 (27%) were high risk. Three patients (2.3%) died from acute toxicity during induction therapy. The median duration of follow-up was 25 months (range 1-65 months). The estimated 5-year OS and EFS was 88±4.6% and 78±4.1%, respectively. The estimated 5-year OS for the standard, intermediate and high-risk groups were 94±5.7%, 93±3.1%, and 59±13%, respectively, and EFS was 94±5.7%, 86.6±4.2%, and 49.9±10%, respectively.

Conclusion: The OS and EFS for standard-risk and intermediate-risk groups were good and comparable to the literature. However, the current study's results should be confirmed in a larger patient population and a longer follow-up period.

Keywords: Children, acute lymphoblastic leukemia, event-free survival, overall survival

Address for Correspondence: Ali Ayçiçek MD, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Pediatric Hematology Oncology, İstanbul, Turkey
Phone: +90 212 909 60 00 **E-mail:** ayciceka@hotmail.com **ORCID ID:** orcid.org/0000-0003-1018-1119
Received: 22.01.2022 **Accepted:** 11.05.2022

CAM & SAKURA MEDICAL JOURNAL

Introduction

Cancer is the 4th most common cause of death in children aged 1 to 15 years old the following infections, heart diseases and accidents in our country (1). Childhood cancer is rare and its incidence is reported as 1/7,000 in children 15 years and younger. Although solid tumors are predominant in adults, hematologic malignancies such as leukemia and lymphoma comprise approximately 40% of childhood cancers (2). Acute leukemia constitutes 97% of all childhood leukemias, and 75-80% of these are acute lymphoblastic leukemia (ALL) (3).

Despite the increase in the prevalence of childhood malignancies, the 5-year survival rate in children with ALL has approached 90% in recent reports because of advances in chemotherapy and supportive care (4). Randomized controlled clinical trials, intensive chemotherapy combinations, central nervous system (CNS) prophylaxis, determining risk groups, and adjusting treatment intensity, and determining residual leukemia cells in the body called minimal residual disease (MRD) showed a significant increase in patients' life expectancy (5,6).

In our study, ALL patients who were diagnosed and treated between 2012 and 2017 in the Pediatric Hematology Oncology Clinic of Sultan Suleyman Training and Research Hospital, in Istanbul, were retrospectively screened. Demographic data, ALL cell type, the risk groups, CNS involvement, acute toxicity related to ALL induction treatment, bone marrow transplantation (BMT) status, relapse/mortality rates and overall survival (OS) and event-free survival (EFS) rates were evaluated.

Material and Methods

A total of 130 ALL patients diagnosed and treated between 2012 and 2016 at the Pediatric Hematology Oncology Clinic of Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, were retrospectively examined. Patient data were obtained from the Turkish Pediatric Oncology Group records and electronic hospital medical records. One case with infant leukemia was excluded from the study and 129 ALL cases aged 1 to 17 years were evaluated. Patients with 25% or higher blast percentage in bone marrow aspiration were diagnosed with acute leukemia and immunophenotyping was used to define the ALL subtype. Bone marrow samples were painted with May Grünwald-Giemsa and were evaluated according to the FAB criteria. The CNS involvement was defined as ≥5 lymphoblasts/mm^3 in cerebrospinal fluid (CSF), and the presence of >10/mm^3 erythrocytes in CSF was considered traumatic lumbar puncture (LP). At the beginning of treatment, the patient was divided into risk groups according to age, leukocyte counts, absolute blast count in the peripheral blood on day 8, MRD level in bone marrow on day 15, t(4;11) and, t(9;22) at the time of diagnosis.

Standard Risk Group (SRG)

Patients aged ≥1 to <6 years at the time of diagnosis, an initial leukocyte count of <20,000/mm^3, patients with <1,000/mm^3 blasts in the peripheral blood on day 8, M1/M2 bone marrow in the bone marrow aspiration on day 15, MRD level <0.1% (complete remission) on day 15, without Ph+ (BCR/ABL+), and t(4;11) (MLL/AF4+) were classified in to the SRG.

High Risk Group (HRG)

Patients with absolute blast count of ≥1,000/mm^3 in the peripheral blood on day 8, or M3 bone marrow with ≥25% blasts on day 15, or FC MRD level more than 10% on day 15, or those with M2/M3 bone marrow on day 33, and, irrespective of treatment response, patients with Ph+ (BCR/ABL+), or t(4;11) (MLL/AF4+) or hypodiploidy (<45 chromosomes) classified in to the HRG.

Medium Risk Group (MRG)

All patients who were not stratified to the standard and HRG were classified in to intermediate risk patients (7).

Relapse Criteria

More than 25% blasts in the bone marrow after the achievement of remission with initial leukemia treatment, and extramedullary leukemia involvement in any site was considered a relapse. Relapse can be isolated bone marrow, CNS and testicular, and ≥2 sites of involvement defined as combined relapse. Relapse 18 months after initial diagnosis defined as very early relapse; defined as early relapse if relapse occurred ≥18 months after initial diagnosis and <6 months after the completion of initial treatment, and defined as late relapse if relapse occurred ≥6 months after the completion of initial treatment. Conditions such as encephalopathy and shock that developed unexpectedly during induction chemotherapy were considered acute toxicity. Overall survival was defined as the time from the date of diagnosis to death from any cause or last follow-up period, EFS was defined as the time from remission until the date of failure (induction failure, relapse or death) and last follow-up time.

Statistical Analysis

Kolmogorov-Smirnov and Lilliefors test was used to determine the distribution of data, and analysis of independent groups was performed by t-test and chi-square test. One sample t-test was used for the comparison of the

literature and the current study's data; OS and EFS were estimated using Kaplan-Meier method and compared with log-rank (Mantel-Cox) test. IBM SPSS 22.0 was used to analyze the study's data. The results are presented as mean ± standard deviation, median and range, and the level of statistical significance was set at $p<0.05$.

Results

There were 86 boys (67%), and 43 girls (33%) and the male/female ratio was 1/2. Three (3%) of male ALL patients and 2 (4%) of ALL female patients had Down syndrome (Trisomy 21). The median follow-up period was 25 months (range: 1-65 months). Mean age of the patients at the time of diagnosis was 6.5±4.3 years (range: 1-17 years). Although the mean age of the diagnosis was higher compared to the literature, no significant difference was found (comparison p=0.105 for 5.9). The mean age of male ALL patients and female ALL patients was 6.9±4.5, and 5.6±4.0, respectively, and there was no significant difference between gender (p=0.97). When evaluated according to risk groups, the highest mean age was found to be in HRG patients (8.3 years) (p=0.014).

According to FAB classification, 106 (82%) patients were B-cell ALL, 22 (17%) patients were T-cell ALL and 1 patient was mix type ALL. After the stratification of ALL patients according to risk groups; there were 76 patients (58%) in MRG, 36 patients (27%) in HRG, and 17 patients (13%) SRG. In the HRG ALL patients, there were 31 (36%) male ALL patients, and 5 female (11%) ALL patients (p=0.014) (Table 1).

While there was no difference between SRG and MRG patients when comparing the risk groups by age (p=0.07), there was a significant difference between HRG patients and both MRG and SRG patients (p=0.01 and p=0.04, respectively). There were no patients with CNS involvement in the CSF examination at the time of diagnosis. Four of the female patients and 3 of the male patients' LP were traumatic. Traumatic LPs were not found to differ by gender (p=0.68). Eight patients underwent BMT, 6 patients were male (75%), and 2 patients were female (p=0.71). Acute toxicity developed during induction therapy in 3 (2%) of 129 patients, including 1 patient with hepatic encephalopathy, 1 with septic shock, and 1 patient was admitted to the intensive care unit due to pulmonary hemorrhage, and all 3 patients eventually died.

Table 1. The distribution of cases by risk groups

	Standard risk	Medium risk	High risk	Total
Male	10	45	31	86
Female	7	31	5	43
Total	17	76	36	129

Three (2.3%) of the cases did not achieve remission during induction, only 1 out 3 patients entered remission after high-risk-1 blocks. Six patients (4%) relapsed. All of these patients relapsed in the first 18 months after diagnosis and were classified as very early relapses. One case relapsed from B-ALL, 1 switched from B-cell ALL to T-cell ALL, and the other one switched from T-cell ALL to B-cell ALL. One patient had CNS+ bone marrow relapse and the others had isolated bone marrow relapse. None of the relapsed patients had testicular involvement. Two patients who developed relapse died of the disease and 4 patients continued to be followed without disease. Two patients underwent BMT and were followed up without disease. AML was not seen in any of our cases as a secondary leukemia. Twelve patients (9.3%) died without disease, 5 (3%) of whom died from septic shock, 1 due to macrophage activation syndrome and 2 due to hepatic encephalopathy. One patient with hepatic encephalopathy had axonal neuropathy leading to permanent sequelae. Four patients died of leukemia and non-treatment causes. Three (2%) patients died of the disease, 2 (1.5%) of these patients died during post-relapse chemotherapy due to septic shock and one due to liver failure. In one of our patients, vincristine was discontinued during reinduction treatment because of severe toxicity.

The median follow-up period was 24 months (range: 1-65 months). Five-year estimated overall OS was 88±4.6%, and EFS was 78±4.1% (Figures 1, 2, 3, 4).

Estimated 5-year OS by gender was found as 93% in female patients, and 86% in male patients (Figure 3). Event free survival by gender was found as 84% in female patients, and 80% in male patients (Figure 4). There was no statistically significant difference between male and female cases in terms of 5-year estimated OS and EFS (p=0.21 and p=0.49, respectively).

Five-year estimated OS according to the risk group was 94%±5.7% in the SRG, 92.9±3.1% in the MRG and 59.3%±3.1 in the HRG patients, respectively (Figure 5). A statistically significant difference was found in the HRG patients for OS compared with SRG and MRG patients (p=0.01).

Estimated 5-year EFS was found to be 94%±5.7% in the SRG, 86.6% in the MRG and ±49.9% in the HRG (Figure 6). The EFS comparison between the risk groups was found to be statistically significant (p<0.001).

The overall OS and EFS rates of 7 patients with traumatic LP (Table 2) were both lower compared to patients without traumatic LP and the difference was significant for EFS comparison (p=0.203, p=0.039, respectively) (Figures 7, 8). In

Table 2. CNS involvement/traumatic LP status according to risk classification

	No CNS involvement	Traumatic LP	Total
Standard risk	17	0	17
Medium risk	73	3	76
High risk	32	4	36
	122	7	129

CNS: Central nervous system, LP: Lumbar puncture

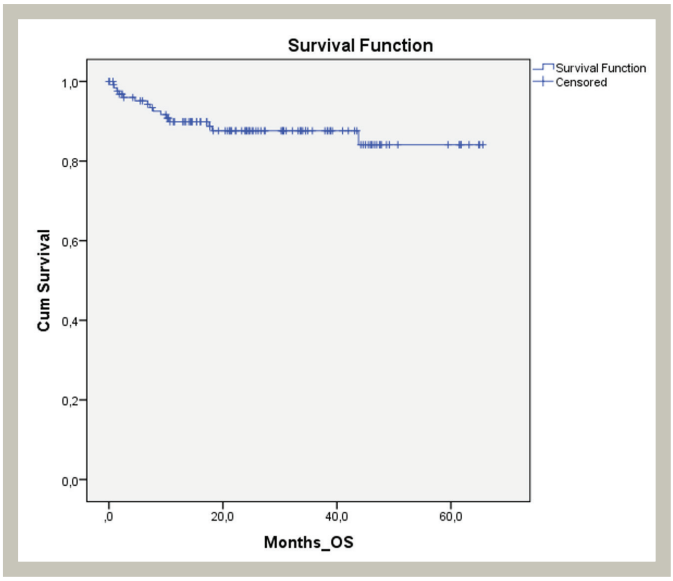

Figure 1. Kaplan-Meier curves of overall survival (OS) of all studied patient (n=129)

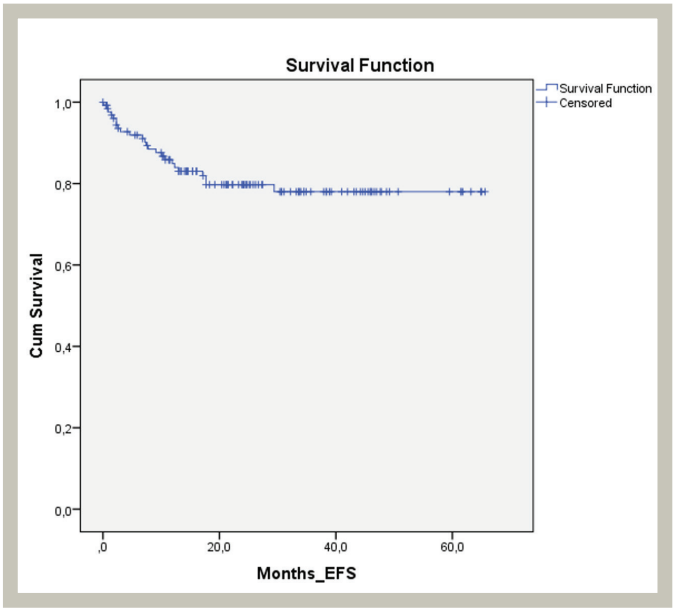

Figure 2. Kaplan-Meier curves of event-free survival (EFS) of all studied patients (n=129)

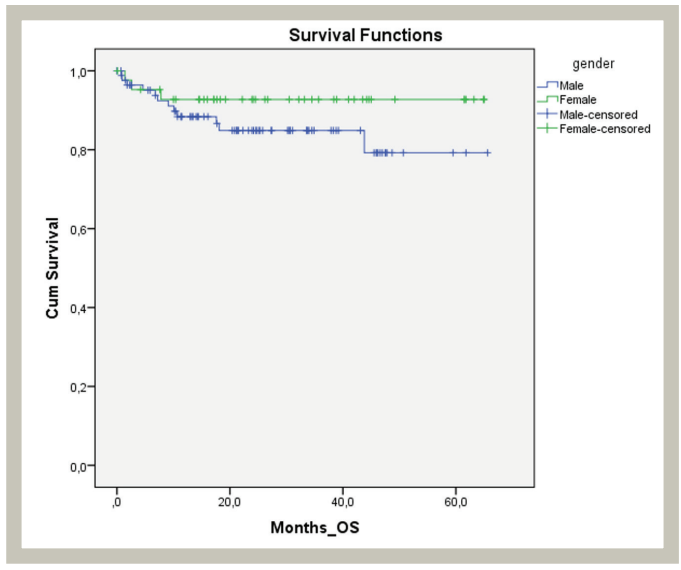

Figure 3. Overall survival (OS) of gender of male (n=86) and female (n=43) patients

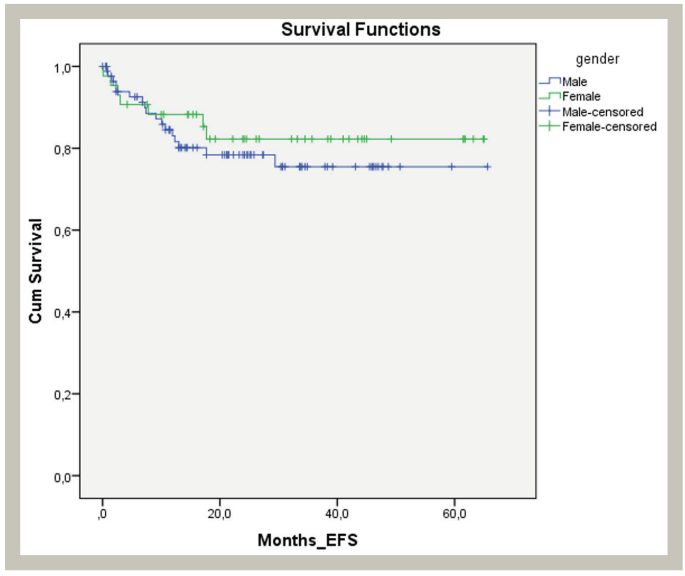

Figure 4. Event-free survival (EFS) of male (n=86) and female (n=43) patients

3 of these patients, 1 developed CNS relapse and 1 with T-cell ALL relapsed, 1 patient died disease-free and 1 patient died of the disease. There were more patients with traumatic LP in HRG patients, so the contribution of variables was compared with the Omnibus test and CNS involvement was found to be significantly higher in HRG patients ($p<0.05$). The main reason for the low survival of patients with traumatic LP was likely due to a high-risk group.

The 5-year estimated OS for B-cell ALL patients in our study was 83%, compared with 88% in patients with T-cell ALL ($p=0.631$) (Figure 9).

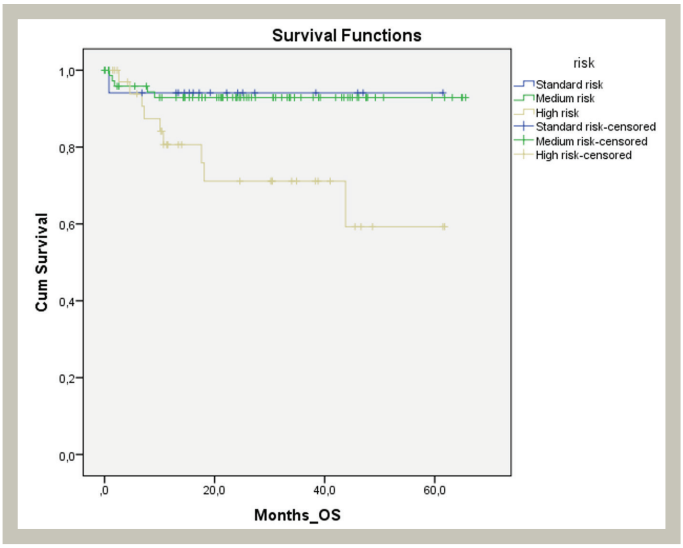

Figure 5. Kaplan-Meier curves of overall survival (OS) for the SRG (n=17), MRG (n=76), and HRG patients (n=36)
SRG: Standard risk group, MRG: Medium risk group, HRG: High risk group

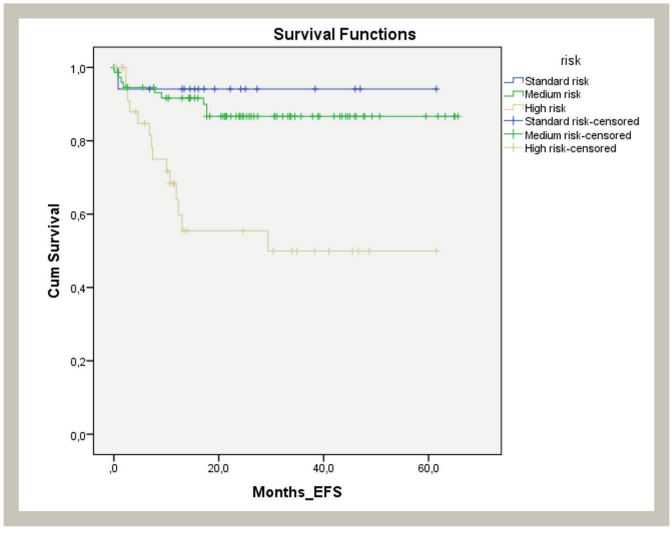

Figure 6. Kaplan-Meier curves of event-free survival (EFS) for SRG (n=17), MRG (n=76), and HRG patients (n=36)
SRG: Standard risk group, MRG: Medium risk group, HRG: High risk group

The 5-year estimated EFS for B-cell ALL patients in our study was 83%, while the EFS for T-cell ALL patients was 57% (Figure 10). Although the p value was close to 0.05, there was no statistically significant difference between the two groups (p=0.06).

Discussion

Leukemia is one of the most common malign diseases in children and accounts for 30% of all childhood cancers (8). Although it varies depending on genetic and environmental factors, ALL comprises 75% of newly diagnosed leukemias and

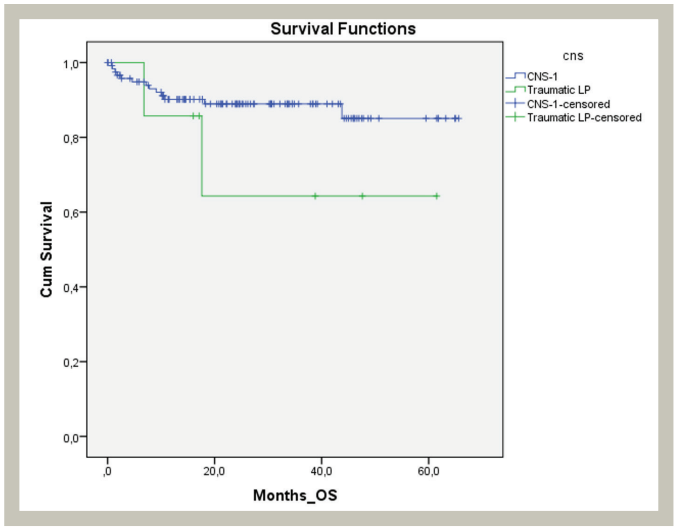

Figure 7. Overall survival (OS) curves of patients without CNS involvement and traumatic LP
CNS: Central nervous system, LP: Lumbar puncture

80% of acute leukemias (9). The incidence of acute leukemias in the United States is 3.4/100,000, while the annual incidence in Turkey is 3/100,000 (10). The incidence rate of ALL in Whites is higher (11). ALL usually develops as the first cancer, rarely developing in the form of secondary cancer (12).

The male/female ratio for ALL is generally reported to be around 1.2-2, and this ratio rises to 4 in T-cell ALL (13,14,15). In the study by Dujua and Hernandez (16) from the Philippines, the rate of male ALL cases was found to be 61.5%. In some studies conducted in our country, ALL was reported to be more common in male, while in some studies, it was reported to be more common in female (17,18). In our study, 86 of the 129 patients (66%) were male, 43 (33%) were girls and the male/female ratio was 2/1. In a study by Koc et al. (17), they reported a male/female ratio of 8/3 in T-ALL. In this study, 16 of 22 patients with T-cell ALL were boys and 6 were girls, and the male/female ratio was found to be 8/3, which was consistent with the literature.

Jabeen et al. (19) reported a mean age of 7.6±0.29 of 255 ALL patients who received BFM protocol. In a study from Turkey by Hazar et al. (18), the mean age of 142 ALL patients who received the TR ALL-2000 protocol was 5.9±4. In our study, the mean age of the ALL-patients was 6.5±4.3, which was higher compared to literature, however the difference was not statistically significant (p=0.105).

B-precursor cells account for 86% of ALL cases, and patients with this immunophenotpe generally enter a standard or intermediate risk group, with a better prognosis. T-cell ALL accounted for 13% of ALL cases. This subtype is associated with older age at presentation, high initial white cell count,

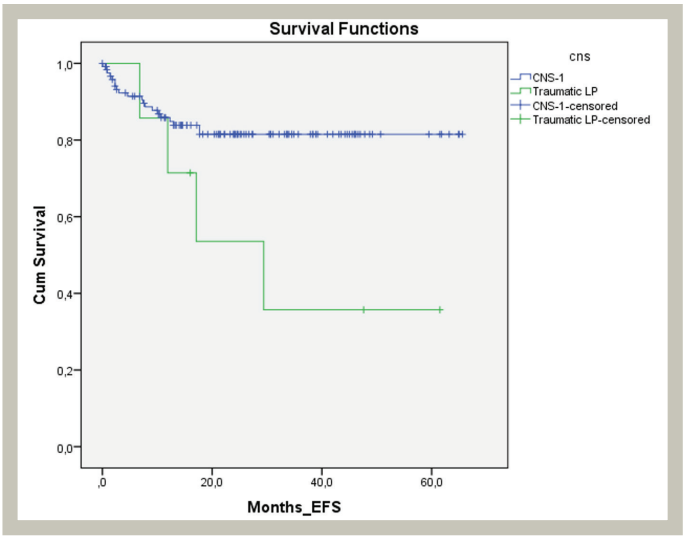

Figure 8. Event-free survival (EFS) curves of patients without CNS involvement and traumatic LP
CNS: Central nervous system, LP: Lumbar puncture

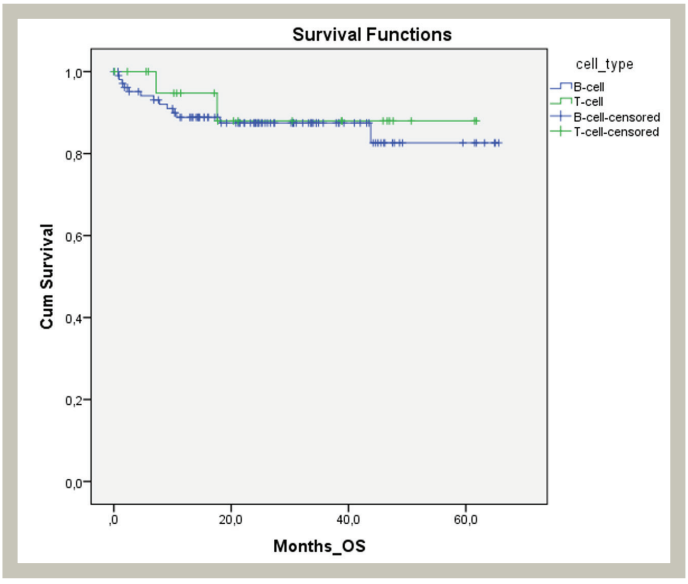

Figure 9. Overall survival (OS) curves of patients according to cell type

CNS involvement, mediastinal mass, and traditionally poor prognosis.

In a multicenter BFM study by Möricke et al. (20), immunphenotypic distribution of 2,169 ALL patients was reported as precursor B-cell ALL in 86.5% of the cases, and was reported as T-cell ALL in 13.3% of the cases. Jabeen et al. (19), reported a rate of 73%, 47%, 3%, and 17% for precursor B-cell ALL, T-cell ALL, mixed type ALL, and unidentified ALL, respectively. In the study by Hazar et al. (18) in Turkey, 78.9% of the cases were precursor B-ALL, 16.2% of were T-cell ALL, and 4.9% could not be defined. In another study from Turkey

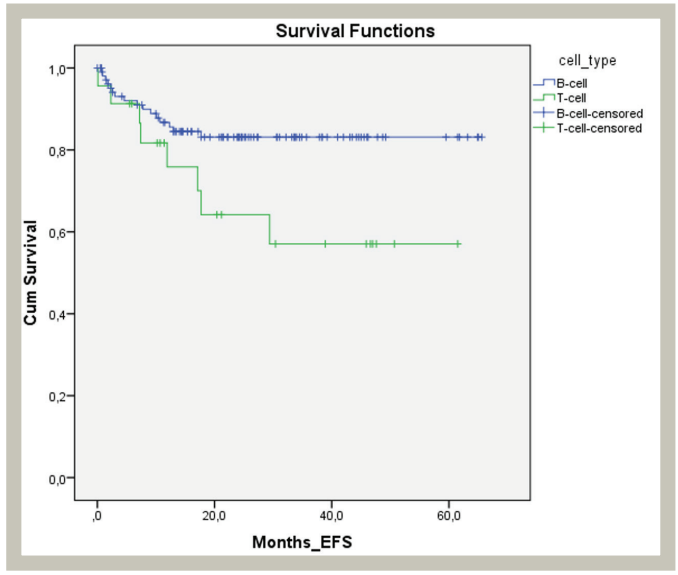

Figure 10. Event-free survival (EFS) curves of patients according to cell type

by Dogru (21), precursor B-cell ALL was found in 89.6% and T-cell ALL in 9.4% of the cases, and 1% was defined as bi-phenotypic. There were 106 cases (82%) of B-cell ALL, 22 (17%) of T-cell ALL, and 1 case (0.7%) of bi-phenotypic ALL in this study, which was consistent with the literature.

In the multicenter BFM study by Möricke et al. (20), 35% of patients were reported as SRG, 53% as MRG and 12% as HRG. In the studies of Hazar et al. (18), 38% of patients reported as SRG, 43.7% as MRG and 18.3% as HRG. In the study by Canbolat Ayhan et al. (22), 32% of ALL patients were in SRG, 45% were in MRG, and 22% were in HRG. In similar studies, 28%-36% of patients reported as SRG, 50%-61% as MRG, and 10%-14% as HRG (23,24). When our patients were evaluated according to risk groups, 13% of the patients in our study group entered SRG, 58% into MRG and 27% into HRG. Compared to the literature, in the current study, HRG patient rate was higher. We think that it was due to the higher mean age of the current study's patient group, as well as treatment response which were evaluated by blast count in the peripheral blood on day 8 and MRD analysis on the 15th day, was also worse.

Schmiegelow et al. (25) defined 14 severe acute toxic effects for childhood lymphoblastic leukemia treatment, which may occur at a frequency of ≤5%-10% during the leukemia treatment. However, they did not report the frequency of deaths that could be related to treatment toxicity (25). Koc et al. (17) reported a frequency of 12.5% acute toxicity, and that was 2% in our study. The low frequency of acute toxicity in the current study might be due to the use of antimicrobial prophylaxis and the supportive care given to the patients during the leukemia treatment. Since there is no detailed

information about the frequency of infections in the literature, a solid conclusion cannot be made in this regard. In this study, acute toxicity related to leukemia treatment was observed in 3 ALL cases (2%), which included hepatic encephalopathy, septic shock and pulmonary hemorrhage, and eventually led to death in all cases.

In a multicenter study by Schrappe et al. (26), induction failure was defined in 1,041 of 44,017 newly diagnosed ALL patients (2.4%). In our country, Orhaner (27), and Degirmenci (28) reported a frequency of 10%, and 3.1% induction failure, respectively. In our study, 3 (2.3%) of 129 patients had induction failure.

In various multicenter studies, the relapse rate in childhood lymphoblastic leukemia was reported to be between 14%-17.5% (16,20,29). In the studies from Turkey, childhood ALL relapse rate was reported to be between 11.5%-19.5% in patients treated with ALL BFM protocol, while Koc et al. (17) reported a 9% relapse rate in patients treated with St. Jude ALL protocol (28,30). In our study, very early recurrence developed in 6 patients (4%). The main reason for our lower relapse rates compared with the literature was the short follow-up period, especially for late relapses.

After the 1960s, the 5-year OS rate for childhood ALL has greatly increased over time (6). Pui et al. (31) reported a 5-year OS of 71.8% in 2000. Following this study, Hussein et al. (29) reported a 5-year OS of 75% in 154 pediatric cases with ALL in 2004, Schmiegelow et al. (32) reported a 5-year OS of 89% in 2007, and Liu et al.'s (33) reported a 5-year OS of 90.6% in 2014. In the results of the BFM-95 multicenter BFM-95 study conducted in our country between 1995 and 2006, the 5-year OS rate was reported as 80% (3). Koc et al. (17) reported a 5-year OS of 77.4% in 2013 from Turkey. In another study, 5-year OS for 256 pediatric ALL patients was reported as 77.4% (28). In our study, 5-year estimated OS was found to be 88%, which was higher than the literature. The possible reason for this might be the shorter follow-up period or the development in supportive treatments.

In addition to improvement in 5-year OS in childhood ALL over time, it was observed in EFS rates. In a 2000 study by Schrappe et al. (5), 6-year EFS was reported as 78%. Although similar drugs are used in various parts of the world, there are small to moderate differences in leukemia treatment protocols with different outcomes. Five-year EFS rates were reported as between 75 and 87% in children with ALL treated with various ALL protocols, including BFM-95, SJCRH-13A, DCOG-9, IC-BFM 2002 and MRC UKALL 2003 (31,32,33,34). Dujua and Hernandez (16) reported a 5-year estimated EFS of 86% in 2016, Takahashi et al. (35) reported a 5-year EFS of 78% in 2017 (16,33). Koc et al. (17) reported a 5-year EFS of 69% in 2012, Degirmenci (28) reported a 5-year EFS of 41.51% in 2016 from Turkey. In our study, 5-year estimated EFS was found to be 78%, which was compatible with the literature.

Male sex is reported as a poor prognostic factor in childhood leukemias (8). The 5-year OS for female and male pediatric ALL patients was reported as 86%, and 70%, respectively, by Hussein et al. (29). The 5-year OS for children with ALL was 76% in girls and 66% in boys in the study by Koc et al. (17). In our study, although the follow-up period was shorter, 5-year estimated OS was 93% in girls and 86% in boys. Möricke et al. (20) reported a 6-year EFS of 81% in girls and 78% in boys in 2,169 pediatric ALL patients treated with the BFM-95 protocol . In the multicenter study by Pui et al. (34), 5-year EFS was 76% in girls and 68% in boys. Takahashi et al. (35) reported a 5-year EFS of 79% for girls and 81% for boys. In a study conducted in Edirne, Turkey, 5-year EFS was reported as 81% in girls and 49% in boys (27). In our study, the 5-year of EFS was 84% in female ALL cases, and 80% in male ALL cases. The 5-year OS and EFS was higher in both boys and girls than that has been reported in the literature. This was likely due to a short follow-up time.

In the study by Takahashi et al. (35), 5-year of OS for SRG, MRG and HRG patients was 96%, 91%, and 81%, respectively. Five-year OS for SRG, MRG and HRG patients was reported as 81%, 79%, and 60%, respectively, in the south eastern region of Turkey (17). In our study, 5-year OS was found to be 94%, 93%, and 59%, for SRG, MRG and HRG patients, respectively, which was compatible with the literature.

In the study by Schrappe et al. (5), EFS rates for SRG B-cell ALL, MRG B-cell ALL, and HRG B-cell ALL, were as 85%, 82%, and 34%, respectively, in 2178 pediatric ALL patients treated by the BFM-90 protocol. In the Takahashi et al. (35) study, EFS rates were found as 87%, 78%, and 65% in SRG, MRG, and HRG patients, respectively. In 2012, Steel et al. reported a 100% EFS rate in SRG, a 57% EFS in MRG and a 55% EFS in HRG B-cell ALL patients, respectively, whereas Koc et al. (17) reported a 76% EFS in SRG, a 69% EFS in MRG and a 53% EFS in HRG B-cell ALL patients, respectively. In our study, 5-year EFS for SRG, MRG, and HRG B-cell ALL patients was found to be 94%, 87%, and 50%, respectively.

In the studies by Bajel et al. (36) and Jabeen et al. (19), CNS involvement rates in ALL were reported as 6.2% and 11%, respectively. There were no patients with CNS involvement in 78 ALL cases reported by Dujua and Hernandez (16). In our country, CNS involvement rate was reported as 1.4% in the studies of Hazar et al. (18). In this study, there were no

patients with CNS involvement at the time of diagnosis among pediatric ALL patients.

In recent pediatric ALL trials, 5-year EFS and OS for B-cell ALL is reported as more than 85% and more than 90%, respectively, however outcomes for T-cell ALL are still 5%-10% lower than B-cell ALL in most studies (37). Hussein et al. (29) reported a 5-year OS of 80% in B-ALL and a 5-yea OS of 60.2% in T-ALL. In the study by Schmiegelow et al. (32), 5 years EFS and OS for B-cell ALL and T-cell ALL were 90% and 66%, respectively. Horibe et al. (38) reported a 5-year OS of 90% in B-ALL patients. Takahashi et al. (35) reported a 92% OS in B-ALL and a 72% OS in T-ALL. In our study, 5-year OS for B-cell ALL was 83%, which was similar to the literature, whereas it was 88% in T-cell ALL, a high survival rate compared to literature, probably due to the small number of T-cell ALL cases and the short follow-up period.

Event free survival for B-cell ALL and T-cell ALL was reported between 72 and 80% and 47%-62%, respectively, in various studies (29,35,38). In our country, Orhaner (27) reported a 70% EFS in B-cell ALL and a 50% EFS in T -cell ALL. In this study, 5-year estimated EFS for B-cell ALL was 83%, and was 57% in T-cell ALL. In the T-cell ALL, a high rate of EFS could not be achieved due to relapse and secondary leukemias.

Study Limitations

There are some limitations to the current study. First, it was a retrospective study a relatively small number of patients. A significant part of the patient data was obtained from patient files. Second, the follow-up time is short. Despite these limitations, we believe that this study's results are important in terms of being the first study of our pediatric hematology and oncology clinic to reveal treatment and toxicity outcomes in patients with ALL.

Conclusion

This study showed that the acute toxicity rate associated with childhood ALL treatment in our center was low with the current median follow-up period. The survival of children with ALL who were classified in standard and intermediate groups were good. However, the current study' results should be confirmed in a larger patient population and in a longer follow-up period.

Ethics

Ethics Committee Approval: Ethics Committee approval was obtained from the University of Health Sciences Turkey, Kanuni Sultan Suleyman Training and Research Hospital (no: 2018/03, decision no: KAEK/20 l8,3,24).

Informed Consent: Informed consent was obtained.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: A.A., Design: A.A., Data Collection or Processing: O.Ö., A.A., S.T., E.P.U., M.G., C.B., Analysis or Interpretation: O.Ö., A.A., Literature Search: O.Ö., A.A., Writing: O.Ö., A.A.

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

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Kutluk T, Yesilipek MA. Turkish National Pediatric Cancer Registry 2002-2008 (Turkish Pediatric Oncology Group and Turkish Pediatric Hematology Society). Pediatr Blood Cancer 2013;(Suppl 15):10067-10067.
2. Hutter JJ. Childhood leukemia. Pediatr Rev 2010;31:234-241.
3. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 2014;64:83-103.
4. Ness KK, Armenian SH, Kadan-Lottick N, Gurney JG. Adverse effects of treatment in childhood acute lymphoblastic leukemia: general overview and implications for long-term cardiac health. Expert Rev Hematol 2011;4:185-197.
5. Schrappe M, Reiter A, Ludwig WD, et al. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90. German-Austrian-Swiss ALL-BFM Study Group. Blood 2000;95:3310-3322.
6. Pui CH, Robison LL, Look AT. Acute lymphoblastic leukaemia. Lancet 2008;371:1030-1043.
7. Stary J, Zimmermann M, Campbell M, et al. Intensive chemotherapy for childhood acute lymphoblastic leukemia: results of the randomized intercontinental trial ALL IC-BFM 2002. J Clin Oncol 2014;32:174-184.
8. Bhojwani D, Yang JJ, Pui CH. Biology of childhood acute lymphoblastic leukemia. Pediatr Clin North Am 2015;62:47-60.
9. Gurney JG, Severson RK, Davis S, Robison LL. Incidence of cancer in children in the United States. Sex-, race-, and 1-year age-specific rates by histologic type. Cancer 1995;75:2186-2195.
10. Celkan T. Acute lymphoblastic leukemia; in: Ozkan A (ed), Pediatric Oncology, Nobel Medical Bookstore, Istanbul, 2009, pp 451-462.
11. National Cancer Institute. SEER Cancer Statistics Review, 1975-2006. Available from: http://seer.cancer.gov/csr/1975-2006/
12. Spector LG, Ross JA, Robison LL, et al. Epidemiology and etiology, in: Pui CH (ed). Childhood leukemias. New York: Cambridge University Press, 2006, pp 48-66.
13. Ishii E, Eguchi H, Matsuzaki A, et al. Outcome of acute lymphoblastic leukemia in children with AL90 regimen: impact of response to treatment and sex difference on prognostic factors. Med Pediatr Oncol 2001;37:10-19.
14. Spallek J, Spix C, Zeeb H, Kaatsch P, Razum O. Cancer patterns among children of Turkish descent in Germany: a study at the German Childhood Cancer Registry. BMC Public Health 2008;8:152.
15. Atay AA, Kürekçi AE, Kesik V, et al. Akut lenfoblastik lösemili olgularýmýzýn retrospektif Analizi. Gulhane Med J 2005;47:183-186.
16. Dujua AC, Hernandez FG. Survival outcome of Filipino children with acute lymphoblastic leukemia treated with modified Berlin-Frankfurt-Muenster/Hong Kong acute lymphoblastic leukemia (BFM95/HKALL97) protocol in a tertiary general hospital from January 2005 to December 2009: a retrospective cohort study. J Pediatr Hematol Oncol 2017;39:e116-e123.
17. Koc A, Aycicek A, Ozdemir ZC, Soker M, Varma M. Outcome of modified St Jude total therapy 13A for childhood acute lymphoblastic leukemia in the southeast region of Turkey. J Pediatr Hematol Oncol 2013;35:36-41.
18. Hazar V, Karasu GT, Uygun V, Akcan M, Küpesiz A, Yesilipek A. Childhood acute lymphoblastic leukemia in Turkey: factors influencing treatment and outcome: a single center experience. J Pediatr Hematol Oncol 2010;32:e317-322.
19. Jabeen K, Ashraf MS, Iftikhar S, Belgaumi AF. The impact of socioeconomic factors on the outcome of childhood acute lymphoblastic leukemia (ALL) treatment in a low/middle income country (LMIC). J Pediatr Hematol Oncol 2016;38:587-596.
20. Möricke A, Reiter A, Zimmermann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. Blood 2008;111:4477-4489.
21. Dogru Ö. Clinical and prognostic importance of genetic and immunphenotypic properties in acute lymphoblastic leukemias (Medicine Thesis). Istanbul: Istanbul University Cerrahpasa Faculty of Medicine; 2009.
22. Canbolat Ayhan A, Timur C, Kalaycik O. A retrospective analysis of complications observed in children with acute lymphoblastic leukemia during chemotherapy. Minerva Pediatr 2017;69:95-105.
23. Reiter A, Schrappe M, Ludwig WD, et al. Chemotherapy in 998 unselected childhood acute lymphoblastic leukemia patients. Results and conclusions of the multicenter trial ALL-BFM 86. Blood 1994;84:3122-3133.
24. Pérez Martínez A, Alonso Ojembarrena A, Ramírez Orellana M, et al. Veinte años de experiencia en el tratamiento de la leucemia linfoblástica aguda [Twenty years of treating childhood acute lymphoblastic leukemia]. An Pediatr (Barc) 2006;65:198-204.
25. Schmiegelow K, Attarbaschi A, Barzilai S, et al. Consensus definitions of 14 severe acute toxic effects for childhood lymphoblastic leukaemia treatment: a Delphi consensus. Lancet Oncol 2016;17:e231-e239.
26. Schrappe M, Hunger SP, Pui CH, et al. Outcomes after induction failure in childhood acute lymphoblastic leukemia. N Engl J Med 2012;366:1371-1381.
27. Orhaner BB. Tr All-2000 protocol for the evaluation of acute lymphoblastic leukemia cases (Specialization Thesis). Edirne: Trakya University Faculty of Medicine; 2012.
28. Degirmenci K. Retrospective evaluation of patients diagnosed with acute lymphoblastic leukemia between 2000 and 2014 (Medicine Thesis). Kayseri: Erciyes University Faculty of Medicine; 2016.
29. Hussein H, Sidhom I, Naga SA, et al. Outcome and prognostic factors of acute lymphoblastic leukemia in children at the National Cancer Institute, Egypt. J Pediatr Hematol Oncol 2004;26:507-514.
30. Köse D, Sarper N, Zengin E, Gelen SA. Induction deaths and treatment-related mortality in childhood acute lymphoblastic leukemia with ALL-BFM protocols. Kocaeli Med J 2021;10:30-37.

31. Pui CH, Yang JJ, Hunger SP, et al. Childhood acute lymphoblastic leukemia: progress through collaboration. J Clin Oncol 2015;33:2938-2948.
32. Schmiegelow K, Forestier E, Hellebostad M, et al. Long-term results of NOPHO ALL-92 and ALL-2000 studies of childhood acute lymphoblastic leukemia. Leukemia 2010;24:345-354. Erratum in: Leukemia 2010;24:670.
33. Liu HC, Yeh TC, Hou JY, et al. Triple intrathecal therapy alone with omission of cranial radiation in children with acute lymphoblastic leukemia. J Clin Oncol 2014;32:1825-1829.
34. Pui CH, Pei D, Sandlund JT, et al. Long-term results of St jude total therapy studies 11, 12, 13A, 13B, and 14 for childhood acute lymphoblastic leukemia. Leukemia 2010;24:371-382.
35. Takahashi H, Kajiwara R, Kato M, et al. Treatment outcome of children with acute lymphoblastic leukemia: the Tokyo Children's Cancer Study Group (TCCSG) study L04-16. Int J Hematol 2018;108:98-108.
36. Bajel A, George B, Mathews V, et al. Treatment of children with acute lymphoblastic leukemia in India using a BFM protocol. Pediatr Blood Cancer 2008;51:621-625.
37. Teachey DT, Pui CH. Comparative features and outcomes between paediatric T-cell and B-cell acute lymphoblastic leukaemia. Lancet Oncol 2019;20:e142-e154.
38. Horibe K, Yumura-Yagi K, Kudoh T, et al. Long-term results of the risk-adapted treatment for childhood B-cell acute lymphoblastic leukemia: report from the japan association of childhood leukemia study ALL-97 Trial. J Pediatr Hematol Oncol 2017;39:81-89.