İSTANBUL UNIVERSITY PRESS

Çocuk Dergisi - Journal of Child 2023;23(3):265-269
DOI: 10.26650/jchild.2023.1341346

RESEARCH ARTICLE / *ARAŞTIRMA MAKALESİ*

Adolescent Acute Lymphoblastic Leukemia: A Retrospective Single-Center Experience

Adolesan Akut Lenfoblastik Lösemileri: Geriye Dönük Tek Merkez Deneyimi

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Citation/Atıf: Pasli Uysalol E, Bayram C, Ozdemir N, Akpinar Tekgunduz S, Aydogan G, Aycicek A. Adolescent acute lymphoblastic leukemia: a retrospective single-center experience. Çocuk Dergisi - Journal of Child 2023;23(3):265-269. https://doi.org/10.26650/jchild.2023.1341346

ABSTRACT

Objective: Acute lymphoblastic leukemia (ALL) is one of the most common malignant diseases in children. This study aimed to determine the clinical and prognostic characteristics of adolescent patients with ALL aged 15–18 years who were followed up in our center.
Materials and Methods: The clinical and laboratory characteristics, treatment responses, and survival and relapse rates of adolescent patients with ALL were retrospectively analyzed
Results: The majority of patients were male. The median age of patients was 16 (range 15–17.9) years. About 36% and 74% of patients were diagnosed with T- and B-cell ALLs, respectively. Then, 32% of patients were stratified in the high-risk group. BCR/ABL t (9;22) positivity was detected in one patient. Recurrence was observed in 6 of 31 patients after completing the treatment. The estimated survival rate in the high-risk group at 32 months was 58%.
Conclusion: Ihe prognosis and outcomes of ALL in adolescent and young adult patients are poor compared to younger age groups. Future clinical trials and advance in chemotherapeutic protocols in this age group will help increase the treatment success rates
Keywords: adolescent, leukemia, survival

ÖZ

Amaç: Akut lenfoblastik lösemi (ALL) çocukluk çağında en sık rastlanan habis hastalıklardan biridir. Çalışmamızda merkezimizde ALL tanısı ile takip ve tedavi edilen, 15-18 yaş arası adölesan hastaların klinik ve prognostik özelliklerini belirlemeyi amaçladık.
Gereç ve Yöntem: ALL'li adolesan hastaların klinik ve laboratuvar özellikleri, tedavi yanıtları, sağkalım ve nüks oranları retrospektif olarak analiz edildi.
Bulgular: Hastaların çoğunluğunu erkekler oluşturmaktaydı.Median yaş değeri 16 (15-17,9) yıl idi. Hastaların %32'si yüksek risk grubundaydı ve %26'sı T hücreli ALL %74'ü B hücreli ALL immunfenotipi göstermekteydi. BCRL/ABL t (9;22) pozitifliği bir hastada saptandı. Altı hastamızda tedavi bitimi sonrası nüks görüldü. Yüksek risk grubunda otuz ikinci ayda tahmini sağ kalım oranı %58 idi.
Sonuç: Ergen ve genç yetişkin hastaların prognozu ve sonuçları diğer küçük yaş gruplarından farklı olarak daha kötüdür. Çocukluk çağında kullanılan protokollerin, bu yaş grubuna özel klinik araştırmalarla geliştirilmesi tedavide başarı oranlarının artmasına katkı sağlayacaktır.
Anahtar Kelimeler: adolesan, çocuk, sağkalım

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Submitted/Başvuru: 11.08.2023 • **Accepted/Kabul:** 19.08.2023 • **Published Online/Online Yayın:** 24.10.2023

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is one of the most common malignant diseases in children. Despite the increase in the prevalence of childhood malignancies, the 5-year survival rate in children with ALL has reached 90% in recent reports as a result of advances in chemotherapy and supportive care.[1,2] At the intersection between children and adults, caring for adolescent and young adult patients with ALL reveal challenges beyond those faced by other age groups. The National Cancer Institute defined the adolescent and young adult cancer population as generally between the ages of 15 and 39 years.[1,3] Although the event-free survival rates of adolescent and young adult patients were previously reported as 30–45% compared to young children, this group of patients treated with pediatric-based approaches may have better outcomes with disease-free survival rates of up to 60%–70%.[1] This study aimed to determine the clinical and prognostic characteristics of adolescent ALL patients aged 15–18 years who were diagnosed and treated in our clinic.

MATERIALS AND METHODS

A total of 31 adolescent patients with ALL, who were diagnosed and treated between January 2009 and January 2022 at our Pediatric Hematology Oncology Clinic, were retrospectively examined. The demographic, clinical, and genetic characteristics of patients and the results of the ALLIC-2009 and EsPhALL-10 treatment protocols were evaluated.

Table 1: Demographic and clinical characteristics of the patients

Median age, year	**16 (15-17,9)**
Sex, n (%)	
Male	22 (71)
Female	9 (29)
Immunophenotype, n (%)	
B-cell ALL	23 (74)
T-cell ALL	8 (26)
Central nervous system involvement, n (%)	
Positive	3 (10)
Negative	21 (90)
Chemotherapy protocol, n (%)	
ALLIC-2009	30 (97)
EsPhALL 10	1(3)
Risk group, n (%)	
High	10 (32)
Medium	21 (68)
Standard	0 (0)
Stem cell transplant, n (%)	
Haploidentical	3(10)
Match unrelated donor	3(10)

Definitions [4]

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 Grunwald–Giemsa and was evaluated based on the FAB criteria. The central nervous system (CNS) involvement was defined as the presence of ≥5 lymphoblast/mm^3 in the cerebrospinal fluid (CSF), and traumatic lumbar puncture (LP) was characterized by the presence of >10/mm^3 red blood cells in the CSF. 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, minimal residual disease (MRD) level in the bone marrow on day 15, and t (4;11) or t (9;22) at the time of diagnosis. Patients aged ≥1 to <6 years at the time of diagnosis, with an initial leukocyte count of <20,000/mm^3, with <1,000/mm^3 blasts of the peripheral blood on day 8, with M1/M2 bone marrow in aspiration on day 15, with MRD level of <0.1% (complete remission) on day 15, without Ph_1 + (BCR/ABL+), or with t (4;11) (MLL/AF4+) were classified as the standard-risk group. Patients with absolute blast count of ≥1,000/mm^3 in the peripheral blood on day 8, M3 bone marrow with ≥25% blasts on day 15, FC MRD level of >10% on day 15, with M2/M3 bone marrow on day 33, and, irrespective of treatment response, with Ph_1 + (BCR/ABL+), with t (4;11) (MLL/AF4+), or with hypodiploidy (<45 chromosomes) were classified as the high-risk group. All patients who were not stratified to standard- or high-risk group were classified into the intermediate-risk group.

Complete remission definitions

1-Bone marrow status: M1 bone marrow: Bone marrow aspirate with <5% lymphoblasts, satisfactory cellularity, and signs of regenerating normal hematopoiesis.

2-The absence of localized leukemic infiltrates/masses based on radiologic or clinical findings.

3-Absence of leukemic cells in the CSF obtained by therapeutic LP on day 33.

Relapse definition

Isolated bone marrow recurrence: More than 25% of blasts in the bone marrow after achieving remission with the initial leukemia treatment

Isolated CNS recurrence: The presence of >5/µL nucleated cells and the presence of blasts on microscopic examination after centrifugation of the CSF sample.

The study was approved by the hospital ethics committee (number: 2022.06.186). Patients signed the informed consent form.

Statistical Analysis: Continuous variables are expressed as medians (ranges), and categorical variables as numbers (percentages). Survival analyses were performed using the Kaplan–Meier method with the IBM SPSS 22.0 (IBM Corporation, Armonk, NY, US) program. Event-free survival

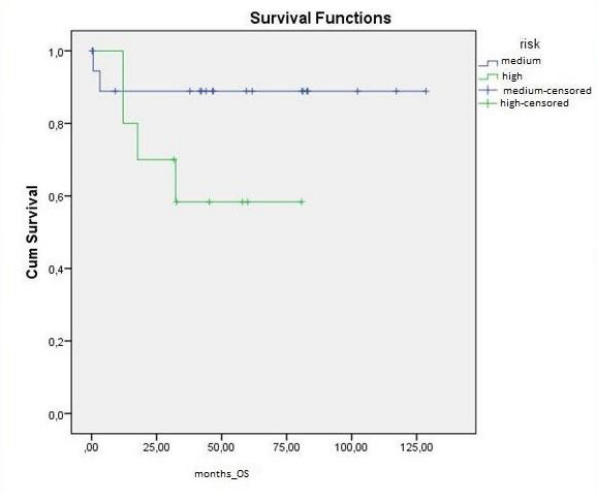

Figure 1: Survival rates by medium (n=21) and high (n=10) risk groups

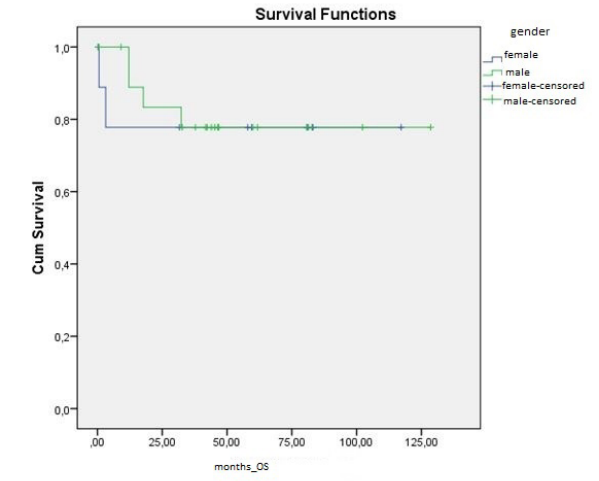

Figure 2: Survival rates by male (n=22) and female (n=9) gender

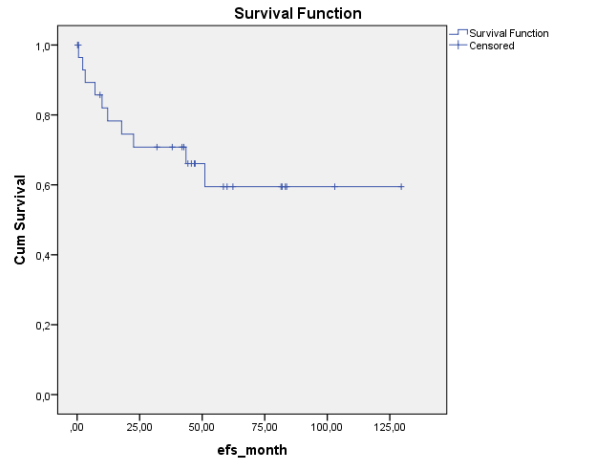

Figure 3: Kaplan-Meier curves of event-free survival (EFS) of all studied patients (n=31)

(EFS) and overall survival (OS) were analyzed using the Kaplan–Meier method and compared with the log-rank (Mantel–Cox) test. OS was defined as the time from the date of diagnosis to death from any cause or last follow-up. EFS were defined as the time from remission until the date of failure (induction failure, relapse or death) or date of the last follow-up.

RESULTS

Of the 31 adolescent patients with ALL, 22 (71%) were males and 9 were females. Their median age was 16 (range, 15–17.9) years. Among them, 10 (32%) were classified in to the high-risk group, and only two (20%) of 10 patients in the high-risk group were females: one due to Philadelphia chromosome positivity and other nine due to the MRD level of >10% and morphologically M3 bone marrow on the 15th day of induction treatment. Demographic and clinical characteristics of the patients are summarized in Table 1. The patient with Philadelphia chromosome positivity was continuously treated with the EsPhALL-10 treatment protocol. A total of 21 of 31 patients were classified into the intermediate-risk group: 8 (26%) with T-cell ALL and 23 with B-cell ALL. Three patients (10%) had CNS involvement at the time of diagnosis. It was observed that the CSF was free of blasts in all of them during treatment. Hematopoietic stem cell transplantation (HSCT) was performed in six patients: from haploidentical donors in three and from a fully matched unrelated donor in the other three. Remission was not achieved in only one patient after the induction therapy. Survival rates were similar between the intermediate- and high-risk groups (p = 0.114) (Figure 1- Survival rates by medium [n = 21] and high [n = 10] risk groups). The estimated survival rate was 58% at the 32-month follow-up in the high-risk group, while it was 89% at the 83-month follow-up in the intermediate-risk group. Survival rates were similar in boys and girls at the 60-month follow-up (p = 0.834) (Figure 2- Survival rates by male [n = 22] and female [n = 9] gender). The 10-month estimated EFS was 82% (Figure 3- Kaplan–Meier curves of event-free survival of all studied patients [n = 31]).

After a median follow-up of 5.2 (range, 0.6–12.2) months, six patients died: three due to sepsis and the others due to acute graft-versus-host disease (GVHD) that developed after HSCT. Of the three patients who died due to acute gastrointestinal GVHD complications, two were transplanted from a haploidentical donor and one from a fully matched unrelated donor. In all six patients, the disease relapsed after the completion of treatment. One of our patients, who was diagnosed at the age of 17 years and 7 months, became pregnant and gave birth to a healthy baby 1 year after the completion of treatment.

DISCUSSION

Adolescents with ALL aged between 15 and 18 years have been historically reported to have inferior survival rates compared to younger children due to an increased rate of induction failure relapses and therapy-related fatalities.[1,3] Thus, adolescent patients with ALL constitute a unique subgroup that still presents specific challenges and needs treatment optimization.[3] Most adolescent patients with ALL have been reported to be

males.[5,6] Compatible with the literature, 71% of patients in the current study were males. Treatment with pediatric protocols in adolescents and young adults with ALL demonstrated a significant survival advantage compared to adult protocols.[1,5,6] In Philadelphia chromosome-positive ALL cases, the outcomes improved after the administration of tyrosine kinase inhibitors together with multiagent chemotherapy.[5,7] The incidence of Philadelphia chromosome-positive ALL is strongly associated with poor outcomes and is found in <3% of ALL patients aged <18 years, although it is one of the most common cytogenetic abnormalities in adult ALLs. The treatment of one patient (3%) with Ph_1 + ALL in our study was continued with the EsPhALL-10 protocol.

ALL in adolescents and young adults accounts for <25% of all ALL cases but causes 80% of ALL-related deaths.[5] Six of our patients (20%) died during treatment: three due to sepsis and three due to acute GVHD after HSCT. Two of the patients who died due to acute gastrointestinal system GVHD were transplanted from a haploidentical and one from a fully matched unrelated donor. While pediatric protocols use higher cumulative doses of drugs, such as asparaginase, vincristine, and steroids, adult protocols more frequently utilize cytarabine and HSCT.[5] Approximately 20% of our patients underwent HSCT, which was more frequent compared to the study by Akhil Rajenda *et al.*[5]

It has been shown that other adverse prognostic features such as intrachromosomal amplification of chromosome 21 and MLL translocation occur more frequently in adolescent and young adult populations.[8] These factors were not encountered in our patient group.

There are a number of biological factors that contribute to low treatment rates in adolescent and young adult patients. T-cell ALL is known to be associated with poor outcomes and occurs in 20–25% of adult ALL cases and 15% in children.[8] Most patients have precursor B (pre-B) ALL, but T-cell ALL is more frequent in the adolescent and young adult groups compared to the pediatric group.[9] In the current study, 8 of 31 patients with ALL (26%) were T-cell ALL and 23 (74%) were B-cell ALL, which was higher as expected than the T-cell ALL ratio compared to younger patients with ALL.

In the analysis results published by the Pediatric Oncology Group, which uses higher-intensity chemotherapy according to the Berlin–Frankfurt–Munster (BFM) protocol, the 5-year OS and EFS rates was reported as 77.5% and 71.5%.[9] Our estimated survival rate at 32 months was 58% in the high-risk group, whereas our survival rate in the medium-risk group was 89% at 83 months. Our estimated EFS rate at 10 months was 82%. Our survival rates at 60-month follow-up were similar in both male and female patients.

In a study by Prasanth Ganesan *et al.*, the presence of BCR-ABL, which was analyzed by reverse transcriptase-polymerase chain reaction or fluorescent in situ hybridization, was detected in 158 of 730 patients.[10] In the current study group, t (9;22) BCRL/ABL positivity was detected only in one patient, and remission was not achieved at the end of induction therapy.

In pediatric patients, the CNS involvement at the time of diagnosis is reported in approximately 3% of cases. It has been reported that this extramedullary leukemia, which manifests itself in the CSF, can be seen in approximately 10% of adolescent and young adult ALL patients.[9] Similarly, in our patient group, three (10%) patients had the CNS involvement at the time of diagnosis, and all patients achieved clearance of blasts from the CSF during the treatment. In the present study, relapse was diagnosed in 6 of 31 patients (19%) after the completion of the treatment, which was lower compared to the literature (40%).[9] All protocols include prophylactic treatment of the CNS to prevent CNS relapse. Some very high-risk cases also require the use of cranial radiation therapy. All studies comparing the cognitive functions in the survivor groups with matched healthy controls report significantly lower scores in the ALL survivor groups.[11] Following cancer treatment, patients often experience late side effects, including the reproductive health problems, which require treatment and follow-up. Male patients who recover from childhood ALL are at a higher risk of long-term infertility, gonadal dysfunction, and poor semen quality due to gonadotoxicity of some treatments, including alkylating agents and testicular irradiation.[12] Many women of reproductive age also desire to have biological children and have cancer. They are concerned that their treatments may affect pregnancy and child health outcomes.[13] While chemotherapy, radiation, and surgical interventions may adversely affect the gametes, they may also affect the uterus and cause comorbidities that affect pregnancy.[13,14] Cyclophosphamide and doxorubicin have the greatest impact on fertility.[15] One of our patient, who was diagnosed at the age of 17 years and 7 months, became pregnant and gave birth to a healthy baby 1 year after the completion of treatment.

The limitation of the current study was the relatively small number of patients.

We think that the development of chemotherapy protocols used in childhood ALL with clinical studies specific to the adolescent age group will contribute to increase the treatment success rates.

Ethics Committee Approval: The study was approved by the Basaksehir Cam and Sakura City Hospital Ethics Committee (Number: 2022.06.186).

Informed Consent: Informed consent was not obtained as it was a retrospective study.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- E.P.U., C.B.; Data Acquisition- E.P.U., G.N.Ö., S.A.T.; Data Analysis/Interpretation- E.P.U., A.A., G.A.; Drafting Manuscript- E.P.U., C..B, N..Ö, S.A.T., G.A., A.A.; Critical Revision of Manuscript- E.P.U., C.B., N.Ö., S.A.T., G.A., A.A.; Final Approval and Accountability- E.P.U., C.B., N..Ö, S.A.T., G.A., A.A.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

Etik Komite Onayı: Çalışma için Basaksehir Cam ve Sakura Şehir Hastanesi Klinik Araştırmalar Etik Kurulu'ndan onay alındı (Numara: 2022.06.186).

Bilgilendirilmiş Onam: Retrospektif bir çalışma olduğu için bilgilendirilmiş onam alınmadı.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Çalışma Konsepti/Tasarım- E.P.U., C.B.; Veri Toplama- E.P.U., G.N.Ö., S.A.T.; Veri Analizi/Yorumlama- E.P.U., A.A., G.A.; Yazı Taslağı- E.P.U., C..B, N.Ö., S.A.T., G.A., A.A.; İçeriğin Eleştirel İncelemesi- E.P.U., C.B, N..Ö, S.A.T., G.A., A.A.; Son Onay ve Sorumluluk- E.P.U., C.B., N.Ö., S.A.T., G.A., A.A.

Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.

Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

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