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Feasibility and Effectiveness of CALGB 10403 protocol in Adolescent and Young Adult Patients with Acute Lymphoblastic leukemia/ Lymphoblastic Lymphoma: A Study at Seyed Al-Shohada Hospital, Isfahan, Iran

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ABSTRACT

Background: Acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) are rare blood cancers with poorer survival in adolescents and young adults (AYAs) than in children. Pediatric-inspired regimens like CALGB 10403 have improved outcomes in AYAs. This study evaluated the effectiveness, feasibility, and treatment-related toxicities of CALGB 10403 in AYAs with ALL/LBL treated at Seyed Al-Shohada Hospital, Isfahan, Iran, from December 2021 to May 2024

Materials and Methods: AYAs aged 17-39 with newly diagnosed ALL/LBL (excluding Burkitt, Ph+, and prior treatment) were included. Baseline characteristics and outcomes of interest (induction response, event-free and overall survivals) were collected. Induction response was assessed via bone marrow (ALL) or CT scan/biopsy (LBL). Minimal residual disease (MRD) was evaluated by flow cytometry. Treatment-related toxicities were monitored and graded per CTCAE criteria. The feasibility of implementing the CALGB 10403 protocol was evaluated by measuring treatment delays.

Results: Seventeen AYA patients with newly diagnosed ALL/LBL (median age 21) were enrolled, mostly male (14/17). Fourteen had ALL, and three had LBL. Extramedullary involvement was seen in 29%, including lymphadenopathy, bulky mediastinal masses, and CNS involvement. Sixteen patients (94%) achieved remission, with no deaths during the induction course. One-year EFS and OS were 77% and 100%, respectively. Common toxicities included hyperbilirubinemia, elevated transaminases, and infections. Treatment delays, mainly from non-adherence, occurred in 53%. Eight patients achieved MRD negativity after Course I.

Conclusion: This study provides insights into the first Iranian experience with the CALGB 10403 protocol for AYAs with ALL/LBL, a regimen that has demonstrated encouraging survival outcomes in U.S. trials.

Keywords: Acute lymphoblastic leukemia (ALL); Lymphoblastic lymphoma (LBL); Adolescents and young adults (AYAs), Pediatric-inspired chemotherapy treatment; CALGB 10403 protocol

INTRODUCTION

Acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) are relatively rare hematologic malignancies characterized by the uncontrolled proliferation of immature lymphoid cells called lymphoblasts. Advancements in treatment have dramatically improved outcomes for children with ALL/LBL, achieving survival rates of approximately 80-90%[1]. However, adolescents and young adults (AYAs), defined as those aged 15 to 39 years, have not experienced the same progress, with survival rates around 30-40%[2]. This disparity highlights the unmet needs in treating ALL/LBL in this age group, a challenge further compounded in settings like Iran, where access to care, resource limitations, and social factors may also influence outcomes.

Previous studies have indicated that the biological behavior of ALL/LBL in AYAs more closely resembles that of pediatrics than that of older adults[3, 4]. As a result, in recent decades, chemotherapy regimens for AYAs with ALL/LBL have transitioned towards pediatric-based treatments, leading to improved survival rates compared to traditional treatment protocols[5]. The key differences between pediatric and traditional adult chemotherapy protocols for ALL and LBL lie in the administration of higher doses of specific chemotherapy agents, such as vincristine and asparaginase derivatives, as well as the implementation of more intensive and extended strategies for the central nervous system (CNS) [6]. The Cancer and Leukemia Group B (CALGB) 10403 protocol, summarized in Table 1, is a recognized treatment regimen for ALL/LBL, comprising five phases: remission induction, consolidation, interim maintenance, delayed intensification, and long-term maintenance[5]. This study aimed to assess the effectiveness of the CALGB 10403 regimen in treating AYAs with newly diagnosed ALL/LBL referred to Seyed-Al-Shohada Hospital in Isfahan, Iran. To this end, the initial induction response, as well as event-free and overall survival, were analyzed. Secondary objectives included evaluating the feasibility of protocol utilization, assessing possible treatment-related toxicities, and adherence to the protocol.

This study could potentially inform clinical practice in Iran and contribute to improved treatment strategies and outcomes for AYA patients with ALL/LBL. The findings will add to the existing knowledge base and help optimize treatment approaches for this vulnerable population.

Table 1: Details of CALGB 10403 treatment protocol

Phases	Duration	Medications, Dosage, Administration route, and Schedule
Remission Induction (Course I)	29 days	* Allopurinol: 300 mg/day (unless allergic), continue until peripheral blasts and extramedullary disease are reduced * Pred: 60 mg/m²/day, PO in two divided doses, on Days 1-28 (Alternative; DEX: 10 10 mg/m², IV in two or three divided doses, on Days 1-28) * Ara-C: 70 mg, IT, on Day 1 * VCR: 1.5 mg/m² (max 2 mg), IV, on Days 1, 8, 15, and 22 * DNR: 25 mg/m², IV, on Days 1, 8, 15, and 22 * PEG: 2500 IU/m², IM, on Day 4 * MTX: 15 mg, IT, on Days 8 and 29 (also on Days 15 and 22 for CNS3)
**If required Extended Remission Induction (Course IA)	14 days	* Pred: 60 mg/m²/day, PO in two divided doses, on Days 1-14 (Alternative; DEX: 10 10 mg/m², IV in two or three divided doses, on Days 1-14) * VCR: 1.5 mg/m² (max 2 mg), IV, on Days 1 and 8 * DNR: 25 mg/m², IV, on Day 1 * PEG: 2500 IU/m², IM, on Day 4 * CTX: 1000 mg/m², IV, on Days 1 and 29
Remission Consolidation (Course II)	50 days	* Ara-C: 75 mg/m², IV or SC, on Days 1-4, 8-11, 29-32, and 36-39 * 6-MP: 60 mg/m², PO, on Days 1-14 and 29-42 * VCR: 1.5 mg/m² (max 2 mg), IV, on Days 15, 22, 43, and 50 * PEG: 2500 IU/m², IM, on Days 15 and 43 * MTX: 15 mg, IT, on Days 1, 8, 15, and 22 (omit on Days 15 & 22 for CNS3)
Interim Maintenance (Course III)	41 days	* MTX: Starting dose 100 mg/m², IV, (escalate by 50 mg/m²/dose on Days 1, 11, 21, 31, and 41) * VCR: 1.5 mg/m² (max 2 mg), IV, on Days 1, 11, 21, 31, and 41 * PEG: 2500 IU/m², IM, on Days 2 and 22 * MTX: 15 mg, IT, on Days 1 and 31
Delayed Intensification (Course IV)	50 days	* VCR: 1.5 mg/m² (max 2 mg), IV, on Days 1, 8, 15, 43, and 50 * DEX: 10 mg/m², PO BID, on Days 1-7 and 15-21 * DOX: 25 mg/m², IV, on Days 1, 8, and 15 * PEG: 2500 IU/m², IM, on Days 4 and Day 43 * CTX: 1000 mg/m², IV, on Day 29 * Ara-C: 75 mg/m², SC, on Days 29-32 and 36-39 * 6-TG: 60 mg/m²/day, PO, on Days 29-42 * MTX: 15 mg, IT, on Days 1, 29, and 36
Maintenance* (Course V)	84 days	* VCR: 1.5 mg/m² (max 2 mg), IV, on Days 1, 29, and 57 * DEX: 6 mg/m²/day, PO in 2 divided doses every 4 weeks, on Days 1-5, 29-33, and 57-61 * 6-MP: 75 mg/m²/day, PO, on Days 1-84 * MTX: 15 mg, IT, on Day 1 (also given on Day 29 of the first 4 courses of maintenance) * MTX: 20 mg/m², PO weekly, on Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78 (held on Day 29 of the first 4 courses of maintenance when IT-MTX is given)

***** Maintenance therapy is a 12-week course that should be followed for 3 years in male and 2 years in female patients from the start of interim maintenance phase.

While patients with precursor T-cell ALL received a total of 24 Gy of prophylactic cranial irradiation (PCI) during the first cycle of maintenance therapy, those with central nervous system (CNS) involvement were administered a total of 18 Gy at the time of presentation.

Pred: Prednisone; **Ara-C:** Cytarabine; **VCR:** Vincristine; **DNR:** Daunorubicin; **PEG:** Pegaspargase; **MTX:** Methotrexate; **CTX:** Cyclophosphamide; **6-MP:** 6-Mercaptopurine; **DEX:** Dexamethasone; **DOX:** Doxorubicin; **6-TG:** 6-Thioguanine; **IT:** intrathecally; **PO:** per os (orally); **SC:** subcutaneous; **BID:** *bis in die* (twice a day).

MATERIALS AND METHODS

Study design and participants

This prospective study was conducted on older adolescents and young adults diagnosed with newly diagnosed Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (LBL) who were treated based on CALGB 10403 chemotherapy protocol at Seyed-Al-Shohada Hospital from December 2021 to May 2024.

Participants aged 17-39 years with a performance status of 0-2 were included. Patients were excluded if they had a Burkitt immunophenotype, Philadelphia chromosome-positive leukemia (Ph^+), or prior ALL/LBL treatment. Exceptions were made for those who had received emergency corticosteroids or hydroxyurea for conditions such as hyperleukocytosis, superior vena cava syndrome, or renal failure due to leukemic infiltration of the kidneys, as well as for those who had received a single dose of intrathecal chemotherapy [7].

Ethical consideration

The study was ethically approved by the Ethics Committee of Isfahan University of Medical Sciences (Reference number: IR.MUI.MED.REC.1402.160) and performed in accordance with the Declaration of Helsinki and its later amendments. Participants were assured that their participation was voluntary and that declining to participate or withdrawing from the study would not negatively impact their treatment. Prior to enrollment, written informed consent was obtained from all eligible patients.

Data collection

For all eligible participants, the following baseline characteristics were collected: age, sex, body mass index (BMI), performance status, disease subtypes and immunophenotypes, cytogenetics, extramedullary involvement, white blood cell (WBC) and platelet (PLT) counts and hemoglobin (HGB) levels. Outcomes of interest, including induction response rate, event-free survival (EFS), and overall survival (OS) were obtained. In fact, for patients with ALL, induction response was evaluated by analyzing bone marrow after either induction or extended induction Course. A response was defined using modified (M) bone marrow criteria, where achieving M0 or M1 status (meaning ≤5% blast cells) indicated a successful response. In contrast, for patients with LBL, at the end of Course I, a remission response was evaluated by conducting a CT scan, according to response evaluation criteria in solid tumors (RECIST) criteria, and subsequent biopsy of the residual mass. EFS was defined as the time from registration in this study to the earliest occurrence of any of the following events: failure to achieve a bone marrow response by day 60, death, relapse at any site, or the development of a second malignant disease. Overall survival (OS) was defined as the time from registration to death resulting from any cause [7].

To determine the effectiveness of treatment and prognosis in patients with ALL, minimal residual disease (MRD), a measure of the number of remaining leukemia cells following treatment, was assessed by three-color flow cytometry at the end of Course I. The MRD negativity was defined as detecting ten or fewer leukemia cells per 10,000 leukocytes ($MRD \leq 10^{-3}$). For patients achieving MRD negativity, surveillance MRD assessments were typically conducted at 3 to 6-month intervals. In contrast, for those with a positive MRD result, the follow-up assessments were performed at the end of each subsequent course until MRD negativity was achieved. Furthermore, in cases of suspected relapse, based on clinical symptoms or periodic complete blood count with differential (CBC-Diff) findings, MRD assessment was repeated.

Treatment-related toxicities per each course were closely monitored, documented, and graded using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, developed by the National Cancer Institute, and medically managed as appropriate.

The feasibility of implementing the CALGB 10403 protocol was evaluated by measuring treatment delays (in days).

Statistical analysis

Data were analyzed by SPSS (v 26.0) and survival curves were generated with GraphPad Prism (v 8.0). Categorical variables were reported as counts (percentages), while quantitative variables were expressed as medians. Survival analysis was conducted using the Kaplan-Meier method to

evaluate event-free survival (EFS) and overall survival (OS). A log-rank test was utilized to compare EFS and OS between male and female participants, as well as among age groups. Statistical significance was defined as $p < 0.05$.

RESULTS

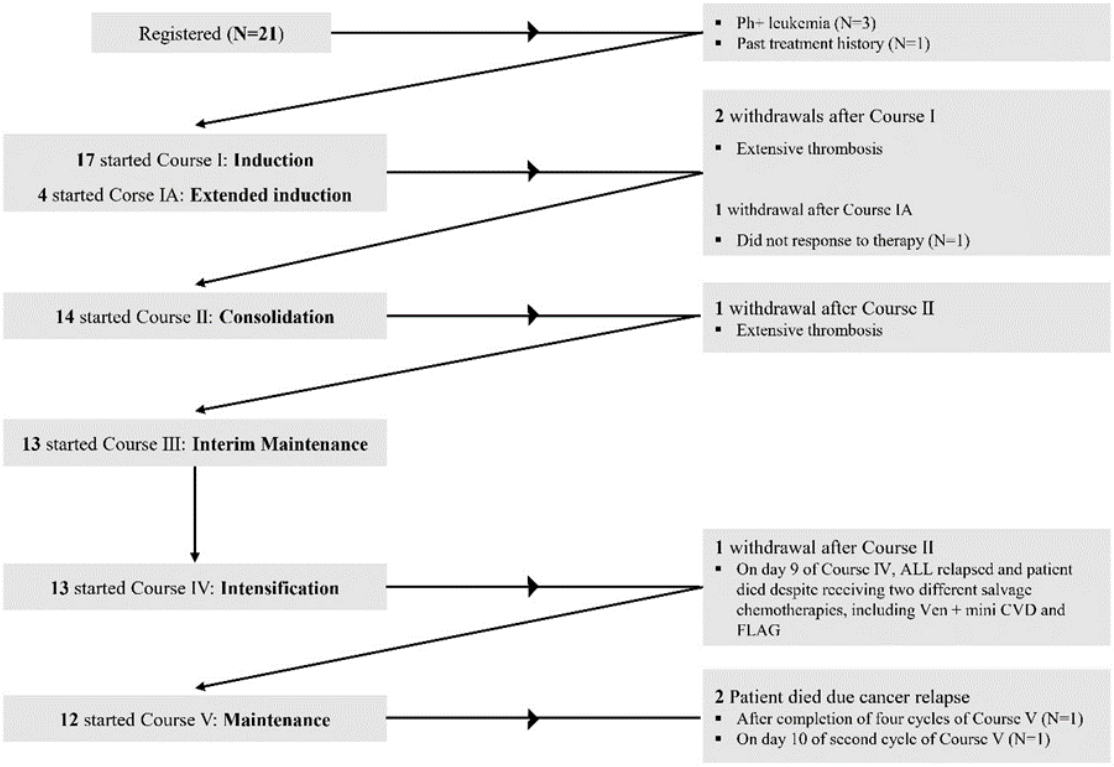

Figure 1. Patient enrollment and progression through treatment courses

As illustrated in Figure 1, 21 patients were registered between December 26th, 2021, and May 20th, 2024. After excluding three patients, 17 individuals remained eligible for the study, whose baseline characteristics are summarized in Table 2. The median age was 21 years, with an age range of 16 to 38 years. The patients were classified into three distinct age groups: 16 to 20 years, 21 to 29 years, and 30 to 39 years. The majority of eligible patients were male, comprising 14 individuals. Among participants, 14 were diagnosed with ALL and only three patients were Lymphoblastic Lymphoma cases. As indicated in Table 2, extramedullary involvement was found in five patients (29.41%), all of whom exhibited lymphadenopathy. Among them, four presented with bulky mediastinal masses, and two had central nervous system (CNS) involvement. Specifically, all three patients diagnosed with T-lymphoblastic lymphoma demonstrated both lymphadenopathy and bulky mediastinal masses. CT scans for two of these patients showed only pleural effusion, one of whom also had CNS involvement, while another patient displayed both pleural and pericardial effusions. Additionally, lymphadenopathy was present in 2 out of 14 patients with ALL. Of these, one patient had a bulky mediastinal mass measuring 117 x 56 mm along with CNS involvement, while the other did not have a mediastinal mass or CNS involvement but presented with severe bilateral pleural effusion and pericardial effusion. Cytogenetic analysis, available for 13 patients, revealed that 61.54% had a normal karyotype (46, XY), while the remaining patients exhibited various chromosomal abnormalities. All three patients with CNS involvement received 18 Gy of prophylactic cranial irradiation (PCI) at

presentation. One of our patients who was diagnosed with the Early T-cell precursor (ETP) subtype of ALL received a total of 24 Gy of PCI post-Course IV and then underwent allogeneic transplantation.

Table 2: Patient baseline characteristics

Characteristic (N=17)	N (%)
Gender	
Male	14 (82.35%)
Female	3 (17.65%)
Age (yr)	
Median	21
Range	17-38
16-20	7 (41.18%)
21-29	7 (41.18%)
30-39	3 (17.64%)
BMI (kg/m^2)	
Median	23.1
Range	20.0-28.0
Underweight (< 18.5)	0
Normal weight (18.5-24.9)	14 (82.35%)
Overweight (25-29.9)	3 (17.65%)
Obese (> 30)	0
WBC (cells/µL)	
Median	16700
Range	1,500-90,000
Leukopenia (< 4000)	2 (11.76%)
Normal (4000 – 11000)	4 (23.53%)
Leukocytosis (> 11000)	11 (64.71%)
HGB (g/dL)	
Median	9.3
Range	6-14.3
anemia (Female < 12, Male< 13)	15 (88.24%)
Normal (Female: 12-16; Male: 14-18)	2 (11.76%)
Platelet (cells/µL)	
Median	51,000
Range	21,000-330,000
Thrombocytopenia (< 150,000)	13 (76.47%)
Normal (150,000-450,000)	4 (23.53%)
Thrombocytosis (> 450,000)	0
Extramedullary involvement	
Lymphadenopathy	5 (29.41%)
CNS involvement	3 (17.65%)
Mediastinal involvement	4 (23.53%)
Performance status	
0	8 (47.06%)
1	8 (47.06%)
2	1 (5.88%)
Types of Disease & Subtypes	
Lymphoblastic lymphoma (LBL)	3 (17.65%)
T- LBL	3 (100%)
B- LBL	0
Acute lymphoblastic leukemia (ALL)	14 (82.35%)
Early pre-B ALL	4 (28.57%)
Pre-B ALL	4 (28.57%)
Pro-B ALL	3 (21.43%)
Early pre-T ALL	1 (7.10%)
T ALL	2 (14.29%)
Cytogenetics (N= 13)	
46, XY	8 (61.54%)
46, XY, t (12;17), t (3;8)	1 (7.69%)
46, XX	2 (15.38%)
54 XXY, der16, t (1;4), der 4	1 (7.69%)
46 XX/58 XX, t (1;6), t (4;12), t (12p), +3, +4, +6, +15, +18, +21	1 (7.69%)

Remission induction

In our study, we found that 16 patients (94%), notably 13 out of 14 patients with ALL and all patients with LBL, achieved an initial remission response. No death occurred during an induction or extended induction Course. Notably, among those patients who achieved remission, two later underwent allogeneic bone marrow transplantation.

Survival analysis

In survival analysis, the median is defined as the time at which 50% of the population has experienced the event of interest. In this study, the events of interest were the occurrence of any pre-defined EFS event and death for OS. As shown in Figure 2A and Figure 3A, neither the median event-free survival (EFS) nor the median overall survival (OS) was reached, as the survival probabilities remained above 50%. However, the estimated one-year and two-year EFS rates were 77% (95% CI: 43% to 92%) and 61.54% (95% CI: 23% to 85%), respectively. The estimated one-year OS was 100%, while the two-year OS was 77% with a 95% CI of 28.5% to 87.87%.

A log-rank test revealed no statistically significant differences between male and female participants in either EFS or OS (Figure 2B and Figure 3B, respectively). The test results indicated $\chi^2 = 1.24$, df = 1, p = 0.26 for EFS and $\chi^2 = 1.30$, df = 1, p = 0.25 for OS. Regarding female participants, the median EFS and median OS were 675 days and 823 days, respectively; conversely, the median EFS and median OS for male participants were not reached. Furthermore, the same analysis for the age groups demonstrated that there were no statistically significant differences in EFS (Figure 2C) or OS (Figure 3C) among the three age categories (16-20 years, 21-29 years, and 30-39 years), as indicated by the log-rank test results of $\chi^2 = 0.696$, df = 2, p = 0.71 for EFS and $\chi^2 = 1.025$, df = 2, p = 0.60 for OS. The median EFS and median OS for the 21-29 age group were recorded at 675 days and 823 days, while the medians for the 16-20 and 30-39 age groups were not reached.

MRD

As presented in Table 3, MRD was assessed for 13 out of 17 patients. Eight patients (61.5%) achieved minimal residual disease (MRD) negativity following the induction course, with MRD levels at or below 10^{-3}. Notably, disease relapse did not occur among them. Unfortunately, the CALGB 10403 protocol was suspended for two of these patients due to severe treatment-related toxicity occurring during Course I. Of the six remaining patients, four maintained negative MRD levels during surveillance. One of these four patients, despite maintaining MRD negativity from Course I through IV, underwent bone marrow transplantation before Course V. The other two patients experienced fluctuating MRD levels before achieving negativity during Course V.

Of the five patients who did not achieve MRD negativity after the initial course of treatment, three patients (60%) remained MRD-positive in subsequent evaluations, with two of these patients experiencing relapse. One patient successfully reached MRD negativity by the end of course II; however, treatment was subsequently discontinued due to the emergence of severe thrombosis. Fluctuating MRD levels were observed in the last patient before MRD negativity was achieved during Course V.

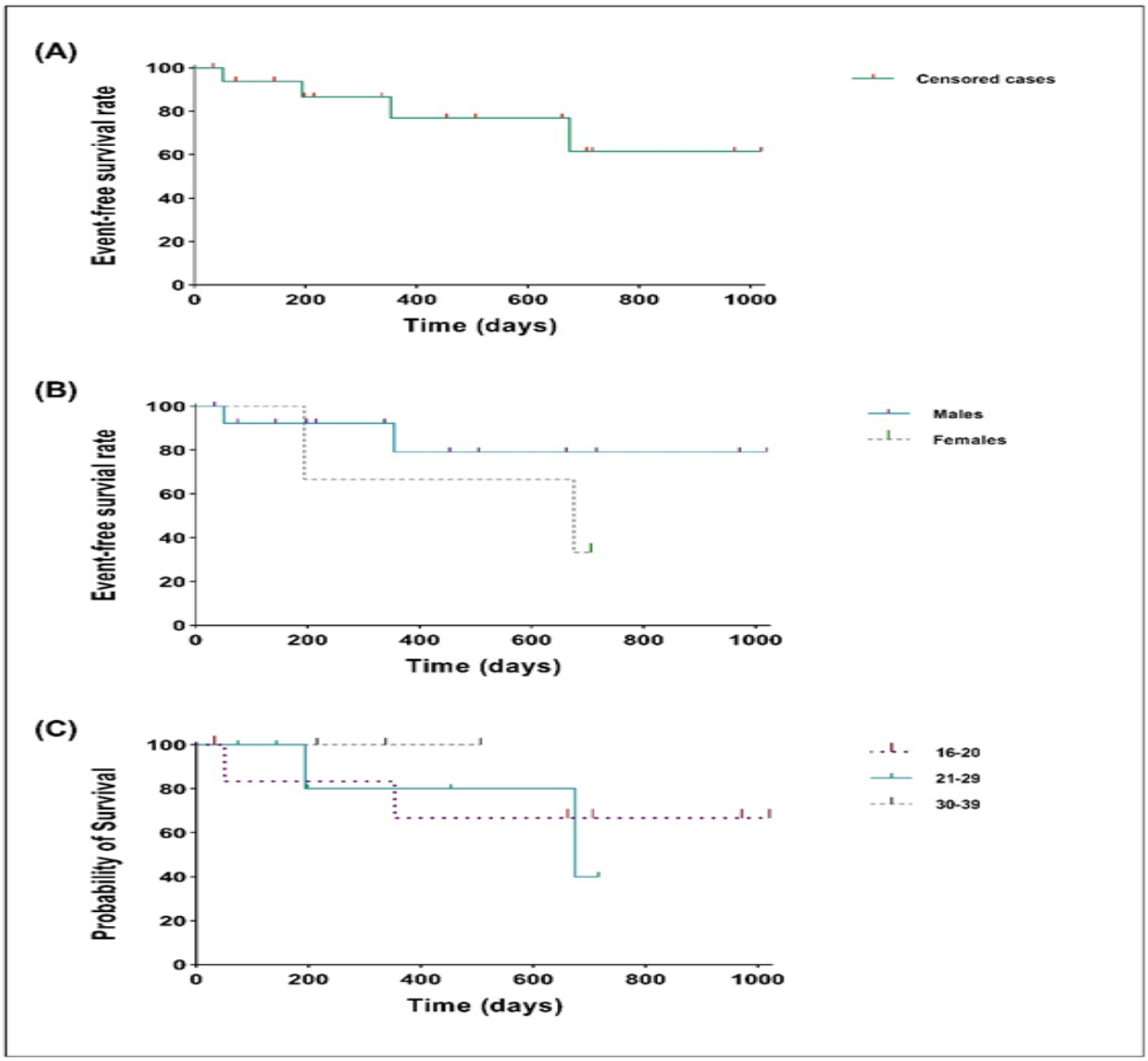

Figure 2. Event-free survival analysis. (A): Event-free survival probability over time for all patients, with censored observations marked; (B) Event-free survival stratified by sex (males vs. females); (C) Probability of event-free survival stratified by age group (16-20, 21-29, 30-39 years)

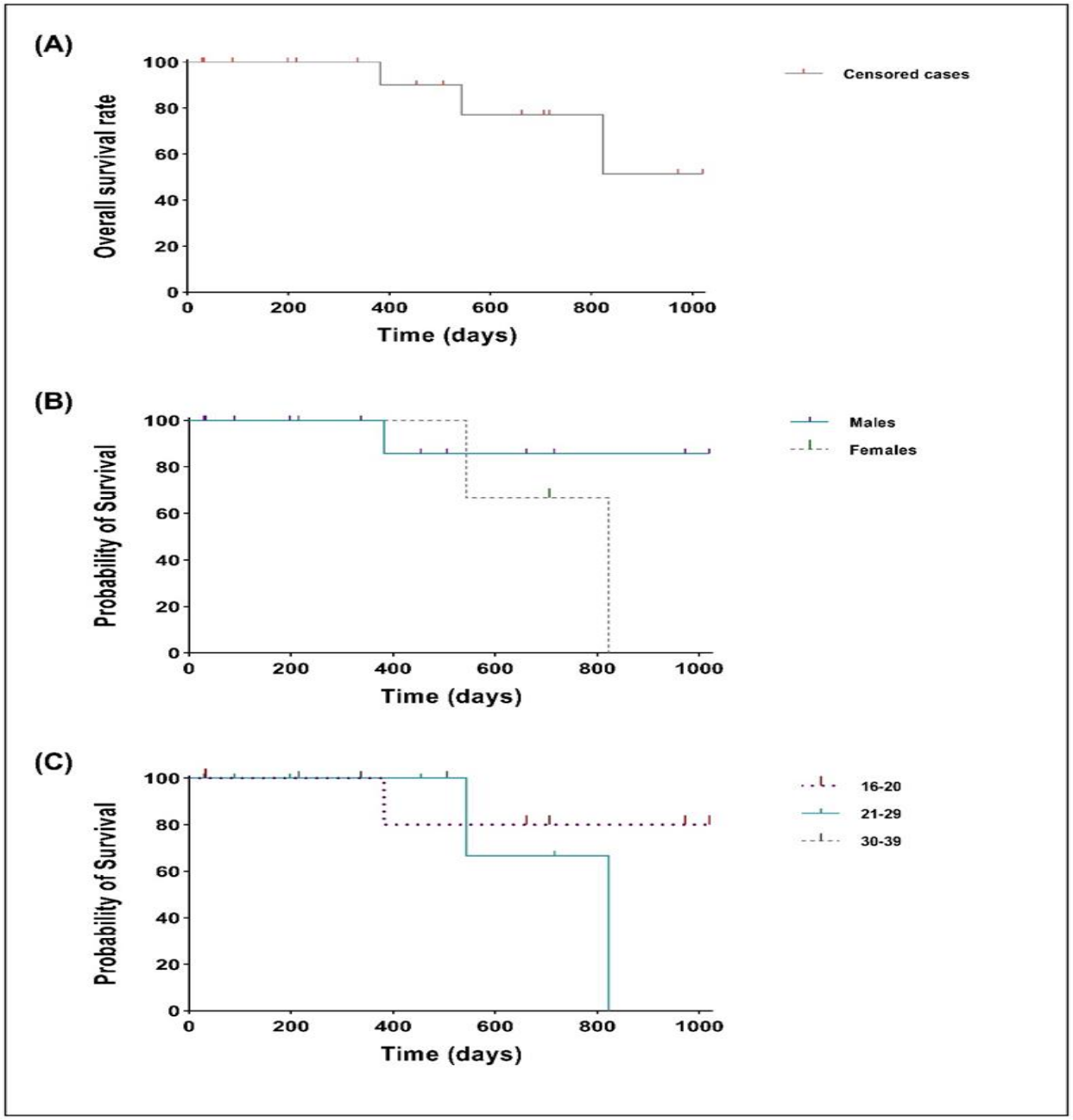

Figure 3. Overall survival analysis. (A): Overall survival for the entire cohort, with censored cases indicated; (B) Overall survival stratified by sex (males vs. females).; (C) Probability of overall survival stratified by age group (16-20, 21-29, 30-39 years)

Table 3: Serial MRD assessments

Patient ID	After C1	After C1A	After C2	After C3	After C4	During C5
PN-01	1.5×10^{-2}	4×10^{-3}	NA	NA	2×10^{-3}	2×10^{-3}
PN-02	$< 10^{-5}$					
PN-03	$< 10^{-3}$	NP	$< 10^{-3}$	NA	$< 10^{-3}$	NA
PN-04	2×10^{-3}	NP	10^{-3}			
PN-05	10^{-3}	NP	NA	10^{-3}	NA	10^{-3}
PN-06	10^{-3}	NP				
PN-07	10^{-3}	NP	10^{-3}	10^{-3}	10^{-3}	#
PN-08	$<10^{-5}$	NP	10^{-3}	NA	4×10^{-3}	10^{-3}
PN-09	10^{-3}	NP	NA	NA	10^{-3}	NA
PN-11	5×10^{-3}	10^{-3}	NA	10^{-3}	3×10^{-3}	10^{-3}
PN-12	6×10^{-3}	NP	NA	8×10^{-3}	3×10^{-3}	Relapse
PN-15	10^{-3}	NP	NA	NA	3×10^{-3}	10^{-3}
PN-16	5×10^{-3}	3×10^{-3}	3×10^{-3}	NA	Relapse	

C: Course; NA: not assessed; NP: not performed
Black-filled cells indicate treatment discontinuation

Adverse events

Table 4 presents a comprehensive summary of the incidence and severity of adverse events, graded according to the Common Terminology Criteria for Adverse Events (CTCAE), observed throughout the courses of the CALGB 10403 protocol. In summary, during Course I, the most prevalent adverse events were hyperbilirubinemia (47%) and elevated transaminases (30%). There was a notable reduction in the frequency of these adverse events during the post-remission treatment. In Course II, infections as well as fever and neutropenia were more frequently reported. The incidence of Grade 3 diarrhea in one of our patients, which occurred two days following the completion of Course II, resulted in an additional four-day hospitalization. In Courses III and IV, infections emerged as the most commonly reported adverse events, with 46% of patients experiencing Grade 1 infections and 15% presenting with Grade 2 infections. Furthermore, renal impairment, indeed elevated creatinine serum levels, and pancreatitis were exclusively noted in Course III, while seizures occurred just in Course IV.

Although no hemorrhage was recorded in Course I, on day 23 of Course II, one of patients experienced a Grade 3 intracerebral hemorrhage (ICH) along with Grade 3 cerebral venous thrombosis (CVT). Additionally, another patient presented with epistaxis, which was graded as 1 during Course IV.

Overall, the most frequently observed adverse events across all courses included infections, hyperbilirubinemia, and fever and neutropenia, followed by elevated transaminases.

The occurrence of CVT, Grade 3 necessitated the discontinuation of the CALGB 10403 protocol for three patients—two in Course I and one in Course II—resulting in the initiation of a hyper CVAD regimen (Cytarabine, Vincristine, and Daunorubicin). One of these patients underwent a matched unrelated donor (MUD) allogeneic hematopoietic stem cell transplant (HSCT) 6.5 months after starting the hyper-CVAD treatment. As of the last follow-up on January 12, 2024, this patient had achieved complete remission with minimal residual disease (MRD) negativity; however, their subsequent status is unknown. The other two patients achieved complete remission after the hyper-CVAD regimen and subsequently started POMP maintenance therapy (prednisone, vincristine, 6-mercaptopurine, and pyrimethamine). By the study's data cutoff on December 21, 2024, one of these patients was waiting for a suitable donor for allogeneic HSCT.

Table 4: Severity of adverse events, classified as mild (Grade 1), moderate (Grade 2), or severe (Grade 3)

Adverse Event	N (%)											
	Course I (N= 17)			Course II (N=14)			Courses III & IV (N= 13)			Overall (N = 17)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Allergic reaction	2 (12%)	1 (6%)	0	1 (7%)	0	0	0	0	0	3 (18%)	1 (6%)	0
Elevated transaminases	2 (12%)	3 (18%)	0	0	1 (7%)	0	1 (8%)	1 (8%)	0	3 (18%)	5 (29%)	0
hyperbilirubinemia	5 (30%)	3 (18%)	0	0	1 (7%)	0	0	1 (8%)	0	5 (29%)	5 (29%)	0
Renal impairment/ creatinine elevation	0	0	0	0	0	0	1 (8%)	1 (8%)	0	1 (6%)	1 (6%)	0
Fever and neutropenia	1 (6%)	2 (12%)	0	0	1 (7%)	3 (21%)	0	0	1 (8%)	*1 (6%)	3 (18%)	5 (29%)
Infection	0	1 (6%)	1 (6%)	1 (7%)	3 (21%)	0	6 (46%)	2 (15%)	0	*8 (47%)	6 (35%)	1 (6%)
Hyperglycemia	2 (12%)	0	0	2 (14%)	0	0	0	0	0	4 (24%)	0	0
Hypertriglyceridemia	0	0	0	0	0	0	0	0	0	0	0	0
Hemorrhage	0	0	0	0	0	1 (7%)	1 (8%)	0	0	1 (6%)	0	1 (6%)
Mucositis	1 (6%)	0	0	1 (7%)	0	0	1 (8%)	0	1 (8%)	3 (18%)	0	1 (6%)
Neuropathy	3 (18%)	0	0	0	0	0	0	0	0	3 (18%)	0	0
Arrhythmia	0	0	0	0	0	0	0	0	0	0	0	0
Pancreatitis	0	0	0	0	0	0	0	1 (8%)	0	0	1 (6%)	0
Thrombosis	0	1 (6%)	2 (12%)	0	0	1 (7%)	0	1 (8%)	0	0	2 (12%)	3 (18%)
Tumor lysis syndrome (TLS)	0	0	0	0	0	0	0	0	0	0	0	0
Thrombocytopenia	0	0	0	0	0	1 (7%)	0	0	1(8%)	0	0	2 (12%)
Diarrhea	0	0	1 (6%)	0	0	1 (7%)	0	0	0	0	0	2 (12%)
Seizure	0	0	0	0	0	0	1(8%)	0	0	1 (6%)	0	0

Percentages are rounded to the nearest whole number.
*In Course V, one of the 12 patients (8.33%) experienced adverse events, including fever and neutropenia (Grade 3) and an infection (Grade 1). This case was included in the overall column statistics.
Six days post-completion of Course IV, one of our patients presented with a dental abscess. This event was not considered an adverse event as defined by CTCAE.

Feasibility assessment

In our study, treatment delays (in days) were attributed to the following three factors: the untimely preparation of pegylated asparaginase (PEG), treatment-related adverse events, and patient non-adherence to scheduled chemotherapy regimens. Of these, patient non-adherence was the most frequent cause of treatment delays, occurring in 53% of patients (9 out of 17), with delays ranging from 2 to 30 days (Table 5). Adverse events thad delayed the regimen included thrombocytopenia, fever and neutropenia, infection, and elevated transaminase.

Table 5: Number of days delayed per course and the status of patients at last follow-up data

Case	Course I	Course IA	Course II	Course III	Course IV	Total	Patient status
1	0	0	0	4	5≈	9	Course V ongoing
2	0					0	Acute adverse events halted protocol
3	0	NP	2	0	0	2	Course V ongoing
4	0	NP	0			0	Acute adverse events halted protocol
5	0	NP	0	0	2	2	Course V ongoing
6	4≈					4	Acute adverse events halted protocol
7	0	NP	0	0	0	0	Allo-transplant prior to Course V
8	0	NP	0	0	0	0	Course V ongoing
9	0	NP	7	30	0	37	Course V ongoing
10	0	0				0	No response to protocol
11	0	0	3≈	0	0	3	Course V ongoing
12	0	NP	7≈	24 (21#+ 3)	2≈	33	Disease relapse followed by death
13	5	NP	12	0	0	17	Course V ongoing
14	0	NP	0	0	0	0	Disease relapse followed by death
15	0	NP	10≈	18 (3#+8+7)	9≈	37	Course V ongoing
16	0	0	19 (4#+12+3)	3	0+	22	Disease relapse followed by death
17	0	NP	11(5≈+2+4≈)	8≈	33 (7#+18+8)	52	Course V ongoing
Total	9	0	71	87	51	218	

The delays due to the inability to prepare Pegaspargase on time are not included.
As none of the patients in this study have fully completed Course V, this table does not account for any potential delays associated with Course V for those patients who have progressed to this stage.
Black-filled cells indicate treatment discontinuation
NP: not performed
≈ The delays in these cases were due to the occurrence of adverse events.
The initiation of the course was delayed, and there were additional postponements during the course itself.
+ Only eight days of this course were completed, and due to a relapse of illness on Day 9, the remaining sessions were discontinued

As outlined in Table 5, these adverse events necessitated a temporary suspension of treatment regimens in 35% of patients, specifically 6 out of 17, resulting in an average delay of 9.5 days. Adverse events were managed through supportive care, dose adjustments, or temporary discontinuation of specific drugs. The delays associated with the preparation of PEG are presented in Table 6. They were mainly due to supply chain issues, which occasionally resulted in the drug being inaccessible at the required times for administration.

Table 6: Number of days delayed due to the inability to prepare Pegaspargase on time

Case	Course I	Course IA	Course II		Course III		Course IV		Total	Patient status
	Day 4	Day 4	Day 15	Day 43	Day 2	Day 22	Day 4	Day 43		
1	1	0	9	0	0	0	0	4	14	Course V ongoing
2	0								0	Acute adverse events halted protocol
3	0		0	0	0	0	0	0	0	Course V ongoing
4	0		3	NR					3+1NR	Course V ongoing
5	0		0	0	0	0	0	0	0	Acute adverse events halted protocol
6	0								0	Allo-transplant prior to Course V
7	0		0	0	0	0	0	0	0	Course V ongoing
8	0		0	0	0	0	0	0	0	Course V ongoing
9	3		14	17	0	NR	NR	0	34+2NRs	No response to protocol
10	0	0							0	Course V ongoing
11	0	0	0	0	NR	0	0	0	1NR	Disease relapse followed by death
12	0		NR	7	NR	0	0	8	15+2NRs	Course V ongoing
13	0		0	0	0	0	0	0	0	Course V ongoing
14	0		0	0	0	0	0	0	0	Disease relapse followed by death
15	0		0	NR	0	NR	0	8	8+2NRs	Course V ongoing
16	0	3	0	0	0	0	NR+		3+1NR	Disease relapse followed by death
17	1		NR	NR	NR	NR	0	NR	1+5NRs	Course V ongoing
Total	5	3	26+2NRs	24+3NRs	0+3NRs	0+3NRs	0+2NRs	20+ 1NR	78+14NRs	

Pegaspargase was administered to the patient immediately upon preparation.
NR: no receive
+ Only eight days of this course were completed, and due to a relapse of illness on Day 9, the remaining sessions were discontinued.

It is important to highlight that when delays were due to the untimely preparation of PEG, the administration of other chemotherapy agents proceeded as scheduled, with PEG being injected promptly upon its availability. In contrast, delays arising from adverse effects or patient non-attendance to treatment schedule resulted in subsequent delays across the entire treatment regimen. An overview of all delays experienced by the subjects participating in the study is provided in Table 7, which indicates that only approximately 24% of patients (n=4) completed the scheduled treatment regimen by the end of Course IV as planned and without any interruptions.

Table 7: Total day delays for each case

Case	Delays due to untimely PEG preparation	Delays due to other reasons	Patient status
1	14	9	Course V ongoing
2	0	0	Acute adverse events halted protocol
3	0	2	Course V ongoing
4	3+1NR	0	Course V ongoing
5	0	2	Acute adverse events halted protocol
6	0	4	Allo-transplant prior to Course V
7	0	0	Course V ongoing
8	0	0	Course V ongoing
9	34+2NRs	37	No response to protocol
10	0	0	Course V ongoing
11	1NR	3	Disease relapse followed by death
12	15+2NRs	33	Course V ongoing
13	0	17	Course V ongoing
14	0	0	Disease relapse followed by death
15	8+2NRs	37	Course V ongoing
16	3+1NR	22	Disease relapse followed by death
17	1+5NRs	52	Course V ongoing

NR: not received

DISCUSSION

Therapeutic approaches for AYAs with ALL/LBL are provided in pediatric or adult cancer settings. Research indicates that adaptation of pediatric ALL/LBL treatments for AYAs is associated with improved outcomes and survival rates compared to adult-based regimens[1-3]. The Cancer and Leukemia Group B (CALGB) 10403 protocol, a pediatric-inspired regimen, was first conducted in the United States and has yielded promising results, with 3-year event-free survival (EFS) and overall survival (OS) of 59% (95% CI, 54%-65%) and 73% (95% CI, 68%-78%), respectively[4]. While this regimen is widely used in the U.S., to the best of our knowledge, this study, conducted at Seyed Al-Shohada Hospital, a leading hematology-oncology center in Iran, is the first effort to implement the CALGB 10403 protocol for the treatment of AYAs with ALL or LBL in Iran.

In ALL, while MRD status is an early prognostic tool for predicting long-term outcomes, the induction response rate is a critical factor for evaluating the early effectiveness of treatment protocols[4, 5]. In our study, 61.5% of patients achieved MRD negativity after Course I, which was notably higher than the rate of 44% reported by Wendy Stock et al[6]. Moreover, 2 out of 5 patients with initial positive MRD experienced disease relapse, which was in line with the previous literature reporting that patients who achieve MRD negativity generally have significantly better outcomes than those who remain MRD positive[5]. Based on our study, it is suggested that the initial assessment of MRD conducted at the end of the induction Course plays a crucial role in making decisions regarding the continuation or discontinuation of treatment protocols for patients with ALL. It is recommended that if MRD negativity is

not achieved after Course I, consideration should be given to bone marrow transplantation, particularly if a fully matched related donor is available, as this can reduce the risk of graft-versus-host disease (GVHD). However, it is important to highlight that MRD positivity at the end of Course I was not necessarily associated with disease relapse. Additionally, our study observed that patients who lost MRD negativity after the induction phase were able to regain it by continuing the treatment regimen through Course V and losing MRD negativity after the induction phase was not associated with disease relapse. Therefore, persistence with the current treatment may be a viable option that could help sustain remission, especially in the absence of a suitable fully matched related donor.

OS and EFS are critical indicators used to evaluate the effectiveness of treatment protocols. In our study, neither median EFS nor median OS was reached during the follow-up period. However, we estimated two-year EFS and OS rates, which were 61.54% (95% CI: 23% to 85%) and 77% (95% CI: 28.5% to 87.87%), respectively. These findings can be compared with those reported by Stock et al. (6), also noting that the median OS was not reached. In contrast to our study, they reported median EFS of 78.1 months (95% CI: 41.8 to not reached). It is important to highlight that Stock et al. evaluated three-year EFS and OS rates, whereas our analysis concentrated on two-year rates due to a shorter follow-up duration in our study.

Treatment-related adverse events are an inevitable challenge in ALL/LBL management. Although the efficacy of the CALGB 10403 protocol has been established, various complications, including hyperglycemia, hepatotoxicity, and febrile neutropenia, have been documented, particularly during the induction phase[6]. These adverse events were largely consistent with those reported in our study. Despite the challenges noted, all adverse events identified in this study were effectively managed without requiring additional hospitalizations or resulting in mortality. Furthermore, 18% of patients experienced severe cerebral venous sinus thrombosis (CVT) during Courses 1 or 2, which represented a substantial proportion. The occurrence of CVT led to the discontinuation of treatment for these individuals; however, the depth of response to the protocol was substantial as these patients achieved MRD negativity following the first course, highlighting the treatment's effectiveness prior to the discontinuation. Considering that the incidence of thrombosis, particularly CVT, constitutes a significant comorbidity that may adversely affect a patient's quality of life, it is recommended to implement proactive measures focused on reducing the risk of thrombosis. Such strategies are likely to enhance patient outcomes and promote overall health.

Since the CALGB 10403 protocol was introduced for AYAs with ALL or LBL in Iran for the first time, it was necessary to carefully evaluate its feasibility. Our study indicated that treatment interruptions were primarily due to treatment-related toxicities, medication shortages, or patient non-attendance at scheduled appointments. Delays in PEG preparation were primarily due to difficulties in its acquisition. The unavailability of domestically produced PEG results in increased costs and potential access barriers. This was further compounded by the lack of insurance coverage for PEG, adding a substantial financial burden for patients and their families. These combined challenges—importation difficulties and lack of insurance coverage—create significant disparities in access to this key component of the CALGB 10403 protocol, ultimately contributing to treatment delays and potentially impacting patient outcomes and overall survival. Despite the mentioned difficulties mentioned, our results were as promising as those reported by leading and high-quality leukemia treatment centers in reference [7].

In conclusion, this study provided valuable insights into the implementation of the CALGB 10403 protocol in Iran, particularly regarding its feasibility and effectiveness. However, the current study had certain limitations, particularly its small sample size, which may restrict the generalizability of the findings to a broader population. It is recommended that future research include both an extended follow-up duration and a larger cohort of patients. This would provide the basis for facilitating protocol optimization, addressing potential resource constraints, reducing treatment-related toxicities,

and allowing for a more in-depth evaluation of long-term outcomes. Furthermore, the challenges related to patient non-adherence to the scheduled regimen, including socioeconomic barriers and resource limitations that can result in suboptimal outcomes, should be addressed through patient education and the provision of psychosocial support.

CONFLICTS OF INTEREST

Authors declare that they have no conflicts of interest.

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