IJHOSCR

Original Article

International Journal of Hematology-Oncology and Stem Cell Research

Outcome of T-Lymphoblastic Leukemia-Lymphoma with Hyper C-VAD Regimen

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Received: 03, Mar, 2025
Accepted: 03, Aug, 2025

ABSTRACT

Background: T-cell lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) are aggressive diseases with dismal prognoses.

Materials and Methods: All adult patients with T-ALL and T-LBL who were candidates for the Hyper-CVAD chemotherapy protocol were included. We evaluated overall survival and progression-free survival in 46 new cases. The T-ALL and T-LBL's number of cases were 32 and 14, respectively.

Results: Two- and 3-year OS were 41.8% (standard error (SE): 7%) and 27.8% (SE: 7%), respectively. Two- and 3-year PFS were 36.9% (SE: 7%) and 25.3% (SE: 7%), respectively. The only variable that had a significant relationship with the duration of PFS and OS was Allogenic SCT. Patients receiving Allogeneic SCT had longer survival time (2-year overall survival of 80% against 20%) ($p<0.001$).

Conclusion: These data support the concept that Hyper-CVAD is not an appropriate and adequate regimen. We need new targeted agents in the T-ALL and T-LBL induction regimen while considering Allogeneic SCT as a Consolidation.

Keywords: T-ALL; T-LBL; Hyper-CVAD chemotherapy; Allogeneic SCT; Progression-Free Survival

INTRODUCTION

The malignant transformation of T-cell progenitors is the source of the severe illnesses known as T-cell lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL)[1]. About 20% of ALL patients are T-ALL[2], whereas 2-4% of adult non-Hodgkin lymphoma cases are T-LBL[3]. According to the 2017 WHO classification, these two illnesses belong to the same category since they have the same immunophenotype and morphology[4]. Less than 20–25% of marrow-infiltrating blasts separate LBL from ALL [4].

The presentation of T-ALL includes hyperleukocytosis, a mediastinal mass, and involvement of lymph nodes, the central nervous system, and other organs[5, 6]. On the other hand, T-LBL typically presents with a mediastinal mass and bone marrow involvement. It's noteworthy that primary central nervous system (CNS) involvement at presentation is rare in T-LBL[7].

The most commonly used chemotherapy regimens in these patients were the Berlin-Frankfurt-Munster (BFM) regimen, the Cancer and Leukemia Group B (CALGB) regimen, the Hyper-CVAD regimen, and the Group for Research and Adult Acute Lymphoblastic Leukemia 2003 (GRAALL 2003) regimen [9, 10]. The MD Anderson Cancer Center (MDACC) reported a 92% complete response rate and a 5-year overall survival rate of around 38% in adults with ALL treated with the Hyper-CVAD chemotherapy protocol[11,12].

DOI:

Although the MDACC reported high CR rates with Hyper-CVAD, subsequent studies and real-world experiences have highlighted issues with relapse and poor long-term survival, particularly in T-cell disease[6,13] .

In this comprehensive study, we conducted a retrospective evaluation to determine the effectiveness of Hyper-CVAD treatment in adults with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) in the southern region of Iran.

MATERIALS AND METHODS

Our research focused on adult patients with T-ALL and T-LBL who underwent the Hyper-CVAD chemotherapy regimen at Namazi and Amir Hospitals in Iran between 2018 and 2023. We meticulously reviewed 221 cases of acute lymphoblastic leukemia/lymphoma, excluding 157 cases with pre-B cell ALL and B cell ALL pathology. Ultimately, after careful evaluation, 46 new cases were included in the study, 32 of which were T-ALL and 14 were T-LBL. The findings from this study are crucial to advancing our understanding of the efficacy of Hyper-CVAD treatment in these specific patient populations.

For 8 cycles, the treatment plan is the following:
Cycle A:
- 4 cycles of Cyclophosphamide 300 mg/m^2 IV in 250 mL of NS every 12 hours on Days 1-3
- Dexamethasone 40 mg IV/PO on Days 1-4 and 11-14
- Methotrexate 12 mg IT on Day 2
- Doxorubicin 50 mg/m^2 IV on Day 4
- Vincristine 2 mg IV in 50 mL of NS on Day 4 and 11.

Cycle B:
- 4 cycles of Methotrexate 1000 mg/m^2 IV in 1250 mL of NS continuous infusion over 24 hours on Day 1
- Cytarabine 3 g/m^2 in 250 mL of NS every 12 hours on Days 2-3
- Methotrexate 12 mg IT on Day 5.

In the study, we do not check for minimal residual disease (MRD). Patients with T-LBL and T-ALL will undergo allogeneic SCT in the first complete remission (CR1), provided a fully matched donor is available. If a donor is not available, the patient will receive 6-mercaptopurine and methotrexate as maintenance treatment for 2.5 years.

Statistical analysis

We used SPSS software (version 23) to analyze the data. The Kolmogorov-Smirnov test was applied to check if the data followed a normal distribution. We presented descriptive statistics as mean and standard deviation or median and range. To illustrate the survival curve for overall survival and progression-free survival (PFS), we conducted a Kaplan-Meier analysis, considering the case of death or disease progression. We used the log-rank test to compare overall survival (OS) and PFS across different groups, with a p-value of less than 0.05 as statistically significant.

RESULTS

A total of 46 patients took part in the study from March 2018 to March 2023. The median follow-up period was 18.5 months (about 3.2 to 93.4 months). Among the patients, 32 (69.6%) were diagnosed with T-ALL and 14 (30.4%) with T-LBL. The average age of patients at diagnosis was 33.8 ± 9.6 years, from 18 to 57 years. The majority of the patients were male (60.9%). A mediastinal mass was in 37% of patients, and 17.4% had CNS involvement at presentation or during the disease. Fifteen percent of patients had more than 100 * 10^9/L white blood cell count (Table 1).

Variables	Value
Age at diagnosis (year), mean ± SD	33.8 ± 9.6
Sex (male), N (%)	28 (60.9)
Disease type, N (%)	32 (69.6)
T-ALL	
T-LBL	14 (30.4)
Mediastinal mass at presentation, N (%)	17 (37)
CNS involvement at presentation, N (%)	8 (17.4)
WBC > 100 * 10^9/L at presentation, N (%)	7 (15)
Allogeneic SCT, N (%)	17 (37)

Table 1: Demographic data and clinical characteristics of patients with T- lymphoblastic leukemia- lymphoma

Twenty-eight percent of patients experienced a relapse before completing the 8th cycle of chemotherapy, and 56% of patients had a recurrence of the disease during the follow-up period. The most common treatment for relapsed patients was MOPAD (methotrexate, vincristine, PEGylated Asparginase, and dexamethasone), which was administered to 50% of patients, followed by the FLAG and ICE regimens. Allogeneic SCT was in 37% of patients. Throughout the follow-up period, 67% of patients passed away.

The 2- and 3-year overall survival (OS) rates were 41.8% (standard error= 7%) and 27.8% (standard error= 7%), respectively, with an average overall survival of 3.1 years (95% CI: 2.2-4.0) (Figure 1). The 2- and 3-year progression-free survival (PFS) rates were respectively 36.9% (SE: 7%) and 25.3% (SE: 7%), respectively, with an average PFS time of 2.8 years (95% CI: 1.9-3.7) (Figure 2).

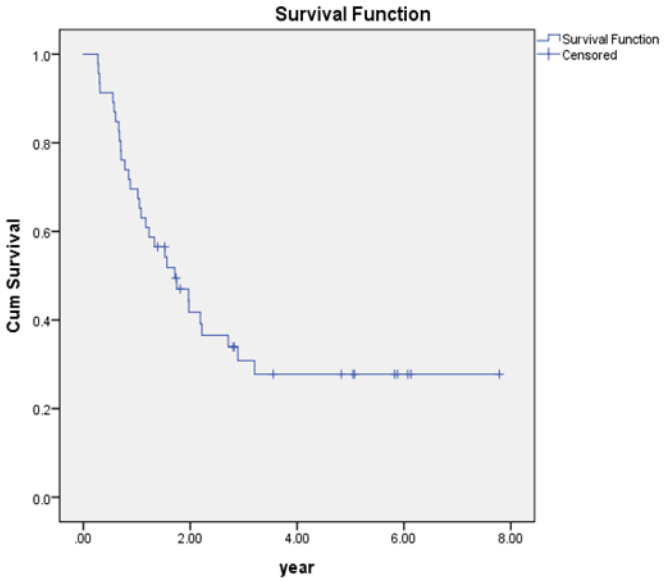


Figure 1. The 2- and 3-year overall survival (OS) rates

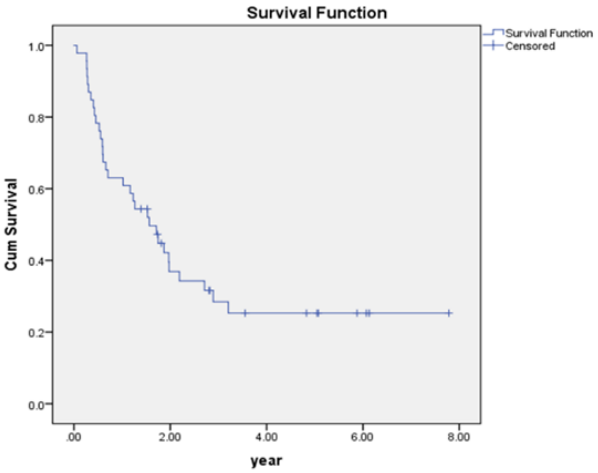
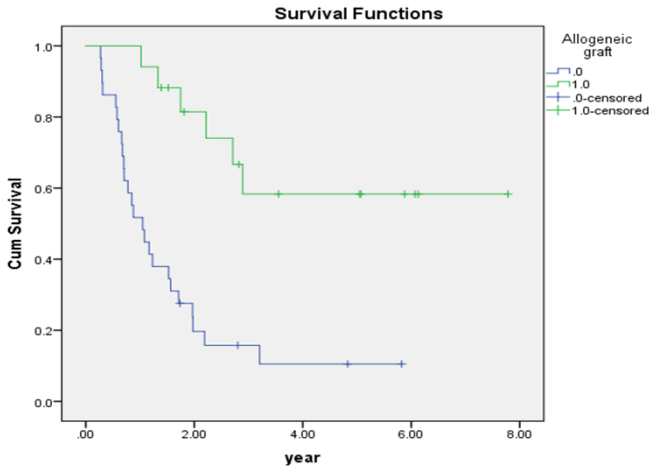


Figure 2. The 2- and 3-year progression-free survival (PFS) rates

The only factor significantly associated with the duration of PFS and OS is allogeneic SCT. The patients who underwent allogeneic SCT showed a significantly longer survival time, with a mean OS of 5.4 years (95% CI: 3.9-6.9) compared to patients who hadn't undergone Allogeneic SCT (mean OS of 1.6 years, 95%CI: 1-2.2) (p-value: <0.001) (Table 1 and Figures 3 A and B). Other factors such as gender, CNS involvement, WBC count of more than 100 * 10^9/L, LDH, and type of disease did not show a significant relationship with OS (P=0.967, P=0.504, P=0.928, P=0.277, P=0.247 respectively) or PFS (P=0.859, P=0.427, P=0.875, P=0.344, P=0.126 respectively).



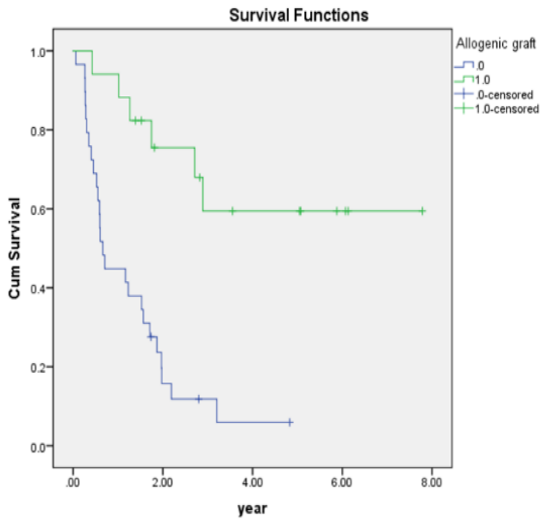


Figure 3 a/b. Comparing survival time duration of patients (a. OS, b. PFS) underwent allogenic SCT with who hadn't undergone allogenic SCT

Table 2: Comparing OS and PFS of patients undergoin allogeneic SCT with those who hadn't undergone allogeneic SCT

Group	Overall Survival (year)		Progression Free Survival (year)	
	Mean	95% CI	Mean	95% CI
Allogeneic SCT	5.4	3.9-6.9	5.3	3.8-6.9
No Allogeneic SCT	1.6	1.0-2.2	1.3	0.8-1.7
P	<0.001		<0.001	

Our study was significant in the number of patients included compared to previous studies. However, the main limitation of our study was the lack of monitoring for minimal residual disease (MRD) and using this information to guide transplantation decisions.

DISCUSSION

An intense multi-agent chemotherapy regimen with central nervous system prophylaxis is the usual treatment for T-cell acute lymphoblastic leukemia (T-ALL). High-risk individuals are highly advised to undergo allogeneic stem cell transplantation (SCT). The following high-risk factors for ALL need to be carefully addressed: complex karyotype[2], non-thymic phenotype (CD1-negative), female gender, positive minimal residual disease (MRD), elevated white blood cell (WBC) count (> 10*10^9/L), hypodiploidy, and specific chromosomal translocations (t (4,11), t (14,23).

Treatment for T-cell lymphoblastic lymphoma (T-LBL) follows a similar regimen as T-ALL. However, the role of allogeneic SCT in T-LBL is less clear. The SCT will be for high-risk patients, including those with central nervous system involvement, resistance to induction chemotherapy, persistent minimal residual disease (MRD), early T-cell precursor (ETP) phenotype, and NOTCH1 mutation.

The Hyper-CVAD regimen, which includes hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternated with high-dose methotrexate and cytarabine (MTx-Ara-

C), is a highly effective therapy for both T-ALL and T-LBL.

In a 2000 study by Kanterjian et al., using the Hyper-CVAD chemotherapy protocol, favorable results were reported[12]. Out of 24 patients with T-ALL treated with Hyper-CVAD, the complete remission rate was 100%, and the 5-year survival rate was 43%[12]. However, a 2014 study by Kozlowski et al., which included 19 T-ALL patients, showed that despite a complete response rate of 89%, Hyper-CVAD had poor efficacy in preventing relapse. Approximately 80% of patients were not transplanted and, after a median time of 9 months from the first complete remission, experienced a relapse[6].

It seems that Molecular response after induction chemotherapy is highly predictive for outcome in patients with T cell ALL.

In a study by Gökbuget et al, , Patients with molecular CR after consolidation had a significantly higher probability of continuous complete remission (CCR; 74% vs 35%; P < .0001) and of overall survival (80% vs 42%; P = .0001) compared with patients with molecular failure. Patients with molecular failure without stem cell transplantation (SCT) in first CR relapsed after a median time of 7.6 months[15].

In another study in 2004, Thomas et al. reported a 91% complete response in 31 patients with T-LBL who received the Hyper-CVAD regimen. The 3-year PFS and OS rates were 62% and 67%, respectively[16].

28% of participants in our research had a disease recurrence prior to finishing the eighth treatment cycle. 56% of patients had a disease recurrence within the 18-month median follow-up period. Overall survival rates were 41.8% (standard error (SE): 7%) at two years and 27.8% (SE: 7%) after three years (Figure 1). According to Figure 2, the progression-free survival rates at two and three years were 36.9% (SE: 7%) and 25.3% (SE: 7%), respectively.

In our study, we found that 67% of patients died during the research period, indicating unsatisfactory results. The only variable that had a significant impact on patient prognosis was Allogeneic SCT. Patients who received Allogeneic SCT had a mean overall survival of 5.4 years (3.9-6.9), while those who did not receive this treatment had a mean overall survival of 1.6 years (1.0-2.2) (P < 0.001).

In a 2018 study by Erkut et al., despite complete response rates of 90% in a certain number of patients treated with Hyper-CVAD, the median OS and PFS were only 17.5 and 12.1 months, respectively[17].

Hyper-CVAD outcomes in this real-world setting were suboptimal without effective consolidation strategies.

These underscore the necessity for new treatment in induction, as relapsed T-ALL is often resistant to standard chemotherapy and glucocorticoids, with a survival rate of less than 50% in adults[17-19].

One potential novel therapeutic strategy is using Nelarabine in the first-line regimen, which is currently being studied[20]. T cell lymphoblasts overexpress the BCL2 protein, making it an attractive therapeutic target[20].

Our study was significant in the number of patients included compared to previous studies. However, the main limitation of our study was the lack of monitoring for minimal residual disease (MRD), using this information to guide transplantation decisions and lack of access to novel therapeutic strategy such as Nelarabine as a first line with chemotherapy drugs.

Other limitations of the study included incomplete records and failure to perform bone marrow sampling at the same time in all patients.

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