Higher Survival Advantage with Hyper-CVAD Chemotherapy Regimen Before Allogeneic Stem Cell Transplantation in Patients with High Risk Adult Acute Lymphoblastic Leukemia: Two-Center Experience

Yüksek Riskli Yetişkin Akut Lenfoblastik Lösemili Hastalarda Allojenik Kök Hücre Transplantasyonu Öncesi Hiper CVAD Kemoterapi Rejimi ile Daha Yüksek Sağkalım Avantajı: İki Merkez Deneyimi

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Öz

Çocukluk çağı akut lenfoblastik lösemi (ALL) tedavisinde umut verici sonuçlar elde edilirken, yetişkin için optimal indüksiyon tedavisi henüz belirlenememiştir. Hyper-CVAD kemoterapi rejimi, yetişkin ALL tedavisinde yaklaşık yirmi yıldır yaygın olarak kullanılan bir tedavi haline gelmiştir. 2014 ve 2020 yılları arasında iki merkezde Hyper-CVAD rejimi ile tedavi edilen 30 hastanın retrospektif analizini gerçekleştirdik. Hyper-CVAD ile tedavi edilen hastalarda (n=30), tam yanıt oranı (TY) %86.7, indüksiyon mortalitesi %10, refrakter hastalık %3.3, medyan genel sağkalım (GS) 38 ay (%95 CI 7.78-68.2 ay), medyan hastalıksız sağkalım (HS) 29 ay (% 95 CI 9-49 ay), 2 yıllık GS oranı % 56.5 ve 2 yıllık HS oranı % 56.7 olarak saptadık. Standart risk (n=12) ALL hastalar için, medyan GS 20 ay (%95 CI 0-43 ay) ve medyan HS 7 ay (%95 CI 0-25 ay) saptadık. Yüksek riskli (n=18) ALL hastalar için, medyan GS 38 ay iken (%95 CI 0-76 ay), medyan HS'a ulaşılamadı. Bu sonuçlar, Hyper-CVAD rejiminin yeni tanı konmuş ve allojenik kök hücre transplantasyonu için uygun olan ALL hastalarının indüksiyon tedavisi için bir seçenek olarak değerlendirilmesi gerektiğini göstermektedir.

Anahtar Kelimeler: Akut Lenfoblastik Lösemi, Hyper-CVAD, Kemoterapi, Transplantasyon, Yetişkin

Abstract

While promising results have been achieved in the treatment of childhood, the optimal initial treatment for adult acute lymphoblastic leukemia (ALL) has not yet been defined. Hyper-CVAD has become a widely used treatment for approximately 2 decades in the treatment of adult ALL. We conducted a retrospective analysis of 30 patients treated with Hyper-CVAD at two centers between 2014 and 2020. In all (n=30) patients treated with Hyper-CVAD, complete response (CR) rate was 86.7%, induction mortality was 10%, refractory disease was 3.3%, the median overall survival (OS) was 38 months (95% CI 7.78–68.2 months), the median disease-free survival (DFS) was 29 months (95% CI 9–49 months), the 2-year OS rate was 56.5%, and the 2-year DFS was rate 56.7%. For standard risk (n=12) ALL patients, the median OS was 20 months (95% CI 0–43 months), and median DFS was 7 months (95% CI 0–25 months). For high risk (n=18) ALL patients, the median OS was 38 months (95% CI 0–76 months), and median DFS was not reached. These results indicate that Hyper-CVAD regimen should be considered as an option for induction treatment of adult ALL patients who are newly diagnosed and eligible for allo-HSCT.

Keywords: Acute Lymphoblastic Leukemia, Hyper-CVAD, Chemotherapy, Transplantation, Adult

Introduction

Acute lymphoblastic leukemia (ALL) is a hematological malignancy with different pathological subtypes of Pre-B cell (most common subtype), pre-T cell, T-cell, and B-cell (1). Combination chemotherapy is the primary treatment modality for ALL patients. Induction chemotherapy protocols were mostly inspired by pediatric regimens, but these treatment protocols were not directly compared in a prospective randomized trial. The most commonly used chemotherapy protocols are Cancer and Leukemia Group B (CALGB), Dana Farber Cancer Institute (DFCI), Berlin-Frankfurt-Munster (BFM), Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) protocols.

Hyper-CVAD regimen/high-dose methotrexate and cytarabine (high dose methotrexate (MTX) and Ara-C) are widely used in many centers. This regimen includes central nervous system (CNS) prophylaxis with intrathecal (IT) methotrexate and cytarabine. The intensive dose phase lasts for six to seven months, followed by 24 to 30 months of maintenance therapy (2). The hyper-CVAD regimen consists of three phases which are induction, consolidation, and maintenance. MD Anderson Cancer Center (MDACC) reported 92% complete

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Başvuru Tarihi / Received: 04.05.2021
Kabul Tarihi / Accepted : 20.08.2022

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response (CR), 38% 5-year overall survival (OS), and 66% 5-year progression-free survival (PFS) in adult ALL patients treated with Hyper-CVAD chemotherapy protocol (2,3).

In this report, we summarized the results of the Hyper-CVAD regimen as a front-line therapy for patients with ALL from two centers.

Material and Method

This study includes newly diagnosed ALL patients who received the Hyper-CVAD regimen between April 2014 and October 2020 in both centers. Clinical and laboratory data and outcomes of therapy were evaluated using the patients' folders. The study was approved by the local Institutional Review Board and Ethics Committee (Local Ethics Committee of Istanbul Medeniyet University (Decision No: 2021/0214)).

For the diagnosis of ALL, bone marrow samples were evaluated morphologically (aspiration and biopsy), and ALL was diagnosed if the lymphoblast ratio was more than 20%. Immunophenotypic evaluation of B cells (CD10, CD19, CD22, sIg, and cIg), T cells (CD2, CD3, CD4, CD5, CD7, and CD8), and precursor cells (tdt, HLA-DR, and CD34) were performed by both immunohistochemical analysis and flow cytometric analysis. At the time of diagnosis, molecular analysis was performed by fluorescent in situ hybridization (FISH) and conventional cytogenetic analysis from bone marrow and/or peripheral blood samples of all patients. Elevated white blood cell (WBC) count (>30×10⁹/L in B-ALL and >100×10⁹/L in T-ALL), older age (>35 years old), the presence of t(9;22) or any additional cytogenetic abnormality (hypodiploidy, t(4;11), t(14;23) and complex karyotype) were considered high risk ALL. Patients without high-risk criteria and with hyperdiploidy or t(12;21) were considered as good risk, while the rest were classified as standard risk ALL (4).

Before starting induction therapy, the patients were evaluated for signs and symptoms of infection, renal failure, uremia, hyperuricemia, tumor lysis syndrome, and other accompanying medical conditions. Additional comorbid conditions accompanying ALL were attempted to be treated appropriately.

Hyper-CVAD chemotherapy protocol is presented in Table 1. Tyrosine Kinase Inhibitor (TKI) (Imatinib) was added to the treatment of patients with Philadelphia chromosome-positive (Ph+) ALL. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) was performed in patients with high-risk disease at the time of diagnosis, who was achieved CR after induction therapy, and had a suitable donor. Allo-HSCT was not planned initially in patients with low and standard risk at diagnosis. Allo-HSCT was also planned in case of relapsed/refractory disease under hyper-CVAD treatment in patients with low and standard risk at diagnosis. For non-transplant patients, after consolidation, POMP (6-mercaptopurine 60 mg/m^2/day per oral (po), vincristine 2 mg intravenous once a month, methotrexate 20 mg/m^2 once a week, prednisone 200 mg po 5 times a month) maintenance therapy was administered for 2 years.

The patients with mature B-cell ALL or lactate dehydrogenase (LDH) level>1125 U/L (higher than 2.5 times the upper limit of LDH reference) were considered high risk for CNS disease and IT prophylaxis was given 16 (8xMTX + 8xARA-C) times; however, for patients with LDH level <1125 U/L, IT prophylaxis was given 8 times. According to institutional guidelines, all patients received trimethoprim/sulfamethoxazole prophylaxis for pneumocystis jiroveci, acyclovir prophylaxis for herpes virus, and fluconazole prophylaxis for fungal infections.

Table 1. Hyper-CVAD chemotherapy protocol

			Chemotherapy Day
1., 3., 5. and 7th cycles			
Cyclophosphamide	300 mg/m^2 TWICE a day	IV infusion	1st to 3rd day
Mesna	600 mg/m^2	IV infusion	1st to 3rd day
Vincristine	2 mg	IV infusion	4th and 11th days
Doxorubicin	50 mg/m^2	IV infusion	4th day
Dexamethasone	40 mg ONCE a day	IV/PO	1st to 4th day, 11th to 14th day
Filgrastim	5 micrograms/kg	SC	5 and continue daily until neutrophil recovery
2., 4., 6. and 8th cycles			
Methylprednisolone	50 mg TWICE a day	IV infusion	1st to 3rd day
Methotrexate	200 mg/m^2	IV infusion	1th day
Methotrexate	800 mg/m^2 over 22 hours	IV infusion	1th day
Calcium folinate (Leucovorin)	15 mg/m^2 every 6 hours *	IV infusion	3-5 days
Cytarabine (Ara-C)	3,000 mg/m^2 TWICE a day **	IV infusion	2nd and 3rd days
Filgrastim	5 micrograms/kg	SC	4 and continue daily until neutrophil recovery
Methotrexate	12 mg	IT	2nd day
Cytarabine	100 mg	IT	8th day

IT: intrathecal, IV: intravenous, PO: per oral. *Every 6 hours until methotrexate level less than 0.05 micromol/L. Start 36 hours after commencement of methotrexate infusion. **For patients over 60 years, the cytarabine dose was reduced to 1000 mg/m^2.

Complete response (CR) was defined as absolute neutrophil count ≥1×10⁹/L, platelet count ≥100×10⁹/L, no blast in peripheral blood, <5% blast in bone marrow, and no extramedullary involvement. Relapse was defined as the recurrence of the disease after CR.

All calculations were made using SPSS 13.0 statistics program. OS was calculated from the initiation date of treatment to death or the patient's last visit. Disease-free survival (DFS) was measured from the date of achievement of CR until evidence of leukemia recurrence or the patient's last visit. Kaplan-Meier curves were generated for survival analyses and Log-rank tests were used to assess differences in OS and PFS between groups.

The study was approved by the local Institutional Review Board and Ethics Committee (Local Ethics Committee of Istanbul Medeniyet University (Decision No: 2021/0214)) and was conducted in accordance with the Helsinki Declaration of 2013.

Results

The clinical characteristics of the 30 (9 female, 21 male) patients treated with Hyper-CVAD are summarized in Table 2. The median age at diagnosis was 46.5 (range 20-74) years. When we grouped patients by age; 9 patients were between 18 and 39 years, 18 patients were between 40 and 65 years, and 3 patients were more than 65 years old. The mean hemoglobin level was 9 (±2.85) g/dL, the mean WBC count was 51.2 (±99.6) ×10⁹/L, the mean platelet count was 95.8 (±129.1) x10⁹/L, and the mean LDH level was 1554 (±1856) U/L at the time of diagnosis. ECOG performance score was 0 for four patients, 1 for twenty-two patients and 2 for four patients. There were no patients with ECOG performance score 3 and 4. While there were no patients with low disease risk, the number of patients with standard and high-risk disease were 12 and 18, respectively. Six patients had Ph+ ALL. One patient had T315I mutation, one had t(2;9) and del(7), one had monosomy 4, and one had hyperdiploidy. When we determined the leukemia subtypes of all patients, there were 25 B-ALL, 4 T-ALL and 1 Mixed Phenotype Acute Leukemia (MPAL) patient. Central nervous system involvement was observed only in one patient at the time of diagnosis.

Twenty-six patients achieved CR after one course of therapy. The median time to CR was 21 (range 15-27) days. Three patients died during induction therapy and one patient was refractory to induction therapy. For salvage therapy FLAG-IDA protocol was administered to the refractory patients and, if CR was achieved after salvage therapy, patients proceed to allo-HSCT. Seventeen of 27 patients underwent allo-HSCT, the other 10 were consolidated with Hyper-CVAD. All of the allo-HSCTs were performed after the first CR. Thirteen patients were followed in remission, one had relapsed, and 3 died due to transplant-related toxicity of the allo-HSCT patients. Of the 10 patients who continued with hyper CVAD, 4 patients were followed in remission, 5 had relapsed, and one patient died due to infection. A total of 6 patients relapsed (1 after allo-HSCT) in the study population and OS of these patients was only 2 months. NRM occurred in 4 patients (1 myocardial infarction, 1 sepsis, 1 engraftment failure, 1 pneumonia) (Table 3).

Table 2. Pretreatment characteristics

Characteristic	All patients (n = 30)
Age (yrs)	46.5 (20-74)
18-39	9
40-65	18
>65	3
Sex, female/male	9/21
Performance score (ECOG scale)	
0	4
1	22
2	4
3	0
4	0
Hemoglobin, g/dL	9 (±2.85)
WBC count, ×10⁹/L	51.2 (±99.6)
Platelet count, ×10⁹/L	95.8 (±129.1)
LDH, U/L	1554 (±1856)
Cell origin, B/T/MPAL	25/4/1
Karyotype	
Diploid	21
Ph positive	6
Hyperdiploid	1
Hypodiploid	0
Other	2
Not done	0
Risk, low/standard/high	0 / 12 / 18
CNS disease at diagnosis	1

ECOG: Eastern Cooperative Oncology Group, WBC: White Blood Cell, LDH: Lactate Dehydrogenase, MPAL: Mixed-Phenotype Acute Leukemia.

The median follow-up of the patients was 14.5 (range 0-72) months. The median OS was 38 months (95% CI 7.78–68.2 months), and the 2-year OS rate was 56.5% for all patients (Figure 1). The median DFS was 29 months (95% CI 9–49 months), and the 2-year DFS rate was 56.7% for all patients (Figure 2).

Comparing the standard risk with high-risk patients, no statistically significant difference was found in terms of OS (p=0.188), but a statistically significant difference was found in terms of PFS (p=0.046). The median OS was 20 months (95% CI 0–43 months), and median DFS was 7 months (95% CI 0–25 months) for standard risk (n=12) patients. The median OS was 38 months (95% CI 0–76 months), and median DFS was not reached for high risk (n=18) patients. At the last of median 14.5 (range 0-72) month follow-up, 18 patients were alive, while 12 patients were dead.

Three patients died (1 sepsis, 1 respiratory failure, 1 pneumonia) during induction therapy.

Neutropenic fever was observed in 21 patients. Fungal infection during induction therapy was observed only in one patient. Intensive care hospitalization during induction therapy was required in 3 patients. During induction therapy, elevated liver enzymes were seen in 5 patients, renal failure was seen in one patient, neuropathy was seen in one patient, and typhlitis was seen in one patient.

Table 3. Treatment outcomes

	All patients (n = 30)
Response	
CR	26
IM	3
Resistant disease	1
Neutropenic fever	21
Fungal infection	1
Intensive care hospitalization	3
Relapse (n=26)	6
Non-relapse mortality (n=25)	4
Survival status	
Alive	18
Dead	12
Cause of death	
R/R disease	6
Infection	3
Other	3
Allogeneic transplantation (n=27)	17
Related	13
Unrelated	4
Achieved CR time (day)	21 (15-27)

CR: Complete Response, IM: Induction Mortality

Discussion

Hyper-CVAD regimen, created at MDACC in 1992 by Kantarjian and colleagues, was inspired by a Burkitt lymphoma regimen developed in the 1980s by the pediatric oncology group at St. Jude Children's Research Hospital (2,5). This protocol incorporated the basic therapeutic principles of the pediatric regimens, with a reduced requirement on asparaginase during the remission induction. For many years, Hyper-CVAD is one of the most frequently used regimens for the treatment of adult ALL in many hematology centers.

In this study, similar to what the MDACC group reported, CR rate was %86.7 (MDACC 92%), refractory disease rate with induction therapy was 3.3% (MDACC 3% in 288 ALL patients with a median age of 40 years). In our study the induction mortality rate was found to be 2 times higher (10% vs 5%) but the median OS was slightly higher (38 months vs 32 months). MDACC group also reported 5-year OS rate was 38% and 5-year CR duration rate was 38% (3). But follow-up time was shorter in our study and the 2-year DFS rate was 56.7% in patients treated with Hyper-CVAD.

In another study by Xu et al., involving 53 adult patients with newly diagnosed adult ALL patients determined that the CR rate was 73.6%, the median OS was 48.7 months, the 2-year OS rate was 82.9%, and the 2-year DFS rate was 87.3%. It should be noted that in this study 32 patients (60.4%) achieved CR after one course of Hyper- CVAD, whereas 7 patients (13.2%) required two or more courses for the achievement of CR (6).

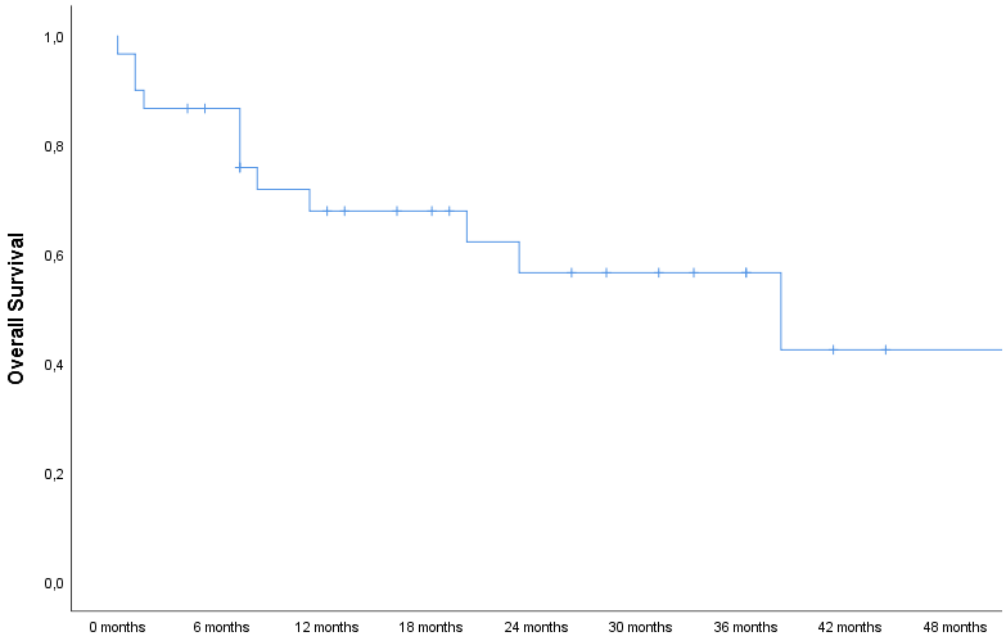

Figure 1. Kaplan–Meier curve for OS

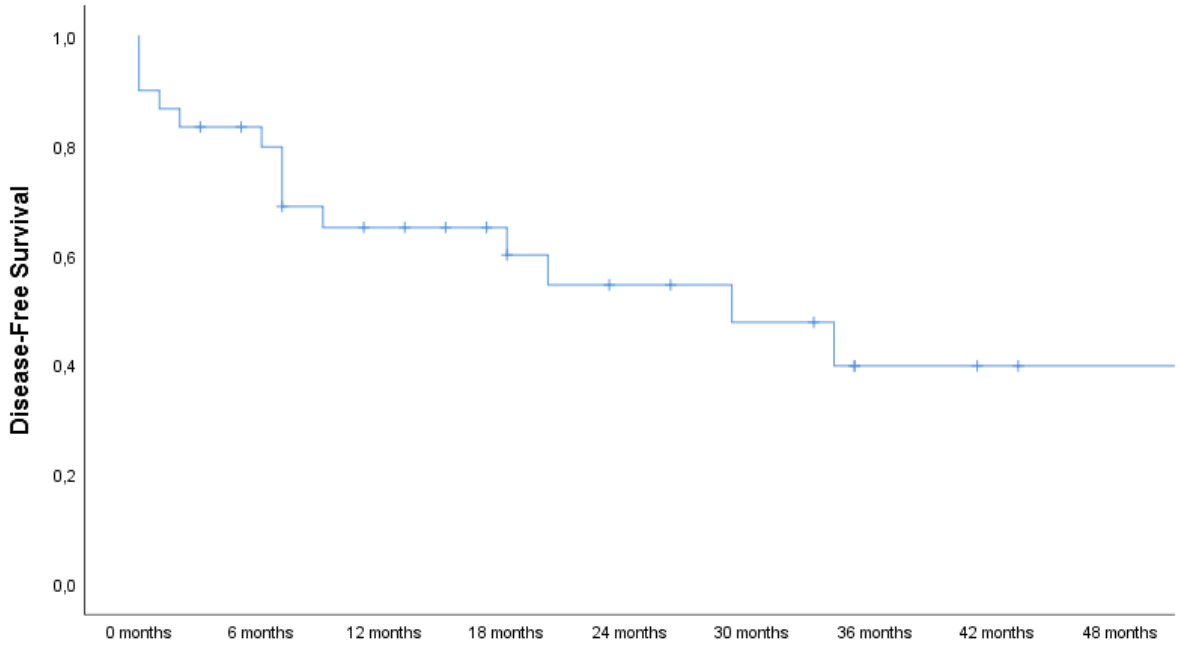

Figure 2. Kaplan–Meier curve for DFS

Buyukasik et al. reported that CR rate was 84.2%, induction mortality rate was 5.2%, refractory disease rate was 10.5% with induction therapy in 57 ALL patients with a median age of 29 years. The median OS was 16.4 months (95% CI 8.3–24.5), median DFS was 13.9 months (4.7–23.1), were observed. Three-years OS and DFS and 5-years OS and DFS rates were 36.8%, 26.3% and 24.9%, 24.9%, respectively (7).

Erkut et al. reported that the CR rate was 90%, median OS was 17.5 months, median DFS was 12.1 months, 2-year OS rate was 30%, and 2-year DFS rate was 28% in 38 ALL patients with a median age of 32 years (8). The summary of Hyper-CVAD outcomes in adult ALL studies are presented in Table-4.

The CR rate of induction therapy in our study was similar to those reported in other studies, however, the IM rate was higher in our study. We think that, this is because the median age and comorbidity of the patients were higher than those in other studies.

When compared with the publications reported in our country, the median OS, median DFS rates, 2-year OS, and DFS rates were significantly better. Probably, this is because most of our patients (63%) have undergone allo-HSCT after achieving CR. Disease relapse and deaths due to all causes were observed more frequently in patients who continued hyper CVAD treatment, compared to patients who underwent allo-HSCT in our study. NRM rate was 16% (n=6), it was observed slightly lower than reported publications in our country (7,8).

Table 4. Summary of Hyper-CVAD outcomes in adult ALL studies

Study	No of patients	Median age (years;range)	CR rate (%)	IM rate (%)	OS	Response, EFS or PFS	No of patients receiving Allo HCT (%)
Kantarjian et al. (3)	288	40 (15-92)	92% (Overall) 81% (After course 1)	5%	38% at 5 years	38% (5 year CR duration rate)	11(4%)
Xu et al. (6)	53	30 (18-66)	73.6% (Overall) 60.4% (After course 1)	NA	82.9% at 2 years	87.3% (2-year DFS)	NA
Buyukasik et al. (7)	57	29 (16-63)	84.2%	5.2%	36.8% at 3 years	26.3% (3-year DFS)	16 (28%)
Erkut et al. (8)	38	32 (17-58)	90%	2%	30% at 2 years	28% at 2 years	13 (34%)

CR: complete response, EFS: event free survival, DFS: disease-free survival, NA:Not available

When we compared the outcomes of high risk (n=18) and standard risk (n=12) patients, interestingly, median OS and DFS results of high-risk patients were observed better than standard-risk patients. The rates of allo-HSCT were significantly different between high-risk and standard-risk patients. 78% of high-risk patients have undergone allo-HSCT, this rate was only %25 in standard-risk patients. We thought that better outcomes of high-risk patients were due to allo-HSCT in this group. During our follow-up, 5 out of 10 patients who continued with Hyper CVAD treatment had a relapse, whereas relapse occurred in only one of 17 patients who were applied allo-HSCT. Morris et al. applied allo-HSCT to 12 high-risk patients with CR with hyper CVAD therapy, and they reported the estimated 5-year OS was 75% and PFS was 82%. In 42 patients who did not undergo allo-HSCT after the first CR estimated 5-year OS, PFS, and EFS for this group was 46%, 36%, and 34%, respectively (9). Based on our study, we can say that allo-HSCT applied for consolidation purposes after Hyper CVAD reverses the negative course of high-risk ALL. We could not investigate the presence of minimal residual disease (MRD) in our patients. If we had detected MRD (+) by flowcytometry in standard risk patients, these patients would also undergo allo-HSCT and the results would probably be better.

If our standard risk ALL patients were continued with allo-HSCT, most likely the results would be better. In the International ALL trial, it has been shown that patients with standard-risk ALL benefit from allo-HSCT. In this study, 5-year OS was 41% in high-risk ALL patients who underwent allo-HSCT and 35% in those without allo-HSCT (p=0.2). While the 5-year OS was 62% in standard risk ALL patients who underwent allo-HSCT, it was 52% in those without allo-HSCT (p=0.02) (4).

We routinely applied trimethoprim /sulfamethoxazole, acyclovir, and fluconazole prophylaxis to our patients. While neutropenic fever was observed in 70%, fungal infection was 3,3%, herpes labialis developed only in a few cases, whereas severe viral infection was not observed. Erkut et al. reported 87% neutropenic fever and 11% aspergillus infection in patients treated with Hyper-CVAD although they have also given prophylaxis (8). We observed that our infection rates were slightly lower.

Since we could not routinely test the blastic proliferative index, patients with LDH level >1125 U/L (higher than 2.5 times the upper limit of LDH reference) were considered high risk for CNS disease and received IT treatment 16 times however, patients with lactate dehydrogenase level <1125 U/L received IT treatment 8 times. CNS relapse developed in only one of our patients while receiving maintenance therapy (POMP). Kantarjian et al. reported among 190 patients without initial CNS leukemia, five (3%) relapsed later isolated CNS disease (2).

The most prominent limitations of our study were the small number of patients and the short median follow-up period. Secondly the median age of our patients is higher than the previous publications that we compared. Another limitation is that we could not test for the blastic proliferative index for CNS disease risk, therefore our CNS prophylaxis schedule was also different than the original hyper-CVAD study.

In conclusion, in our retrospective study, Hyper-CVAD regimen has resulted in a high CR rate in adult ALL patients. These results indicate that Hyper-CVAD regimen should be considered as an option for the induction treatment of adult ALL patients who are newly diagnosed and eligible for allo-HSCT.

Ethics Committee Approval: The study was approved by the local Institutional Review Board and Ethics Committee (Local Ethics Committee of Istanbul Medeniyet University (Decision No: 2021/0214)).

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