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Venetoclax-based treatment in adult relapsed/refractory acute lymphoblastic leukemia and lymphoblastic lymphoma: a single-center real-world experience

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ABSTRACT

Aims: Relapsed/refractory (R/R) acute lymphoblastic leukemia and lymphoblastic lymphoma (ALL/LBL) remain clinically challenging entities with limited effective salvage options, particularly in T-cell and early T-cell precursor (ETP) subtypes. Venetoclax has shown encouraging activity in preclinical and early clinical studies; however, real-world data are still scarce. This study aimed to evaluate venetoclax-based regimens in adult patients with R/R ALL/LBL treated at a single-center.

Methods: This retrospective analysis included 13 adults with R/R ALL/LBL who received venetoclax-based therapy between 2019 and 2025. Clinical characteristics, prior treatments, cytogenetics, venetoclax dosing schedules, treatment combinations, response rates and survival outcomes were extracted from institutional records. Responses were assessed using bone marrow evaluation, multiparameter flow cytometry for measurable residual disease (MRD) and PET-CT for extramedullary disease. Overall survival (OS) and progression-free survival (PFS) were estimated using Kaplan-Meier analysis.

Results: The median age was 30 years, and most patients had T-ALL/LBL (61.5%), including two with ETP-ALL/LBL. Patients were heavily pretreated (median 3 prior lines); 38.5% had relapsed after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Venetoclax was administered with various backbones, most commonly FLAG (46.2%) or nelarabine/asparaginase (23.1%). Venetoclax treatment duration ranged from 7–28 days per cycle, with shorter schedules frequently used in individualized regimens. The overall CR/CRi rate was 84.6%, including 38.5% MRD-negative CR. Complete metabolic response (CMR) was achieved in 3 patients with extramedullary disease. Both patients with ETP-ALL/LBL achieved deep responses (CMR or MRD-negative CR), aligning with the biological venetoclax sensitivity of this subtype. Following venetoclax-based therapy, 7 patients (53.8%) proceeded to allo-HSCT. Median OS was 7 months and median PFS was 5 months, comparable to previously published real-world series. Toxicities were manageable; although Grade ≥3 cytopenias were universal, prolonged cytopenias were infrequent with 7-14-day venetoclax courses. Infectious complications included febrile neutropenia (84.6%), mucormycosis (7.7%) and invasive aspergillosis (7.7%). No patient discontinued therapy due to toxicity.

Conclusion: Venetoclax-based regimens demonstrated substantial activity in a young, heavily pretreated R/R ALL/LBL population, yielding high CR/CRi rates, MRD-negative remissions and successful transition to allo-HSCT in over half of patients. Efficacy in the ETP-ALL/LBL subgroup and manageable toxicity with shorter venetoclax schedules highlight the practicality of individualized real-world use. These findings support venetoclax-based combinations as a promising salvage and bridging strategy in R/R ALL/LBL, warranting further prospective evaluation.

Keywords: Venetoclax, acute lymphoblastic leukemia, lymphoblastic lymphoma, relapsed and refractory, hematopoietic stem cell transplantation

INTRODUCTION

Relapsed and refractory (R/R) acute lymphoblastic leukemia (ALL) poses a significant clinical challenge, with long-term survival rates in adults remaining below 10%.[1] Thus, novel approaches to improve outcome are needed. Over the last decade, significant therapeutic advancements have emerged in the management of R/R B-cell acute lymphoblastic leukemia (B-ALL), most notably with the regulatory approval of novel agents such as blinatumomab, inotuzumab ozogamicin, and CD19-directed chimeric antigen receptor T-cell therapies.[2-4] Although multiple salvage treatments exist for B-ALL, effective options for R/R T-cell acute lymphoblastic leukemia (T-ALL) remain limited. Nelarabine has shown activity as a

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monotherapy in this context; however, remission durations are typically brief. Additionally, unlike B-ALL, there are currently no commercially available CAR T-cell therapies for T-ALL patients.[5] T-ALL and T-cell lymphoblastic lymphoma (T-LBL) are aggressive malignancies that arise from precursor T-lymphocytes. T-ALL/LBL constitutes approximately 85–90% of lymphoblastic lymphoma (LBL) cases. It also constitutes 2–4% of Non-Hodgkin lymphoma.[6] The advancement of targeted therapeutic strategies in T-ALL/LBL has been limited and clinical outcomes for patients with R/R T-ALL/LBL remain markedly poor.

Venetoclax, a small-molecule inhibitor of B-cell leukemia/lymphoma-2 (BCL-2), has shown promising antitumor activity in preclinical models and early-phase clinical trials, particularly in ETP acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL).[7,8] BCL-2 is an anti-apoptotic protein overexpressed in many hematological malignancies, including ALL and elevated levels of BCL-2 and BCL-XL have been reported across ALL subtypes such as T-ALL, B-ALL, TCF3-HLF ALL, and MLL-AF4 ALL, suggesting that inhibition of BCL-2 may have important clinical relevance. However, accumulating evidence and clinical experience with venetoclax indicate that treatment response often depends on the strength of apoptotic signals and the interplay among other BCL-2 family members.[9] Retrospective analyses in children and adults have also suggested the efficacy of chemotherapy plus venetoclax combinations in patients with R/R ALL who have received multiple prior treatments.[9,10] However, there is still limited real-world data on the use of venetoclax in R/R ALL. In this study, we present the data of thirteen patients with R/R ALL/LBL who were followed up in our center and who received venetoclax-based therapy. These real-world data may provide valuable insights in the R/R patient population.

METHODS

The study was conducted with the permission of the İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 05.07.2023, Decision No: 2023-25). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective analysis included 13 adult patients (≥18 years) diagnosed with R/R ALL/LBL who received venetoclax-based therapy at our institution between 2019 and 2025. Clinical and demographic characteristics including prior treatment regimens, history of hematopoietic stem cell transplantation, disease status, and outcomes associated with venetoclax therapy were systematically documented using a standardized data collection form. Venetoclax was administered as part of treatment following off-label approval in all cases. Inclusion criteria comprised adults (≥18 years) with a confirmed diagnosis of R/R ALL/LBL who received venetoclax-based therapy and had sufficiently detailed clinical records. Patients with incomplete baseline data or missing follow-up information were excluded from the study.

Relapse was defined as disease recurrence following a documented remission or post-transplantation while refractory disease was characterized by failure to achieve remission despite prior therapies. Complete response (CR) was defined as <5% blasts in the bone marrow with an absolute neutrophil count of ≥1×109/L and a platelet count of ≥100×109/L, along with complete resolution of all sites of extramedullary disease. Complete remission with incomplete count recovery (CRi) was defined as the same as CR, but without complete peripheral blood count recovery. MRD was assessed via multiparameter flow cytometry with a sensitivity threshold of 1×10^{-4} on fresh bone marrow aspiration samples. CMR was defined according to Lugano criteria as complete disappearance of all lesions and Deauville score ≤3 on positron emission tomography-computed tomography (PET/CT).

OS was defined as the time from the date of the first venetoclax-based treatment administration to death or the last follow-up examination. Patients who were alive at the data cut-off date were censored at the last known date of survival. PFS was defined as the time from the first venetoclax-based treatment administration to documented disease progression or death from any cause. OS and PFS were estimated using the Kaplan-Meier method.

Statistical Analysis

Response was evaluated by bone marrow aspiration/biopsy. The response to extramedullary disease was assessed using PET-CT. Adverse events were graded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All calculations were performed using descriptive statistics. Continuous variables are presented as medians (range), while categorical variables are expressed as counts (n) and percentages (%). No further comparative analyses were performed due to the limited sample size.

RESULTS

A total of 13 adult patients with R/R ALL/LBL were included in this study. The median age was 30 years (range, 20-42) and the majority were male (n=9, 69.2%). 3 patients (23.1%) had an ECOG performance status of 0, 9 patients (69.2%) had a score of 1 and 1 patient (7.7%) had a score of 2. T-ALL was the most common subtype (n=8, 61.5%), followed by ETP-ALL/LBL (n=2, 15.4%), T-LBL (n=2, 15.4%) and B-ALL (n=1, 7.7%). None of the patients had any comorbidities.

At the diagnosis, cytogenetic analysis revealed abnormal findings in 5 patients (38.5%) which included FISH-detected CDKN2A deletion (n=1), 1p and 11p deletion (n=1) and NGS-detected mutations such as RUNX (variant allele frequency [VAF] 31%) and GATA2 (VAF 37%) (n=1), IDH2 (VAF 47%), KRAS (VAF 45%), and NOTCH1 (VAF 7%) (n=1) and concurrent NOTCH1 (VAF 45%) and PTEN (VAF 58%) alterations (n=1).

CNS involvement was observed in 3 patients (23.1%) and extramedullary involvement was present in 4 patients (30.8%). 8 patients (61.5%) had refractory disease and 5 patients (38.5%) had relapsed disease. The median number of prior therapy lines was 3 (range, 1-5). Previous allo-HSCT had been performed in 5 patients (38.5%). Prior to venetoclax treatment, the patient's absolute neutrophil count was 3.8×10^3/μL (range, 0.4-12) and the platelet count was 121×10^3/μL (range, 18-419). Only 1 patient had an absolute neutrophil count below 1×10^3/

μL. Patient demographics and clinical characteristics are summarized in Table 1.

Table 1. Patients demografics and clinical characteristics

Characteristic	All patients (n=13)
Age, years (range)	30 (20-42)
Gender	
Male, n (%)	9 (69.2%)
Female, n (%)	4 (31.8%)
ECOG PS, n (%)	
0	3 (23.1%)
1	9 (69.2%)
2	1 (7.7%)
ALL/LBL subtype n (%)	
T-ALL	8 (61.5%)
T-LBL	2 (15.4%)
B-ALL	1 (7.7%)
ETP-ALL/LBL	2 (15.4%)
Karyotype, n (%)	
Normal	8 (61.5%)
Other*	5 (38.5%)
CNS involvement, n (%)	3 (23.1%)
Extramedullary involvement, n (%)	4 (30.8%)
Refractory disease, n (%)	8 (61.5%)
Relapse disease, n (%)	5 (38.5%)
Previous allo-HSCT, n (%)	5 (38.5%)
Median prior lines of therapy (range)	3 (1-5)
Baseline blood parameters, median (range)	
Neutrophil ($\times 10^3$/uL)	3.8 (0.4-12)
Platelets ($\times 10^3$/uL)	121 (18-419)
LDH (U/L)	352 (127-5291)

* Other: Includes FISH-detected CDKN2A deletion (n=1), 1p and 11p deletion (n=1); and NGS-detected mutations such as RUNX (VAF 31%), GATA2 (VAF 37%) (n=1); IDH2 (VAF 47%), KRAS (VAF 45%), NOTCH1 (VAF 7%) (n=1); NOTCH1 (VAF 45%) and PTEN (VAF 58%) (n=1). ECOG PS: Eastern cooperative oncology group performance status, CNS: Central nervous system, ALL: Acute lymphoblastic leukemia, LBL: Lymphoblastic lymphoma, ETP: Early T-cell precursor, LDH: Lactate dehydrogenase, allo-HSCT: Allogeneic hematopoietic stem cell transplantation

Venetoclax was combined with the following chemotherapy regimens: FLAG (fludarabine, cytarabine, G-CSF) in 6 patients (46.2%), nelarabine plus asparaginase (L-asp/Peg-asp) in 3 patients (23.1%), De-Angelis regimen (high-dose methotrexate, procarbazine, vincristine, intrathecal chemotherapy) in 1 patient (7.7%), azacitidine, daratumumab plus dexamethasone in 1 patient (7.7%), cladribine plus cytarabine (Ara-C) in 1 patient (7.7%) and FLEND (fludarabine, etoposide, nelarabine) plus asparaginase in 1 patient (7.7%). The Venetoclax dose and duration were adjusted based on factors such as the intensity of the backbone regimen, the expected duration of cytopenias, azole interactions, and disease burden. None of the patients had prior exposure to venetoclax. The median number of venetoclax cycles was 1 (range, 1–2). Therapeutic features and regimen details are summarized in Table 2.

The median venetoclax dose was 400 mg (range, 100–400) and the median treatment duration was 21 days per cycle (range, 7-28). In 8 patients, venetoclax was added to the backbone regimen for 7 days without ramp-up dosing. Among these, 1 patient developed tumor lysis syndrome. In contrast, the remaining 5 patients received venetoclax for 14 to 28 days with a ramp-up schedule. None of them experienced tumor lysis syndrome. The FLAG-venetoclax regimen was administered to 6 patients, 5 of whom received venetoclax for seven days, while 1 received venetoclax for 14 days. In another patient treated with the DE-ANGELIS protocol, venetoclax was given for 14 days. Among patients receiving nelarabine combined with asparaginase (L-asp/Peg-asp), 2 received venetoclax for 7 days and 1 received venetoclax for 14 days. 1 patient receiving FLEND plus asparaginase was treated with venetoclax for 7 days. In a patient treated with azacitidine, daratumumab and dexamethasone, venetoclax was administered for 28 days. Additionally, in 1 patient receiving cladribine and cytarabine, venetoclax was administered for 28 days.

Table 2. Therapeutic features and regimen details

Characteristic	Value
Venetoclax based protocol (n, %)	
De-angelis	1 (7.7%)
Nelarabine+asparaginase (L-asp/Peg-asp)	3 (23.1%)
Azacitidine+daratumumab+dexamethasone	1 (7.7%)
FLAG	6 (46.2%)
Cladribine+Ara-C	1 (7.7%)
FLEND+asparaginase	1 (7.7%)
Treatment duration with Venetoclax (days per cycle) median (range)	21 (7-28)
Venetoclax dose (mg) median (range)	400 (100-400)
Co-administration of antifungal agent, n (%)	
Micafungin	4 (30.8%)
Fluconazole	4 (30.8%)
Posaconazole	1 (7.7%)
Voriconazole	1 (7.7%)
None	3 (23.1%)
Number of treatment cycles median (range)	1 (1-2)

Asp: Asparaginase, FLAG: Fludarabine, cytarabine, G-CSF, FLEND: Fludarabine, etoposide, nelarabine,
De-Angelis: High-dose methotrexate, procarbazine, vincristine, intrathecal chemotherapy

The dose of venetoclax was reduced when administered concomitantly with an azole antifungal agent. Venetoclax dosage was reduced by 50% with concomitant fluconazole use and by 75% with concomitant posaconazole or voriconazole use. Antifungal prophylaxis was administered in 10 patients (76.9%). Specifically, micafungin was used in 4 patients (30.8%), fluconazole in 4 (30.8%), posaconazole in 1 (7.7%) and voriconazole in 1 (7.7%). The patient who received voriconazole had previously developed invasive pulmonary aspergillosis during earlier lines of therapy. Three patients (23.1%) did not receive any antifungal prophylaxis.

The median duration of neutropenia was 14 days (range, 7-30), while neutrophil recovery occurred at a median of day 21 (range, 14-36). The median duration of thrombocytopenia was 12 days (range, 2-27), and platelet recovery was achieved at a median of day 23 (range, 12-29).

With venetoclax-based treatment, CR was achieved in 2 patients, both of whom were MRD-negative. CRi was observed in 6 patients (3 MRD-negative, 3 MRD-positive). In 3 patients, CMR was confirmed by PET-CT imaging. At the initiation of treatment, these 3 patients (23%) had multiple lymphadenopathies and/or bulky mediastinal mass with bone marrow blast counts below 5%. Therefore, treatment response was assessed using PET-CT and CMR was achieved in all 3 cases. MRD-negative CR was achieved in 5 patients (38.5%) who received the following treatment combinations: DE-ANGELIS plus venetoclax (14 days-200 mg), FLAG plus venetoclax (14 days-100 mg), FLAG plus venetoclax (7 days-400 mg), nelarabine plus Peg-asparaginase with venetoclax (14 days-100 mg) and nelarabine plus L-asparaginase with venetoclax (7 days-400 mg). 1 patient (7.7%) had refractory disease. 1 patient (7.7%) died before response evaluation, so response evaluation could not be performed. One of our 2 patients diagnosed with ETP-ALL/LBL achieved CMR on PET-CT. The other patient diagnosed with ETP-ALL/LBL underwent allo-HSCT with MRD-negative CR.

Following venetoclax-based therapy, allo-HSCT was performed in 7 patients (53.8%). All patients who underwent allo-HSCT were in CR at the time of transplant (3 MRD-negative, 1 MRD-positive, 3 CMR confirmed by PET-CT). In 1 patient who had previously undergone allo-HSCT, venetoclax-based therapy was used to bridge to a second allo-HSCT.

Among patients who did not undergo allo-HSCT after venetoclax treatment, 3 patients (23.1%) received subsequent therapies, including blinatumomab (n=1), FLEND (n=1) and FLAG (n=1). All 3 patients were heavily pretreated. The patient treated with blinatumomab experienced both bone marrow and extramedullary relapse (liver involvement) following the first allo-HSCT. Blinatumomab was initiated due to persistent MRD positivity after treatment with cladribine, cytarabine and venetoclax. A second allo-HSCT was subsequently performed. As of the ninth month post-transplant, the patient remains in remission. Over the course of treatment, this patient received a total of 6 lines of therapy. The other patien, who received FLEND, relapsed after the first HSCT and was subsequently treated with FLAG-venetoclax. FLEND had been administered for refractory disease; however, the response remained refractory. The patient was then treated with the BFM protocol, which achieved an MRD-negative remission and enabled a second allo-HSCT. However, the patient relapsed again and died due to sepsis and mucormycosis. This patient underwent a total of 11 lines of therapy. The other patient treated with FLAG relapsed after the first HSCT and was subsequently started on a regimen including nelarabine, peg-asparaginase and venetoclax. Due to persistent MRD positivity, FLAG therapy was initiated. The patient later chose to discontinue treatment and was discharged at his own request. The disease was progressed and the patient died. This patient received a total of 7 lines of therapy. The remaining 3 patients (23.1%) received no further treatment after venetoclax-based therapy. Two of the patients died following the response evaluation: one due to disease progression and the other due to viral and fungal infections. The third patient died of sepsis before a response evaluation could be performed.

Two patients (15.4%) who underwent allogeneic HSCT after venetoclax-based bridging therapy continued venetoclax maintenance therapy after transplantation. 1 of these patients received azacitidine in combination with venetoclax due to post-transplant MRD positivity but was switched to daratumumab after 3 cycles because MRD negativity could not be achieved. This patient experienced disease relapse in the fifth month of daratumumab treatment. The second patient remains in remission and is currently in the third year of follow-up, receiving single-agent venetoclax at a dose of 200 mg. Treatment response and outcomes following venetoclax-based therapy are summarized in Table 3.

Table 3. Treatment response and outcomes following venetoclax-based therapy

Parameter	Value
Duration of neutropenia (days) median (range)	14 (7-30)
Neutrophil recovery day median (range)	21 (14-36)
Duration of thrombocytopenia (days) median (range)	12 (2-27)
Platelet recovery day median (range)	23 (12-29)
Venetoclax treatment response	
CR	2 (15.4%)
CRi	6 (46.2%)
CMR	3 (23.1%)
PD	1 (7.7%)
NE	1 (7.7%)
Subsequent therapy	
Allogeneic HSCT	7 (53.8%)
Other*	3 (23.1%)
None	3 (23.1%)
Post HSCT maintenance venetoclax	2 (15.4%)
Survival status	
Death	9 (69.2%)
Alive	4 (30.8%)

*Blinatumumab (n=1), FLEND (n=1), FLAG (n=1)
CR: Complete remission, CRi: Complete remission with incomplete count recovery, CMR: Complete metabolic response, PD: Persistent disease, NE: Not Evaluable, HSCT: Hematopoietic Stem Cell Transplantation

The treatment was generally well tolerated. No patients discontinued therapy due to treatment-related toxicity. Grade 3 or higher treatment-related hematologic adverse events included neutropenia (13/13, 100%), anemia (6/13, 46.2%) and thrombocytopenia (11/13, 84.6%). Treatment-related non-hematologic adverse events included febrile neutropenia (11/13, 84.6%), gastrointestinal bleeding (1/13, 7.7%), sinonasal mucormycosis (1/13, 7.7%) and invasive pulmonary aspergillosis (1/13, 7.7%). The patient who subsequently developed mucormycosis had exhibited primary refractory disease. Mucormycosis emerged early during the initiation of second-line therapy. This patient received the FLAG-venetoclax regimen (venetoclax 200 mg for 7 days) in conjunction with fluconazole prophylaxis. The patient who developed pulmonary aspergillosis had undergone

heavily pretreatment and was diagnosed with ETP-ALL/LBL. Throughout all lines of treatment, the patient experienced prolonged periods of neutropenia. Pulmonary aspergillosis developed while the patient was receiving azacitidine, daratumumab, dexamethasone, and venetoclax (400 mg for 28 days). The infection occurred during a period of profound neutropenia despite ongoing micafungin prophylaxis. At the time of analysis, 9 patients (69.2%) had died and 4 (30.8%) were still alive. 5 patients died due to disease progression, 2 patients died due to infections occurring during the neutropenic period following venetoclax-based treatment and the other 2 patients died due to infection complications observed in the early and late stages of HSCT. All four alive patients remained in remission post-HSCT, three of whom proceeded to transplant following venetoclax-based treatment. With a median follow-up time of 7 months, the median PFS was 5 months (95% CI, 1.8-8.1; Figure 1) and the median OS was 7 months (95% CI, 4.0–9.9; Figure 2).

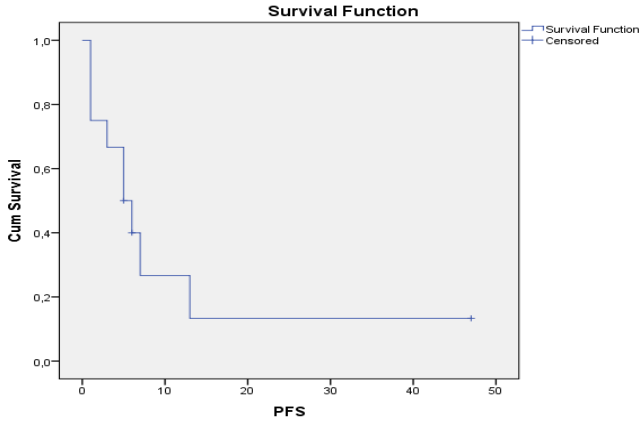

Figure 1. The median PFS was 5 months (95% CI, 1.8-8.1)

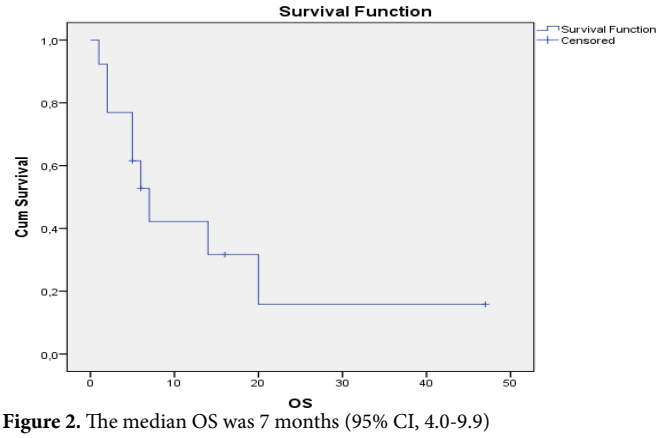

Figure 2. The median OS was 7 months (95% CI, 4.0-9.9)

DISCUSSION

Previous case reports have described the use of venetoclax in patients with ALL/LBL.[11-16] Several phase I/II trials have explored its efficacy in both adult and pediatric populations with newly diagnosed or R/R disease.[7,8,17-20] Preclinical studies have shown that BCL-2 expression is highest in early thymic progenitors and decreases with T-cell maturation, suggesting that precursor T-cell ALL/LBL-particularly the ETP subtype-may be especially sensitive to venetoclax.[21] Accordingly, clinical reports have highlighted venetoclax activity in R/R T-ALL, with increasing focus on its potential role in ETP-ALL.[15,22]

In frontline T-ALL/LBL, Ravandi et al.[19] added venetoclax to HyperCVAD, nelarabine, and PEG-asparaginase, demonstrating superior 2-year PFS and duration of response (DOR) (87.9% and 93.6%, respectively) compared to historical controls. Similarly, Luskin et al.[17] investigated venetoclax combined with mini-HyperCVAD in both newly diagnosed and R/R ALL, reporting a 90.9% MRD-negative CR rate in newly diagnosed patients and a 37.5% CR rate in the R/R subgroup, which included T-ALL cases. 8 R/R patients were primarily T-ALL (5/8, 62.5%) and frequently had TP53 (6/8) and had undergone intensive prior treatment (median 2 treatment lines; 62.5% relapsed after HSCT).

In the R/R setting, venetoclax has shown promising activity in various combination regimens. Shi et al.[18] combined venetoclax with daratumumab and the CAGE regimen, achieving a CR rate of 47.6% in R/R T-ALL/LBL patients, with ETP-ALL cases showing 100% bone marrow remission. These findings suggest that this regimen may serve as an effective salvage therapy for patients with R/R disease and as a potential bridge to HSCT for those achieving CR.[18] Cao et al.[20] administered venetoclax with azacitidine in 18 R/R T-ALL/LBL patients, achieving an ORR of 88.9%, though hematologic toxicity was notable. After the treatment, 66.7% of patients underwent allo-HSCT.20 Pullarkat et al.[8] explored a triplet of venetoclax, low-dose navitoclax and chemotherapy in heavily pretreated ALL/LBL patients, reporting a CR rate of 60%, with one-third achieving MRD negativity. 28% of patients proceeded to HSCT or CAR-T therapy following remission.8 In a smaller study by Short et al.,[7] venetoclax with mini-HCVD led to a CR/CRi rate of 57% and MRD negativity in 45% of responders, though response durations were limited (median DOR: 6.3 months).

In real-world settings, Canaani et al.[9] reported venetoclax-based regimens in a small mixed cohort of T-ALL and B-ALL patients, noting ORRs of 55% with chemotherapy combinations and 46% when combined with navitoclax. While encouraging, these regimens were applied uniformly without adjustment for individual patient variables. Similarly, Carpentier et al.[10] presented one of the earliest real-world experiences of venetoclax in R/R T-ALL/LBL, reporting a 60% response rate and a median OS of 7.7 months. However, the fixed administration schedule led to notable prolonged cytopenias and MRD assessment was not available, limiting the evaluation of response quality. More recently, Fan Yang et al.[23] incorporated venetoclax into a daratumumab-anchored regimen (Daratumumab+venetoclax+CAGE) in high-risk R/R T-ALL/LBL, including post-allo-HSCT patients, achieving a CR/CRi rate of approximately 50%. The study highlighted CD38-targeting as a rationale for combining daratumumab and venetoclax, although the therapy followed a fixed design.

Unlike phase I/II trials, our study reflects real-world individualized use of venetoclax in R/R ALL/LBL. Our cohort consisted of younger, heavily pretreated patients, 38.5% of

whom had relapsed after allo-HSCT. In this challenging population, we achieved a complete remission rate (CR, CRi) of 84.6% and an MRD-negative CR rate of 38.5% with venetoclax-based therapy and more than half of the patients (53.8%) successfully progressed to transplantation. This rate further supports the notion that venetoclax-based combinations are not only effective as salvage therapy but also serve as a successful bridging strategy. In terms of survival outcomes (OS=7 months, PFS=5 months), our results are consistent with those reported by Canaani et al.[9] (OS, 7.7 months) and Richard-Carpentier et al.[10] (OS, nearly 7 months). This finding indicates that, despite heterogeneous patient populations across different centers, venetoclax provides a comparable clinical benefit. It is noteworthy that patients with ETP-ALL/LBL, a biologically high-risk subgroup, also achieved remission. Notably, achieving an MRD-negative CR in the ETP-ALL/LBL subgroup is consistent with the results reported in the literature.

Furthermore, our study encompasses a broader range of chemotherapy regimens compared to the current literature, including FLAG, nelarabine/asparaginase, and FLEND as backbone regimens. Shorter venetoclax schedules appear to be clinically effective and feasible based on our observational findings. This diversity demonstrates the adaptability of venetoclax-based therapy across different treatment intensities and clinical settings. Beyond efficacy, our experience also highlights important real-world challenges; namely, drug-drug interactions with antifungal agents and the necessity for individualised venetoclax dose and duration adjustments outside of clinical trial settings. The inclusion of MRD-based response assessment further strengthens our findings by objectively documenting deep remissions.

These results underscore the practical applicability of venetoclax-based regimens in the routine treatment of R/R ALL/LBL. Our data demonstrates that venetoclax can serve as a treatment option that can be integrated with various chemotherapy or targeted approaches and can induce remission and transition to curative HSCT even in patients who have undergone intensive prior therapy or have relapsed after transplantation.

Limitations

This study has some limitations. The small sample size, retrospective design and lack of a control group prevent definitive conclusions about the contribution of adding venetoclax to chemotherapy. The combination of venetoclax with different chemotherapy regimens, while reflecting real-world practice, makes it difficult to compare outcomes between treatment regimens and determine the optimal combination strategy. Additionally, the individualised dosing and administration schedules of venetoclax have led to variability in drug exposure, complicating the interpretation of toxicity and efficacy. Pharmacokinetic interactions between venetoclax and concomitant antifungal therapies may also have influenced the results; however, this has not been systematically analysed.

CONCLUSION

Prospective evaluation of venetoclax-based therapies in larger and more diverse ALL cohorts is needed to better characterize their safety and define their role in clinical practice. While our findings suggest that venetoclax-based regimens are feasible and can be integrated into various treatment backbones, the optimal timing, dosing and combination strategies remain uncertain. As with many novel agents, earlier incorporation may offer potential benefit, but this requires cautious interpretation and further confirmation. Additional studies are warranted to determine the most appropriate and least toxic approaches for using venetoclax in ALL.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 05.07.2023, Decision No: 2023-25).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Surgical and medical practices: S.Y.K., L.K., S.M., H.S.B., A.H.A; Concept: S.Y.K.; Design: S.Y.K., L.K.; Data collection or processing: A.H.A, S.M.; Analysis or interpretation: S.M., S.Y.K.; Literature search: L.K., S.Y.K.; Writing: S.Y.K., L.K.

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