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Venetoclax combination with Cladribine, idarubicin, Cytarabine for relapsed T-Cell acute lymphoblastic leukemia/lymphoblastic lymphoma treatment: A case report and literature review

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ABSTRACT

Acute lymphoblastic leukemia (ALL) represents only 20 % of adult acute leukemias, while Lymphoblastic lymphoma is even rarer, accounting for 2 % of adult non-Hodgkin lymphomas. T-acute lymphoblastic leukemia (T-ALL) and T-lymphoblastic lymphoma (T-LBL) are neoplasms characterized by the presence of immature T-cell precursors or lymphoblasts. Relapsed T-ALL or LBL is associated with a very poor prognosis, necessitating the exploration of novel therapeutic approaches. This case report describes the use of Venetoclax in combination with Cladribine, Idarubicin, and Cytarabine (CLIA) as salvage therapy for relapsed T-ALL/T-LBL. The treatment regimen resulted in remission and negative minimal residual disease. However, it was accompanied by delayed count recovery, febrile neutropenia, and Central Line-Associated Bloodstream Infection. The management of central nervous system involvement was challenging due to low platelet counts requiring transfusion support. The findings highlight the need for further investigation into the efficacy and optimal therapeutic regimen for relapsed T-ALL/T-LBL. Additionally, the case emphasizes the importance of early salvage therapy and potentially consolidative hematopoietic stem cell transplantation for improved survival outcomes in relapsed T-ALL/T-LBL patients.

1. Introduction

Acute lymphoblastic leukemia (ALL) represents only 20 % of adult acute leukemias, while Lymphoblastic lymphoma (LBL) is even rarer, accounting for 2 % of adult non-Hodgkin lymphomas [1]. T-ALL and T-LBL are neoplasms characterized by the presence of immature T-cell precursors or lymphoblasts, with >90 % of cases displaying a precursor T-cell immunophenotyped. Mutations in the NOTCH pathway, including NOTCH1 and FBXW7, are found in approximately 60 % of adult T-ALL patients and have been associated with improved overall survival (OS), particularly in the absence of RAS or PTEN abnormalities. Notably, T-LBL commonly presents with a hematological emergency, such as superior vena cava syndrome, upper airway obstruction, and pericardial or pleural effusions. Additionally, involvement of lymph nodes, skin, bone, gonads, liver, and spleen is frequently observed [1].

Central nervous system (CNS) disease is more prevalent in patients with bone marrow involvement and can serve as a site of relapse. Prognosis in T-ALL and T-LBL is influenced by various factors, including clinical, cytogenetic, immunophenotypic, and molecular variables. However, the prognostic significance of many molecular markers remains uncertain.

Relapsed T-ALL or LBL is associated with a very poor prognosis, with a 5-year OS rate of only 5 % [2] Treatment strategies that involve early salvage therapy and the possibility of consolidative hematopoietic stem cell transplantation (HSCT) are predictive of better survival outcomes. These findings underscore the urgent need for novel and effective

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therapies for T-ALL that can induce minimal residual disease (MRD) negative responses and facilitate a potentially curative HSCT [3].

Relapsed T-ALL/T-LBL poses a significant clinical challenge, as treatment options for these patients are limited. Salvage therapies using various regimens have shown varying outcomes.

Venetoclax is a BH3-mimetic antagonist of the BCL-2 anti-apoptotic protein, inhibiting BCL-2′s suppression of pro-apoptotic proteins like BAX, which leads to mitochondrial outer membrane permeabilization (MOMP) and apoptosis [4] Venetoclax single agent has been shown to play a crucial role in the normal development of T-cells [5] and to alter proliferation in human T-ALL cell lines particularly in ETP phenotype. However, the rapid emergence of resistance may limit the use of this drug as a single agent and it showed clinical activity in patients with T-ALL in combination with chemotherapy [6].

Here, we present a case report of the use of Cladribine, Idarubicin, and Cytarabine as salvage therapy for a patient with relapsed T-ALL and T-LBL.

2. Case description

A 23-year-old male patient with no prior history of chronic medical conditions was referred from a peripheral hospital due to the presence of a mediastinal mass and symptoms suggestive of superior vena cava obstruction. The patient reported experiencing neck swelling, enlargement of multiple lymph nodes, along with symptoms such as shortness of breath, dysphagia, a productive cough with whitish sputum, generalized fatigue, and reduced oral intake for a duration of two weeks.

A Complete blood count (CBC) was performed, revealing a hemoglobin level of 13.3 g/dL, WBC count of 7.93 × 10^3/μL, and a differential count that showed 10 % circulating blasts. The platelet count was 479 × 10^3/μL. Upon presentation, bone marrow aspiration (Fig. 1) and trephine biopsy (Fig. 2) were conducted, revealing a hypercellular marrow with approximately 50 % cellularity. The bone marrow was diffusely infiltrated by blasts, accounting for 85 % of the cells, consistent with a diagnosis of T-ALL. These blasts tested positive for CD5, CD2, CD7, CD99, CD4, CD8, s-CD3 (18 %), CD38, CD58, and c-CD3, while they tested negative for CD34, TdT, and CD1a.

A chest Computed Tomography (CT) scan revealed the presence of a large infiltrative anterior mediastinal mass measuring 20 cm x 9 cm x 12 cm. The mass extended superiorly to the thoracic inlet and inferiorly to the cardio phrenic region (Fig. 3). This mass caused significant stenosis and near occlusion of the superior vena cava and both brachiocephalic veins. Additionally, multiple enlarged lymph nodes were observed in the cervical supraclavicular, cardio phrenic, and upper abdominal retroperitoneal regions. A core biopsy of the mediastinal mass was performed, confirming histologic and immunophenotypic features consistent with Lymphoblastic T-cell lymphoma. Immunohistochemistry staining revealed positive results for CD99, CD5, CD2, CD7, CD43, CD3, TDT, CD4, and CD8, while stains for CD20, PAX5, Epstein-Barr Virus, Cd1a, cd34, Pan-CK, MUM-1, CD30, BCL2, BCL6, and Ki67 were negative. Imaging studies did not show any evidence of central nervous system (CNS) involvement, although cerebrospinal fluid (CSF) analysis revealed the presence of an atypical aberrant T-cell population, raising suspicion for T-cell lymphoma.

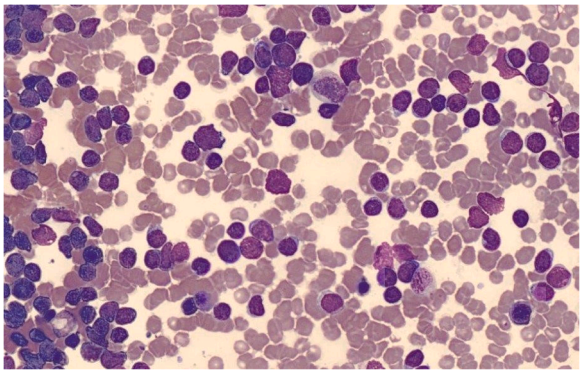

Fig. 1. The bone marrow aspirate shows heavy infiltration by immature mononuclear cells; the blasts are variable in size with an open chromatin, high N/C ratio, and inconspicuous nucleoli. Few of the blasts demonstrate the hand-mirror sign. No Auer rods are identified. The normal trilineage hematopoiesis is markedly reduced.

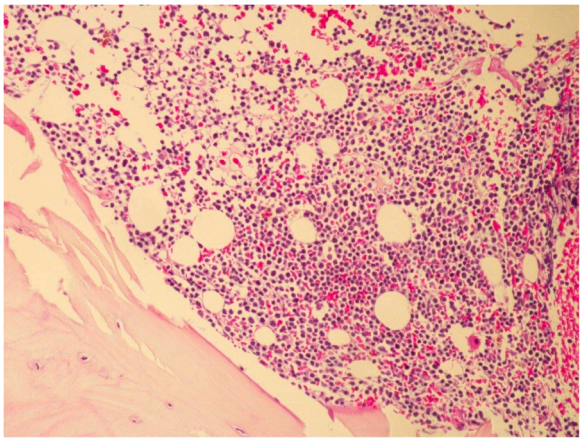

Fig. 2. Hypercellular bone marrow (cellularity is ~90 %) diffusely infiltrated by sheets of immature mononuclear cells. Few preserved trilineage hematopoiesis, mainly megakaryopoiesis.

The patient was initiated on the AALL0232 protocol. On day 33 of the protocol, a bone marrow biopsy (BMB) was performed, which showed no evidence of persistent blasts based on immunomorphological examination. Flow cytometry analysis of the bone marrow did not detect the presence of leukemia blasts. One month after treatment initiation, a repeat CT scan demonstrated a significant reduction in the size of the previously observed mediastinal mass and intrathoracic lymphadenopathies. A follow-up PET-CT scan performed at the same time showed no suspicious FDG-avid nodal disease or solid organ involvement (Fig. 4). The treatment course was complicated by upper limb deep venous thrombosis, right-sided weakness with generalized tonic-clonic seizures, acute/subacute ischemic changes in the brain, hyperdense dilated superior sagittal sinus related to acute thrombosis, febrile neutropenia, extensive anal and perianal inflammation, and small abscesses. Repeat bone marrow biopsy showed no residual disease after the consolidation phase.

Prior to commencing the maintenance phase, the patient experienced left facial and periauricular pain, along with tinnitus and sensitivity to sound. Subsequently, the patient developed left-sided lower motor neuron facial nerve palsy, which had limited improvement with prednisolone treatment. The patient also experienced moderately severe holocephalic headaches, described as band-like in nature, without visual changes or autonomic features. Over time, the symptoms became bilateral and increasingly debilitating, resulting in an inability to close both eyes. At the same time, the frequency and severity of the headaches worsened. Notably, the patient responded well to Pregabalin, with effective pain relief and headache management. The MRI brain revealed mild thickening in both facial nerves with more pronounced enhancement on the left side. CSF analysis indicated the presence of query cells, accounting for 79.7 % of the gated cells, characterized by dim CD45 expression and low SSC. These cells tested positive for CD3, CD5, CD8, CD2, CD7, CD99, and Cy-CD3, while CD4, CD34, and TdT were negative. The patient was started on the HyperCVAD arm B protocol and received two cycles of treatment, including intrathecal chemotherapy injections with Methotrexate, Cytarabine, and hydrocortisone. Subsequent CSF analysis showed no malignant cells. However, the patient was found to have 65 % peripheral blood blast cells, with flow cytometry revealing 37

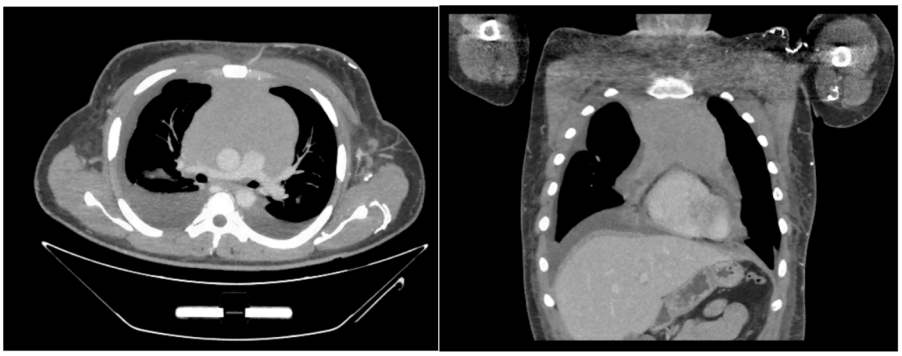

Fig. 3. Initial CT Scan with IV Contrast. The image reveals a large infiltrative anterior mediastinal mass that extends superiorly to the thoracic inlet and inferiorly to the cardiophrenic region. The dimensions of the mass are measured as 20 cm craniocaudal x 9 cm anteroposterior x 12 cm on transverse diameter. The mass is causing significant stenosis, nearly occluding the superior vena cava and both brachiocephalic veins. There is evidence of acute thrombosis involving the left subclavian vein and left axillary vein. Notably, there are prominent chest wall collaterals observed. The mass is exerting pressure on the lower aspect of the trachea and both bronchi. Multiple enlarged supraclavicular and cardiophrenic lymphadenopathy are visible, along with small bilateral axillary lymph nodes. Additionally, there is a moderate pericardial effusion and a bilateral moderate pleural effusion, with the right side showing greater accumulation.

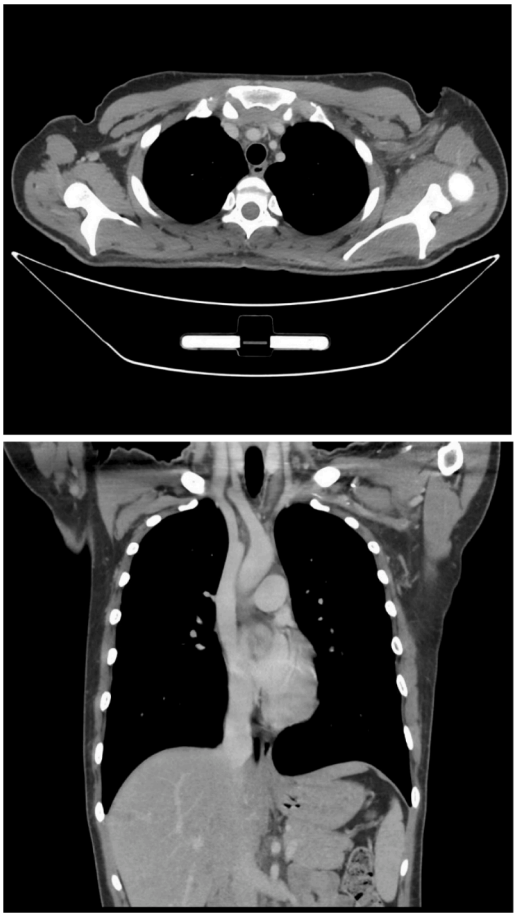

Fig. 4. Post induction CT Scan with IV contrast showing interval complete resolution of previously seen large infiltrative anterior mediastinal mass that extends superiorly to reach at the thoracic inlet and inferiorly to reach the cardiophrenic region. There is interval significant resolution of multiple intrathoracic lymphadenopathies. Also, there is interval resolution of previously seen moderate pericardial effusion as well as bilateral moderate pleural effusion.

% T-lymphoblasts. The query cell population with positive CD45 expression and low SSC was identified. These cells were positive for CD5, CD3, CD7, CD2, CD58, CD38, cy-CD3, and CD99, while they were negative for CD34, CD1A, TDT, CD4, and CD8, with all other tested myeloid and B-lineage antigens also being negative.

Considering the patient's refusal for a bone marrow examination, the tumor board committee opted to begin treatment with CLIA Cladribine/Idarubicin/Cytarabine) in combination with Venetoclax for a duration of 7 days. The treatment plan also included the resumption of triple intrathecal chemotherapy injections, which had been temporarily halted due to thrombocytopenia. However, the treatment course was complicated by deep neutropenia, thrombocytopenia, and a central line-associated bloodstream infection (CLABSI). On day 25, a repeat bone marrow examination was conducted, demonstrating no remaining disease based on both morphology and flow cytometry analysis, and the CSF cytology was negative as well. As a result, it was decided to proceed with allogeneic stem cell transplantation from a matched sibling donor. The conditioning protocol involved Cyclophosphamide, Total Body Irradiation (TBI), and a cranial radiation boost, which achieved engraftment of absolute neutrophil counts (ANC) on day +32. However, the course was complicated by hemorrhagic cystitis with a positive BK virus. Additionally, the patient developed acute kidney injury, which was medication-related. Furthermore, a pulmonary infection was observed, and a high-resolution computed tomography (HRCT) of the chest revealed ground glass opacity in the right lung.

Bone marrow evaluation on day +30 showed blasts comprising 2–3 % based on morphology and 1.8 % based on flow cytometry. However, on day +49, a circulating blast count of 20 % was detected. Post-transplant chimerism analysis was conducted on day +51, revealing 100 % donor DNA. To manage the disease, the patient was initiated on Hydroxyurea for cytoreduction and received transfusion support as needed. Additionally, a Do Not Resuscitate (DNR) status was initiated. Unfortunately, the patient passed away on day +59 due to cardiopulmonary arrest.

3. Discussion

To our knowledge, this is the first case report describing the use of Venetoclax in combination with CLIA (Cladribine, Idarubicin, and Cytarabine) in relapsed T-ALL/T-LBL, which resulted in complete remission (CR) post-induction. This regimen has previously been used for acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS) [7] Limited treatment options for relapsed and refractory T-ALL/T-LBL necessitate further research into novel therapies.

Although Nelarabine is an FDA-approved therapy for relapsed T-ALL and T-LBL, with a CR rate of 41 %, a median overall survival (OS) of 20 weeks, and an OS rate of 28 %, [8] it was unfortunately unavailable at our institute. Several studies have shown higher expression of BCL2 in T-ALL blasts compared to normal subjects, which may explain the poor

outcomes observed in adult patients with T-ALL [9] Similarly, high expression of BCL2 has been observed in T-LBL blasts. Although T-ALL and T-LBL represent different clinical presentations of the same disease and are often treated with identical regimens, BCL2 inhibitors have shown higher efficacy in T-LBL compared to T-ALL [10] Venetoclax has demonstrated clinical activity as a single agent in relapsed/refractory early T-cell precursor ALL (ETP-ALL) [1,11].

Several combinations with Venetoclax have been explored to treat relapsed/refractory T-ALL. For example, Venetoclax plus Dacogen was administered to five patients, four of whom (80 %) achieved MRD negativity [12] Another combination of Venetoclax and Daratumumab plus CAG (Cytarabine, Aclarubicin, and G-CSF) was used as concurrent chemotherapy [13]. Six out of seven (85.7 %) patients achieved MRD negativity, with four patients (57.1 %) attaining MRD negativity after one cycle. Subsequently, five out of six (83.3 %) MRD-negative patients underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT). In a Phase I study, Venetoclax was combined with Mini-Hyper-CVD in older adults (>60 years) with untreated and relapsed/refractory ALL. The overall response rate (ORR) was 100 %, with nine out of ten (90 %) achieving CR and one patient achieving a partial response [14]. In Richard-Carpentier et al.'s study, Venetoclax was combined with Hyper-CVAD, fludarabine, Cytarabine, idarubicin, pegylated-asparaginase, nelarabine, vincristine, or Dacogen, resulting in remission and hematological recovery in 60 % of patients, with a median OS of 7.7 months and relapse-free survival (RFS) of 4.0 months [15] In another study, combining Venetoclax with low-dose navitoclax and chemotherapy showed promising preliminary results in relapsed/refractory ALL or LBL, including patients with prior stem cell transplantation, with a median OS of 6.6 months [16] Based on the evidence supporting the use of Venetoclax combinations in relapsed/refractory T-ALL, we combined Venetoclax with CLIA.

In our patient's treatment course, we observed delayed count recovery, febrile neutropenia, and central line-associated bloodstream infection (CLABSI) as potential complications associated with the use of Venetoclax in combination with CLIA. To control CNS involvement, we continued weekly triple intrathecal chemotherapy injections, although this was challenging due to low platelet counts requiring transfusion support. Ultimately, the primary goal of salvage therapy for relapsed T-ALL/T-LBL was achieved by bridging the patient for allogeneic stem cell transplantation.

The rapid emergence of drug resistance may limit the effectiveness of Venetoclax [17]. resistance arises from various mechanisms, including mutations in BCL2 that decrease drug affinity, BAX mutations that impair localization, and MCL1 upregulation via chromosomal amplification and NF-κB activation. Additionally, methylation of the PUMA promoter and altered NOXA transcripts contribute to resistance, [4] alongside metabolic adaptations such as changes in oxidative phosphorylation and fatty acid metabolism [18] To overcome Venetoclax resistance, researchers are exploring both direct MCL1 inhibitors (e.g., S63845, AMG-176) and indirect strategies involving deubiquitinase and CDK9 inhibitors [19]

A review of the literature reveals that various combinations of chemotherapy agents and novel therapies have been used in the treatment of T-ALL and T-LBL. Nelarabine combination therapy with cyclophosphamide and Etoposide has reported CR rates of 35 % to 71 % in children and 60 % in adults [20] Other agents, such as Clofarabine, have also shown modest responses in T-ALL, although their efficacy in T-ALL/T-LBL specifically requires further investigation. In one study, the ORR (CR/CRi + PR) was 35 % [21].

Other novel agents have been utilized in studies with limited numbers but have shown promising results. For example, Bortezomib was used in combination with chemotherapy for patients with relapsed T-ALL [22]. The results demonstrated an encouraging CR rate of 68 % among 22 patients. Among the ten LBL patients included in this study, seven patients had an overall response, including CR. The OS rate was 67 % for MRD-negative patients, compared to 43 % for MRD-positive patients. Another agent, daratumumab, was also utilized in combination with chemotherapy and studied in pediatric and young adult patients with relapsed/refractory T-ALL. Among pediatric ALL patients, ten patients (41.7 %) achieved CR at the end of Cycle 1 (with a 90 % confidence interval of 24.6–60.3 %). The ORR was 83.3 %, with CR in 13 patients (54.2 %) and CRi (complete response with incomplete hematologic recovery) in seven patients (29.2 %). In young adult ALL patients, the ORR was 60.0 % (all CR), and in LBL lymphoma patients, the ORR was 40.0 % (all CR) [23]

New clinical trials have been conducted to evaluate new agents to overcome challenges in T-ALL. One of these agents is Menin inhibition with revumenib has been evaluated for KMT2A-rearranged relapsed or refractory acute leukemia, including patients with T-ALL. The achieved CR + CRh rate was 22.8 %, with an ORR rate of 63.2 % [24]

Lu et al. published the results of a phase 1 trial using CD7-targeted chimeric antigen receptor (CAR) T cells for patients with T-ALL and T-LBL. On day 28, all six included patients (100 %) achieved CRi and MRD negativity. Five patients received consolidative allo-HSCT at a median time of 57.5 (42–92) days after infusion, with one death secondary to grade 3 acute graft-versus-host disease (GVHD) [25].

4. Conclusion

This case report highlighted the combination of Venetoclax with CLIA as a potential salvage option for relapsed T-ALL/LBL in a single patient case as there is no standard, and a need for larger clinical trials to validate these findings and to explore the long-term outcomes of such treatment protocols, is needed.

Informed consent

Informed consent has been taken form the patient to use the patient data for research purposes.

CRediT authorship contribution statement

Alaa Eldein Yahia: Writing – review & editing, Writing – original draft, Supervision, Software, Methodology, Data curation. **Ibrahim Motabi:** Writing – review & editing, Supervision, Resources, Project administration. **Abdullah A. Alsakkaf:** Writing – review & editing, Software. **Kamal Alzahrani:** Writing – review & editing. **Laila M. Alsuhaibani:** Software. **Bilal Albtoosh:** Project administration. **Abdullah Khaled AlBathi:** Software. **Abdullah M. Alrajhi:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

All authors declare that they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2025.100506.

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