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CASE REPORT

A complete response with daratumumab, venetoclax, azacitidine and dexamethasone in a heavily pre-treated, chemo-refractory early T-precursor acute lymphoblastic leukemia/lymphoma patient

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Abstract

Early T-precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) is a rare and aggressive subtype of T-cell leukemia with poor prognosis and resistance to standard treatments. We report a 21-year-old male with ETP-ALL/LBL who, after an initial complete remission with the HOELZER protocol, experienced early relapse and was refractory to subsequent FLEND and BFM protocols. Following disease progression and complications, he was treated with a combination of daratumumab, venetoclax, azacitidine, and dexamethasone. This regimen achieved complete remission after one cycle. This case highlights the potential of this combination therapy as an effective treatment for refractory ETP-ALL/LBL, suggesting further research is warranted to validate its efficacy and safety.

Keywords Early T-precursor acute lymphoblastic leukemia/Lymphoma · Daratumumab, Venetoclax · Azacitidine · Dexamethasone · Allogeneic hemopoietic stem cell transplantation

Introduction

Early T-precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) is a rare, distinct subtype of T-ALL characterized by genomic instability, a dismal prognosis and refractoriness to standard chemotherapy [1]. The clinical course is aggressive and management of patients with ETP-ALL/LBL is challenging. The outcome of patients is poorer than that of other subtypes of T-ALL in previous studies [2]. Despite the availability of several salvage chemotherapy protocols, the rates of successful response remain insufficient [3]. Allogeneic hemopoietic stem cell transplant (allo-HSCT) remains an important part of the therapy for ALL including high-risk subgroups such as ETP-ALL/LBL. The dismal outcomes of ETP-ALL/LBL with standard chemotherapy have led others to explore the use of different approaches including hypomethylating agents, monoclonal antibodies and BCL-2 inhibitors [4]. ETP-ALL is characterised by the absence of the T cell surface markers CD1a and CD8, minimal or absent expression of CD5, and abnormal expression of myeloid and haematopoietic stem cell markers such as CD13, CD33, CD34 and CD117. These findings suggest that the addition of myeloid-directed therapies

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might improve the poor outcome of ETP ALL [5]. Favorable therapeutic efficacy has been observed with these novel therapies [6], but further studies are needed to better evaluate their clinical utility. Herein, we report a case with R/R ETP-ALL/LBL who relapsed early after first-line combination chemotherapy and was refractory to second- and third-line chemotherapy protocols but successfully achieved complete remission (CR) with daratumumab, venetoclax, azacitidine and dexamethasone combination therapy.

Case

A 21-year-old male patient presented with newly onset cervical lymph nodes in August 2020. PET-CT showed increased FDG uptake in bilateral cervical, mediastinal, paracaval, prevascular, right upper and lower paratracheal, subcarinal, right bronchopulmonary, right hilar and paraesophageal lymphadenopathies at the level of the malignancy (SUV max 3.8–11). He was diagnosed with ETP-ALL/LBL after evaluation of cervical lymph node biopsy at a local hospital. The immunohistochemical staining of the neoplastic cells demonstrated that expressed CD3+, CD7+, CD34+, CD117, HLA-DR+, CD13+, CD33+, CD11b, CD65+; CD8-, CD1a- and had a Ki-67 index of 90%. Bone marrow biopsy and flow cytometric analysis showed no increase in blasts. Bone marrow cytogenetics showed normal karyotype and revealed no numerical and no structural abnormalities. Next-generation sequencing and fluorescence in situ hybridization did not reveal any prognostically or therapeutically relevant variant. He had no central nervous system (CNS) involvement. First-line treatment was initiated with the HOELZER protocol. He received intrathecal prophylaxis. After the induction phases, PET-CT showed complete remission and there was no finding in favour of ETP-ALL involvement in the bone marrow. A CR was achieved and the entire protocol was completed. Allo-HSCT was not planned in CR1 at the local hospital, and no donor screening was performed. The last dose of maintenance treatment was administered in April 2023. He was admitted to our hospital for routine follow-up 3 months after completion of the HOELZER regimen. On presentation to our center, he complained of shortness of breath and fatigue. His laboratory values were normal. PET-CT was performed with suspicion of recurrence and showed 9 cm pleural effusion, 2.7 × 2 cm lesion in the right lung lower lobe pleural-based, 3 × 2 cm lesion in the right atrial neighbourhood and multiple 2 × 2 cm lesion in the paraesophageal area with malignant increased FDG uptake (SUV max 7.5–9.4). A biopsy was performed from the pleura-based lesion by video assisted thoracoscopic surgery. It was consistent with ETP-ALL relapse. In our centre, second line chemotherapy was initiated with FLEND protocol (nelarabine, fludarabine and etoposide) + PEG-asparaginase with allogeneic transplantation planning. Intrathecal CNS prophylaxis was given. At the end of 1 cycle of FLEND + PEG-asparaginase, PET-CT showed progressive disease. Therefore, the BFM 2000 was initiated as third-line chemotherapy. On the first day of the BFM 2000 protocol induction 1 A (initial 7 days of prephase with methylprednisolone and then methylprednisolone day 1–28 then taper over 10 days and cease; daunorubicin IV 30 mg/m2 days 8, 15, 22, 29; vincristine IV 1.5 mg/m2 days 8, 15, 22, 29; L-asparaginase IV 5000 IU/m2 days 12, 15, 18, 21, 24, 27, 30, 33; methotrexate IT 12 mg days 1, 12, 33), the patient was diagnosed with catheter thrombosis and pulmonary thromboembolism, for which anticoagulant therapy was started. After the BFM 2000 protocol induction 1 A, progression was again detected on PET-CT. Right lung lower lobe pleural-based soft tissue mass 3.7 × 2.5 cm with dimensional progression and increased thickness on pleural surfaces in the right cardiophrenic area (SUVmax: 8.3–11.5). The remaining areas were stable in size and uptake appeared stable. Subsequently, daratumumab (16 mg/kg every 2 weeks iv), venetoclax (100 mg d1, 200 mg d2, 400 mg day3-28), azacitidine (75 mg/kg d1-7 for 28 days) and dexamethasone (40 mg/weekly) protocol was initiated as a bridge to allo-HSCT. After explaining the unapproved nature of this treatment, the rationale for its use and the potential side effects of the drug, written informed consent was obtained. The regimen was well tolerated. Micafungin prophylaxis was also initiated to prevent any fungal infections. Grade 4 neutropenia occurred. Throughout the treatment period, erythrocyte and platelet replacement was not required. Neutropenic fever occurred once. No opportunistic infections were observed. After 1 cycle of treatment, the patient achieved a CR on PET-CT (Fig. 1). During all these treatments, the donor screening of the patient could not be carried out due to problems with the payment of the health insurance. Therefore, the second cycle of treatment was started to ensure the continuity of the response. Micafungin prophylaxis was also continued to prevent any fungal infections. A total of 2 treatment cycles were administered. However, grade 4 neutropenia occurred again in the 2nd cycle. On the 7th day of neutropenia, invasive pulmonary aspergillosis, haemophilius influenza type B and gram-negative sepsis developed. The patient was admitted to the intensive care unit and died due to ARDS.

Discussion

Venetoclax, a targeted BCL-2 inhibitor, emerged as a promising component in ETP-ALL/LBL treatment. This followed the identification of BCL2 as significantly expressed during the DN1 stage of early T-cell progenitors and

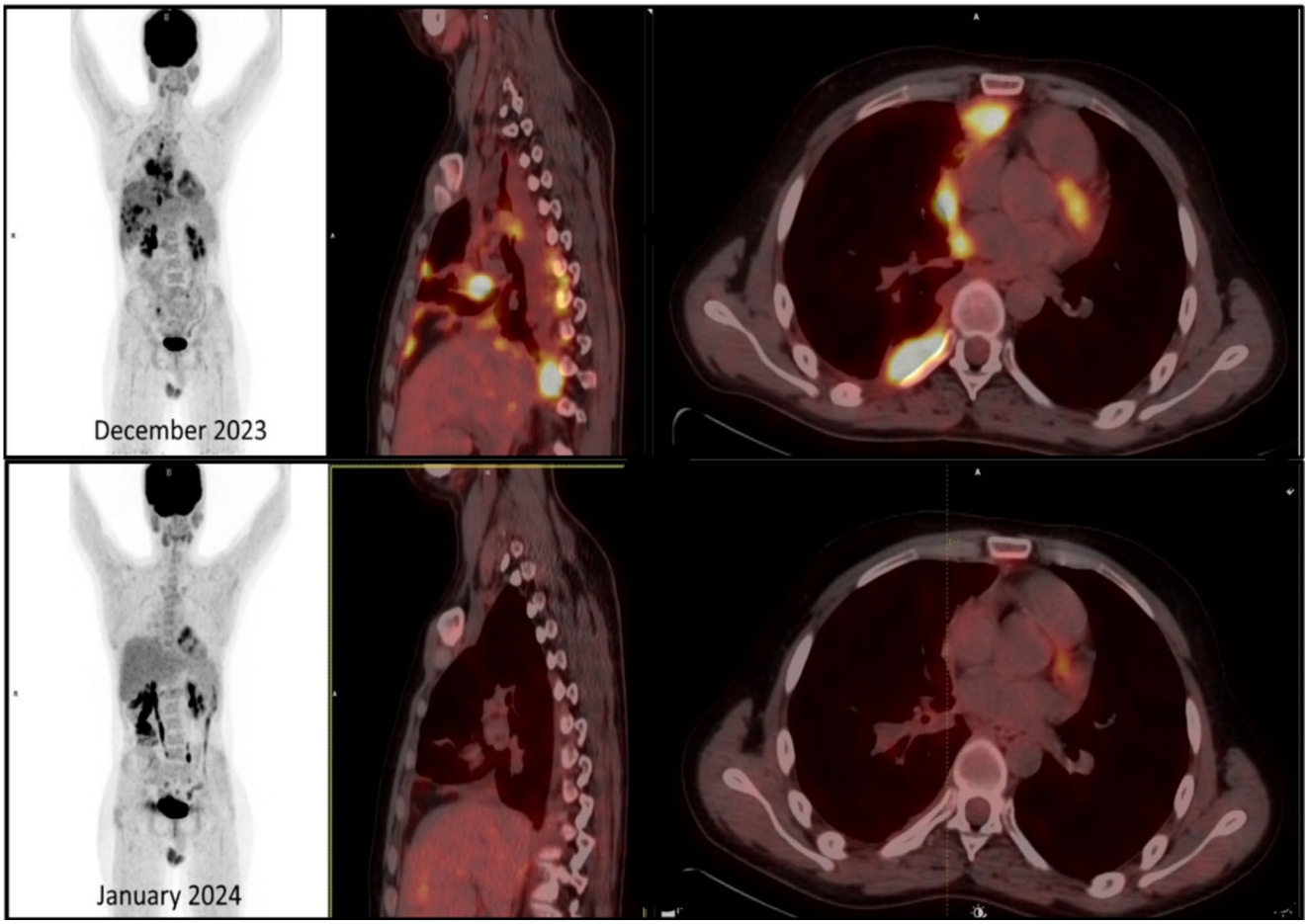

Fig. 1 In December 2023, nodular pleural lesions in the right hemithorax exhibited increased FDG uptake with an SUV of 11.5. The size and metabolic activity of these pleural mass lesions decreased significantly in January 2024 (Deauville score of 2)

research revealing ETP-ALL/LBL's reliance on BCL-2 for its anti-apoptotic function [7]. Subsequently, the efficacy of venetoclax against ETP-ALL/LBL was validated in patient-derived xenograft models of ETP-ALL/LBL leukemic cells [8]. Venetoclax, combined with other agents, has shown promise in treating ETP-ALL/LBL [2]. A Clinical trial demonstrated encouraging clinical efficacy of combination therapy with venetoclax in R/R T-ALL patients [6]. The successful outcome of venetoclax combination with other agents in achieving remission with minimal residual disease negativity and facilitating a bridge to allogeneic HSC transplant in adult patients with ETP-ALL/LBL was also documented in a case report [9]. Furthermore, venetoclax can also be combined with other therapeutic agents as demonstrated in a study where the combination of venetoclax with daratumumab and the CAGE regimen resulted encouraging remission rate in bone marrow, particularly in ETP-ALL/LBL patients [10].

Daratumumab, a monoclonal antibody targeting CD38, exerts its antitumor activity through multiple mechanisms, including antibody-dependent and complement-dependent cytotoxicity [11]. A preclinical study on ETP-ALL/LBL PDX models has demonstrated that CD38 expression is not affected by other cytotoxic chemotherapies and also its downregulation was not observed after the use of daratumumab in xenotransplant models thus suggesting its sustained efficacy as a potent target even under the influence of other chemotherapeutic agents [12]. A case report also highlights the rapid induction of morphological remission and achieving MDR negativity without significant toxicity after multiple administrations and enabling subsequent allo-HSCT. Daratumumab also demonstrated encouraging efficacy in achieving MDR negativity in patients who had relapsed after the second allo-HCST thus overall suggesting daratumumab as a potent and well-tolerated therapeutic candidate for ETP-ALL/LBL patients [4]. In a study by Prejzner et al., daratumumab was used as 16/mg/kg iv every 2 weeks with a different combination in 2 patients [13]. Considering this study, we preferred to use this dose and achieved a complete response with this regimen.

Combining azacitidine with venetoclax, particularly due to the commonly observed hypermethylation association

with PRC2 mutations offers a rational strategy [2]. A study on AML patients has demonstrated azacitidine can upregulate the expression of the proapoptotic protein thereby enhancing the sensitivity of leukemic cells to venetoclax-induced apoptosis [14]. Due to the co-expression of myeloid markers in ETP-ALL/LBL cases [5], this combination therapeutical strategy can be a good candidate to treat ETP-ALL/LBL patients. A case series including two ETP-ALL/LBL patients has also demonstrated ventoclax and azacitidine combinations as a reliable and safe approach for salvage therapy [15]. The combination of Venetoclax and Azacitidine has recently emerged as a promising treatment for relapsed/refractory (R/R) T-cell acute lymphoblastic leukemia (T-ALL) and lymphoblastic lymphoma (LBL), including ETP-ALL. A Phase 2 multicenter trial presented at ASH 2023 demonstrated that Venetoclax, in combination with Azacitidine, was an effective salvage regimen, with an overall response rate of 88.9%. The results from this study, which showed a median overall survival (OS) of 24.1 months, support its use as a viable option for R/R T-ALL/LBL patients who have failed other therapies [16]. A retrospective study demonstrated the potential efficacy and safety of daratumumab in treating relapsed/refractory ALL patients, showing continued effectiveness even in combination with chemotherapy. Although the optimal chemotherapy regimen for use with daratumumab is still undetermined, adding novel drugs like venetoclax is suggested as a promising approach [17].

Our case demonstrates the potential impact of daratumumab, venetoclax, azacitidine and dexamethasone combination therapy in achieving complete remission in a patient with heavily pre-treated, R/R ETP-ALL/LBL. This case provides the rationale for further study of the synergistic effect of this combination, which may provide a new and effective option in the treatment of R/R ETP-ALL/LBL. To the best of our knowledge, this is the first report in the R/R ETP-ALL/LBL setting and therefore data on long-term follow-up results, safety and toxicity profile are unknown. These limitations emphasise the need for larger case series.

Author contributions S.Y.K., Ö.G.S. and L.K. were the treating physicians and participated in the study design and writing of the manuscript. S.Y.K., M.V. and R.A. contributed to the writing of the manuscript and discussion of the case with the literature review. Ö.G.S and S.M. reviewed the manuscript. T.Ç. participated in the radyological analyses. All authors have read and approved the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent for publication was obtained from the patient. All the authors have reviewed the manuscript and approved it for publication.

Conflict of interest The authors declare no competing interests.

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