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Case Report

Negative Impact of Gemtuzumab Ozogamicin on CD33-Positive Early T-Cell Precursor Acute Lymphoblastic Leukemia: A Case Report

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Keywords

Early T-cell precursor acute lymphoblastic leukemia · Gemtuzumab ozogamicin · CD33 · Antibody-drug conjugate

Abstract

Introduction: Early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) is a rare subtype of T-cell leukemia that phenotypically expresses mature T-cell markers and immature myeloid markers such as CD33. Gemtuzumab ozogamicin (GO) is a novel agent for the CD33 molecular targeting antibody conjugated to the cytotoxic agent calicheamicin. GO is anticipated to be effective against ETP-ALL. In vivo studies promise antileukemic effects in cell lines; however, clinical reports to support this research are lacking. We treated a patient who suffered from CD33-positive ETP-ALL using GO. ***Case Presentation:*** We treated an 81-year-old man who suffered from ETP-ALL. The patient's leukemia expressed T cell and myeloid markers including cyCD3, CD5, CD7, CD33, and HLA-DR. Initially, the patient was treated using a standard chemotherapy regimen for acute lymphoblastic leukemia comprising cyclophosphamide, daunorubicin, vincristine, L-asparaginase, and prednisolone. The induction chemotherapy produced the expected complete hematological response; however, bone marrow blasts remained. Following consolidation chemotherapy, the patient maintained a full hematological response. Thereafter, we changed the consolidation regimen to nelarabine, which did not reduce bone marrow blasts effectively. After two courses of nelarabine therapy, we finally used GO at an 8 mg/m^2 weekly dose after confirming that CD33 expression was still positive in the patient's residual leukemic cells. GO was ineffective in treating the patient's leukemia, and peripheral blasts increased 30 days following treatment. The patient died 81 days after initiating GO therapy. ***Conclusion:*** This is the first clinical case of GO having a

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negative impact on ETP-ALL. Because the GO resistance mechanism for ETP-ALL has not been fully elucidated, treatment modification should be considered to achieve optimal clinical efficacy.

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Introduction

Early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) is an extremely aggressive type of T-cell leukemia [1]. ETP-ALL is a T-cell neoplasm composed of T-cell lineage-committed cells with limited early T-cell differentiation [2]. According to genuine clinical evidence, ETP-ALL was refractory to established chemotherapy protocols for common acute lymphoblastic leukemia (ALL) [2]. ETP phenotype ALL has a poor prognosis without optimal standard chemotherapy. ETP-ALL has stem cell markers such as CD34, CD117, HLA-DR, CD13, CD33, CD11b, and CD65 that are phenotypically distinct. ETPs are a subset of thymocytes that have immigrated from the bone marrow [3]. The oncogenesis of ETP-ALL is caused by activating mutations in the neurogenic locus notch homolog protein 1 (NOTCH1), leading to T-cell acute lymphoblastic leukemia transformation [4]. NOTCH1 activation in early T-cell proliferation causes abnormal lymphogenesis and T-cell neoplasm. NOTCH1 regulates lymphoid development in the thymus before T-cell commitment [5]. Furthermore, ETP-ALL can coexpress myeloid markers as bilineate phenotypes.

Genetic analysis of adult ETP-ALL showed DNMT3A and RUNX1 mutations, which are more common in acute myeloid leukemia [1]. However, immunophenotypic analysis of ETP-ALL revealed that lymphoblasts expressed some myeloid or stem cell markers, such as CD17, CD34, HLA-DR, CD13, CD33, CD11b, and CD65 [6]. Consistent with these previous studies, clinical samples from patients confirmed that ETP-ALL clone clusters express high levels of CD33, suggesting that CD33 may be a definitive molecular target of ETP-ALL. Furthermore, ETP-ALL demonstrated in vitro data suggesting that anti-CD33-targeted therapy should be investigated in this disease subset [7, 8]. In this basic research, evidence [7] was obtained for CD33-positive ALL, so clinical evidence for ETP-ALL should also be warranted. It is critical to develop an optimal treatment for relapsed and refractory ALL [9]. According to the current research, treating ETP-ALL with the anti-CD33 monoclonal agent gemtuzumab ozogamicin (GO) may be beneficial. However, no prior research has investigated the clinical efficacy of GO in ETP-ALL.

Case Presentation

We treated an 81-year-old man with ETP-ALL who had fatigue and phenotypic expression of T cell and myeloid markers like cyCD3, CD5, CD7, CD33, and HLA-DR. A screening test was performed to detect the absence of chimeric genetic abnormalities in patients with leukemia. Target sequences for leukemogenesis genes identified aberrant mutations in DNMT3A (T691Nfs), KMT2A (E1728D), KRAS (G13D), and IDH2 (R140Q). The patient's blastic cells had a normal male chromosome, 46, XY. We initially treated the patient using a standard induction therapy for common ALL in Japan, JALSG ALL202 [10], which comprises cyclophosphamide (800 mg/m^2, day 1), daunorubicin (30 mg/m^2, days 1–3), vincristine (1.3 mg/m^2, days 1, 8, 15, 22), L-asparaginase (300 U/m^2, days 11, 13,16,18, and 20), and prednisolone (100 mg/body, from day −3). L-asparaginase-induced liver function abnormality for 9 days (days

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34–42) prolonged persists in grade 2. As the first clinical portend, prephase 100 mg/day prednisolone for 3 days was ineffective. The induction therapy produced a hematological complete response with immunophenotypically detectable residual diseases. The first course of consolidation therapy, which included cytarabine (2.0 g/m^2, days 1–3), etoposide (100 g/m^2, days 1–3), and dexamethasone (33 g/body, days 1–3), kept hematological complete response stable. The same response was obtained with the second consolidation therapy, which included methotrexate (MTX) (2.4 g/m^2, day 1), vincristine (1.4 mg/m^2, day 1), and 6-mercaptopurine (25 mg/m^2, day 3). During this second consolidation therapy, MTX excretion was delayed for 17 days with more than 0.01 μM. This caused renal dysfunction because grade 2 creatinine increased for 22 days (days 4–25) and grade 3 creatinine increased for 8 days (days 5–12). In this second consolidation course, increased MTX concentration prohibited 6-mercaptopurine administration after day 2. We used nelarabine 1,500 mg/m^2 (on days 1 and 3) as the third consolidation therapy. Because nelarabine was given to the patient with grade 2 peripheral neuropathy, day 2 nelarabine was skipped. However, nelarabine did not reduce the abnormal blastic cells phenotypically in flow cytometry. Simultaneously, CD33 was kept alive in leukemia cells. Finally, we used GO at a weekly dose of 8 mg/m^2. At 33 days after GO treatment, the patient's bone marrow showed 40% leukemic progression (a clinical course is shown in Fig. 1), with CD33 molecules still strongly expressed. Therefore, we shifted our treatment strategy to palliative care. At the end of his last hospitalization, WBC was 19,630/mL and peripheral blasts were 56.0%. He died because of the progression of his leukemia. The patient died from ETP-ALL 81 days after starting GO therapy. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536424).

Discussion

Relapsed and refractory ALL lacks a standard therapy [11]. In common B-ALL, hematologists prefer molecular targeted therapy such as inotuzumab ozogamicin (InO) (CD22 targeted) and blinatumomab (CD19 targeted) as salvage chemotherapy [12]. However, in early T-cell precursor (ETP) ALL does not express surface antigens targeted by monoclonal antibody-drug conjugates. The only available salvage agent for the treatment of relapsed and refractory T-cell ALL is nelarabine; however, its clinical efficacy for ETP-ALL is unknown, although the prognosis for ETP-ALL is similar to non-ETP T-ALL with modern approaches [13]. Our patient was corticosteroid-resistant, and the previous two regimens' refractoriness prompted him to try a novel agent. Therefore, we decided to use GO as a third-line therapy following nelarabine failure, based on molecular targeting evidence [7]. A review found GO to be a promising regimen, though a selective clinical trial was lacking at the time of this case study.

In an in vitro study, the efficacy of GO for ETP-ALL was found to be promising. CD33 expression as a molecular target has been confirmed in nearly all ETP-ALL [7, 8], and a basic in vitro trial would support biological efficacy. Based on the preclinical data of GO for ETP-ALL, a clinical trial is required to investigate the clinical potential of GO for ETP-ALL [8]. In an in vitro assay using the human ETP-ALL cell line, Loucy specifically inhibited the progression of tumor cells by treating it with an anti-CD33 antibody-conjugated alkylating agent [8]. A novel description in the review article [13] suggested that CD33-targeted antibody therapy could be effective. However, to date, no promising clinical case report or large-scale clinical trial involving CD33 target therapy for ETP-ALL has been published. Therefore, we conducted a clinical case study to evaluate its safety and primary efficacy. The current study is the first

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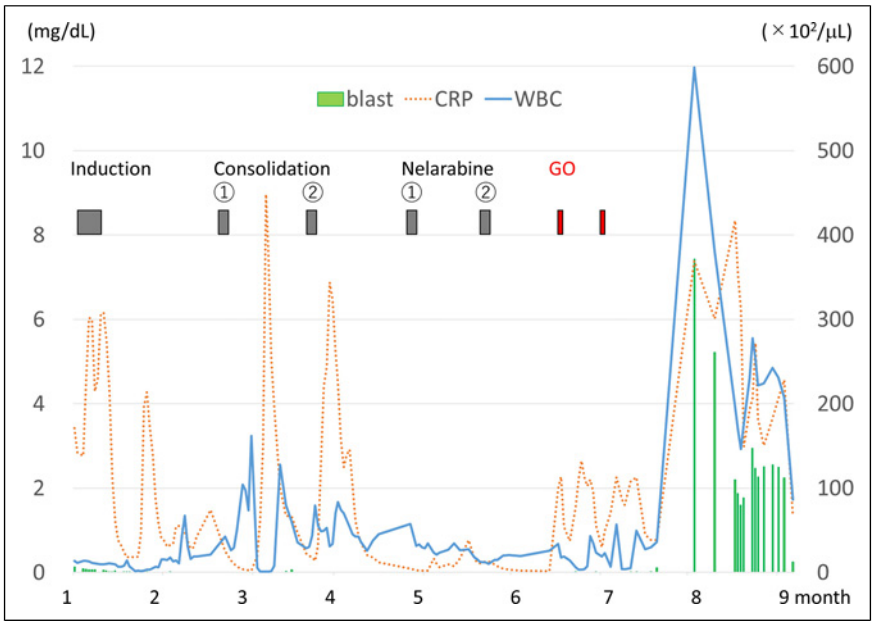

Fig. 1. Clinical course of the patient. Although induction therapy aided in blast cell reduction, it did not result in complete remission (CR) phenotypically. Following consolidation therapy and salvage chemotherapy with nelarabine, hematological progression but not CR was slowed. A trial with GO to induce remission was unsuccessful in the patient's leukemia cells. GO, gemtuzumab ozogamicin.

clinical experience to demonstrate that GO has a negative clinical impact on ETP-ALL. The treatment failure in this study was attributed to the rapid progression of ALL cells. We found no evidence that the ALL cells of the patient avoided GO therapy owing to a lack of CD33 molecules.

The reason why GO did not produce a promising result in our case is a matter of scientific interest. The mechanism of resistance of GO in ETP-ALL has not been completely investigated owing to a lack of clinical experience with this specific antibody-drug conjugate. In InO, loss of target antigen expression for CD22 is the main escape mechanism for antibody-directed therapy in ALL [14]. Other resistant mechanisms for InO have been identified, including CD22 downregulation, alternative CD22 splicing, and high Bcl-2 expression [14]. However, in our case, we observed initial resistance despite ensuring CD33 expression before GO treatment. Therefore, GO must bind to ETP-ALL cells. Gemtuzumab binds to CD33 on the surface of leukemic cells and is internalized intracellularly with a component of the anticancer drug calicheamicin, allowing for cytotoxic effects. In general, antibody-drug conjugates have three distinct modes of action: (1) antibody-dependent cellular cytotoxicity, (2) complement-dependent cytotoxicity, and (3) direct cytotoxicity [15]. In the mode of action, GO must have been internalized after binding to tumor cells in our case. However, GO did not prevent the proliferation of ALL cells. This resistant mechanism, to the best of our knowledge, is caused by Bcl-2 overexpression [14]. Furthermore, the disease risk of ETP-ALL in this case was potentially low due to the possibility of harboring genetic background, DNMT3A, KMT2A, KRAS, and IDH2 mutations. DNMT3A and IDH2 mutations were both poor risk factors for AML [16]. KRAS mutation was associated with a poor outcome in ALL [17].

To summarize, there is not enough clinical evidence to support GO therapy for ETP-ALL. Therefore, treatment setting modification, such as timing of use or combined modality, should be reconsidered to achieve optimal response.

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Statement of Ethics

We obtained approval from the Kagawa University Hospital Institutional Review Board (H23-023). This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The subject has given their written informed consent to publish their case (including publication of images). Written informed consent was obtained from the patient for publication of this study prior to the patient's passing away for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

O.I. and M.U. managed the patient's case, contributed to the literature search, and wrote the manuscript. H.F. and M.U. made substantial contributions to the concept and design of this report and took part in critical discussions. H.F. qualified the patient's data and suggested important intellectual content. M.U. was involved in supervision of the manuscript and managed the research. All authors approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this published article and its online supplementary material. Data are available on request due to privacy/ethical restrictions. Further inquiries can be directed to the corresponding author.

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