Inotuzumab ozogamicin is an effective treatment for CD22-positive acute undifferentiated leukemia: A case report

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Abstract

Acute undifferentiated leukemia (AUL) is a rare subtype of leukemia that expresses no lineage-specific markers; no optimal treatment for AUL has been established. Here, we report a 16-year-old female with CD22-positive refractory AUL who responded well to inotuzumab ozogamicin (InO). Minimal residual disease negativity was achieved using InO, followed by HLA-mismatched unrelated bone marrow transplantation (BMT). Although grade II veno-occlusive disease/sinusoidal obstruction syndrome occurred, it improved immediately. She remained disease-free at 10 months post-BMT, without severe complications (grade III–IV). This case demonstrates the feasibility of a treatment strategy using InO against CD22-positive AUL.

BRIEF REPORT

Inotuzumab ozogamicin is an effective treatment for CD22-positive acute undifferentiated leukemia: A case report

Running title: Inotuzumab ozogamicin for CD22-positive AUL

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Abbreviations

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
AUL	Acute undifferentiated leukemia
BM	Bone marrow
BMA	Bone marrow aspiration
BMT	Bone marrow transplantation
CR	Complete remission
EBMT	European Society for Blood and Marrow Transplantation
GVHD	Graft-versus-host disease
InO	Inotuzumab ozogamicin
MPO	Myeloperoxidase
MRD	Minimal residual disease
TAC	Tacrolimus
VOD/SOS	Veno-occlusive disease/sinusoidal obstruction syndrome
WHO	World Health Organization

Keywords: acute undifferentiated leukemia, inotuzumab ozogamicin, stem cell transplantation, veno-occlusive disease/sinusoidal obstruction syndrome

ABSTRACT

Acute undifferentiated leukemia (AUL) is a rare subtype of leukemia that expresses no lineage-specific markers; no optimal treatment for AUL has been established. Here, we report a 16-year-old female with CD22-positive refractory AUL who responded well to inotuzumab ozogamicin (InO). Minimal residual disease negativity was achieved using InO, followed by HLA-mismatched unrelated bone marrow transplantation (BMT). Although grade II veno-occlusive disease/sinusoidal obstruction syndrome occurred, it improved immediately. She remained disease-free at 10 months post-BMT, without severe complications (grade III–IV). This case demonstrates the feasibility of a treatment strategy using InO against CD22-positive AUL.

INTRODUCTION

Acute undifferentiated leukemia (AUL) is a rare subtype of acute leukemia that expresses neither lymphoid nor myeloid lineage-specific markers. AUL is reported to be 0.2–1% of all acute leukemias.[1] Due to the rarity of AUL, an optimal treatment regimen has not been established. According to the treatment protocol for mixed phenotype leukemia, first-line chemotherapy is usually acute lymphoblastic leukemia (ALL)-type therapy, with patients who cannot achieve complete remission (CR) considered for acute myeloid leukemia (AML)- or combined-type therapy;[2,3]however, when first- and second-line treatment are ineffective, the choice of alternative therapy is very limited.

In the 2016 revised World Health Organization (WHO) classification, multiple antigens are required for B-lineage identification, including a combination of CD19 with CD79a, cytoplasmic (cy) CD22, and/or CD10.[4] Expression of limited B-lineage-associated antigens, such as CD22, has been reported in some cases of AUL.[5]

CD22 is a glycoprotein widely expressed on normal B cells, as well as B-ALL cells.[6] Inotuzumab ozogamicin (InO) is a CD22-targeted antibody-drug conjugate of calicheamicin, which is approved for treatment of relapsed/refractory CD22-positive B-cell ALL. Bhojwani et al. reported that use of InO for 51 children with relapsed/refractory ALL, who were heavily pretreated, resulted in 67% of patients achieving CR, and InO was well-tolerated;[7]however, no study has reported the efficacy of InO for CD22-positive AUL. Here, we report a case of CD22-positive AUL resistant to ALL- and AML-type therapy that achieved minimal residual disease (MRD)-negative CR using InO and who was able to undergo stem cell transplantation.

RESULTS

Case report

A 15-year-old female presented to our hospital for evaluation of dyspnea on effort and pancytopenia. Bone marrow aspiration (BMA) showed 76.6% blasts, which were negative for myeloperoxidase (MPO) and 2–3 times the size of small lymphocytes (Fig. 1A, 1B, and 1C). Flow cytometric analysis revealed that the blasts expressed surface cyCD22, cyCD79a, CD34, CD38, and HLA-DR, and partially expressed CD19, but lacked cyCD3, MPO, and specific features of other lineages, such as monocytes, megakaryocytes, or plasmacytoid dendritic cells. Karyotype analysis revealed 46, XX, add(2)(q31), add(6)(p21), add(16)(q22), del(20)(q11.2q13.3). No known chimeric transcripts (e.g., rearrangements of *KMT2A* , or *BCR-ABL1*) were detected. Immunophenotype analysis met the criteria of B-cell precursor ALL,[4]and she received ALL-oriented induction therapy;[8]however, BMA after induction chemotherapy showed $> 90\%$ blasts, which expressed only CD34, CD7, and CD13, and partially expressed cyCD79a and HLA-DR, but not CD19 or surface and cyCD22. Given the lack of expression of lineage-specific markers and the fact that less than two myeloid associated markers were detected,[5] she was diagnosed with AUL and treated with AML-oriented chemotherapy.[9] After re-induction therapy, partial remission was achieved, with approximately 10% blasts in the bone marrow (BM); however, she could not obtain morphological CR after two courses of consolidation therapy. She subsequently received a clofarabine-containing regimen (clofarabine 40 mg/m^2, cyclophosphamide 400 mg/m^2, and etoposide 150 mg/m^2, daily for 5 consecutive days), which is used for relapsed/refractory ALL and AML;[10,11] however, she achieved only partial remission (8.0% blasts in the BM). CD22 expression was transiently lost after induction therapy, but the blasts became positive for surface CD22 again and remained negative for CD19 after re-induction therapy (Figure. 1D, 1E, and 1F). Hence, based on the persistent expression of CD22 after re-induction therapy, she received InO (0.8 mg/m^2 on day +1, and 0.5 mg/m^2 on days +8 and +15) at 16 years of age, which has approval for use in young adults by the Patient Safety Unit, Kyoto University Hospital. She experienced an acute adverse effect of slight transient elevation of aspartate aminotransferase and alanine aminotransferase (grade I, National Cancer Institute Common Terminology Criteria for Adverse Events, version 5). Hematological toxicity was only thrombocytopenia, which recovered within approximately 3 weeks. After one course of InO, she attained MRD-negative CR, as determined by flow cytometry. Therefore, she proceeded to receive bone marrow transplantation (BMT) from an HLA-7/8 allele-matched unrelated donor, with a myeloablative conditioning regimen consisting of total body irradiation (12 Gy in 6 fractions) and melphalan (180 mg/m^2). Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus (TAC) and short-course methotrexate (15 mg/m^2 on day +1 and 10 mg/m^2 on days +3, +6, and +11). She received low molecular-weight heparin, ursodeoxycholic acid, and antithrombin for veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) prophylaxis. She was infused with a cell dose of 2.4×10^8/kg body weight. From day +6, she had fever with fluid retention and a rash on her face and extremities, and received methylprednisolone for pre-engraftment immune reaction. Neutrophil engraftment was confirmed on day +19. From day +25, she became platelet transfusion-dependent, with elevated lactase dehydrogenase and undetectable serum haptoglobin. Although she did not have findings of increased schistocytes or renal dysfunction, we considered probable thrombotic microangiopathy. Approximately 3 weeks after reduction of TAC, she responded to platelet transfusion, with recovery of serum haptoglobin level. From day +35, she experienced abdominal swelling and her body weight increased by 5–6%. Abdominal ultrasonography revealed ascites and slight hepatomegaly, without diminished portal venous flow. She never exhibited elevated serum bilirubin or liver tenderness. She met the diagnostic criteria for pediatric VOD/SOS (grade II), suggested by the European Society for Blood and Marrow Transplantation (EBMT).[12] She received recombinant human soluble thrombomodulin and coadministration of albumin and furosemide for 1 week, and the ascites and hepatomegaly resolved in a few weeks.[13] She presented with grade II acute GVHD (stage 2 skin and stage 1 gastrointestinal) from around day +36 and was treated with prednisolone and short-course methotrexate (7.5 mg/m^2 on days +70, +77, and +84). She responded well to prednisolone; however, there was repeated acute GVHD after weaning off prednisolone. At last follow up, she was 10 months post-BMT and received prednisolone and tacrolimus without GVHD. She was free from disease, with no other severe complications.

DISCUSSION

Because AUL is an extremely rare disease, optimal treatment has not been established and, particularly in relapsed/refractory cases, therapy options are limited. A few B-lineage associated markers, such as CD22, are expressed in some cases of AUL.[4] Weinberg et al. reported that 6 of 24 (25%) AUL cases showed partial or full CD22 co-expression,[5] and in our case, CD22-positive AUL indicated a treatment strategy using InO against relapsed/refractory disease.

Use of InO increases the risk of VOD/SOS after stem cell transplantation.[14] Our patient also met the proposed EBMT pediatric criteria for VOD/SOS.[12] Although the severity grading was moderate (grade II) and VOD/SOS improved immediately with symptomatic therapy in this case, careful judgment should be made regarding administration of InO for AUL. Further accumulation of cases is needed to allow evaluation of the efficacy and safety of InO as a bridging therapy to stem cell transplantation in patients with CD22-positive AUL.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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FIGULRE LEGENDS

Figure 1. (A–C) Microscopic images of bone marrow smears at onset. Blasts were negative for MPO and 2–3 times the size of small lymphocytes with a 60–90% nucleus-to-cytoplasm ratio, delicate chromatin, irregular nuclear contours, prominent nucleoli, and no cytoplasmic granules. (A) May-Giemsa-stained sample; magnification, ×200. (B) May-Giemsa-stained sample; magnification, ×1000. (C) MPO-stained sample; magnification, ×400. (D–F) Flow cytometric analysis before administration of InO, showing a population of blasts expressing surface CD22 and dim CD45, but lacking CD19.

Figure 2. Clinical course until day +100 post transplantation. PIR, pre-engraftment immune reaction; GV-HD, graft-versus-host disease; VOD, veno-occlusive disease; SOS, sinusoidal obstruction syndrome; rhTM, recombinant human soluble thrombomodulin; MTX, methotrexate; mPSL, methylprednisolone; PSL, prednisolone; TAC, tacrolimus.

Figure 1

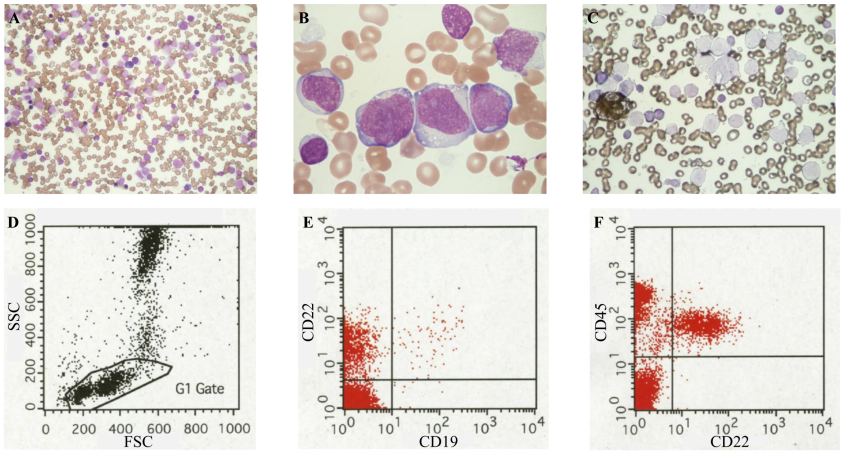

Figure 2