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Total body irradiation-based haploidentical hematopoietic stem cell transplantation using posttransplant cyclophosphamide after administration of inotuzumab ozogamicin: A case report

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ABSTRACT

Owing to the poor prognosis of relapsed or refractory acute lymphoblastic leukemia (ALL), hematopoietic stem cell transplantation (HSCT) followed by effective salvage therapy is required. Inotuzumab ozogamicin (INO) was developed for ALL refractory to standard chemotherapy. However, previous reports suggest that sinusoidal obstruction syndrome (SOS) risk increases in patients with HSCT receiving INO, especially with dual alkylating agents. We report a case of relapsed Philadelphia chromosome-negative B-ALL where the patient underwent haploidentical HSCT using fludarabine/total body irradiation conditioning and posttransplant cyclophosphamide. Successful engraftment was achieved without SOS development.

1. Introduction

The prognosis of relapsed or refractory acute lymphoblastic leukemia (ALL) is poor because traditional salvage chemotherapy is not effective. Recently, inotuzumab ozogamicin (INO), an anti-CD22 antibody conjugated to calicheamicin, was developed for relapsed or refractory ALL. The rate of complete remission (CR) is significantly higher with INO than with standard chemotherapy [1]. However, it has been reported that the incidence of sinusoidal obstruction syndrome (SOS) as a transplant-related adverse effect significantly increases after INO administration [2]. An expert panel published a recommendation to avoid SOS in patients who received INO as salvage chemotherapy before hematopoietic stem cell transplantation (HSCT), suggesting that multiple alkylating agents, especially busulfan, should not be used in the conditioning regimen [3].

We report the case of a patient with relapsed Philadelphia chromosome-negative B-ALL who received INO for salvage therapy.

This investigation was approved by the ethics committee at Okayama University Hospital.

2. Case report

A 29-year-old man with Philadelphia chromosome-negative B-ALL had been treated in another hospital. He achieved CR after induction chemotherapy and continued consolidation chemotherapy. Although he had been in CR after the third course of consolidation chemotherapy, he had a relapse during the fourth. For reinduction therapy, he was treated with INO (0.8 mg/m^2 on day 1, 0.5 mg/m^2 on days 8 and 15). The percentage of lymphoblasts after the first course of INO was 15%. However, he finally achieved a second CR (0.1% lymphoblasts) after the second course of INO. He was transferred to our hospital for allogeneic HSCT.

At the time of admission, laboratory tests showed white blood cell count 1.56 × 10^9/l, blasts 0%, red blood cell count 429 × 10^{10}/l, hemoglobin concentration 13.0 g/dl, and platelet count 53.0 × 10^9/l. Although the serum level of aspartate transaminase (AST) was slightly increased (34 U/l; normal range, 13–30 U/l), alanine aminotransferase (ALT) (30 U/l; normal range, 10–42 U/l) and total bilirubin (0.81 mg/dl; normal range, 0.40–1.50 mg/dl) were within the normal range.

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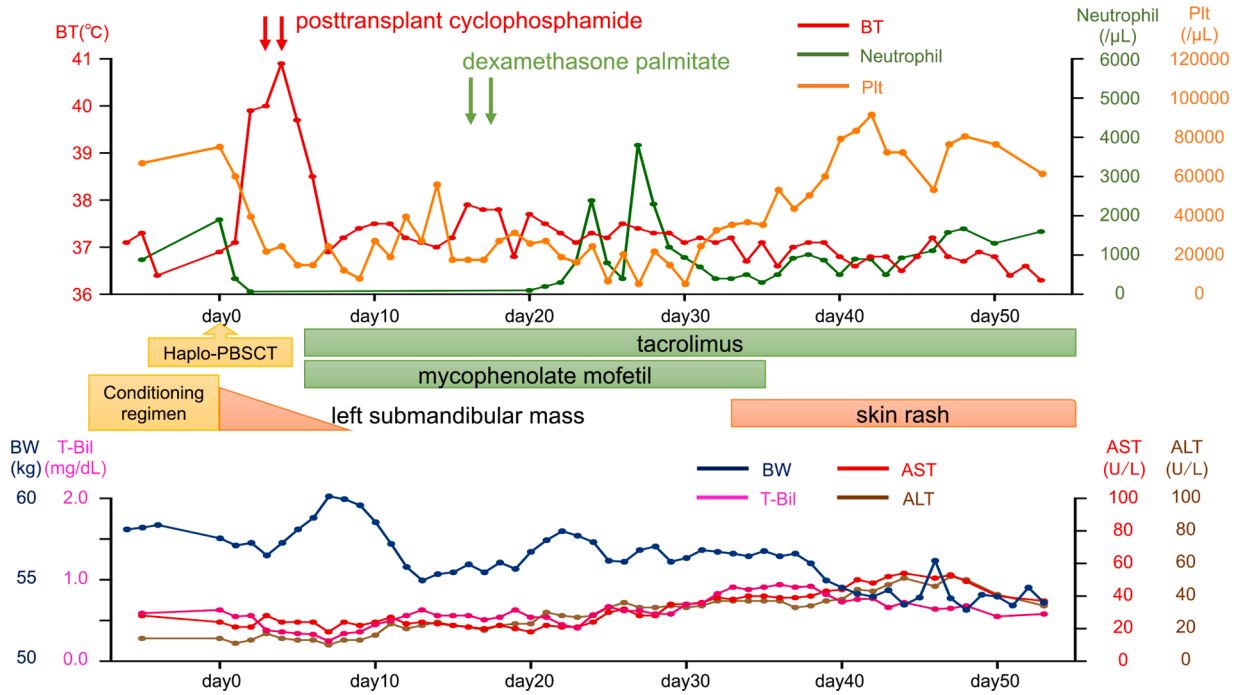

Fig. 1. Clinical course of the patient. ALT, alanine aminotransferase; AST, aspartate transaminase; BT, body temperature; BW, body weight; Haplo-PBSCT, haploidentical peripheral blood stem cell transplantation; Plt, platelet; T-Bil, total bilirubin.

Hepatitis B surface antigen, anti-hepatitis B surface and core antibodies, and anti-hepatitis C virus antibody were negative. Contrast-enhanced computed tomography did not detect any extramedullary lesions. Bone marrow aspiration showed no lymphoblasts in the smear, and flow cytometric analysis detected <1.0% blasts. Minimal residual disease analysis by measuring immunoglobulin heavy chain rearrangement was not performed.

The conditioning regimen for HSCT comprised fludarabine 30 mg/m^2/day from days −7 to −5 and total body irradiation (TBI) of 12 Gy delivered in six fractions from days −4 to −2, followed by peripheral blood stem cell transplantation (PBSCT) from a haploidentical sibling donor. He received posttransplant cyclophosphamide (PT-CY) 40 mg/kg on days +3 and +4. Posttransplantation immunosuppression was initiated on day +5 with intravenous tacrolimus (target level, 10–12 ng/ml) and oral mycophenolate mofetil (MMF; 15 mg/kg body weight twice daily) for graft-versus-host disease (GVHD) prophylaxis. The total infused dose of CD34-positive cells was 4.64 × 10^6 cells/kg body weight. Ursodeoxycholic acid (200 mg/body, thrice daily) for veno-occlusive disease (VOD)/SOS prevention was initiated on day −7.

The disease status before initiation of the conditioning regimen was CR. However, swelling of the left submandibular mass appeared on day −2. Bone marrow examination on day −1 showed blast-like cells, approximately 7% of total nuclear cells. A needle biopsy of the mass lesion on day 0 showed that the lymph node was infiltrated by lymphoblasts later. He received PBSCT on day 0, 39 days after the last INO administration.

The left submandibular mass gradually improved and disappeared around day +7. On day +17, we performed bone marrow examination because his peripheral blood did not show any recovery of neutrophils. The bone marrow examination showed a hypocellular marrow with no blasts; however, there were 39% macrophages, suggesting hemophagocytosis. On days +17 and +18, we administered dexamethasone palmitate 5 mg/day, and neutrophil engraftment was finally observed on day +22. Administration of MMF was gradually decreased from day +30 and terminated after 7 days. Bone marrow examination on day +31 showed normocellular marrow without lymphoblasts, suggesting CR. Fluorescence in situ hybridization of the bone marrow fluid indicated complete donor chimerism. On day + 34, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography found no extramedullary infiltration of ALL. He developed a skin rash and was diagnosed with acute GVHD on day +35; however, no other acute GVHD features were observed in the liver and intestine. Grade I skin acute GVHD was improved by treatment with topical steroids. He was discharged on day +52. During the hospitalization period, we did not observe any laboratory results or signs suggesting SOS. Fig. 1 shows the clinical course of the patient. Unfortunately, his ALL recurred in the bone marrow on day +89, and he died on day +158.

3. Discussion

SOS, a syndrome originally referred to as VOD, is characterized by painful hepatomegaly, jaundice, and weight gain with fluid retention. Liver damage results from nonthrombotic sinusoid obstruction due to endothelial cell injury [4]. Analysis of 135 articles from 1979 to 2007 shows that the median SOS incidence after HSCT was 13.7%. The mortality rate for severe SOS is 84.3% [5]. SOS remains one of the most severe complications after HSCT.

Kantarjian et al. showed that the frequency of SOS was much higher in patients receiving INO than in those receiving standard chemotherapy, 13% and <1%, respectively. Of these, 82% of SOS were grade 3 or worse. They also demonstrated that conditioning regimens containing two alkylating agents, compared to one, were associated with an increased SOS risk, with the levels of last available pre-HSCT bilirubin ≥ the upper limit of normal (ULN) and pre-HSCT AST or ALT < 1.5 times the ULN [2]. Based on these findings, an expert panel published recommendations to avoid HSCT conditioning regimens containing dual alkylating agents, thiotepa, or both; use prophylactic agents; and avoid hepatotoxic agents in combination with conditioning regimens containing high-dose alkylating agents [3]. They also recommended limiting treatment with INO to two cycles in patients proceeding to HSCT [3], as SOS incidence is 8% with one cycle of INO, 19% with two, and 29% with more than two [2].

In our case, the patient received two cycles of INO and achieved CR. As he did not have a human leukocyte antigen (HLA)-matched sibling

donor and could not wait for an HLA-matched unrelated donor, we chose to administer haploidentical HSCT from a sibling donor using PT-CY for GVHD prophylaxis. As he was not in CR, even after the first course of INO, we decided to use a myeloablative conditioning regimen to eradicate minimal residual disease. To reduce SOS risks, we had to avoid conditioning regimens including alkylating agents. In previous report published by Solomon et al., there was only one death caused by SOS among 82 patients [6]. Therefore we chose fludarabine and TBI 12 Gy.

The patient underwent haploidentical transplantation using PT-CY without SOS; however, he experienced ALL recurrence during the conditioning regimen. Previous studies have shown that the 1-year overall survival rate of patients who went directly to first HSCT after CR was 56.1%, whereas the 1-year progression-free survival rate of posttransplant patients after INO administration was 41.2% and the 1-year overall survival rate was 45.1% in all patients [7]. Therefore, it is important to perform HSCT under CR. As our patient experienced relapse during conditioning regimen, other additional treatments after CR achieved by INO might have been required. Currently, blinatumomab and chimeric antigen receptor T-cell therapy have been approved for relapsed or refractory ALL [8, 9]. Neither of these treatments was available for this patient at that time in Japan. However, these treatments should be considered as salvage therapy now.

Recently, a noninvasive method using ultrasound was recently developed for early detection of SOS [10]. Early detection and immediate treatment might reduce the incidence of SOS after administration of INO. Although INO increases the risk of SOS, INO is still an important option for patients with refractory ALL before undergoing transplantation. Thus, we believe that strategies to avoid SOS even after INO should be established.

In summary, we reported a case of TBI-based HLA haploidentical PBSCT using PT-CY after INO administration. In cases where PT-CY is required for GVHD prophylaxis, Flu/TBI conditioning might be an attractive option as a no-alkylating-agent preparative regimen. Further studies on this conditioning regimen are warranted.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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