A Case of Daratumumab-Induced Significant Decrease in Donor-Specific HLA Antibodies and Remission Induction Before Haploidentical Stem Cell Transplantation in a Refractory B-ALL Patient

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Abstract

Objective: To explore the method of eliminating donor-specific anti-HLA antibodies (DSA) in haploidentical stem cell transplantation (haplo-SCT). Methods: We present a refractory B-cell acute lymphoblastic leukemia (ALL) patient who had strongly positive DSA, but had no human leukocyte antigen–matched donor. Although CD38 expression on leukemia cells was negative, daratumumab combined with etoposide and venetoclax therapy was chosen for her. Results: She achieved a significant decrease in DSA levels and complete remission on the combination therapy with daratumumab. She then received a haplo-SCT from a daughter as a donor and had a successful engraftment of donor stem cell. In haplo-SCT, strongly positive DSA levels, directed against donor HLA antigens, could be significantly reduced by daratumumab therapy before transplantation and successfully bridge subsequent haplo-SCT. Conclusion: Although CD38 expression is negative in leukemia cells, refractory B-ALL patients may still benefit from combination therapy with daratumumab. We need further clinical observation.

Keywords

acute lymphoblastic leukemia, haploidentical stem cell transplantation, donor-specific anti-HLA antibodies, daratumumab

Introduction

Acute lymphoblastic leukemia (ALL) is a highly heterogeneous disease with a high risk of relapse, mainly due to high-risk cytogenetic abnormalities. Allogeneic hematopoietic stem cell transplantation (allo-HSCT), especially the human leukocyte antigen (HLA)-matched sibling donors (MSDs) and matched unrelated donors (MUDs), is an important option for the prevention of ALL recurrence. The limited availability of MSDs and MUDs limits the acceptance of allo-HSCT for ALL patients. Haploidentical stem cell transplantation (haplo-SCT) has become an important alternative approach for such patients. However, the donor-specific anti-HLA antibodies (DSA) are considered an important barrier for the successful engraftment of donor stem cell. Identification of DSA is one of the important causes of primary graft failure (PGF) in haplo-SCT and other types of HLA-mismatched donor transplantation. These antibodies are considered to have a weak to low level of mean fluorescence intensity (MFI) if the values range from 1,000 to 3,000; moderate-level MFI, values from 3,000 to 5,000; and strong-level MFI, values >5,000.

Several desensitization strategies have been used to decrease the total antibody load of DSA to reduce the risk of
PGF: plasmapheresis or immunoabsorption, monoclonal antibody to CD20+ B lymphocytes (rituximab), inhibitors against antibody-producing plasma cells (bortezomib), intravenous immunoglobulins, donor HLA antigen (platelet or white blood cell) infusions, and inhibition of complement cascade. These desensitization strategies have been used in solid organ transplantation and allo-HSCT. They improved the risk of PGF and the survival rate of patients in transplantation of partially mismatched hematopoietic stem cell donors.

Here we present a patient with refractory B-cell ALL, with strongly positive DSA levels, directed against donor HLA antigens. Before her haplo-SCT, we chose daratumumab combined with chemotherapy for this patient, and she achieved a significant decrease in DSA levels and complete remission (CR).

**Medical History Presentation**

A 36-year-old female patient was diagnosed with common B-cell ALL. After one course of VDCLP (vincristine, daunorubicin, cyclophosphamide, l-asparaginase, and prednisolone), two cycles of CAM (cyclophosphamide, cytarabine, and 6-mercaptopurine), and two courses of high-dose methotrexate combined with venetoclax chemotherapy, her disease did not achieve CR with 30.36% leukemia cells in the bone marrow (BM) by flow cytometry (FCM) (Fig. 1A). Except for a daughter haploid donor, she had no sibling donor and HLA-matched or HLA-mismatched unrelated donor for her allo-HSCT. Unfortunately, strong MFI level values were found in her DSA test (immunomagnetic beads liquid chip technology) (Table 1). In addition, her ABO blood group could not be detected because of the loss of erythrocyte antigen expression.

Although CD38 expression on leukemia cells was negative, daratumumab (16 mg/kg) combined with etoposide and venetoclax therapy was chosen for her. After one cycle of combination therapy, she achieved CR with a significant decrease in DSA levels (Fig. 1B, Table 1). At the same time, her erythrocyte antigen expression recovered, and her ABO blood group could be detected. After a second course of the same combination therapy, the DSA levels remained low and stable (Table 1); consequently, she was prepared to receive haplo-SCT from her daughter as a donor.

To further reduce DSA levels, she received corticosteroids (40 mg/day, from day -7 to day 0) and high-dose immunoglobulin (0.5 g/kg, on day −2, −1) before allo-HSCT. She did not receive plasmapheresis prior to haplo-SCT because of insufficient plasma; in addition, she did not receive rituximab because she had contracted pneumonia during the previous combination chemotherapy. The myeloablative conditioning regimen included total body irradiation (3 Gy/day, for 3 days), cyclophosphamide, fludarabine, and cytarabine. Graft-versus-host disease prophylaxis consisted of antithymocyte globulin, cyclosporin A, and mycophenolate mofetil. The dose of CD34+ cells from the donor was $4.81 \times 10^6$ cells/kg and the dose of CD3+ T cells from the donor was $7.12 \times 10^8$ cells/kg. On the day of the donor stem cell
infusion, her DSA levels continued to decline to negative (Table 1). She achieved minimal residual disease (MRD)-negative Cri by FCM at 14 days after haplo-SCT, while the donor chimerism according to short-tandem repeat was 98.12% at 14 days and 100.00% at 28 days after haplo-SCT. Her BM was myelodysplastic at 14 days and hyperplastic 28 days after haplo-SCT. Moreover, her neutrophils and platelets were engrafted 17 and 21 days after haplo-SCT, respectively. The DNA copies of Epstein–Barr virus (EBV) and cytomegalovirus (CMV) in the blood measured by quantitative polymerase chain reaction were monitored weekly after haplo-SCT. She received intrathecal chemotherapy to prevent central nervous system leukemia monthly after haplo-SCT. Thereafter, the MRD-negative status in the BM, full donor chimerism in the BM, negativity of EBV, and CMV DNA copies in the peripheral blood were maintained for 90 days.

Discussion

In our study, the patient with refractory B-ALL achieved a significant decrease in DSA levels and CR with the combination therapy of daratumumab, etoposide, and venetoclax. She then received a haplo-SCT from a daughter as a donor and had a successful engraftment of donor stem cells. This patient benefited from daratumumab in two ways. (1) Her strongly positive DSA levels directed against donor HLA antigens achieved a significant decrease. (2) Although the leukemia cells had CD38-negative expression, this refractory B-ALL patient achieved CR.

It was an important cause of PGF in the following haplo-SCT because of an association between DSA-positivity and PGF in the haplo-SCT noted in the previous studies. In a study of 122 haplo-SCT recipients, the incidence of DSA-positivity was 18%, and PGF occurred in 32% of the DSA-positive recipients and in only 4% of DSA-negative recipients. Compared with DSA-negative recipients, the time of haploid stem cell engraftment was significantly delayed in DSA-positive recipients (18 vs 19 days). Desensitization strategies to decrease the antibody load of DSA, including plasmapheresis, rituximab, bortezomib, intravenous immunoglobulin, and donor HLA antigen infusion, have been suggested in DSA-positive recipients. However, the results of these desensitization strategies have only been published in some case reports or small studies. Daratumumab is a human monoclonal antibody that binds to CD38-expressing cells; it has been used in the treatment of relapsed multiple myeloma. Daratumumab targeting plasma cells that express the protein CD38, a type II transmembrane glycoprotein, may be an effective method of plasma cell depletion, which promotes desensitization. In one study, daratumumab significantly reduced anti-HLA antibodies and anti-HLA DSA in animal models, and in two transplant clinical patients before and after solid organ transplantation. Nevertheless, in allo-HSCT, especially haplo-SCT, daratumumab was used to treat immune dysregulation induced by incomplete immune recovery following allo-HSCT. This includes warm autoimmune hemolytic anemia, refractory cold agglutinin disease, Evans syndrome, and pure red cell aplasia following allo-HSCT. However, studies of allo-HSCT in hematologic malignancy, which are similar and show reduction in anti-HLA antibodies and anti-HLA DSA by daratumumab in solid organ transplant candidates, have not been reported.

Despite CD38-negative expression in her leukemia cells, this patient with refractory B-ALL achieved CR on the day of transplantation.

Table 1. Change in DSA Levels After Daratumumab Therapy.

| Molecular specificity | Specificity | Before therapy | After first therapy | After second therapy | Day 0 (immunoglobulin) | Day 7 |
|-----------------------|-------------|----------------|--------------------|----------------------|------------------------|-------|
| HLA-I (MFI)           |             |                |                    |                      |                        |       |
| A*32:01               | A32         | 19,138.89      | 10,256.38          | 10,640.21            | 12,144.49              | Negative |
| B*52:01               | B52         | 16,160.91      | 8,482.32           | 7,455.16             | 8,721.4                | Negative |
| HLA-II (MFI)          |             |                |                    |                      |                        |       |
| DRB 1*04:04           | DR4         | 19,606.25      | 12,341.13          | 9,289.78             | 8,258.89               | Negative |
| DRB 1*04:01           | DR4         | 19,131.51      | 11,638.18          | 9,386.64             | 8,862.2                | Negative |
| DRB 1*04:03           | DR4         | 16,333.14      | 9,105.7            | 7,601.77             | 7,239.81               | Negative |
| DRB 1*04:05           | DR4         | 15,719.31      | 8,961.4            | 6,366.44             | 6,141.03               | Negative |
| DRB 1*04:02           | DR4         | 14,776.56      | 7,920.72           | 7,103.39             | 6,332.34               | Negative |

DSA: donor-specific anti-HLA antibodies; HLA: human leukocyte antigen; Immunoglobulin: intravenous immunoglobulin, 1g/kg; MFI: mean fluorescence intensity of microbead reaction. The bold-faced indicates a different match between the patient and the donor.
combination therapy with daratumumab. In a preclinical study, the protein CD38 on leukemic cells was demonstrated to be expressed at varying degrees in 37 acute myeloid leukemia (AML) and 12 T-cell ALL patients, who were newly diagnosed. It has also been indicated that daratumumab is significantly effective in a T-ALL patient-derived xenograft (PDX) model and in AML-PDX. Some case reports have indicated that daratumumab is effective in relapsed/refractory T-ALL patients. However, treatment with daratumumab in relapsed/refractory B-ALL was only reported in one case report. In our refractory B-ALL patient, why is the combination therapy with daratumumab effective in the state of CD38-negative expression in leukemia cells, despite having received venetoclax therapy before?

Conclusion

In haplo-SCT recipients, daratumumab therapy before transplantation could significantly reduce strongly positive DSA levels directed against donor HLA antigens and successfully bridge subsequent haplo-SCT. Whether refractory B-ALL patients might still benefit from combination therapy with daratumumab despite negative CD38 expression in their leukemia cells still need further clinical observation and investigation.

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Authors Contributions

Concept and design: DQ and ZXL.
Drafted or revised the manuscript: LX.
Acquisition of data: ZHB and ST.
Writing, review, and/or revision of manuscript: DQ.

Ethical Approval and Consent to Participate

The patient agreed to the use of her specimens and data for our study in accordance with the Declaration of Helsinki.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

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