Leukemia Research Reports 17 (2022) 100314

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Case report

Daratumumab as a Frontline Immunosuppression for Pure Red Cell Aplasia after Major ABO-mismatched Allogeneic Hematopoietic Stem Cell Transplantation

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ARTICLE INFO

Keywords:
Daratumumab
Pure red cell aplasia
Major ABO-mismatched

Introduction

Pure red cell aplasia (PRCA) is one of the important complications after ABO-mismatched allogeneic hematopoietic stem cell transplantation (allo-HSCT). This PRCA is caused by residual recipient plasma cells secreting isohemagglutinins, which attack donor erythroid precursors. The incidence of PRCA in patients who underwent major ABO-mismatched HSCT was 10-30% depending on the conditioning regimens and blood phenotype of donor and recipient which highest incidence among O positive recipient and A positive donor as well as the anti-isohemagglutinins titer before HSCT. The reduced-intensity conditioning regimen has the highest rates of PRCA among other regimens [1–2]. Patients become red blood cell (RBC)-transfusion dependent leading to iron overload and increased risks of transfusion complications. In addition, PRCA was reported to be associated with severe pancytopenia [3].

To decrease anti-donor isohemagglutinins is the cornerstone for treatments via four main approaches. First, rapid tapering or withdrawal of immunosuppressants and/or donor lymphocyte infusion aims to enhance the graft-versus-plasma-cell effect [4]. Second, antibody producing memory B cells and plasma cells are eradicated by using rituximab, high-dose corticosteroids or bortezomib [5]. Third, isohemagglutinins are directly eliminated by plasmapheresis [6]. Finally, stimulation of erythroid progenitors or hematopoietic stem cells using recombinant erythropoietin-stimulating agents or eltrombopag are applicable as well [7]. However, the benefits of these treatments appear to be variable and require a long period of time, ranging from 3 to16 months, for the recovery of donor erythroid cells. Furthermore, these treatments increase the risks of graft-versus-host disease (GVHD) and opportunistic infections.

Recent studies have demonstrated the efficacies of daratumumab for post-HSCT PRCA which was resistant to various treatments [8–11]. Daratumumab, an IgG1k anti-CD38 monoclonal antibody that can target plasma cells producing anti-donor isohemagglutinins, is therefore, specific to disease pathogenesis. This study has reported daratumumab administrations as a frontline immunosuppressive therapy for PRCA after major ABO-mismatched HSCT in a patient who had no clinical response to the immunosuppressant taper for 2 months.

Case report

A 49-year-old male was diagnosed with acute myeloid leukemia (AML). Bone marrow examination and cytogenetic study showed 40% myeloblasts and 20 metaphases of 45, X, -Y, t(8;21)(q22;q22), respectively. The molecular studies of *NPM1, FLT3*-ITD and *FLT3*-TKD mutations were all negative. He achieved a complete remission after 3+7

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https://doi.org/10.1016/j.lrr.2022.100314
Received 13 October 2021; Received in revised form 23 February 2022; Accepted 10 April 2022
Available online 13 April 2022

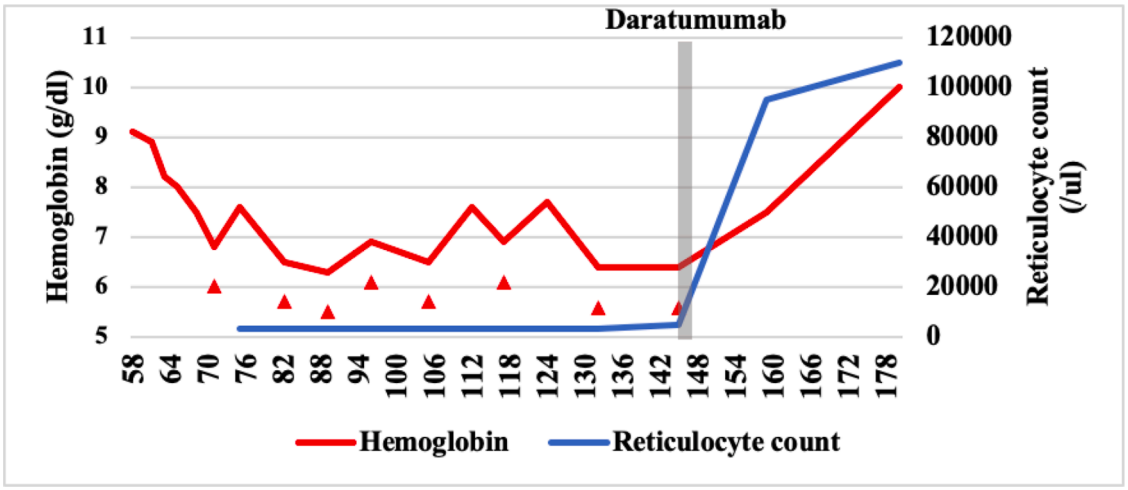

Fig. 1. The hemoglobin levels and absolute reticulocyte counts during the course of pure red cell aplasia (PRCA) post ABO-mismatched allo-HSCT. The red, and blue line represents hemoglobin levels, and absolute reticulocyte counts, respectively. Each red triangle refers to an incidence of red blood cell transfusion. The grey bar indicates s daratumumab infusion.

induction chemotherapy. Although t(8;21) without *c-Kit* mutation conferred a favorable risk in Western countries, this may not be a good risk cytogenetics in Asian patients who had a loss of sex chromosome [12].

After received the first consolidation therapy with high-dose cytarabine, he underwent human leukocyte antigen-matched allo-HSCT from his sister. The major ABO incompatibility was identified as B positive donor and O positive recipient blood types. There was no information of anti-A and anti-B titer before transplantation. The myeloablative conditioning regimen was fludarabine and 4-day busulfan. The GVHD prophylaxis was post-transplantation cyclophosphamide (50mg/kg/day for 2 days) plus cyclosporin and mycophenolate mofetil. The peripheral blood stem cell dose was 7.17 $\times$ 10^6 CD34+ cells/kg.

The platelet and white blood cell engraftment were detected on day +16 and day +21, respectively. Afterward, he developed calcineurin inhibitors induced thrombotic microangiopathy and acute kidney injury from both cyclosporin and tacrolimus. Mycophenolate mofetil was only continued as GVHD prophylaxis. Bone marrow evaluation on day +35 showed a complete remission and the female donor karyotype.

On day +71 post-HSCT, he presented with dyspnea on exertion from anemic symptom. His laboratory investigation revealed hemoglobin 6.8 g/dL with reticulocytopenia (0.1%, 3000/μL), white blood cell count 3.86 $\times$ 10^9/L, platelet count 123 $\times$ 10^9/L and direct comb test was negative. The bone marrow was reassessed showing hypocellularity with the absence of erythroid precursors and myeloblasts compatible with PRCA. The cytogenetic study and whole blood chimerism exhibited female donor karyotype and full donor chimerism. Parvovius B19 and cytomegalovirus were undetectable by polymerase chain reaction. He was diagnosed with PRCA caused by major ABO-mismatched allo-HSCT on day +89. Rapid tapering of mycophenolate mofetil and weekly RBC-transfusion were given. No acute GVHD symptom was detected. On day +117, anti-B IgG titer and anti-B IgM titer were 1:256 and 1:8, respectively. Although anti-B IgG titer gradually decreased to 1:64 on day +145, he still had reticulocytopenia and required weekly RBC transfusion. With no improvement for 2 months after mycophenolate mofetil withdrawal and weekly transfusion, daratumumab was administered at 16 mg/kg starting on day +146. A signed informed consent was obtained from the patient for off-label and compassionate use of daratumumab. Manageable infusion reactions from daratumumab were observed.

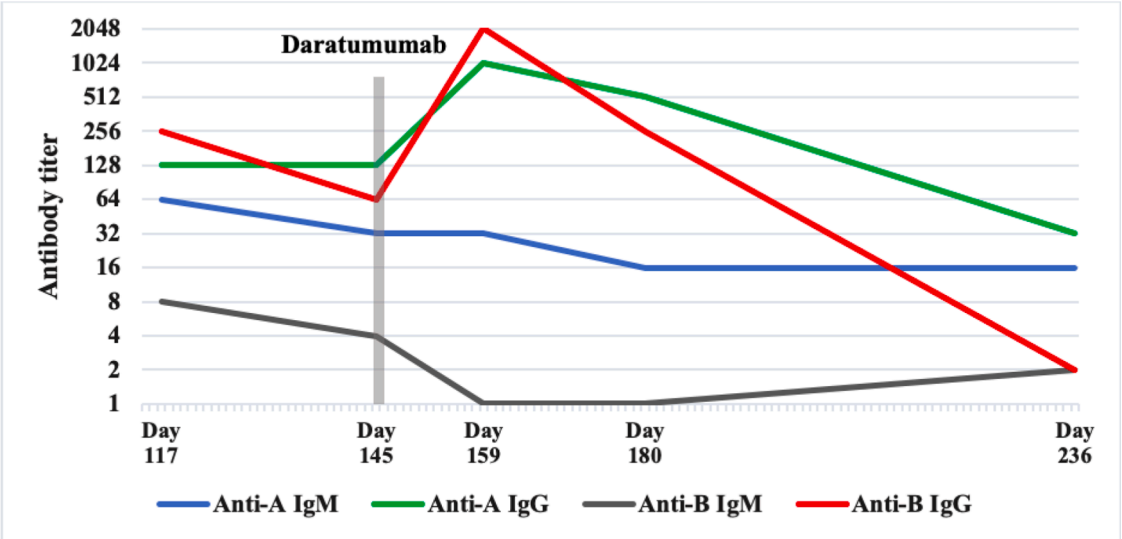

Fig. 2. ABO isoagglutinin titer during the treatment course of pure red cell aplasia (PRCA) post ABO-mismatched allo-HSCT. The blue, green, dark, red, and grey line represents anti-A IgM titers, anti-A IgG titers, anti-B IgM titers, and anti-B IgG titers, respectively. The grey bar indicates daratumumab infusion.

After the first infusion of daratumumab, reticulocyte counts rapidly increased and hemoglobin started to rise. There was no RBC-transfusion requirement after a single dose of daratumumab. No further daratumumab was administered due to the marked clinical improvement (Fig. 1). Anti-B IgG titer increased to 1:2048, albeit hemoglobin improvement 2 weeks after daratumumab (Fig. 2). Anti-A IgG titer rose to 1:1024 while anti-B IgM titers went down. Daratumumab interfering ABO blood type test was the reason leading to an spurious increase in anti-A and anti-B IgG titers [13]. This effect could persist for 2-6 months post daratumumab infusion [14]. We can negate daratumumab interference by using dithiotreitol (DTT) to destruct CD38 on reagent RBC, however we did not perform in this case. After 3 months of a single dose of daratumumab, his ABO blood type turned to donor B blood group with extremely low-titer anti-B IgG and IgM as shown in figure 2.

Discussion

Here, we presented use of daratumumab as the first-line immunosuppressive agent for PRCA after ABO incompatible HSCT in a patient who failed to response after tapering of GVHD prophylaxis drugs. This was consistent with previously reported efficacies in cases resistant to rituximab/bortezomib/high-dose steroid [8–11]. Furthermore, recent studies have demonstrated the successes of daratumumab in various antibody-related refractory diseases including systemic lupus erythematosus and hemophilia A with inhibitor [15]. Our case showed a rapid response after the first dose of daratumumab similar to three previous case reports [8–11]. A sharp increase in reticulocyte counts after the first daratumumab infusion similarly found in our patient was also described in former cases [8, 11]. Although 2-6 weekly doses of daratumumab were administered in the literatures [8–11], a single dose daratumumab was sufficient in our patient. This was possibly because it was used as the early-line therapy. However, a larger study is required to verify this finding.

Aung FM, et al. demonstrated that the significant risk factor associated with PRCA development after ABO mismatched allo-HSCT was the fludarabine and busulfan conditioning regimen, especially in reduced-intensity settings [1]. Our patient received a myeloablative dose of busulfan plus fludarabine. In addition, he received post-transplantation cyclophosphamide which had an activity against plasma cells. To the best of our knowledge, no PRCA after ABO mismatched HSCT cases with post-transplantation cyclophosphamide as GVHD prophylaxis was previously mentioned. In addition to conditioning regimen, anti-titers of Ig-A, Ig-B before ABO incompatibility HSCT should be determined. However, we did not perform in this patient. Whether these factors associated with the clinical courses of PRCA remains to be determined.

Previous studies showed no daratumumab interference on isohemagglutinin titer testing at one [10] or two months [9] after infusions. Besides reticulocyte counts and hemoglobin, the isohemagglutinin titer is commonly used for predicting PRCA treatment responses. Our case showed falsely high anti-A/anti-B IgG titers as the effects of daratumumab at second and fourth week after the infusion. In fact, daratumumab can interfere with blood compatibility testing as a result its use should be aware. Importantly, monitoring of IgG titers should be continued for 1-2 months after the last dose of daratumumab or processed with dithiothreitol [13,14].

Currently, the standard treatment of PRCA after ABO incompatible HSCT has not been established. The treatment strategies after GVHD prophylaxis withdrawal and RBC-transfusion has been suggested as follows: watch and wait approach, rituximab, corticosteroids, bortezomib, and plasmapheresis. The balance of immunosuppressive treatment toxicity and a long-term PRCA complication with watch and wait strategy should be considered for individual PRCA patient management.

In conclusion, we have reported an excellent outcome of using a single dose of daratumumab as an early-line treatment for PRCA after ABO-mismatched HSCT. The agent was well tolerated. However, rapid tapering of immunosuppressant plus RBC transfusion for 2-3 months after PRCA diagnosis should be applied primarily as spontaneous recovery may be noticed.

Inform consent

A signed informed consent was obtained from the patient for off-label and compassionate use of daratumumab.

Declaration of Competing Interest

All authors report no conflict of interest.

Acknowledgement

The authors were grateful to all participants who assisted in this patient. The compassionate use of daratumumab (Darzalex) was supported by Janssen-Cilag (Thailand) Ltd.

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