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Case Report

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Pure Red Cell Aplasia After ABO-Incompatible Allogeneic Hematopoietic Stem Cell Transplantation Successfully Treated With Daratumumab: Report of Two Cases

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Abstract

Pure red cell aplasia (PRCA) is a potential complication after ABO-incompatible allogeneic hematopoietic stem cell transplantation (HCT). In case where PRCA persists beyond 60 days post-HCT, spontaneous resolution is rare, and therapeutic intervention is typically required. However, there is currently no established standard of care for its management. We report two cases of post-transplant PRCA that were refractory to conventional therapies, including erythropoietin and rituximab, and were successfully treated with daratumumab. These cases underscore the potential role of daratumumab as an effective therapeutic option in the management of PRCA following ABO-incompatible HCT. Given the limited data available on its use in this setting, our report contributes with valuable clinical evidence supporting its efficacy and safety.

Keywords: Pure red cell aplasia; Allogenic hematopoietic stem cell transplant; Daratumumab

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HCT) is a potentially curative therapy for various hematologic disorders [1]. The ABO blood group system has been used in donor selection alongside other factors that influence HCT outcomes. Since human leukocyte antigen (HLA) and ABO blood group systems are inherited independently, ABO incompatibility has been reported in up to 50% of transplants, with studies showing contradictory effects on transplant survival [1-3]. Transplant complications observed in ABO-incompatible transplants include autoimmune hemolytic anemia (AIHA), pure red cell aplasia (PRCA), and, in rare cases, passenger lymphocyte syndrome [2]. PRCA typically arises in the context of major or bidirectional ABO incompatibility between donor and recipient, with an incidence ranging from 7.5% to 30% [4]. It is clinically characterized by anemia, reticulocytopenia, and red blood cell transfusions persisting for 30 to 90 days post-transplant. Bone marrow aspirates or biopsies reveal a marked reduction or complete absence of erythroid precursors [5]. The pathogenesis of PRCA is primarily attributed to the persistence of high titers of anti-donor isohemagglutinins targeting erythroid precursors. Conditioning regimens with reduced intensity or toxicity, such as fludarabine-busulfan, may predispose patients to PRCA due to the survival of recipient plasma cells which continue to produce isohemagglutinins [4, 6, 7]. Interestingly, the development of graft-versus-host disease (GVHD) appears to confer a protective effect against PRCA, likely through immune-mediated elimination of residual recipient plasma cells [8].

Therapeutic options described for post-transplant PRCA include: reduction of immunosuppression, plasmapheresis, high-dose erythropoietin (EPO), donor lymphocyte infusions (DLIs), anti-thymocyte globulin (ATG), rituximab, corticosteroids, and daratumumab, among others [9-12]. Daratumumab is a human IgG1κ monoclonal antibody directed against the CD38 antigen, which is highly expressed on plasma cells. The mechanisms of action of daratumumab include complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and apoptotic signaling [13]. In the context of PRCA following allo-HCT, cases successfully treated with daratumumab have been described [8, 9, 11, 14-17]. It has also been successfully used in the management of autoimmune hemolytic anemia (AIHA) [18] and Evans syndrome after HCT [19].

Our objective was to describe two cases of post-HCT PRCA successfully treated with daratumumab.

Case Reports

Case 1

A 46-year-old female was diagnosed with chronic neutrophilic

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Table 1. Clinical Summary of Two Patients Receiving Post-Transplantation Daratumumab for Anemia-Associated ABO Major Incompatibility

Case	Age (years)/ gender	Diagnosis	ABO (donor/ recipient)	TCI (intensity)	Previous treatments	Days post-HCT at daratumumab beginning	No. of doses
1	46/F	Chronic neutrophilic leukemia	B+/O+	Intermediate	EPO, rituximab	+266	4
2	58/M	MDS with excess blasts II	A+/O+	Intermediate	EPO, rituximab	+194	4

EPO: erythropoietin; HCT: hematopoietic stem cell transplantation; MDS: myelodysplastic syndrome; TCI: transplant conditioning intensity.

leukemia with CSF3R mutation. First-line treatment was decided with HCT with an HLA-mismatched unrelated donor (9/10), with major ABO incompatibility (donor group B+/recipient O+). Conditioning was with fludarabine/busulfan, with intermediate intensity [20]. As prophylaxis for GVHD, she received tacrolimus, rabbit ATG, and methotrexate on days +1, +3, and +6. The infused cellularity was $CD34^+$: 7.01×10^6/kg (peripheral blood). As an intercurrence, she presented febrile neutropenia, without microbiological isolation. Neutrophil engraftment occurred 14 days after transplantation, and the minimum platelet count during transplantation was 35,000 kJ/µL. The patient presented slow red blood cell (RBC) engraftment with persistent anemia with a low reticulocyte count and no signs of hemolysis, requiring a transfusion of two units of RBCs weekly to maintain hemoglobin levels above 7 g/dL, and was unresponsive to EPO treatment. No signs of acute GVHD were observed. Cytomegalovirus (CMV) viral load and a direct Coombs test were negative. Donor chimerism in whole blood at days +30 and +60 was 92% and 96%, respectively. Bone marrow biopsy revealed findings consistent with PRCA. Following the exclusion of secondary causes, parvovirus B19, CMV, and GVHD, a diagnosis of post-transplant PRCA was established. Due to the ongoing transfusion requirement, the patient's ferritin level rose to 1989 ng/mL, and iron chelation with deferasirox was initiated. As transfusion dependence persisted beyond day +100, rituximab was administered at a dose of 375 mg/m^2 weekly for four consecutive weeks. Given the lack of clinical response, daratumumab therapy was initiated 1 month after the final rituximab dose. The patient received four weekly intravenous infusions of daratumumab at 16 mg/kg, each preceded by premedication with intravenous dipyrone and hydrocortisone. Transfusion independence was achieved after the third dose of daratumumab (Table 1). At 755 days post-transplant, the patient remains in sustained hematological recovery, with no evidence of disease relapse or GVHD.

Case 2

A 58-year-old male was diagnosed with myelodysplastic syndrome with excess blasts 2, classified as high risk with a revised International Prognostic Scoring System (R-IPSS) score of 4.5. Following cytoreduction with five cycles of azacytidine, the patient underwent allo-HCT from a 10/10 HLA-matched unrelated donor. The stem cell source was bone marrow, and the transplant involved major ABO incompatibility (donor blood group A+, recipient O+). Conditioning was performed using an intermediate intensity fludarabine-busulfan regimen [20]. GVHD prophylaxis included methotrexate, tacrolimus, and rabbit ATG. The infused graft contained $CD34^+$ cells at a dose of 4.18×10^6/kg (bone marrow). During the post-transplant period, the patient developed febrile neutropenia and was treated with piperacillin-tazobactam for 5 days. Neutrophil and platelet engraftment occurred on days +12 and +17 days, respectively. RBC engraftment was delayed, with persistent anemia, reticulocytopenia, and no evidence of hemolysis. Weekly transfusions of one RBC unit were required to maintain hemoglobin levels above 7 g/dL. The patient did not respond to EPO therapy. No signs of acute GVHD were observed. CMV viral load and direct Coombs test were negative. Donor chimerism at days +30 and +60 was 92% and 99%, respectively. Bone marrow biopsy findings were compatible with PRCA. In the context of anemia with reticulocytopenia and a bone marrow biopsy confirming PRCA, after excluding secondary causes (parvovirus B19, CMV, and GVHD), a diagnosis of post-transplant PRCA was made. As transfusion dependence persisted beyond day +100, rituximab was initiated at a dose of 375 mg/m^2 weekly. The patient's ferritin level was elevated at 3,665 ng/mL, and he exhibited intolerance to deferasirox. Due to ongoing transfusion requirements, daratumumab therapy was initiated 1 month after the final rituximab dose. The patient received four weekly intravenous infusions of daratumumab at 16 mg/kg, each preceded by premedication with intravenous dipyrone and hydrocortisone. Transfusion independence occurred 15 days after initiating daratumumab (Fig. 1, Table 1). Ferritin levels progressively declined, until reaching 679 ng/mL at last follow-up. At 1,180 days post-transplant, the patient remains with sustained hematological recovery, with no evidence of disease relapse or GVHD.

Discussion

We reported two cases of PRCA following allo-HCT. Both patients underwent a major ABO-incompatible transplant, received a busulfan-based, reduced-toxicity, intermediate-intensity conditioning regimen, and they did not develop GVHD after transplant, illustrating key risk factors associated with PRCA in the post-transplant setting. After a prolonged period of transfusion dependence, both patients achieved successful erythroid recovery after treatment with daratumumab.

When PRCA persists beyond 60 days after HCT, spontaneous resolution is uncommon, and therapeutic intervention is generally warranted due to the significant morbidity associated with transfusion dependence [17]. Currently, there is no approved standard of care for its management [12]. Although

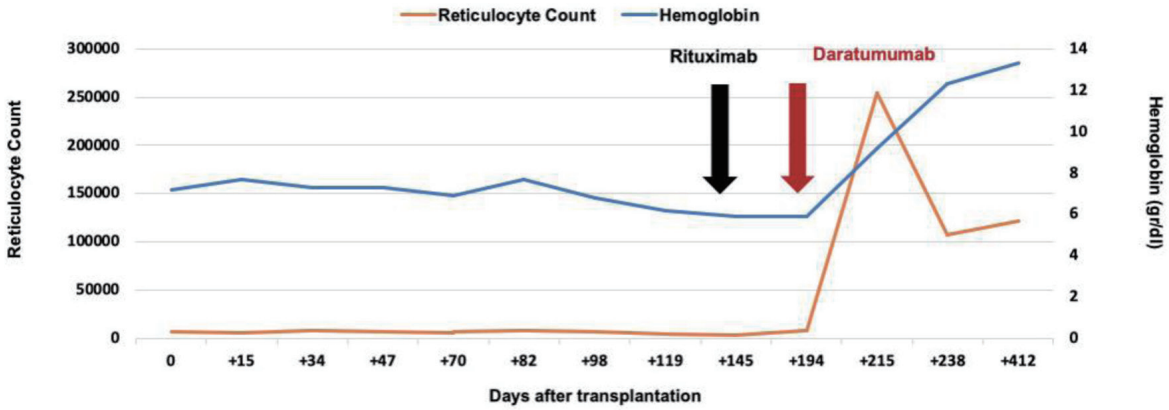

Figure 1. Curve of hemoglobin and reticulocytes values, and response to treatment with daratumumab. Changes in hemoglobin concentration (blue line, right y-axis) and absolute reticulocyte count (orange line, left y-axis) in a patient after allogeneic hematopoietic cell transplantation with ABO major incompatibility (case 2). The x-axis indicates days after transplantation. The black arrow marks the initiation of rituximab treatment, and the red arrow marks the initiation of daratumumab treatment. A marked increase in reticulocyte count and gradual recovery of hemoglobin were observed following daratumumab administration.

EPO has shown benefit in select cases, its use is not supported as a standard treatment due to inconsistent responses and the lack of consensus in the literature [3]. Similarly, rituximab and DLI have demonstrated limited efficacy in this context [3].

Considering the potential of daratumumab to eliminate the recipient residual plasma cells, cases of post-transplant PRCA were reported since 2018. A systematic review of seven studies involving 28 patients treated with daratumumab for post-HCT PRCA reported an overall response rate of 85%, with 20 patients achieving a complete response (CR) and four patients achieving partial response (PR). The median time to response was 4 weeks (range: 2 - 8 weeks). Among those who achieved CR, 17 maintained their response at a median follow-up of 12 months. The most frequently reported adverse event was neutropenia, ocurring in 35% of cases [21]. Weverling et al [22] described 14 patients with PRCA after ABO-incompatible allo-HCT treated with daratumumab in seven Dutch bone marrow transplant centers. Transfusion independence was achieved in 93% of patients, with a median time to response of 14 days. No unexpected adverse events or relapses were reported at a median follow-up of 383 days [22]. Consistent with these findings, our case report further supports the rapid and sustained efficacy of daratumumab in resolving PRCA.

Neither of our patients experienced adverse events during daratumumab treatment. However, a recent multicenter study involving 45 patients with post-transplant PRCA [23] reported serious adverse events, primarily infections, in seven patients treated with daratumumab. In that study, daratumumab was administered either as first-line (36%) or in subsequent lines, with a median time from PRCA diagnosis to treatment initiation of 88 days. Infusion schedules and total doses varied (range 1 - 8), and no correlation between treatment regimen and adverse events was informed [23].

Our two cases received four doses of daratumumab, with one patient showing response after the second dose. This may suggest that a limited course of daratumumab can achieve durable remission with a favorable safety profile. To limit the number of infusions until the development of reticulocytosis and normalization of the ABO-titer has been proposed with the potential of reduce adverse events [22].

Our two patients received daratumumab after +194 and +266 days after transplant, showing by this point a significant iron overload after a large number of transfusions. This highlights the potential role of this therapy earlier in the course of PRCA development. The accumulating evidence from case series, systematic reviews, and now larger real-world cohorts reinforces the role of daratumumab as an effective and well-tolerated option for PRCA following allo-HCT.

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Conflict of Interest

The authors have no conflict of interest.

Informed Consent

Not applicable.

Author Contributions

Conceptualization: EJB and ALB; methodology: EJB, ALB, MM, and LRC; resources: EJB, ALB, and MJG; visualization (tables and figures): VAD and ELP; writing - original draft

preparation: EJB, ALB, MM, and LRC; writing - review and editing: EJB, ALB, ELP, and VAD; supervision: ALB, ELP, and VAD; project administration: ALB and EJB. All authors have read and agreed to the published version of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

AIHA: autoimmune hemolytic anemia; ATG: anti-thymocyte globulin; CMV: cytomegalovirus; DLI: donor lymphocyte infusion; EPO: erythropoietin; GVHD: graft-versus-host disease; HCT: hematopoietic stem cell transplantation; MDS: myelodysplastic syndrome; PCR: polymerase chain reaction; PR: partial response; PRCA: pure red cell aplasia; CR: complete response; RCB: red blood cell; R-IPSS: revised International Prognostic Scoring System; TCI: transplant conditioning intensity

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