BRIEF REPORT

Daratumumab for Delayed Red-Cell Engraftment after Allogeneic Transplantation

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SUMMARY

Daratumumab, a human IgG1κ monoclonal antibody targeting CD38, is used to treat multiple myeloma. We describe successful treatment with daratumumab in a case of treatment-refractory pure red-cell aplasia after ABO-mismatched allogeneic stem-cell transplantation. The patient was a 72-year-old man with the myelodysplastic syndrome who received a transplant from an HLA-matched, unrelated donor with a major ABO incompatibility (blood group A in the donor and blood group O in the recipient). The patient had persistent circulating anti-A antibodies and no red-cell recovery 200 days after transplantation. Standard treatments had no effect. Within 1 week after the initiation of treatment with daratumumab, he no longer required transfusions.

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Allogeneic stem-cell transplantation is a curative treatment option for patients with malignant hematologic diseases, including myelodysplastic syndromes. In 25 to 50% of transplantations, HLA-matched allogeneic stem-cell donors have some degree of ABO blood-group incompatibility with the recipient, since HLA and ABO genes are inherited independently.[1]

ABO incompatibility is classified as either major ABO incompatibility caused by recipient antibodies directed against donor red cells or minor ABO incompatibility due to passive transfer of donor antibodies directed against recipient red cells. A consequence of ABO incompatibility caused by persistent recipient antibodies directed against donor red cells is that red-cell recovery may be delayed for several months.[2] The recipient's bone marrow is characteristically devoid of erythroid precursors (pure red-cell aplasia). The incidence of pure red-cell aplasia after transplantation ranges from 6 to 30%[3,4] and varies according to the conditioning regimen. The risk of pure red-cell aplasia is increased in blood group O recipients of transplants from blood group A donors.[5,6] These patients typically have no detectable reticulocytes, remain dependent on red-cell transfusions, and are at risk for transfusion-associated iron overload.

The optimal management of pure red-cell aplasia after transplantation remains unclear. Current therapies include tapering of immunosuppressive agents, administration of erythropoiesis-stimulating agents, administration of glucocorticoids, plasma exchange, administration of rituximab, and donor lymphocyte infusions.[4,7-10]

Daratumumab is a human IgG1κ monoclonal antibody directed against CD38, which is expressed at high levels on plasma cells. The mechanisms of action of daratumumab include complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and apoptotic signaling.[11] Successful use of daratumumab for the treatment of autoimmune hemolytic anemia after transplantation was reported in a single case report involving a

patient who had had no response to multiple previous therapies, including rituximab.[12] We describe the use of daratumumab in a transfusion-dependent patient who had no response to other treatment options for pure red-cell aplasia after transplantation. We hypothesized that targeting CD20-negative but CD38-positive plasma cells directly with daratumumab would decrease red-cell antibody production and allow for red-cell recovery.

CASE REPORT

A 72-year-old man with the myelodysplastic syndrome presented for evaluation. He had had thrombocytopenia and leukopenia for 2 years. Bone marrow biopsy revealed a hypercellular aspirate with megakaryocytic dysplasia, increased blasts (7%), and fibrosis. Cytogenetic studies showed a complex karyotype with loss of the Y chromosome, trisomy 1, del 1p, and del 20q.

Given the high-risk disease, allogeneic stem-cell transplantation was planned. During the donor search, the recipient received four cycles of hypomethylating chemotherapy.

A matched, unrelated donor was identified with a major ABO incompatibility (blood group O in the recipient and blood group A in the donor). From day –5 to day –2 (i.e., from 5 days to 2 days before transplantation), the patient received a reduced-intensity conditioning regimen consisting of fludarabine at a dose of 30 mg per square meter of body-surface area per day and busulfan at a dose of 0.8 mg per kilogram of body weight twice a day. For prophylaxis against graft-versus-host disease (GVHD), methotrexate was given on days 1, 3, and 6 after transplantation and tacrolimus was started on day –3.

On the day of transplantation, the patient received the peripheral-blood stem-cell transplant at a dose of 5.01×10^6 CD34+ cells per kilogram. The hematopoietic progenitor-cell product was not depleted of red cells because it contained less than 30 ml of red cells.

Engraftment was prompt, with white-cell recovery on day 18 after transplantation and platelet recovery on day 25. Chimerism studies showed a high level of donor chimerism (94% donor leukocytes with a 57% T-cell subset) on day 25. Bone marrow biopsy showed no evidence of disease on day 30. However, there was a paucity of erythroid precursors on bone marrow examination. Erythroid elements accounted for less than 1% of total cellularity, raising concern about post-transplantation pure red-cell aplasia. Despite the recovery of white cells and platelets, the patient continued to have anemia and required red-cell transfusions. Evaluation for hemolysis revealed a normal haptoglobin level and a negative direct antiglobulin test. No reticulocytes were present. The patient was repeatedly typed as O-positive, with no detectable donor type A cells in his circulation.

Throughout the post-transplantation course, the patient received transfusions of only type O red cells.[2] Reverse blood typing (i.e., testing for ABO antibodies) confirmed O type and was positive for anti-A antibodies. Anti-A IgG and IgM isohemagglutinins were detected but were not separately quantitated. The anti-A antibody titer was 1:512 on day 77 and peaked at 1:1024 between days 126 and 211 after transplantation (Fig. 1).

Tapering of immunosuppressive therapy with tacrolimus was started on day 105 and was stopped on day 196. The anti-A antibody titer and reticulocyte level did not improve after immunosuppressive therapy was tapered. High-dose glucocorticoids were started on day 209 after transplantation and slowly tapered over a period of several weeks, with no effect on the hemoglobin level and hematocrit or the anti-A antibody titer. Treatment with rituximab, at a dose of 375 mg per square meter given weekly for 4 weeks, was started on day 235. Although the anti-A antibody titer decreased to 1:128, the hematocrit and reticulocyte count did not increase. After treatment with rituximab, the patient remained transfusion-dependent, with no reticulocytes. To treat persistent anemia, he received darbepoetin alfa at a dose of 300 μg weekly, but there was no improvement in the hematocrit or reticulocyte count; he continued to require 1 to 2 units of red cells per week. Daratumumab was administered at a dose of 16 mg per square meter weekly, starting on day 390 and continuing for 6 weeks, with premedication to prevent infusion toxicity (methylprednisolone [Solu-Medrol, Pfizer] at a dose of 40 mg given intravenously, fexofenadine at a dose of 60 mg given orally, famotidine at a dose of 20 mg given intravenously, and diphenhydramine at a dose of 25 mg given intravenously).

Starting the week after the first dose of dara-

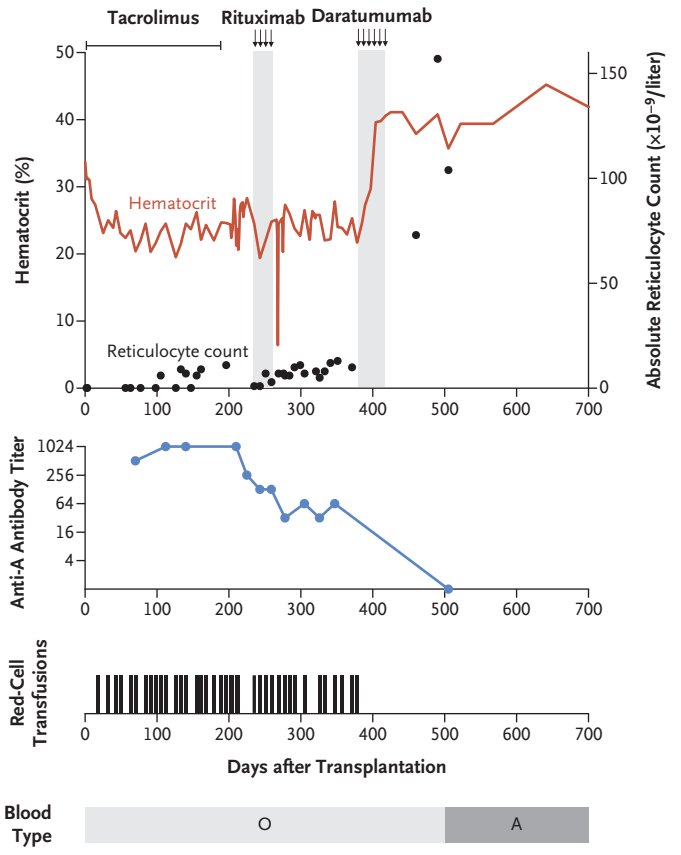

Figure 1. Results of Treatment with Daratumumab for Pure Red-Cell Aplasia in the Recipient of a Stem-Cell Transplant from a Donor with a Major ABO Mismatch.

Shown are the hematocrit, reticulocyte count, anti-A antibody titer, red-cell transfusion requirement, and blood type before and after treatment first with rituximab and then with daratumumab (shading). The variation in the hematocrit after rituximab therapy reflects continued management with red-cell transfusions; the patient received a transfusion immediately before the initiation of daratumumab therapy. The patient received four doses of rituximab and six doses of daratumumab, as indicated by the arrows.

tumumab, the patient no longer required red-cell transfusions. After two doses of daratumumab, a brisk reticulocytosis developed and the hematocrit increased from 27.2% to 39.6%. At this time, the patient became transfusion-independent. Given the stable hematocrit and elevated iron levels, therapeutic phlebotomy was started 2 months after treatment with daratumumab.

At the most recent clinic visit, 700 days after transplantation and 10 months after the initiation of treatment with daratumumab, the patient had a normal hemoglobin level (14.5 g per deciliter) and hematocrit (41.9%), and the reticulocyte count was 2.8%. After treatment with daratumumab, the patient's blood type converted to A-positive, with no detectable anti-A antibodies. The direct antiglobulin test became positive as a result of daratumumab therapy. The binding of daratumumab to CD38 on red cells can complicate measurement of IgG anti-A antibody titers and was resolved with standard dithiothreitol treatment in this case.[13] The IgG anti-A antibody titer with the use of dithiothreitol-treated reagent red cells was 0. A bone marrow biopsy performed 6 months after daratumumab therapy revealed a normal number of erythroid precursors and no evidence of recurrent myelodysplastic syndrome.

DISCUSSION

The patient received a diagnosis of post-transplantation pure red-cell aplasia, defined by persistent reticulocytopenia and an absence of erythroid precursors in the bone marrow, as well as an absence of infection, drug toxicity, and relapse.[14] Persistently elevated anti–donor isohemagglutinins with high anti-A antibody titers (peak titer, 1:1024) for more than 200 days after transplantation were the cause of the pure red-cell aplasia.

Delayed red-cell recovery and transient pure red-cell aplasia after nonmyeloablative allogeneic hematopoietic stem-cell transplantation with major ABO incompatibility, as seen in this patient, has been documented in multiple studies.[4,8,15,16] Use of allogeneic transplants from a donor with blood group A in a recipient with blood group O, as in the case we describe, is associated with an increased risk of pure red-cell aplasia.[5,6] One explanation for this may be higher levels of anti-A antibodies and the prolonged presence of anti-A antibodies as compared with anti-B antibodies.[5] Although ABO antibodies are usually IgM isotype, persons with blood group O may have IgG isohemagglutinins, which might explain the longer duration.[2] The increased antigenicity of A antigens as compared with B antigens and individual interactions may also contribute to this observation.

For transplant recipients who have pure red-cell aplasia caused by persistently elevated isohemagglutinins, the first therapeutic approach is the tapering of immunosuppressive agents to promote a graft-versus-plasma-cell effect.[4,17,18] In

our case, the reduction of immunosuppressive therapy had some effect on anti-A isohemagglutinin titers, which decreased by a factor of 2 and probably represented graft-versus-plasma-cell activity. GVHD did not develop in this patient, and despite the decrease in isohemagglutinins, no improvement in erythropoiesis or reticulocyte levels was seen.

Other strategies for the treatment of post-transplantation pure red-cell aplasia include erythropoietin therapy, glucocorticoid therapy, plasmapheresis, rituximab therapy, and donor lymphocyte infusions.[7,9,19,20] This patient had no response to erythropoietin, glucocorticoids, or rituximab. Although rituximab led to a decrease in anti-A isohemagglutinin titers, the reticulocyte count and erythropoiesis did not improve. Plasmapheresis was considered, but because of its temporary effect, we proceeded with other options.

Donor lymphocyte infusions are a treatment option for refractory cases[9] but are associated with considerable risks, with acute or chronic GVHD developing in 50 to 60% of patients.[21] This patient had no signs of GVHD, and his bone marrow showed 94% donor chimerism, with no evidence of recurrent myelodysplastic syndrome. We were concerned that the risk might outweigh the benefit of donor lymphocyte infusions and therefore discussed alternative strategies.

Given the pathophysiology of post-transplantation pure red-cell aplasia due to residual isohemagglutinin-producing plasma cells, we hypothesized that a selective treatment targeting these plasma cells should eliminate the pathogenic plasma-cell population and overcome the refractory pure red-cell aplasia. Rituximab targets mature B lymphocytes but not CD20-negative plasma cells, which may explain why anti-CD20 treatment was not effective in this patient.[22,23] Plasma cells are CD38-positive,[24,25] and anti-CD38 therapy with the use of daratumumab is very effective in the treatment of multiple myeloma.[26,27] Supporting evidence for our use of daratumumab in a patient with pure red-cell aplasia after allogeneic stem-cell transplantation with a major ABO mismatch came from a case report of treatment with this agent in a patient with post-transplantation autoimmune hemolytic anemia, which was refractory to previous treatment with rituximab.[12] In that case, daratumumab decreased the patient's transfusion requirement. No adverse effects after daratumumab infusion were noted, with a limited follow-up period of 20 days.[12] A less directed approach to targeting plasma cells can be achieved with other reagents that are active in multiple myeloma, such as bortezomib, which has been reported in a few cases.[28,29] However, we were concerned about the side-effect profile of bortezomib and chose the more directed targeting approach with daratumumab.

Because of the previous use of rituximab in this patient, we waited for six half-lives (one half-life of rituximab is estimated to be 22 days[30]) before starting daratumumab. We used the standard dose of daratumumab for myeloma (16 mg per square meter).[26] The infusions were given with hypersensitivity premedications, with no adverse events. Daratumumab was very effective for this patient, who had refractory post-transplantation pure red-cell aplasia. He did not require transfusions after the first dose of daratumumab, and the hematocrit and hemoglobin level increased to normal values after two doses. We speculate that the prompt response to daratumumab can be explained by the 5-day half-life of IgM,[31] with three half-lives elapsed at the time of the maximal response. In addition to rapid resolution of transfusion dependence, anti-A antibodies disappeared. A repeat bone marrow biopsy revealed normal erythroid precursors. Either spontaneous resolution of post-transplantation pure red-cell aplasia or a late response to rituximab is very unlikely in this case. Concerns about possible immunomodulatory effects of daratumumab were raised before infusion, but we did not observe GVHD or opportunistic infections with follow-up 10 months after treatment with daratumumab; the differential blood count remained normal.

Post-transplantation pure red-cell aplasia is a well-recognized complication after ABO-incompatible allogeneic stem-cell transplantation. Most cases resolve spontaneously or with immunomodulatory or immunosuppressive treatments. The results in this patient with refractory post-transplantation pure red-cell aplasia suggest that direct targeting of residual host plasma cells with an anti-CD38 agent such as daratumumab might be a valid treatment option to consider in patients with no response to standard treatments.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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