Annals of Hematology & Oncology

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Austin Publishing Group

Case Presentation

Daratumumab Effectively Treats Refractory Immune Hemolytic Anemia after Hematopoietic Stem Cell Transplantation: Case Report

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Received: February 25, 2020; **Accepted:** April 06, 2020; **Published:** April 13, 2020

Abstract

Immune hemolytic anemia following allogeneic hematopoietic stem cell transplantation is often refractory to initial therapeutic interventions, and can lead to significant morbidity and mortality. Long-lived auto reactive plasma cells may play a role in treatment-resistant autoimmune disease. We describe a patient with severe post-transplant immune hemolytic anemia, refractory to multiple lines of therapy including plasma-cell directed therapy with bortezomib. Treatment with daratumumab, an antibody directed at CD38, resulted in a rapid and sustained resolution of her hemolysis. Daratumumab may represent an effective strategy in patients with refractory post-transplant immune hemolytic anemia.

Keywords: Hematopoietic stem cell transplantation; Immune cytopenia; Autoimmune hemolytic anemia

Case Presentation

A 17-year-old female with high risk acute myeloid leukemia underwent a haploidentical Hematopoietic Stem Cell Transplantation (HSCT) from her brother, with major ABO incompatibility (blood group B in the donor and A in the recipient). Post-transplantation cyclophosphamide was given for prevention of Graft-Versus-Host-Disease (GVHD). Two months later, due to primary graft failure, a second HSCT was performed. Her father was the haploidentical, ABO compatible donor (blood group A in donor and recipient). The patient was conditioned with fludarabine (30 mg/m^2/day x 5 days) and alemtuzumab (20 mg/dose x 5 days) and received a filgrastim-mobilized peripheral blood stem cell graft. Post-transplantation cyclophosphamide was given on Day +3 and +4 (50 mg/kg/dose x 2 days) as well as tacrolimus and Mycophenolate Mofetil (MMF) for GVHD prevention. Neutrophil engraftment occurred on day +25. At day +180, the patient was clinically well with 100% donor chimerism, and immune suppression was discontinued.

At day +240, she presented with pallor, fatigue and jaundice. Her hemoglobin was 54 g/L with 5% reticulocytes. Her Direct Antiglobulin Test (DAT) was positive; further testing revealed a mixed warm and cold hemolytic anemia (IgG binding C3 along with cold agglutination). Platelet count was 48 x 10^9/L. Bone marrow aspirate and biopsy showed a mildly hypocellular marrow with megakaryocytes and normoblasts present.

The patient was treated with a pulse of 2 mg/kg/day of methylprednisolone and two doses of Intravenous Immunoglobulin (IVIG) (0.4 g/kg/dose), but had no sustained increase in her hemoglobin. She was then treated with four doses of rituximab (375 mg/m^2/dose at weekly intervals) but did not respond. Sirolimus was then given for eight months. Although hemolysis persisted on sirolimus, transfusions requirements decreased. However, the patient developed severe hypertriglyceridemia, necessitating discontinuation of sirolimus. MMF (12 mg/kg PO BID) and plasmapheresis (three cycles) were tried, but both failed to produce a sustained response. DAT remained positive and she required 5-10 units of red blood cells transfused per month.

At day +574, treatment with bortezomib was initiated. The patient received two courses (1 mg/m^2 dose during the first course and 1.3 mg/m^2/dose during the second course, given on days +1, 4 ,8 and 11 each course). Each course was given with plasmapheresis in order to remove circulating antibodies, thus increasing protein production and leading to enhanced cell killing [1]. Her hemolysis did not improve after bortezomib. At day +651, she underwent laparoscopic splenectomy, but this too failed to mitigate the hemolysis. Of note, the patient's ongoing thrombocytopenia did resolve after splenectomy. As persistence of hemolysis post splenectomy suggested the possibility of a predominantly complemented-mediated disease, she was then treated with three doses of eculizumab (900 mg/dose) but did not respond. The patient remained on steroids since presenting with Immune-Mediatedhemolytic Anemia [IHA], and received intermittent pulses during periods of brisk hemolysis.

The therapeutic measures described resulted in multiple adverse effects, including insulin-dependent diabetes mellitus, hypertension and osteonecrosis as well as severe hypertriglyceridemia. Following splenectomy, the patient suffered a bilateral pulmonary embolism and was treated with low molecular weight heparin. She also developed transfusion-related iron overload and was placed on iron chelation therapy.

At day +750, sixteen months after the onset of IHA, the patient was still requiring 2-3 transfusions per week and her DAT remained positive. Her peripheral CD19 count was 0, suggesting that hemolysis may be triggered by plasma cell- generated antibodies rather than B cells. She was then treated with daratumumab. She received a total of six doses at 16 mg/kg/dose, given at weekly intervals. Daratumumab

Citation: Malkiel S, Wheaton L, Calderwood L, Kirby M, Ali M, Schechter T, et al. Daratumumab Effectively Treats Refractory Immune Hemolytic Anemia after Hematopoietic Stem Cell Transplantation: Case Report. Ann Hematol Oncol. 2020; 7(3): 1292.

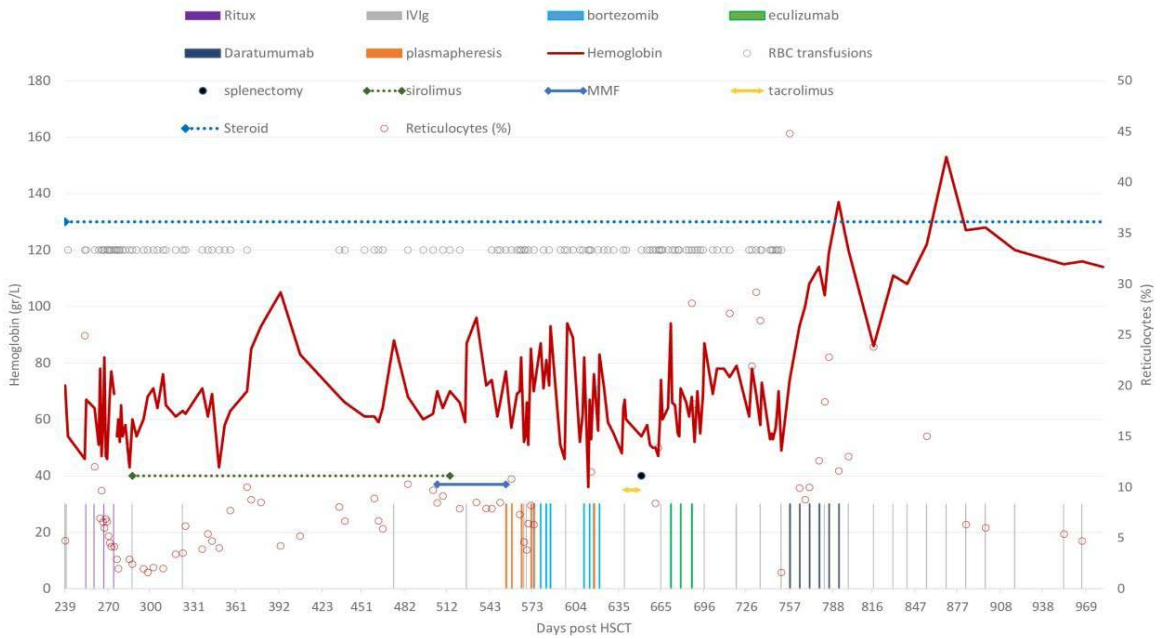

Figure 1: Course of treatment and laboratory parameter response.

was well tolerated. Her hemoglobin began to rise after the first dose, and she has not required a transfusion since. Currently, nine months after beginning daratumumab, the patient has no evidence of hemolysis and her hemoglobin is stable (Figure 1). Her CD19 count is 33/μL. She continues to receive IVIG on a regular basis and is tolerating a very slow wean of prednisone, her only immunosuppressive therapy. She remains fully engrafted with >95% donor cells from her father, confirmed by PCR. She has no evidence of GVHD. No other adverse effects were observed.

Discussion

Autoimmune cytopenias are a well-described entity after allogeneic Hematopoietic Stem Cell Transplant (HSCT), with IHA affecting 2-6% of recipients [2-6]. First-line treatment options for IHA include steroids and IVIG, but up to 60% patients do not have a sustained response to these agents [2-4]. Rituximab, cyclophosphamide and MMF have been utilized as second-line therapy. For those with refractory disease, anemia may lead to significant treatment-related morbidity and a mortality rate as high as 50% [2,5]. This case report demonstrates the highly resistant behavior that can characterize post-HSCT IHA, with hemolysis persisting in the face of B cell depletion, splenectomy and complement blockade. It also illustrates the significant morbidity associated with such a clinical course. Patients with treatment-refractory post-transplant IHA are thus in need of new therapeutic options.

The mechanisms driving post-transplant IHA are incompletely understood. The use of unrelated donors and T cell depletion strategies and the occurrence of chronic GVHD have been described as risk factors [3,4,6], implicating immune dysregulation and incomplete immune reconstitution in the pathogenesis of this condition. For example, if recovery of regulatory T cells is delayed during immune reconstitution, autoreactive lymphocyte clones may develop through homeostatic expansion [6]. Autoreactive B cells give rise to autoreactive plasma cells, which may play an important role in treatment-refractory autoimmune disease [7]. The recognition that autoimmunity can persist after effective depletion of peripheral B cells, has led to the identification of long-lived plasma cells as a potential therapeutic target in refractory IHA.

Daratumumab is a human monoclonal antibody directed at the CD38 glycoprotein, which is highly expressed on multiple myeloma cells and normal plasma cells. Daratumumab was approved for the treatment of refractory multiple myeloma in 2015. The use of daratumumab for IHA was first reported in 2016 [8], in a 19-year-old female with post-transplant autoimmune hemolytic anemia refractory to multiple therapies, including rituximab. The authors hypothesized that her ongoing hemolysis was due to a population of CD20-/CD38+ plasma cells. Daratumumab administration resulted in dramatic increase in her hemoglobin and reduced transfusion needs. Three new cases of use of daratumumab in AIHA have since been reported; all patients responded well [9,10]. Successful use has also been reported in two cases of refractory post-transplant pure red cell aplasia [11,12].

No major adverse effects were associated with the daratumumab in any of the reported subjects. Most had delayed recovery of humoral immunity, requiring IVIG substitution for up to 12 months. In multiple myeloma, daratumumab has been shown to deplete CD38-positive immunoregulatory cells, promoting cytotoxic and helper T cell expansion and a shift from naïve T cell toward effector memory T cell phenotype [13]. Yet,in the post-HSCT setting no authors have reported GVHD or other immune-mediated phenomena after treatment with daratumumab, nor did our own patient have evidence of GVHD.

The response to daratumumab in our patient occurred despite

complete resistance to plasma cell directed therapy with bortezomib. The previously reported patients had also failed to respond to bortezomib [9,10]. Bortezomib causes reversible inhibition of the 26S proteasome and prevents the degradation of misfolded protein, resulting in death of both short- and long-lived plasma cells. Bortezomib has become increasingly integrated into the treatment of autoimmune disease. It has been used successfully in refractory antibody-mediated hematologic disease, including post-transplant IHA [14,15]. It is unclear what factors determine response to this therapy.

In conclusion, this case provides further support for the use of daratumumab in difficult-to-treat post-transplant IHA, even after failure of proteasome inhibitors. Daratumumab was rapidly effective and very well tolerated in our patient. There is no current consensus regarding the treatment of patients with post-transplant IHA who fail first and second-line therapies. Until such time that a clinical trial is available, daratumumab should be considered on a compassionate use basis when other therapies have failed. Ultimately, earlier incorporation of daratumumab into therapy may reduce morbidity and mortality.

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