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Post-Allogeneic Hematopoietic Stem Cell Transplantation Eculizumab as Prophylaxis Against Hemolysis and Thrombosis for Patients with Hematologic Disorders Associated with Paroxysmal Nocturnal Hemoglobinuria Clones

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Paroxysmal nocturnal hemoglobinuria (PNH) is frequently seen in the context of other aplastic anemia and myelodysplastic syndromes and is associated with hemolysis and increased thromboembolic events. Allogeneic hematopoietic stem cell transplantation (alloHCT) is the sole curative treatment but is associated with significant morbidity. The terminal complement inhibitor eculizumab reduces hemolysis and thromboembolic events and is the sole Food and Drug Administration-approved therapy for PNH. Prophylactic administration of this agent in the early post-transplantation setting to prevent hemolysis and thrombosis has not been described in the literature. We describe our institutional experience of 8 patients with PNH who underwent alloHCT and who received at least 1 dose of eculizumab within 30 days of alloHCT for prevention of thrombosis and hemolysis. One patient with underlying aplastic anemia who received bone marrow stem cells failed to engraft. Another patient experienced steroid-refractory grade IV acute graft-versus-host disease and died of a fungal infection. The other patients engrafted well; no hemolysis, thrombotic events, or infections associated with encapsulated bacteria occurred in any of the 8 patients.

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal hematologic disorder marked by the acquisition of a somatic mutation in the *PIG-A* gene with diminished expression of the GPI-anchored proteins CD55 and CD59 on the cell surface. Because CD55 and CD59 normally serve to block complement activation, their absence on the erythrocyte surface results in complement-mediated hemolysis, and clinical manifestations include hemolytic anemia and thrombotic events, which can be both arterial and venous. Although PNH can be an isolated diagnosis, in which case it is called classic PNH, it also frequently occurs in the setting of a separate acquired bone marrow disease, such as aplastic anemia (AA) and myelodysplastic syndrome (MDS).

Therapy for PNH is directed against clinical manifestations of the disease, such as venous thrombosis and hemolytic anemia. The only approved pharmacologic therapy specifically for this disease is eculizumab (Soliris), a humanized monoclonal antibody that binds to complement component C5, thereby preventing its cleavage into components C5a and C5b, which in turn prevents formation of the complement membrane attack complex [1]. Its use to treat PNH has been shown to decrease hemolysis, transfusion requirements, and thrombosis while improving quality of life [2]. Allogeneic hematopoietic stem cell transplantation (alloHCT) for PNH is curative, but its related morbidity is nontrivial, especially in patients with previous thrombotic events [3,4], limiting its applicability in PNH absent a concurrent diagnosis of MDS or AA. More recent data suggest that reduced-intensity conditioning alloHCT can be done safely with acceptable survival [5]. Nonetheless, there are patients with MDS or AA with significant PNH clone sizes who

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require alloHCT, and the increased complement activation occurring during the conditioning regimen may increase the risk of intravascular hemolysis.

At our institution, for patients with PNH who have been receiving eculizumab and proceed to alloHCT, we have opted to continue this agent immediately post-alloHCT to prevent withdrawal hemolysis. Although eculizumab has been given as management of established post-transplantation thrombotic microangiopathy [6,7], prophylactic administration to prevent peritransplantation hemolysis and thrombosis in the early post-transplantation setting has not been described in the literature. Here we summarize our institutional experience with 8 patients with PNH undergoing alloHCT who received at least 1 dose of prophylactic eculizumab within 30 days post-transplantation.

METHODS

Patients who underwent alloHCT for PNH between 2007 and 2017 and who had received at least 1 dose of eculizumab within 30 days of transplantation for prophylaxis and not for treatment of thrombotic microangiopathy were included. Eight such patients were identified. All of these patients had previously received eculizumab for management of PNH-related hemolysis. Institutional Review Board approval was obtained.

RESULTS

Patient demographic and clinical characteristics are summarized in Table 1. The median duration of follow-up was 36 months (range, 1 to 86 months). No patients underwent alloHCT purely for PNH without another concurrent diagnosis; 4 patients had AA (all with severe AA), 3 patients had MDS, and 1 patient had primary myelofibrosis. Two of the patients with AA had received previous immunosuppressive therapy. All 8 patients received reduced-intensity conditioning, and graft source was bone marrow in 5 patients; all 4 patients with AA received bone marrow stem cells, and 1 patient with MDS received bone marrow stem cells as well. Donors were 10/10 HLA-matched in all cases, and graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus and sirolimus in 6 patients and cyclosporine and methotrexate in the other 2 patients. None of the patients in this cohort had experienced previous thrombosis, and all patients had been treated with eculizumab before transplantation. All patients had been receiving eculizumab before alloHCT; the last date of eculizumab administration before alloHCT is specified in Table 1. Patient 1 had been receiving maintenance eculizumab up until shortly before undergoing alloHCT at another institution, and the final date of administration could not be confirmed with available records.

The schedule of eculizumab administration was somewhat variable but generally subscribed to the biweekly maintenance dosing schedule. Patient 3 had eculizumab held due to a perforated viscus and severe septic shock and then subsequently received 2 doses on days +23 and +30 at the discretion of the treating physician in the context of multiorgan failure and severe limb ischemia and graft failure. Patient 7 received only 1 dose because of severe septic shock that developed the following week, which subsequently resolved. Patient 4 received only 1 dose at the discretion of the treating physician. The eculizumab dose was 900 mg i.v. for each administration with the exception of one 600-mg i.v. dose given to 1 patient on day +6 that was the last of 4 weekly loading doses followed by a 900-mg i.v. dose on day +13.

All but 1 patient engrafted, with the median day of neutrophil engraftment at day +15 (range, days +12 to +28). The patient with graft rejection had underlying AA and received a bone marrow graft. One patient with AA (patient 3) died of

Table 1
Demographics and Clinical Characteristics

Patient	Age, yr	Sex	Disease	Donor	Conditioning	Source	Day of Last Pre-HCT Eculizumab Dose	Pre-HCT PNH Clone Size (% gran/RBC)	Days to Neutrophil Engraftment	Days to Platelet Engraftment	Eculizumab Post-HCT (Days Given)	Follow-Up, mo
1	60	Male	AA	Sibling	Cy/ATG	BM	Unknown	36/0	28	21	+3, +17	51
2	25	Male	AA	Sibling	Flu/Cy/ATG	BM	-13	6/NA	20	18	+2, +16	52
3	32	Male	AA	Sibling	Cy/ATG	BM	-14	23/NA	NA	NA	+2, +23, +30	1
4	29	Female	AA	MUD	Flu/Mel	PBSCs	-18	70/30	12	11	+7	86
5	38	Male	MDS	Sibling	Flu/Mel	BM	-21	68/6	15	15	+8, +22	6
6	58	Female	MDS	MUD	Flu/Mel	PBSCs	-1	60/10	12	10	+6, +13	59
7	63	Male	MDS	MUD	Flu/Mel	PBSCs	-12	89/10	14	N/A	+2	3
8	46	Male	PMF	MUD	Flu/Mel	BM	-11	73/12	23	23	+2, +16, +30	20

Cy indicates cyclophosphamide; ATG, antithymocyte globulin; Flu, fludarabine; BM, bone marrow; NA, not applicable; MUD, matched unrelated donor; Mel, melphalan; PBSCs, peripheral blood stem cells; PMF, primary myelofibrosis.

Escherichia coli sepsis on day +32 before engraftment, and another patient (patient 7) died on day +88 from multiple infections (refractory CMV reactivation and fungal pneumonia) in the setting of steroid-refractory grade IV acute GVHD involving the lower gastrointestinal tract; this patient also did not have successful platelet engraftment. No patients had clinical hemolysis after transplantation or infection from encapsulated organisms. Two patients developed grade III-IV acute GVHD (patients 1 and 7) and 4 patients developed grade II-IV acute GVHD, and only 5 patients were evaluable for chronic GVHD at 2 years, of whom 2 had mild chronic GVHD (patients 4 and 8). No patient relapsed with the PNH clone, although 1 patient with AA with a detectable monosomy 7 (patient 1) developed MDS at 4 years after alloHCT and died 89 days after a second alloHCT. All patients who survived to day +100 underwent reevaluation of PNH clone size by flow cytometry, and all showed either complete clearance of the PNH clone or a PNH clone size of $<1\%$ in both the granulocytes and erythrocytes. No patient experienced a hemolytic or thrombotic event after alloHCT. Of the 6 patients who survived to day +100, 5 were still alive at last follow-up, with the only death occurring in the patient who developed MDS after alloHCT.

DISCUSSION

Of note, none of the patients in our cohort had previous thrombosis, which has been identified as an adverse prognostic factor for survival post-alloHCT in patients with PNH [3]. Recently, Vallet et al [8] reported outcomes for 21 patients with PNH who had received eculizumab before alloHCT, noting grade II-IV acute GVHD in 7 patients (33%) and grade III-IV acute GVHD in 4 patients (19%). Three patients died of fungal infection, 2 patients died of acute GVHD, and 1 patient died of relapsed MDS. Engraftment did not seem to be affected. Three patients received eculizumab post-alloHCT as well, 1 for a hemolytic crisis on day +27, another for engraftment failure, and a third for early disease relapse with recurrent hemolysis [8]. DeZern et al [9] reported a series of 8 patients with PNH (7 with concurrent severe AA) who received pre-transplantation eculizumab as bridging therapy before the start of conditioning. Five of these patients had experienced at least one previous thrombotic event. Of note, 5 patients received a haploidentical donor transplant, and the other 3 received a matched unrelated donor transplant. No infections from encapsulated organisms were seen, and there were no thrombotic or hemolytic events post-alloHCT; engraftment also did not appear to be delayed. Our data, although limited by a small number of patients, suggest that the use of eculizumab in the early post-transplantation setting is feasible and safe, without obvious toxicities specifically related to the drug. Furthermore, the patients in this series also received pre-HCT eculizumab as described by DeZern et al [9].

The lack of overt hemolysis in these patients with a PNH clone size as large as 89% may indicate its potential therapeutic benefit in reducing the risk of withdrawal hemolysis early post-HCT. The data also illustrate real-world management of patients with PNH who undergo alloHCT and describe a standardized institutional practice that has not been previously documented in the literature. Although the small sample size precludes any conclusive statements about early post-transplantation use of eculizumab, our experience as summarized here highlights its feasibility and supports further clinical studies in patients with sizable PNH clones who are at risk for active withdrawal hemolysis during alloHCT.

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