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Eculizumab Bridging Before Bone Marrow Transplant for Marrow Failure Disorders is Safe and Does Not Limit Engraftment

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Abstract

Background.—Paroxysmal nocturnal hemoglobinuria (PNH) often develops secondary to other bone marrow failure (BMF) disorders, especially aplastic anemia (AA). Patients with the AA/PNH syndrome may require treatment with both eculizumab to reduce intravascular hemolysis and the risk of thrombosis and allogeneic stem cell transplant for the severe BMF. There has been concern that eculizumab could adversely affect the outcomes for transplant in these patients.

Methods.—This is a retrospective, single-center study of SAA/PNH patients treated with eculizumab immediately prior to the start of conditioning for transplant. Metrics of engraftment and infectious outcomes are described.

Results.—Eight patients with SAA/PNH and PNH-related symptoms were treated with eculizumab and then proceeded to transplant. All were successfully transplanted without adverse events related to C5 blockage prior to conditioning. All were also cured of their both PNH and SAA.

Conclusions.—Eculizumab is safe and efficacious in patients with PNH clones who require transplant. This is sometimes required to “bridge” patients before BMT and does not appear to adversely impact outcomes even when using HLA matched unrelated or haploidentical donors.

Keywords

aplastic anemia; transplant; eculizumab; paroxysmal nocturnal hemoglobinuria

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal, hematopoietic stem cell disorder that manifests with hemolytic anemia and thromboembolism as a result of a population of cells deficient in glycosylphosphatidylinositol anchored proteins (GPI- APs).[1] Eculizumab has been shown to improve anemia, decrease intravascular hemolysis, and reduce the risk of

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thrombosis in PNH.[2] PNH often develops secondary to acquired aplastic anemia (AA), and patients with the AA/PNH syndrome have poorer outcomes than those with PNH alone.[3] Acquired aplastic anemia is an immune-mediated bone marrow failure (BMF) disorder that presents with a hypocellular marrow and resultant pancytopenia.[4,5] Patients with severe aplastic anemia (SAA) have life-threatening pancytopenia,[6] and require treatment with immunosuppressive therapy (IST) with an antithymocyte globulin-containing regimen or allogeneic stem cell transplantation.[7,8] As many as 40% of AA patients have a PNH population of cells at diagnosis. This PNH clone[9,10] is considered a marker of acquired marrow failure[11] and its presence may or may not be associated with manifestations of classical PNH disease such as thrombosis or hemolysis.[1] SAA patients with large PNH clones[12] may require both eculizumab to stop thrombosis and definitive therapy (IST or transplant). A previous report specifically of PNH patients transplanted after treatment with eculizumab, has shown almost 30% of mortality, mainly due to infections and acute graft-versus-host disease (GvHD).[13] It is not known if this would be true in AA patients transplant as well. Here we review our single institution experience with allogeneic transplantation in SAA/PNH patients who required eculizumab as a bridge to transplant.

METHODS

We retrospectively reviewed our single institutional experience in patients who received eculizumab in advance of their conditioning for allogeneic transplantation for SAA/PNH. This was a retrospective study performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. Follow up was from Day 0 of a patient's BMT to June 1, 2018. These patients were transplanted between July 2010 and May 2018. All patients meeting criteria were reviewed from January 2008 until July 2018. Infections were documented from the clinical records.

Donors and grafts

Eligible donors included related family members who shared at least 1 HLA haplotype and unrelated matched/mismatched donors. Donor bone marrow was harvested with a target yield of 4×10^8 nucleated cells/kg recipient ideal body weight and infused on day 0. The marrow was unmanipulated except that major incompatible ABO grafts were red blood cell depleted by buffy coat preparation and minor ABO incompatible grafts were plasma depleted as per institutional standards. HLA phenotyping was performed as described previously.[14] Unrelated donors were selected in accordance with the standard National Marrow Donor Program policies.

Eculizumab dosing, Conditioning and GVHD Prophylaxis

All patients had received eculizumab using a 25 to 45 minute intravenous (IV) infusion. An induction dose of eculizumab 600 mg every 7 ± 2 days for 4 doses in patients who had received drug for PNH symptoms; then eculizumab 900 mg 7 ± 2 days later; followed by a maintenance dose of eculizumab 900 mg every 14 ± 2 days. The maintenance dose was given to patients for whom only 1-3 doses prior to BMT were utilized. All patients discontinued eculizumab with the start of conditioning. Dosing was not continued thereafter.

The transplant conditioning regimen began with rabbit anti-thymocyte globulin (ATG) dosed at 0.5 mg/kg on day −9 and 2 mg/kg on days −8 and −7. Fludarabine was administered 30 mg/m^2 IV daily for 5 days, from day −6 to day −2 (total dose received 150 mg/m^2). Cyclophosphamide was given 14.5 mg/kg IV daily for 2 days from day −6 to day −5 and administered as a 1-2 hour infusion (total dose received 29 mg/kg) and total body irradiation (TBI) administered at delivered in a single dose of 200 cGy on day −1 for all patients who received nonmyeloablative transplants. One patient (Patient 6) received oral busulfan (dosed to AUC 800-1400 μmol*min/L Days −6 to −2) and CY (50 mg/kg on days −4, −5).

The marrow graft was infused on day 0. PTCy was administered at 50mg/kg/day IV on days +3 and +4 post-transplant. G-CSF was given SQ starting on day +5 at 5 mcg/kg/day until absolute neutrophil count (ANC) was greater than 1.5 $\times l0^9$/L for 3 days. Mycophenolate mofetil (MMF) was given day 5 through 35 and tacrolimus day 5 through day 365.

Supportive Care

Blood product replacement and other supportive care measures were per institution practices. Standard oral antibiotic prophylaxis with a quinolone and an azole was begun on day 0. Bacterial prophylaxis was continued through neutrophil recovery while fungal prophylaxis through approximately day 60 as per clinical suspicion for any dormant fungal disease. Patients received standard *Pneumocystis jiroveci* and anti-herpes and varicella prophylaxis for 1 year. Magnesium levels were kept above 1.5 mg/dL. All blood products, except for the allograft, were irradiated with 25 Gy prior to transfusion. The thresholds of red blood cell (RBC) and platelet transfusions were hematocrit < 25% and platelet count < $20 \times 10^3/mm^3$. Cytomegalovirus (CMV)–seronegative patients with seronegative donors were given transfusions from CMV-seronegative donors, or leukocyte reduced blood products if CMV-negative products were unavailable. Patients were monitored for CMV reactivation by weekly measurement of CMV copy number by PCR of serum until day 60. Preemptive therapy with ganciclovir would have been initiated when ≥ 500 copies of CMV/mL serum were detected. Patients were monitored weekly for EBV and therapy in these subjects was not required here.

Engraftment and Chimerism Analysis

Neutrophil engraftment was defined as an ANC >1.0 $\times 10^9$/L measured for three consecutive measurements on different days. Red cell engraftment was counted as days from last packed RBC transfusion and platelet engraftment defined as a platelet count greater than $50 \times 10^3/mm^3$ for 7 days without transfusion.

Patients had chimerism studies done on peripheral blood or bone marrow on days 30, 60, 180, and 360, and yearly thereafter. Chimerism was measured by PCR analysis of variable number of nucleotide tandem repeats unique to donors or recipients on total peripheral blood and isolated $CD3^+$ T cells.

Statistical Analysis

Baseline characteristics and demographics are reported descriptively with continuous variables summarized by median and range. Responses to therapy were defined as above.

RESULTS

Johns Hopkins Hospital is a tertiary referral hospital where a total of 63 SAA/PNH patients underwent curative allogeneic BMT with documented presence of a PNH clone >20% in the granulocytes since 2008 which was the population reviewed. Of these patients, 8 had received eculizumab per clinical indication as determined by the treating provider prior to start of conditioning for transplant. All patients discontinued eculizmab completely after the start of conditioning. Patient 1 was initially treated with ATG/CSA for aplastic anemia but present years later with Budd-Chiari and a large PNH clone. He was started on eculizumab but remained red cell and platelet dependent due to a combination of breakthrough hemolysis and underlying bone marrow failure. Patient 5 had classical PNH but continued to have breakthrough intravascular hemolysis despite receiving 1500 mg of eculizumab IV every 12 days. The remaining patients met criteria for severe aplastic anemia but were bridged with eculizumab because of document or suspected thrombosis. Patient characteristics are shown in Table 1. The median age of the patients was 24.5 (range, 17-47) years with 50% male. Median follow up time is 37 (range, 2-83) months. The median granulocyte clone percentage was 80.75% (range, 28-100). The median doses of eculizumab varied widely from 2-156 with median of 16 doses pre transplant. Time prior to the Day-9 start of conditioning is noted in Table 1. ATG has also been shown to cause hypercoagulability through complement mediated mechanisms;[15,16] eculizumab was dosed up until the start of conditioning to not further precipitate complement activation and risk for a thrombotic event peri-transplant. It was not continued as the complement would be blocked for the next two weeks in these patients and by then the chemotherapy was presumed to sufficiently myelosuppress the PNH hematopoiesis. . Donor and cell dose information are provided in Table 2. All patients with related donors were transplanted from haploidentical donors. All SAA patients are alive. The single PNH patient (Pt 5) (who had concomitant Crohn’s disease) succumbed to colon cancer, attributed to his antecedent inflammatory bowel disease, 4.5 years after transplant. All patients engrafted with no unsuspected complications. These outcomes are shown in Table 3. There were no severe infections or infections with encapsulated bacteria among these 8 patients peri-transplant . The median time to neutrophil engraftment was 19.5 days (range 14-41). The median time to red cell engraftment was 22 day (range 14-115). Lastly the median time to platelet engraftment was 26 days (Range 22-190). Patient 4 did have longer time to engraftment than other patients attributed to BK virus in the urine as well as noncompliance with mycophenolate mofetil, possibly leading to low Day 30 T cell chimerism. This patient had platelet transfusion independent over $10 \times 10^3/mm^3$ from day 27 forward but did not achieve sustained values over $50 \times 10^3/mm^3$ until Day 190. In all patients, the PNH clones were eliminated as demonstrated by negative flow cytometric assays post-transplant.

DISCUSSION

Eculizumab is an FDA-approved humanized monoclonal antibody for the treatment of PNH and in clinical trials has been shown to improve anemia, decrease intravascular hemolysis, reduce the risk for thrombosis, and markedly improve quality of life for most PNH patients. [1,2,17] Patients with severe aplastic anemia and moderate to large PNH clones at diagnosis or following immunosuppressive therapy can experience severe morbidity due to thrombosis,

even in the presence of severe thrombocytopenia. These patients often present with pain (frequently abdominal) and elevated d-dimers. Eculizumab is highly effective in controlling the thrombotic complications of PNH but does not improve bone marrow failure. Small studies describing the concomitant use of eculizumab with immunosuppressive therapy in aplastic anemia have been described but its use immediately prior to bone marrow conditioning regimens has not been studied.[18,19] A common clinical query to AA/PNH experts in the field is if there are potentially detrimental effects from complement blockage prior to BMT for patients given previous reports[13]. ATG is commonly used for conditioning, especially in nonmalignant diseases, to facilitate engraftment and to mitigate GVHD; its mechanism of action is both complement dependent and independent.[2] One could hypothesize that the blockage of terminal complement by eculizumab could predispose to or adversely affect transplant outcomes. Here, we demonstrate comparable engraftment rates to other reported AA patients receiving BMT without increased infections rates.[20,21] The patients' duration of therapy with eculizumab also did not impact outcomes. The source of donor, haploidentical or unrelated, also was not affected by its use.

The major limitations of this study are the relatively small patient sample, the retrospective analysis, and the possibility of selection bias in choosing which patients required eculizumab therapy per BMT. However, treatment decisions were made by the authors with lengthy experience in treating BMF as well as patients with indications to treat a thrombotic event or risk with PNH clone per published guidelines.[1,2,22] Moreover, both PNH and AA are rare diseases for which transplant is increasingly utilized, but it is unlikely that there will be a prospective trial to evaluate this role for eculizumab. BMT is also still indicated for the rare PNH patient whose hemolysis is not controlled by eculizumab; however, with newer complement inhibitors this latter indication may become obsolete.[23,24]

In conclusion, eculizumab before transplant for patients with SAA/PNH is safe and well-tolerated. We advocate the use of eculizumab for "bridging" therapy in these patients in need of transplant who have a moderate to large size PNH clone (>20%) and suspected or documented thrombosis in patients prior to ATG- containing and other conditioning regimens so that patients do not have peri-transplant PNH-related complications.

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Highlights

- A retrospective review of AA/PNH patientd who got eculizumab before bone marrow transplant
- Nonmyeloablative conditioning and post-transplant cyclophosphamide for GVHD prophylaxis
- All 8 patients engrafted, are transfusion independent, without increased transplant-related complications due to eculizumab

Table 1:

Patient Characteristics.

Pt	Age (years)/Sex	Primary Diagnosis	Use of IST Pre BMT	Granulocyte Clone (%)*	Thrombotic event PreBMT	D-Dimer Pre Ecu (mg/L)	D-Dimer Post Ecu (mg/L)	Retic (K/mm^3)	LDH (U/L)	HGB (g/dL)	Doses pre BMT	Time from Last Ecu Dose to Day −9 (days)
1	35 M	SAA	Y	92	Buddchiari	>20	0.52	84	919	5.5	48	12
2	27 F	SAA	Y	69.5	None	4.0	0.42	42	199	6.8	32	7
3	23 M	SAA	Y	99	Facial artery	>30	0.68	7.1	348	6.8	15	1
4	25 F	SAA	Y	97	Pulmonary embolism and superior mesenteric artery	27	0.49	19.4	63	6.6	17	1
5	47 M	PNH	N	100	None	NA	7	340	517	9.7	156	2
6	24 F	SAA	Y	65	Abdominal vein	>30	0.76	9.2	157	8.1	6	1
7	22 F	SAA	N	49	None	0.41	0.28	55.8	280	7.9	3	1
8	17 M	SAA	N	28	Abdominal vein	1.49	0.23	37.5	250	6.6	2	1

Pt = patient; IST = immunosuppressive therapy; BMT = bone marrow transplant; Ecu = eculizumab; Retic= absolute reticulocyte count; LDH = lactate dehydrogenase; HGB = hemoglobin

*All laboratory measurements noted at time pointimmediately prior to the start of eculizumab to indicate the additional clinical indications for initiation of drug

Day −9 was start of conditioning regimen in all patients

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Table 2:

Donor Characteristics

Pt	Donor Age (yrs)	Donor Sex	Donor Relationship	Degree of HLA Mismatch	Patient ABO	Donor ABO	Patient CMV	Donor CMV	Nucleated cells/kg	Infused graft CD34+ cells/kg	Infused graft CD3+ cells/kg	Product processi ng
1	38	F	Related	5/10	O+	O+	Nonreactive	Nonreactive	3.77E+08	4.60E+06	4.07E+07	None
2	24	M	Related	5/10	O+	O+	Nonreactive	Nonreactive	7.98E+08	5.18E+06	4.79E+07	None
3	37	F	Unrelated	10/10	O+	O−	Nonreactive	Reactive	2.92E+08	1.90E+06	3.55E+07	None
4	23	M	Unrelated	10/10	A+	A+	Nonreactive	Reactive	4.08E+08	2.78E+06	2.80E+07	None
5	13	M	Related	5/10	O+	O+	Nonreactive	Reactive	8.0E+08	20.8E+06	5.7E+07	None
6	27	M	Unrelated	10/10	A+	A+	Reactive	Reactive	3.5E+08	3.1E+06	4.1E+07	None
7	54	M	Related	5/10	A+	A+	Nonreactive	Nonreactive	3.80E+08	2.74E+06	3.02E+07	None
8	19	M	Related	5/10	B−	B+	Nonreactive	Reactive	5.56E+08	7.00E+06	5.62E+07	None

Table 3:

Transplant Outcomes by Patient.

Pt	Neutrophil engraftment (day)	Red cell engraftment (day)	Platelet engraftment (Day)	Day 30 T Cell (% donor)	Day 30 Myeloid (% donor)	GVHD	Viral infections	Bacterial Infections	Post Granulocyte Clone (%)
1	19	16	28	100	100	None	None	None	0
2	24	20	31	100	100	None	None	None	0
3	20	27	33	>95	>95	None	CMV, BK	Enteroccus in the urine without pyyruia	0
4	41	115	190	22	100	None	BK	None	0
5	18	24	22	100	100	None	CMV	None	0
6	21	24	24	100	100	None	None	Enteroccus in the urine without pyyruia	0
7	19	19	23	100	100	None	HHV6, BK	C difficile in stool	0
8	14	14	18	100	100	None	None	Sinusitis without organism identified	0

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