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Successful reduced-intensity conditioning hematopoietic stem cell transplantation (HSCT) for paroxysmal nocturnal hemoglobinuria (PNH) with aplastic anemia in two children

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Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) is an extremely rare cause of bone marrow failure in children. We report two children who presented with pancytopenia, and were diagnosed with PNH with severe aplastic anemia. Both children underwent upfront, successful hematopoietic stem cell transplantation with reduced-intensity conditioning. One patient had a syngeneic donor, and one patient had a 10/10 matched unrelated donor. Neither patient developed GVHD, infections, or recurrent PNH. Reduced-intensity conditioning hematopoietic stem cell transplantation is a reasonable therapy for PNH with marrow failure in children.

Keywords

stem cell transplantation; paroxysmal nocturnal hemoglobinuria; pediatric

1 INTRODUCTION

PNH is a rare hematologic disorder characterized by hemolytic anemia, thrombosis, and/or varying degrees of bone marrow failure secondary to disordered regulation of the complement cascade. Affected hematopoietic stem cells acquire a deficiency in an anchoring protein glycosylphosphatidylinositol (GPI) which normally allows two complement inhibitory proteins, CD55 and CD59, to connect to cell surfaces. Clinically, this improper activation of the complement cascade results in erythrocyte hemolysis, pancytopenia with aplastic anemia, and/or thrombosis.[1] The etiology of the GPI deficiency has been linked to a mutation of the X-linked PIG-A gene.[1] PNH has two main phenotypes: intravascular

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CONFLICT OF INTEREST STATEMENT

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hemolysis and pancytopenia due to marrow failure.[2] The diagnosis of PNH relies on flow cytometry of peripheral blood using a fluorescein-tagged proaerolysin variant to evaluate for deficiency of GPI.[3]

Treatment of PNH depends on the severity of disease and supportive care including blood transfusions and/or immunosuppressive therapy may be used.[2] Eculizumab, a humanized monoclonal antibody that targets the complement protein C5, leads to inhibition of the terminal complement cascade[2,4] and results in reduced intravascular hemolysis and better control of complement-mediated symptoms; unfortunately eculizumab will not treat the underlying bone marrow failure.[3] Hematopoietic stem cell transplant (HSCT) is the only curative therapy for PNH, and may be indicated for patients with severe bone marrow failure secondary to PNH.[3,5] HSCT for PNH has been performed using both myeloablative and reduced intensity conditioning (RIC) regimens.[6] In this case report, we present the clinical course of two teenage patients with PNH who have successfully undergone HSCT with RIC.

2 CASE REPORTS

Patient #1 is a 16 year-old male identical twin with history of asthma who presented with a month-long history of headache and fatigue; complete blood count (CBC) was notable for pancytopenia: White blood cell count $3.0 \times 10^9/L$, hemoglobin 6.9 g/dL, platelets $38 \times 10^9/L$, reticulocyte count 3.2%, $57 \times 10^9/L$. Subsequent flow cytometry confirmed PNH (Figure 1); loss of expression of GPI-linked proteins in monocytes (29% loss of FLAER/CD14), granulocytes (27% loss of FLAER/CD24), and erythrocytes (3% loss of CD59). Bone marrow biopsy revealed significant hypocellularity (10%) with aplastic anemia; in addition, bone marrow cytogenetics was notable for deletion 13q14q22 on 2/20 karyotypes. The patient's identical twin brother was confirmed to be a perfect HLA match. Prior to transplant, the patient had symptomatic anemia, and did require packed red blood cell transfusion. The patient proceeded with a syngeneic peripheral blood stem cell transplant from his identical twin brother (twin brother tested negative for PNH). He underwent a 5-day RIC regimen with fludarabine 30 mg/m²/day on days -5 to -2, cyclophosphamide 60 mg/kg/day on days -3 to -2, and horse ATG 30 mg/kg/day on days -4 to -2. He received no additional GVHD prophylaxis given that he had a syngeneic donor. On day +7 from the transplant, with an ANC of 0, he developed fever to 41.6 C, systolic hypotension, and extensive confluent maculopapular rash over his trunk and extremities requiring transfer to the pediatric intensive care unit for pressor support. Cultures were negative and symptoms resolved immediately with prednisone, suggesting late onset ATG reaction versus engraftment syndrome. He engrafted on day +12 and his ANC rapidly rose over the following days. He was discharged from the hospital on day +16. He did not have any further complications. He is currently >20 months post-transplant with normal blood counts, no signs of GVHD, and no signs of recurrence of his PNH.

Patient #2 is a 15 year-old male with history of depression and anxiety who presented when he was noted to be pancytopenic: White blood cell count $2.8 \times 10^9/L$, hemoglobin 7.4 g/dL, platelets $25 \times 10^9/L$, reticulocyte count 4.0%, $77.2 \times 10^9/L$. Flow cytometry confirmed PNH (Figure 1); loss of expression of GPI-linked proteins in monocytes (79% loss of FLAER/CD14), granulocytes (25% loss of FLAER/CD24), and erythrocytes (45% loss of CD59).

Bone marrow biopsy showed severe aplastic anemia and hypocellularity. Cytogenetics were normal. The patient had no full siblings. Both immunosuppressive therapy and stem cell transplant were offered to the patient and family, and they felt strongly to proceed with upfront transplant with a matched unrelated donor. Prior to transplant, the patient had symptomatic anemia and required packed red blood cell transfusions, though did not have other complications. The patient underwent HSCT with a 10/10 HLA-matched unrelated 49-year-old male donor. He received reduced intensity conditioning with fludarabine 30 mg/m² ×4 days on days -5 to -2, cyclophosphamide 50 mg/kg ×2 days on days -3 to -2, low dose total body irradiation (2 Gy) ×1 on day -1, and alemtuzumab 10 mg ×4 days on days -7 to -4. Tacrolimus and Methotrexate were additionally used for GVHD prophylaxis. He experienced significant fluid overload and subsequent hypertension with the infusion of bone marrow and required anti-hypertensive therapy with amlodipine until discharge. He engrafted on day +14. He was discharged from the hospital on day +21. Approximately two months after transplant, he experienced asymptomatic CMV reactivation with detectable but too low to quantify CMV PCR titer. He was started on empiric valganciclovir, and his CMV PCR immediately turned negative and has remained so throughout. He never developed GVHD and tacrolimus was weaned off by 9 months post-transplant. He is currently >17 months post-transplant with normal blood counts, >97% donor chimerism, no signs of GVHD, and no signs of recurrence of his PNH.

3 DISCUSSION

PNH is rare in adults, though is even rarer in children, with only a few published series.[7–9] PNH may have a slightly different phenotype in children, as multiple reports show that children are more likely to have marrow failure than their adult counterparts.[7,8] HSCT remains the only curative therapy available.

We report two children with PNH and aplastic anemia who underwent upfront, successful HSCT with RIC. One patient had an identical twin donor (matched sibling) and the other had a 10/10 matched unrelated donor. Both patients did well post-HSCT and did not have complications after discharge.

There are very few reported pediatric patients with PNH being treated with HSCT. Published transplanted patients are summarized in Table 1. To our knowledge, there are only reports of 20 children with PNH undergoing allogeneic HSCT, and all are from retrospective case reports or case series.[7–13] In contrast to our report, the majority of children have received myeloablative conditioning regimens, with various regimens and various donors. Also, in contrast, the majority of reported patients (14 of 20) received immunosuppressive therapy prior to HSCT, typically consisting of cyclosporine, ATG, +/-prednisone.[7–10,13] Only one prior report of pediatric patients undergoing HSCT for PNH includes RIC.[9] Previously reported survivals have been good, with 16 of 20 children surviving HSCT without recurrent PNH. Our experience adds to the safety and efficacy of RIC for this population.

Identical twin donors are obviously rare, though as PNH is acquired, PNH is the ideal disease for this donor choice. Four prior case reports of syngeneic donor HSCT for PNH exist. One child and one adult received myeloablative conditioning with syngeneic donor,

and both survived.[14] Conversely, one child received no conditioning, and one adult received single agent cyclophosphamide, and both patients had relapse of PNH, suggesting that that more conditioning is required than single agent cyclophosphamide to eradicate the PNH clone.[12,15] Our patient was successfully transplanted with syngeneic donor with a fludarabine/cyclophosphamide and hATG conditioning regimen, thus lending evidence that RIC is effective for PNH with syngeneic donors.

In conclusion, our two pediatric case reports add to the growing literature of HSCT as a therapy for PNH. Similarly to patients with de novo severe aplastic anemia, RIC HSCT may be considered as first-line therapy for children and young adults with PNH, both with HLA-matched sibling donors, as well as with HLA-matched unrelated donors.

ABBREVIATIONS

HSCT	hematopoietic stem cell transplantation
PNH	paroxysmal nocturnal hemoglobinuria
GVHD	graft versus host disease
GPI	glycosylphosphatidylinositol
RIC	reduced intensity conditioning
CBC	complete blood count
FLAER	fluorescein-labeled proaerolysin
ANC	absolute neutrophil count
ATG	anti-thymocyte globulin
CMV	cytomegalovirus
PCR	polymerase chain reaction
HLA	human leukocyte antigen

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FIGURE 1.

Flow for PNH clones in granulocytes and monocytes. (A) Patient #1 pre-transplant, showing loss of FLAER/CD24 in granulocytes and loss of FLAER/CD14 in monocytes. (B) Patient #1 post-transplant. (C) Patient #2 pre-transplant, showing loss of FLAER/CD24 in granulocytes and loss of FLAER/CD14 in monocytes. (D) Patient #2 post-transplant

TABLE 1.

Review of pediatric PNH patients having undergone HSCT[7–13]

Reference	Number of patients	Pre-HSCT therapy	BMT Donor	Conditioning	Outcome
Curran KJ et al	n=5	4 of 5 received immunosuppressive therapy prior	MSD (n=1)	Myeloablative (5): TBI based (3); non-TBI based (2)	3 of 5 alive
			MUD (n=2)		
			MMUD (n=2)		
Mercuri A et al	n=5	3 of 5 received immunosuppressive therapy prior	Data not provided	Data not provided	5 of 5 alive
van den Heuvel-Eibrink MM et al	n=5	4 of 5 received immunosuppressive therapy prior	MSD (n=2)	Myeloablative in 2: (Bu/CY/Mel); Reduced intensity conditioning in 3: CY, ATG or Campath, low dose TBI	4 of 5 alive
			MUD (n=3)		
Ware RE et al	n=1	1 of 1 received immunosuppressive therapy prior	Data not provided	Data not provided	1 of 1 alive
Graham ML et al	n=1	0 of 1 received immunosuppressive therapy prior	Syngeneic (identical twin)	Myeloablative: TBI/CY	1 of 1 alive
Endo M et al	n=1	0 of 1 received immunosuppressive therapy prior	Syngeneic (identical twin)	No conditioning	1 of 1 alive (+PNH recurrence)
Flotho C et al	n=2	2 of 2 received immunosuppressive therapy prior	MUD (n=2)	Myeloablative: TBI/CY (1); Bu/CY (1)	2 of 2 alive
Current study (Andolina JR et al)	n=2	0 of 2 received immunosuppressive therapy prior	Syngeneic (identical twin) (n=1)	Reduced intensity conditioning: Flu/CY/ATG (1); Flu/CY/200 cGy TBI/Campath (1)	2 of 2 alive
			MUD (n=1)		
TOTAL	n=22	14 of 22 received immunosuppressive therapy prior	Syngeneic (n=3) MSD (n=3) MUD (n=8) MMUD (n=2) No data (n=6)	Myeloablative (n=10) Reduced intensity (n=5) None (n=1) No data (n=6)	18 of 22 alive & disease-free