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Hematopoietic Stem Cell Transplantation in Paroxysmal Nocturnal Hemoglobinuria: Experience from a Tertiary Care Center

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Abstract:

BACKGROUND: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired hematological disorder characterized by episodic intravascular hemolysis. Despite newer therapies such as eculizumab, hematopoietic stem cell transplantation (HSCT) remains the only curative therapy.

MATERIALS AND METHODS: An observational analytical retrospective study was conducted comprising eight PNH patients who had undergone HSCT at our center. From January 2014 to December 2020, we performed HSCT in 8 PNH patients, 5 female and 3 male, with median age of 32 years (range: 15–38 years).

RESULTS: Seven patients had pancytopenia, associated with marrow hypocellularity. One patient presented with a thrombotic episode. Seven had matched sibling donor (MSD) transplant and one underwent haploidentical transplant. The median time from diagnosis to transplant was 7 months (range: 1–38 months). All received reduced intensity conditioning (RIC): Flu-Bu-Cy-A TG for MSD transplants and Flu-A TG-Post Cy in haploidentical transplants. Median CD34+ stem cell dose was 5.5 × 106/kg (range 3.4–5.8 × 106/kg). All had successful engraftment. Acute graft versus host disease (GVHD) Grade I–III occurred in six patients. Chronic GVHD occurred in two patients. One patient succumbed to Grade III liver GVHD. Rest seven patients are alive till date and transfusion independent. The overall survival was 87.5% at a median of 26 months.

CONCLUSIONS: HSCT is the only curative therapy for PNH. With the use of RIC, the outcomes of PNH patients can be improved. The incidence of GVHD is high with RIC regimens but can be managed with prompt immunosuppression.

Keywords:

Aplastic anemia, hematopoietic stem cell transplantation, paroxysmal nocturnal hemoglobinuria

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired hematological disorder characterized by episodic intravascular hemolysis. The patients present with episodic hemoglobinuria and life-threatening venous thromboses, resulting frequently in an abbreviated life span.[1,2] Apart from episodic hemolysis, patients may develop venous thrombosis or marrow failure.[3] Thrombotic events remain the most important prognostic indicator of survival. Marrow hypoplasia occurs in 10%–31% of patients.[4,5] PNH, by itself, cannot produce aplasia, but the PNH clones seem to have a survival advantage in an environment of bone marrow failure (BMF) (due to other cause), resulting in clonal selection of PNH clones.[2,4] The disease is usually chronic with a median survival of 10 years.[6]

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With the advent of complement inhibitors such as eculizumab,[7,8] hemolytic and thrombotic features can be overcome, but these therapies do not cure the disease and are not effective in treating marrow failure. Hematopoietic stem cell transplantation (HSCT) remains the only modality of cure for PNH. There is a paucity of data on allogeneic HSCT in patients with PNH in India. Here, we present retrospective analysis of PNH patients undergoing allogeneic HSCT at our center.

Methods

From January 2014 to December 2020, eight patients with PNH underwent HSCT at the bone marrow transplant unit of our tertiary care center were eligible for this retrospective study. Patients were diagnosed with PNH – either in the classical form (with hemolysis or thrombosis) or predominantly with BMF. None of the patients had features of myelodysplasia. PNH clone was detected using FLAER (fluorescent aerolysin) based flow cytometry on granulocytes and monocytes at the time of diagnosis. In addition to flow cytometry, a bone marrow examination was performed in all these patients. We used the minimal essential diagnostic criteria laid down by the International PNH Interest group.[9]

All patients were treated with reduced intensity conditioning (RIC) regimens. The conditioning regimen employed was Flu-BU-CY-ATG for matched sibling donor (MSD) transplants and Flu-ATG-Post CY-Post Rituximab for haploidentical transplant. Graft versus host disease (GVHD) prophylaxis used was cyclosporine and methotrexate (for MSD transplants) and MMF-Cyclosporine/Tacrolimus and Rituximab for haploidentical transplants. Cyclosporine was administered at 1.5 mg/kg intravenous twice daily. Intravenous methotrexate was given at a dose of 15 mg/m^2 at day +1, and 10 mg/m^2 on days +3, +6, and +11. Cyclosporine trough levels were monitored regularly and doses adjusted accordingly. Few patients with MSD transplants received MMF (at 15 mg/kg/dose thrice a day) once they developed cyclosporine toxicity.

The stem cell source was peripheral blood in all patients. Supportive treatment, including antimicrobials and blood products, was given according to standard practices. Patients were closely monitored for acute and chronic GVHD and graded as per standard guidelines. Cytomegalovirus (CMV) copies were routinely assessed with quantitative real-time polymerase chain reaction. Posttransplant donor chimerism was analyzed by fluorescence *in situ* hybridization (X-Y) or short tandem repeat technique. The PNH clone was evaluated at Day 30 posttransplant by flow cytometry. Data were collected from medical records and analyzed for individual patient, and transplant characteristics, complications, and posttransplant outcomes. The Institutional Review Board and Ethics committee approved the study.

Results

The median age was 32 years (range: 15–38 years). Five patients were female and three males. Seven patients presented with pancytopenia associated with bone marrow hypoplasia with no features of dysplasia. One female patient had classical PNH with central nervous system (CNS) thrombosis at presentation. Before transplant, five patients were on cyclosporine and danazol combination, and three patients on steroids and danazol. In addition, the patient with CNS thrombosis received warfarin. Median time from diagnosis to transplant was 7 months (range: 1–38 months).

Seven patients underwent MSD transplant and one underwent haploidentical transplant. The median CD34+ cell count was 5.5×10^6/kg (range: 3.4–5.8×10^6/kg). The median time to neutrophil and platelet engraftment was 14 days (range; 12–16 days) and 18 days (range: 15–22 days), respectively. All patients engrafted successfully.

Six patients developed Grade I–III acute GVHD. Chronic GVHD occurred in two patients: Grade I and Grade II, respectively. All patients except one with acute GVHD responded to immunosuppressive agents. One patient with Grade III liver GVHD succumbed [Table 1].

CMV viremia was detected in two patients after 2 months of HSCT, which was treated with IV Ganciclovir as per protocol. One patient developed hemorrhagic cystitis and was managed conservatively. No patient developed veno-occlusive disease. By day +100 posttransplant, 100% donor chimerism was achieved in all patients. None of the patients developed graft rejection or graft failure. One patient developed thrombotic thrombocytopenic purpura on day +27 due to cyclosporine toxicity and was treated with daily plasma exchange therapy till improvement of counts. She had 99% chimerism at day +30 but succumbed to Grade III liver GVHD. Rest seven patients are alive till date and transfusion independent. The median duration for complete disappearance of PNH clone posttransplant was 2 months (range: 1–12 months). At a median follow-up period of 26 months (range: 3–68 months), overall survival (OS) was 87.5% [Figure 1].

Discussion

In this study, we have reviewed the outcome of eight PNH patients postallogeneic HSCT. Data on PNH transplantation from India are scarce. The two main

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Table 1: Patient and transplant characteristics

Age/sex	Baseline PNH clone (%)	Treatment prior to transplant	Type of transplant	Conditioning	Stem cell dose	Neutrophil/ platelet engraftment	GVHD	Posttransplant complications	Final status
33/female	90	Cy, dan	MSD	Flu-Bu-Cy-ATG	5.5	+12, +15	I (skin)	HC	Alive
28/male	24	Cy, pred	Haplo	Flu-ATG	3.4	+16, +18	No	No	Alive
32/male	55	Cy, dan	MSD	Flu-Cy	5.7	+15, +17	I (skin)	No	Alive
33/female	32	Pred, dan	MSD	Flu-Bu-Cy	5.3	+16, +18	II (GI, liver)	No	Alive
24/female	53	Cy, dan	MSD	Flu-Bu-Cy-ATG	5.6	+13, +15	No	No	Alive
32/female	65	Pred, dan	MSD	Flu-Bu-Cy-ATG	5	+15, +22	I (skin)	HC	Alive
21/female	65	Pred, dan	MSD	Flu-Bu-Cy-ATG	5.3	+16, +22	III (liver)	VOD, TTP	Expired
38/male	11	Cy, dan	MSD	Flu-Cy	5.8	+14, +19	II (gut, skin)	No	Alive

Cy=Cyclosporine; Dan=Danazol; Pred=Prednisolone; MSD=Matched sibling donor; Haplo=Haploidentical; HC=Hemorrhagic cystitis; VOD=Veno-occlussive disease; PNH=Paroxysmal nocturnal hemoglobinuria; GVHD=Graft versus host disease; ATG=Antithymocyte globulin; TTP=Thrombotic thrombocytopenic purpura; Flu=Fludarabine; Bu=Busulfan; GI=Gastrointestinal

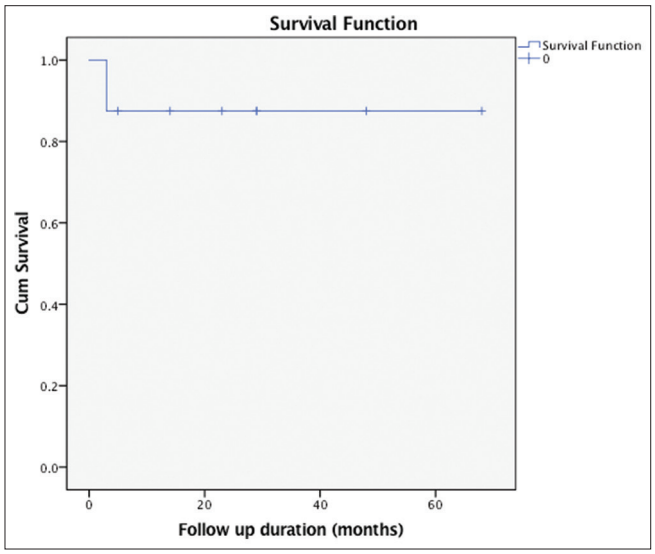


Figure 1: Overall survival

registry studies on HSCT in PNH are the International Bone Marrow Transplant Registry (IBMTR) (1978–1995) that included 57 patients and the Gruppo Italiano Trapianto Midollo Osseo including 26 patients. The recent publication by Polish Adult Leukemia Group (Multicenter Analysis) (2002–2016) comprised 78 patients.[10-12] The primary indications for transplantation in these studies and in our series were AA/PNH overlap. One female patient presented with classical PNH and thrombosis. The Polish group had 27 patients with classical PNH presenting with thrombosis in 12% and hemolysis in 81%.[11] The IBMTR study had 32% of patients who presented with severe aplastic anemia.[10]

In our study, the stem cell source was peripheral blood for all the patients. We used Busulfan and ATG-based RIC. In the Polish Study, almost all patients (94%) received reduced toxicity conditioning, 66% treosulfan based, and 67% ATG based. Peripheral blood was used as stem cell source in 72% and an identical sibling donor was used in 24%.[12] All our patients had successful engraftment and complete disappearance of PNH clone within 60 days of transplant. The Polish study had 96% of patients with successful engraftment;[12] the IBMTR group had 77% with sustained engraftment.[10] In the Polish Study, complete disappearance of clone was seen in 70% of patients, and subclinical clone size in 25% of patients; within a median duration of 133 days.[12] Six out of eight patients (75%) had Grade I–III acute GVHD in our study. Chronic GVHD occurred in two patients. In comparison, in the Polish study, acute GVHD Grade II–IV was seen in 23%, and chronic GVHD was noted in 10.8% and 3.7% of patients in the BMF/PNH and classical PNH group, respectively.[12]

Majority of the patients in our study are alive and transfusion independent. At a median follow-up period of 26 months, the OS was 87.5%. In the Polish Study, with a median follow-up of 5.1 years, the 3-year OS was 88.9% and 85.1% in the cPNH and BMF/PNH groups, respectively. The IBMTR group had a survival of more than 60% in those with sustained engraftment.[10,12]

HSCT still remains the only cure for PNH patients. The decision to do a transplant depends on many factors such as number of previous transfusions received, response to nontransplant therapy such as cyclosporine, steroids, and androgens, donor availability, size of the PNH clone as well as degree of marrow failure.[13,14] With the use of RIC, morbidity and mortality can be reduced in patients of PNH but at the cost of increased rates of GVHD. The use of RIC leads to graft-versus-PNH effect which helps to eradicate the PNH clone with acceptable toxicity and improved OS.[15] The most important limitation of our study is its retrospective nature. We studied a small group of patients with a short duration of follow-up. However, our study contributes to the existing knowledge of HSCT in the treatment of PNH. Especially in a country like India, where Eculizumab is not readily available, HSCT is an important modality for treatment in PNH. A large-scale multicenter study with a more number of subjects and formation of a PNH registry in India is the need of the hour.

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Conflicts of interest
There are no conflicts of interest.

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