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Excellent Outcomes of Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Paroxysmal Nocturnal Hemoglobinuria: A Single-Center Study

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A B S T R A C T

We analyzed the outcomes of 44 patients with paroxysmal nocturnal hemoglobinuria (PNH) who received allogeneic hematopoietic stem cell transplantation (allo-HSCT) (haploidentical [haplo]-donors, 25; matched sibling donors [MSDs], 15; and matched unrelated donors, 4) between July 2007 and May 2018. All patients achieved successful donor engraftment. The median time was 12 days (range, 7 to 26) for myeloid engraftment and 13 days (range, 11 to 75) for platelets. The cumulative incidences were 15.91% and 2.27% for grades II to IV and grades III to IV acute graft-versus-host disease (GVHD), respectively, with a median follow-up time of 36 months (range, 4 to 132). The cumulative incidences were 26.73% for chronic GVHD and 9.70% for moderate to severe chronic GVHD. No patients relapsed. The probabilities of 3-year overall survival (OS) and GVHD-free, failure-free survival (GFFS) were 90.4% ± 4.6% and 85.6% ± 5.4%, respectively. The 3-year OS rates of the haplo-donor and MSD groups were 86.5% ± 7.3% versus 93.3% ± 6.4% ($P = .520$). The 3-year GFFS rates of the haplo-donor and MSD groups were 78.3% ± 8.6% versus 92.9% ± 6.9% ($P = .250$). The preliminary results indicated that allo-HSCT is a feasible option for patients with PNH; however, this should not be considered as a first-choice therapy, because the results seemed to only suggest rather than confirm that haplo-HSCT and MSD-HSCT exerted similar therapeutic efficacies.

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired hematopoietic stem cell disorder that manifests with hemolysis (classic PNH) due to loss of expression of the CD55 and CD59 proteins, leading to uncontrolled complement activation that causes hemolysis and other PNH manifestations [1]. Glycosyl phosphatidylinositol–anchored protein deficiency is usually due to somatic mutations in phosphatidylinositol glycan class A, a gene involved in the first step of glycosyl phosphatidylinositol anchor biosynthesis [2]. Consequently, stem cells affected by PNH and their progeny are deficient in glycosyl phosphatidylinositol–anchored proteins. CD55 and CD59 are 2 relevant complement regulatory proteins, and their absence is fundamental to PNH pathophysiology [3].

The clinical features of PNH differ in Western and Asian populations. For example, Western patients are reported to experience more thrombotic events, whereas Asian patients are particularly predisposed to bone marrow (BM) failure [4,5]. PNH prognoses vary greatly, ranging from indolent to life-threatening, partly because of the risk of evolution to myelodysplastic syndrome or acute leukemia [6].

PNH management has entered the era of complement inhibitory therapy. Classic PNH has been reported to be treated with eculizumab. Eculizumab therapy does not affect the disease's BM failure component [7]. Despite being the only curative treatment for PNH, allogeneic hematopoietic stem cell transplantation (allo-HSCT) is not recommended as a first-line therapy for classic PNH [8,9]. Because of the known treatment-related toxicity, this approach to management is recommended only for patients with underlying BM abnormalities,

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life-threatening complications, or refractory transfusion-dependent hemolytic anemia [4,10]. However, the European Society for Blood and Marrow Transplantation previously reported a 30% overall mortality rate in PNH patients transplanted between 1978 and 2007 [11]. In previous studies we reported 18 PNH patients who underwent allo-HSCT at our center, either from HLA-haploidentical (haplo-) donors (n = 10) or HLA-matched donors (5 from sibling donors [MSDs] and 3 from unrelated donors [MUDs]). The median follow-up period was 14.5 months (range, 6.0 to 79.0), and 9 of 10 patients in the haplo-HSCT group and all patients in the HLA-matched HSCT group were alive and transfusion-independent [12]. Haplo-HSCT is now increasingly applied as a curative therapy for patients with hematologic diseases. However, few reports exist on the use of haplo-HSCT to treat PNH. Our study evaluated the outcomes of HSCT treatment in 44 patients with PNH, especially in those who underwent haplo-HSCT at our center.

METHODS

Patients

All 44 patients with PNH who underwent allogeneic HSCT at our center between July 2007 and May 2018 were enrolled in this study. Eligibility for HSCT included a diagnosis of classic PNH or clinical PNH (PNH clone > 5%) in patients with PNH with BM failure, patients with evidence of clonal evolution (eg, myelodysplastic syndrome, leukemia), and nonresponders to agent therapy. No enrolled patients showed evidence of dyshematopoiesis or chromosomal abnormalities. In all cases the PNH diagnosis was confirmed by both clinical manifestation and hematologic tests (Ham's test and flow cytometric analysis of CD55 and CD59 expression). None of the enrolled patients was treated with eculizumab because the drug was unavailable in China. Iron chelation therapy was administered when serum ferritin was >1000 μg/L to reduce the level to below 1000 μg/L before transplantation.

The ethics committee of the First Affiliated Hospital of Soochow University approved this study. All patients provided written informed consent before therapy.

HLA Typing and Donor Selection

Donors were selected based on HLA typing, age, gender, health conditions, and willingness to donate. HLA-MSDs were the first-choice treatment. When an MSD was unavailable, we chose HLA-MUDs. Patients without a suitable HLA-MUD (>8/10 matching HLA-A, -B, -C, -DR, and -DQ loci) were eligible for HLA-haplotype transplantation.

Conditioning Regimen

Transplant days were named sequentially; for example, days before transplant were preceded by "–," the first day of stem cell infusion was named "day 1," and days after the last stem cell infusion were preceded by "+." Patients with an MSD were treated with the fludarabine/cyclophosphamide–based regimen, which consisted of fludarabine 30 mg/m^2/day i.v. on days −7 to −2, cyclophosphamide 50 mg/kg/day i.v. on days −4 to −3, and antithymocyte globulin (ATG; rabbit, Thymoglobulin; Genzyme, Cambridge, MA) 2.5 mg/kg/day i.v. on days −8 to −4. Patients with MUDs or haplo-donors were treated with the busulfan/cyclophosphamide–based regimen, which consisted of busulfan 3.2 mg/kg/day i.v. on days −7 and −6, cyclophosphamide 50 mg/kg/day i.v. on days −5 to −2, and ATG 2.5 mg/kg/day i.v. on days −5 to −2.

Graft Collection and Infusion

HSC mobilization in donors was performed via subcutaneously injecting granulocyte colony-stimulating factor at 10 mg/kg/day from day −4. For patients with MSDs, BM grafts were collected on day 0 via BM aspiration in the operating room. The targeted mononuclear cell (MNC) counts from the BM were 6 to 8×10^8/kg of recipient weight. The following day peripheral blood stem cells (PBSCs) were collected by apheresis using a Cobespectra device (Gambro BCT, Lakewood, CO) if the targeted MNC count was unmet. For patients with MUDs, PBSCs were harvested to ensure a target MNC count of 6 to 8×10^8/kg of recipient weight. For patients with haplo-donors, BM grafts were harvested on day 0 to achieve a target MNC count of 2 to 4×10^8/kg of recipient weight, and PBSCs were collected the following day. The total number of cells from the BM and peripheral blood should achieve the targeted MNC count of 6 to 8×10^8/kg of recipient weight. If the cell numbers were insufficient, more PBSCs were collected on the following day. Fresh unmanipulated BM and PBSCs were infused into the recipient on the day of collection.

Graft-versus-Host Disease Prophylaxis and Treatment Strategy

Patients with MSDs received cyclosporine A (CsA) for acute graft-versus-host disease (aGVHD) prophylaxis. CsA at 3 mg/kg/day was continuously infused over 24 hours from day −4 until the day the patient switched to oral intake, maintaining the requested whole blood trough level of 200 to 300 ng/mL for 12 months after HSCT. CsA was gradually tapered thereafter and withdrawn completely over the next 2 to 3 months. Patients with MUDs or haplo-donors received CsA (from day -7), mycophenolate mofetil, and short-term methotrexate for aGVHD prophylaxis. Mycophenolate mofetil at 1.0 g (or .5 g for children) p.o. was administered twice daily from day −7 to +30 and then gradually tapered until day +60. Methotrexate was administered at 15 mg/m^2/day on day +1 and at 10 mg/m^2/day on days +3, +6, and +11. During the CsA tapering process, if GVHD occurred in any organ, CsA was continued and adjusted to the therapeutic concentration. aGVHD was treated with 1 to 2 mg/kg/day of methylprednisolone. For steroid-refractory aGVHD, second-line immunosuppressive therapy was administered, including tacrolimus, CD25 monoclonal antibody, mycophenolate mofetil, and methotrexate.

Supportive Care and Post-Transplant Surveillance

From the beginning of the preparative regimen, all patients were in sterile rooms with strict reverse isolation. Patients began selective gut decontamination with fluconazole (200 mg twice daily), albendazole (200 mg once daily for 3 days), and levofloxacin (gentamycin for children; 200 mg twice daily) before conditioning. During the conditioning and immunosuppressive periods, prophylactic antibiotics and antifungal and antiviral therapies were administered. Trimethoprim/sulfamethoxazole (4 tablets daily, twice per week) was administered to prevent *Pneumocystis jiroveci* infection. Beginning on day +7, granulocyte colony-stimulating factor was administered at 5 μg/kg/day until myeloid recovery (absolute neutrophil count $\geq 2 \times 10^9$/L for 3 consecutive days). Heparin and prostaglandin E_1 were administered to prevent veno-occlusive disease. Prophylactic i.v. immunoglobulin (400 mg/kg) was used once weekly for the first month after HSCT. Irradiated and leukodepleted blood products were administered to maintain hemoglobin levels > 60 g/L and platelet counts > 20×10^9/L.

Multiplex fluorescent short tandem repeat analysis was used weekly in the peripheral blood to assess donor cell chimerism from the time of neutrophil recovery. Cytomegalovirus and Epstein-Barr virus viremias were monitored weekly using a real-time PCR-based method. If cytomegalovirus-positive DNA was found, ganciclovir or foscarnet was administered as preemptive therapy.

Definitions and Post-Transplant Evaluations

The first day the absolute neutrophil count was $>.5 \times 10^9$/L for 3 consecutive days was defined as neutrophil engraftment. The first day platelet counts were $>20 \times 10^9$/L without transfusion support for 7 consecutive days was defined as platelet engraftment. Primary graft failure was defined as failure to achieve neutrophil engraftment after HSCT until day +100 post-HSCT. Secondary graft failure was defined as the development of absolute neutrophil count $< .5 \times 10^9$/L after achieving initial engraftment. Delayed platelet recovery was defined as platelet engraftment achieved after >30 days. Relapse was defined as disease recurrence. Early mortality was defined as death within 60 days after HSCT. Death without disease progression was defined as transplant-related mortality.

GVHD-free, failure-free survival (GFFS) was defined as survival without grades III to IV aGVHD, moderate to severe chronic GVHD (cGVHD), or treatment failures. Death, primary or secondary graft failure, and relapse were considered treatment failures. aGVHD was scored per the criteria proposed by the 1994 consensus conference [13]. cGVHD was scored per the National Institutes of Health consensus criteria [14]. After HSCT, recipient BM and peripheral blood samples were drawn monthly during the first 3 months and every 3 to 6 months for the next 1 to 2 years.

Statistical Analysis

Survival curves were calculated using Kaplan-Meier analysis and compared using the log-rank test. All statistical analyses were based on the data available on August 31, 2018 and were performed using SPSS, version 16.0 (SPSS, Chicago, IL). All P values were 2-sided and considered statistically significant at $P < .05$.

RESULTS

Patient Characteristics and Donors

Forty-four patients diagnosed with PNH who underwent HSCT were included in this study. Table 1 shows the data for all patient and donor characteristics at the time of transplant. At the time of transplant the median age was 28.5 years (range, 6 to 54), and the median disease duration was 6 months (range, 3 to 240). Patients had received various treatments

Table 1
Characteristics of PNH Patients (N = 44) and Donors

Variable	Value
Clinical characteristics	
Median age, yr (range)	28.5 (6-54)
≤20 years, n (%)	9 (33.33)
21-40 years, n (%)	25 (56.82)
>40 years, n (%)	10 (22.73)
Sex, male/female	26/18
PNH classification at transplantation, n (%)	
Classic PNH	15 (34.09)
PNH-AA syndrome	29 (65.91)
Median time from diagnosis to transplantation, mo (range)	6.0 (3.0-240.0)
Conditioning regimen, n (%)	
Fludarabine + Cy + ATG (HLA-identical sibling)	15 (34.09)
Bu + Cy + ATG	
HLA-MUDs	4 (9.09)
HLA-haplo-donors	25 (56.82)
Conditioning regimen of classic PNH, n (%)	
Fludarabine + Cy + ATG	8 (53.33)
Bu + Cy + ATG	7 (46.67)
Conditioning regimen of PNH-AA syndrome, n (%)	
Fludarabine + Cy + ATG	7 (24.14)
Bu + Cy + ATG	22 (75.86)
Donor type, n (%)	
HLA-identical sibling	15 (34.09)
HLA-MUDs	4 (9.09)
HLA-haplo-donors	25 (56.82)
GVHD prophylaxis, n (%)	
CsA (HLA-identical sibling)	15 (34.09)
CsA + MMF + MTX	
HLA-MUDs	4 (9.09)
HLA-haplo-donors	25 (56.82)
Donor median age, yr (range)	38 (11-57)
Donor-recipient sex match, n (%)	
Male–male	17 (38.64)
Male–female	14 (31.82)
Female–male	9 (20.45)
Female–female	4 (9.09)
HLA matched in haplo-HSCT, n (%)	
5/10	23 (92.00)
6/10	1 (4.00)
7/10	1 (4.00)
Haploidentical donor–recipient relationship, n (%)	
Mother–child	2 (8.00)
Father–child	10 (40.00)
Child–mother	2 (8.00)
Child–father	2 (8.00)
Siblings	9 (36.00)
Blood types of donor to recipient, n (%)	
Matched	28 (63.64)
Major mismatched	8 (18.18)
Minor mismatched	6 (13.64)
Major and minor mismatched	2 (4.55)
Source of graft, n (%)	
BM (HLA-identical sibling)	3 (6.82)
Peripheral blood	8 (18.18)
HLA-identical sibling	4 (9.09)
HLA-MUDs	4 (9.09)
BM + peripheral blood	33 (75.00)
HLA-identical sibling	8 (18.18)
HLA-haplo-donors	25 (56.82)

Cy indicates cyclophosphamide; Bu, busulfan; MMF, mycophenolate mofetil; MTX, methotrexate.

before transplantation such as steroids, androgens, cyclosporine, ATG, and growth factors. Twenty-nine patients had PNH–aplastic anemia (PNH-AA) syndrome. Of the 44 donors (31 men, 13 women), 19 were HLA-identical (15 siblings and 4 unrelated) and 25 were haploidentical. The median age of donors was 38 years (range, 11 to 57).

Hematopoietic Recovery

The median MNC and $CD34^+$ cell values were 10.68×10^8/kg (range, 3.83 to 33.40) and 4.00×10^6/kg (range, .68 to 8.42). All patients achieved engraftment and complete chimerism (>95%), and 3 patients (haplo-donors) demonstrated delayed platelet recovery. The median time to neutrophil recovery was 12 days (range, 7 to 26), and the median time to platelet recovery was 13 days (range, 11 to 75) (Table 2).

GVHD Incidence and Severity

The cumulative incidences on day +100 were 27.27% for grades I to IV aGVHD, 15.91% for grades II to IV aGVHD, and 2.27% for grades III to IV aGVHD (Figure 1A). The cumulative incidence of cGVHD was 26.73% and that of moderate to severe cGVHD was 9.70% (Figure 1B).

Table 2
Clinical Outcomes after HSCT

Variable	Value
Median neutrophil recovery, days (range)	12 (7-26)
Median platelet recovery, days (range)	13 (11-75)
Delayed platelet recovery, n (%)	3 (6.82)
aGVHD, n (%)	
Grade I	5 (11.36)
Grade II	6 (13.64)
Grade IV	1 (2.27)
Chronic GVHD, n (%)	
Mild	6 (13.64)
Moderate	2 (4.55)
Infection, n (%)	
Febrile neutropenia	3 (6.82)
Pulmonary infections	6 (13.64)
Septicemia	2 (4.55)
Anal infection	4 (9.09)
CMV viremia	1 (2.27)
EBV viremia	1 (2.27)
TRM	4 (9.09)
Causes of death, n (%)	
GVHD	1 (2.27)
Infection	2 (4.55)
Thrombotic microangiopathy	1 (2.27)
Median follow-up time among living patients, mo (range)	36 (4-132)

TRM indicates transplant-related mortality; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

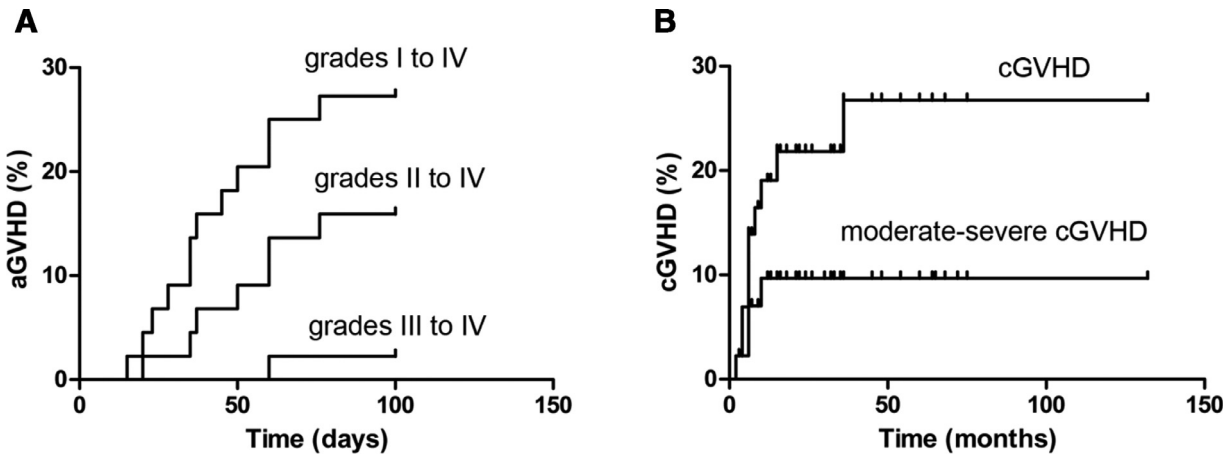

Figure 1. The cumulative incidences of GVHD. (A) The cumulative incidence of aGVHD grades I to IV on day +100 was 27.27%, of grades II to IV aGVHD on day +100 was 15.91%, and of grades III to IV on day +100 was 2.27%. (B) The cumulative incidence of cGVHD was 26.73% and of moderate to severe cGVHD was 9.70%.

Infectious Complications and Transplant-Related Toxicities

Seventeen patients (38.64%) experienced infection (Table 2). Grades II to IV organ toxicities during the +40 days were evaluated as hepatic (6.82%) and renal (4.55%). No patient died because of lethal organ toxicities during the first 40 days after HSCT.

Relapse, Transplant-Related Mortality, and Survival

The median follow-up time among living patients was 36 months (range, 4 to 132). No patient relapsed during the follow-up period. The 12-month transplant-related mortality rate was 9.95% (Figure 2). The causes of transplant-related mortality included GVHD in 1 case, thrombotic microangiopathy in 1 case, and infection in 2 cases. The probabilities of 3-year overall survival (OS) and GFFS were 90.4% ± 4.6% and 85.6% ± 5.4%, respectively (Figure 3A,B). The probabilities of 3-year OS for haplo-donors and MSDs were 86.5% ± 7.3% and 93.3% ± 6.4%, respectively, with no significant differences between the groups ($P = .520$) (Figure 3C). The probabilities of 3-year GFFS between these 2 groups did not statistically differ (78.3% ± 8.6% versus 92.9% ± 6.9%, $P = .250$) (Figure 3D). The probabilities of 3-year OS for the classic PNH and PNH-AA syndrome groups were 100.0% ± .0% and 85.5% ± 6.7%, showing no differences between these 2 groups ($P = .144$) (Figure 3E). The probabilities of 3-year GFFS between the 2 groups also did not differ (100.0% ± .0% versus 78.5% ± 7.8%, $P = .069$) (Figure 3F).

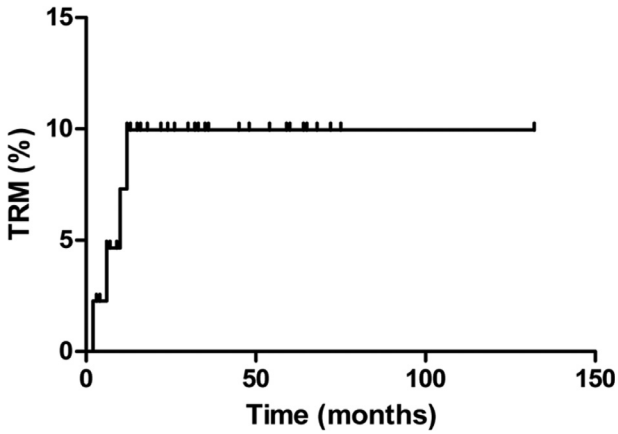

Figure 2. The transplant-related mortality rate during follow-up for 12 months.

DISCUSSION

Eculizumab, a monoclonal antibody against complement protein 5, stops the intravascular hemolysis in PNH and has been shown to significantly reduce hemolysis and improve anemia and patient quality of life [15,16]. Nonetheless, eculizumab does not affect underlying stem cell abnormalities or the associated BM failure. Furthermore, not all patients have a favorable response to eculizumab. Genetic variants in complement protein 5 are associated with a poor response to eculizumab, and allo-HSCT should be recommended in these patients. In addition, eculizumab is currently unavailable in China. Patients with ongoing BM failure from AA are less likely to benefit from eculizumab. For these patients, therapy should address the underlying BM failure. Patients meeting criteria for severe AA with PNH clones continue to be good candidates for HSCT if they are young and have suitable donors [17].

Few single-center studies have been published on HSCT for PNH [18,19], and these studies included few patients. The International Bone Marrow Transplant Registry reported a 2-year survival probability of 56% in 48 recipients who received HLA-identical sibling transplants between 1978 and 1995 [20]. The European Society for Blood and Marrow Transplantation reported the largest cohort of 211 PNH patients [11]. Of these patients, 65% received grafts from HLA-identical siblings and the remainder from HLA-MUDs [11]. The 5-year OS probability was 68%, with infections and GVHD being the main causes of death. Moreover, reports on the outcomes of PNH patients who received haplo-HSCT are rare. Here, we report the characteristics and outcomes of 44 patients with PNH who underwent HSCT at our center. Remarkably, these 44 patients included 25 transplant recipients from HLA-haploidentical related donors. The present study showed that allo-HSCT yielded favorable outcomes in PNH patients, all patients achieved engraftment, no patients relapsed during the follow-up period, and the probabilities of 3-year OS and GFFS were 90.4% ± 4.6% and 85.6% ± 5.4%, respectively. The 3-year OS and GFFS did not differ between the haplo-donor and MSD groups. Although the 3-year OS and GFFS tended to be better in the PNH group than in the PNH-AA syndrome group, the present cohort size was small; thus, a conclusion cannot yet be confirmed.

In a considerable percentage of PNH patients, suitable matched donors are unavailable or cannot be identified within a reasonable time. Finding suitable HLA-identical sibling donors for Chinese patients is even more difficult because of

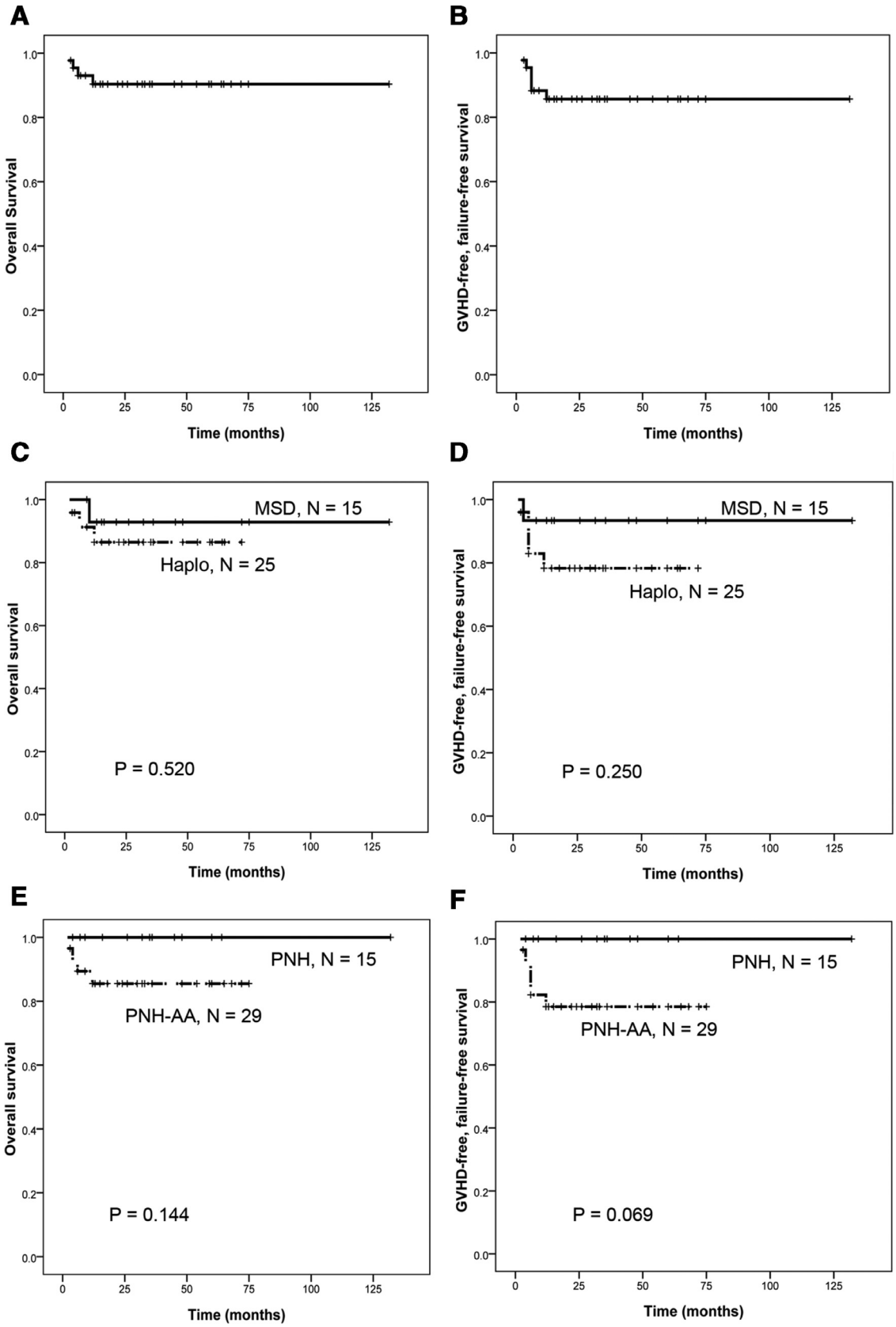

Figure 3. Patient OS and GFFS as assessed using Kaplan-Meier analysis. (A) The probability of 3-year OS was 90.4% ± 4.6%. (B) The probability of 3-year GFFS was 85.6% ± 5.4%. (C) The probabilities of 3-year OS in the haplo-donor group and MSD group were 86.5% ± 7.3% versus 93.3% ± 6.4%, without significant differences between the 2 groups ($P = .520$). (D) The probabilities of 3-year GFFS in the haplo-donor and MSD groups were 78.3% ± 8.6% versus 92.9% ± 6.9 %, without significant differences between the 2 groups ($P = .250$). (E) The probabilities of 3-year OS in the classic PNH group and PNH-AA syndrome group were 100.0% ± .0% versus 85.5% ± 6.7%, without statistical differences between the 2 groups ($P = .144$). (F) The probabilities of 3-year GFFS in the classic PNH and PNH-AA syndrome groups were 100.0% ± .0% versus 78.5% ± 7.8%, without statistical differences between the 2 groups ($P = .069$).

the national population policy. Furthermore, the often long periods of time for seeking MUDs can permit disease progression before treatment. Haplo-HSCT virtually ensures the opportunity for most patients to benefit from HSCT and offers the advantage of immediate accessibility to transplantation therapy. Brodsky et al. [21] published the first report of successful HLA haplo-HSCT in 3 PNH patients in 2008. Two of their patients achieved long-term survival, whereas 1 died from graft failure. In this study we report the outcomes of 25 consecutive PNH patients treated with HSCT from an HLA-haploidentical related donor. The 3-year OS and GFFS probabilities were 86.5% ± 7.3% and 78.3% ± 8.6%, respectively. These results seem to suggest rather than confirm that transplant-related complications and outcomes did not differ significantly between the haplo-HSCT and MSD-HSCT groups in our study. In this study all 25 haplo-HSCT patients who received the busulfan/cyclophosphamide conditioning regimen attained successful engraftment, indicating that haplo-HSCT with busulfan/cyclophosphamide conditioning could attain excellent engraftment for PNH patients. However, these haplo-HSCT results were achieved using a specific protocol (including BM + PBSCs, CsA + mycophenolate mofetil, and ATG) used extensively in China but to a lesser extent in Western countries.

Transplantation is the only curative therapy for PNH; however, the risks associated with this option could be significant. In the era of complement inhibitory therapy, the most challenging issue is identifying those patients who are most likely to benefit from transplantation. More prospective trials are needed to develop strategies for identifying such patients. Because eculizumab is currently unavailable in China, whether allo-HSCT (including haplo-HSCT) can be recommended as a first-line therapy for PNH should be addressed in future studies.

In conclusion, our data confirm that patients with PNH can be cured with allo-HSCT, also from alternative donors, with a low incidence of transplant-related mortality (9.95%) and no relapses. This may be relevant for patients not responding to eculizumab and for countries where the drug is currently unavailable. However, our study is limited by its retrospective nature and relatively few patients. Further large-scale, multicenter, cooperative prospective studies should be conducted to completely evaluate our results.

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Authorship statement: L.L., S.L., and Y.Z. contributed equally to this work. M.M. and D.W. designed the study. L.L. analyzed the data and wrote the paper. S.L. and Y.Z. analyzed the data and revised the paper. H.Z., Q.W., H.T., F.C., H.Q., X.T., Y.H., C.F., Z.J., S.C., and A.S. performed the research and contributed essential reagents. All authors were involved in analyzing and interpreting the results and read, commented on, and approved the final version of the manuscript.

REFERENCES

1. Vallet N, de Fontbrune FS, Loschi M, et al. Hematopoietic stem cell transplantation for patients with paroxysmal nocturnal hemoglobinuria previously treated with eculizumab: a retrospective study of 21 patients from SFGM-TC centers. *Haematologica*. 2018;103:e103–e105.
2. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. *Blood*. 2014;124:2804–2811.
3. Parker CJ. The pathophysiology of paroxysmal nocturnal hemoglobinuria. *Exp Hematol*. 2007;35:523–533.
4. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. *JAMA*. 2005;293:1653–1662.
5. Rotoli B, Luzzato L. Paroxysmal nocturnal haemoglobinuria. *Ballieres Clin Haematol*. 1989;2:113–138.
6. Ge M, Li X, Shi J, Shao Y, Zheng Y. Clinical features and prognostic factors of Asian patients with paroxysmal nocturnal hemoglobinuria: results from a single center in China. *Ann Hematol*. 2012;91:1121–1128.
7. Socié G, Mary JY, de Gramont A, et al. Paroxysmal nocturnal haemoglobinuria: long-term follow-up and prognostic factors. French Society of Haematology. *Lancet*. 1996;348:573–577.
8. Parker CJ. Management of paroxysmal nocturnal hemoglobinuria in the era of complement inhibitory therapy. *Hematol Am Soc Hematol Educ Progr*. 2011;2011:21–29.
9. Saso R, Marsh J, Cevreska L, et al. Bone marrow transplants for paroxysmal nocturnal haemoglobinuria. *Br J Haematol*. 1999;104:392–396.
10. Santarone S, Bacigalupo A, Risitano AM, et al. Hematopoietic stem cell transplantation for paroxysmal nocturnal hemoglobinuria: long-term results of a retrospective study on behalf of the Gruppo Italiano Trapianto Midollo Osseo (GITMO). *Haematologica*. 2010;95:983–988.
11. Peffault de Latour R, Schrezenmeier H, Bacigalupo A, et al. Allogeneic stem cell transplantation in paroxysmal nocturnal hemoglobinuria. *Haematologica*. 2012;97:1666–1673.
12. Tian H, Liu L, Chen J, et al. Haploidentical hematopoietic stem cell transplant in paroxysmal nocturnal hemoglobinuria. *Leuk Lymph*. 2016;57:835–841.
13. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus conference on acute GVHD grading. *Bone Marrow Transplant*. 1995;15:825–828.
14. Filiovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease. I. Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2005;11:945–956.
15. Parker C. Eculizumab for paroxysmal nocturnal haemoglobinuria. *Lancet*.. 2009;373:759–767.
16. Kelly RJ, Hill A, Arnold LM, et al. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. *Blood*. 2011;117:6786–6792.
17. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. *Blood*. 2014;124:2804–2811.
18. Hegenbart U, Niederwieser D, Forman S, et al. Hematopoietic cell transplantation from related and unrelated donors after minimal conditioning as a curative treatment modality for severe paroxysmal nocturnal hemoglobinuria. *Biol Blood Marrow Transplant*. 2003;9:689–697.
19. Lee JL, Lee JH, Lee JH, et al. Allogeneic hematopoietic cell transplantation for paroxysmal nocturnal hemoglobinuria. *Eur J Haematol*. 2003;71:114–118.
20. Saso R, Marsh J, Cevreska L, et al. Bone marrow transplants for paroxysmal nocturnal haemoglobinuria. *Br J Haematol*. 1999;104:392–396.
21. Brodsky RA, Luznik L, Bolaños-Meade J, et al . Reduced intensity HLA-haploidentical BMT with post transplantation cyclophosphamide in nonmalignant hematologic diseases. *Bone Marrow Transplant*. 2008;42:523–527.