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Review Article

Progress in clinical research on allogeneic hematopoietic stem cell transplantation for the treatment of paroxysmal nocturnal hemoglobinuria

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ABSTRACT

Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal proliferative disease of hematopoietic stem cells that is clinically characterized by hemolysis, thrombosis, and bone marrow failure. In recent years, significant progress has been made in the complement inhibitor-based treatment of PNH, but the only curative treatment is still hematopoietic stem cell transplantation (HSCT). This article reviews the research progress on allogeneic HSCT for PNH, systematically summarizes the overview, indications, influencing factors, and treatment outcomes of allogeneic HSCT for PNH, and provides an analysis of HSCT for PNH.

1. Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a nonmalignant clonal proliferative disease of hematopoietic stem cells that is clinically characterized by intravascular hemolysis, thrombotic tendency, and bone marrow failure.[1] The onset of PNH is mostly caused by acquired mutations in the

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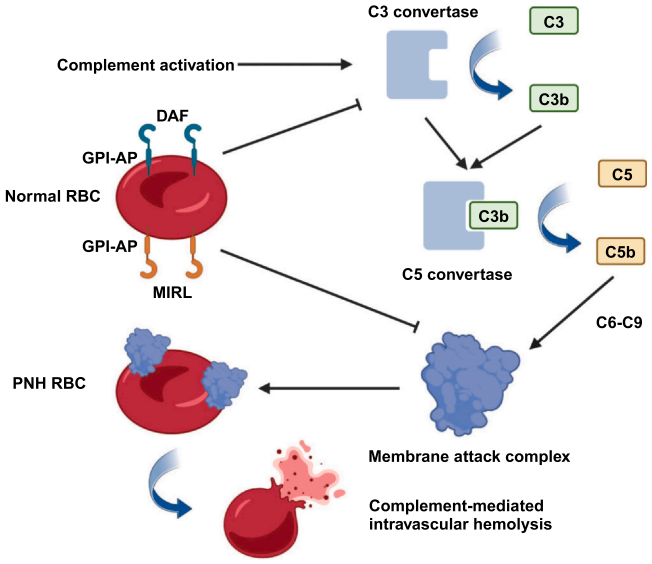

Fig. 1. Pathogenesis of paroxysmal nocturnal hemoglobinuria. RBC, red blood cell; PNH, paroxysmal nocturnal hemoglobinuria; GPI-AP, glycated phosphatidylinositol anchor protein; DAF, decay accelerating factor; MIRL, reactive hemolytic membrane inhibitor. (Created with BioRender.com).

phosphatidylinositol N-acetylglucosamine transferase subunit A (*PIG-A*) gene located on the X chromosome p22.1,[2] leading to abnormal synthesis of glycated phosphatidylinositol anchor protein (GPI-AP) in hematopoietic stem cells, resulting in the loss of two complement regulatory proteins on the surface of red blood cells in the offspring of affected stem cells due to the absence of GPI-AP. The loss of expression of these two proteins, decay accelerating factor (DAF, CD55) and membrane inhibitor of reactive lysis (MIRL, CD59) triggers complement pathway mediated intravascular hemolysis[3] (Figs. 1 and 2). The exact prevalence of PNH has not yet been determined, the overall prevalence is about 3.81/100,000 according to previous studies.[4]

According to the subtype classification of the International PNH Interest Group, PNH is divided into three subtypes, namely classical PNH (cPNH), PNH in the setting of another bone marrow failure, and subclinical PNH.[5,6] Due to the current clinical consensus that subclinical PNH does not require special treatment for PNH clones,[5,6] and most clinical studies have focused on two subtypes: classical

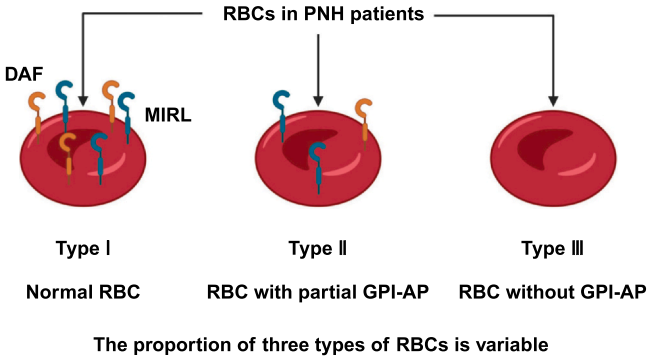

Fig. 2. Heterogeneity of red blood cells in paroxysmal nocturnal hemoglobinuria patients. RBC, red blood cell; PNH, paroxysmal nocturnal hemoglobinuria; DAF, decay accelerating factor; MIRL, reactive hemolytic membrane inhibitor; GPI-AP, glycated phosphatidylinositol anchor protein. (Created with BioRender.com).

paroxysmal nocturnal hemoglobinuria (cPNH) and PNH in the setting of another bone marrow failure syndrome, the focus of this article is also on cPNH and PNH in the setting of another bone marrow failure.

The existing first-line treatment for PNH is the complement C5 inhibitor such as eculizumab and ravulizumab,[7–14] which has shown great therapeutic efficacy.[8,9,15–17] However, this first-line treatment is ineffective for about less than 10% of patients,[10,15,16,18–23] may result in uncontrolled anemia and thrombosis or associated side effects such as infection leading to poor clinical outcomes,[24–30] and may not be effective for possible bone marrow failure.[31–33] Therefore, hematopoietic stem cell transplantation (HSCT), the only curative method, is an effective treatment option.

HSCT can reconstruct the hematopoietic system by replacing dysfunctional hematopoietic stem cells in PNH patients with functional stem cells from histocompatible healthy donors, eliminating PNH clones completely and fundamentally correcting symptoms such as hemolysis and thrombosis.[34,35] Approximately 2%–4% of patients with intractable PNH do not respond to complement inhibitors and require HSCT (detailed discussion can be found in the next part).[24,25] Partly due to the unavailability of first-line treatment, among PNH patients undergoing HSCT, 40.5% do not have accompanying bone marrow failure.[22] Allogeneic hematopoietic stem cell transplantation (allo-HSCT) via matched related donors (MRDs) and/or haploidentical donors (HIDs) is considered the only curative treatment for PNH.

2. Indications for HSCT for the treatment of PNH

First-line treatment, eculizumab has been proven to be effective at treating PNH in more than 90% of patients, and its safety is good.[10,15,16,18–23] However, due to the potential manifestations of bone marrow failure, genetic polymorphisms of complement genes, suboptimal inhibition of complement C5, or extravascular hemolysis in patients (Fig. 3),[21,36–44] only approximately 10% of patients maintain normal

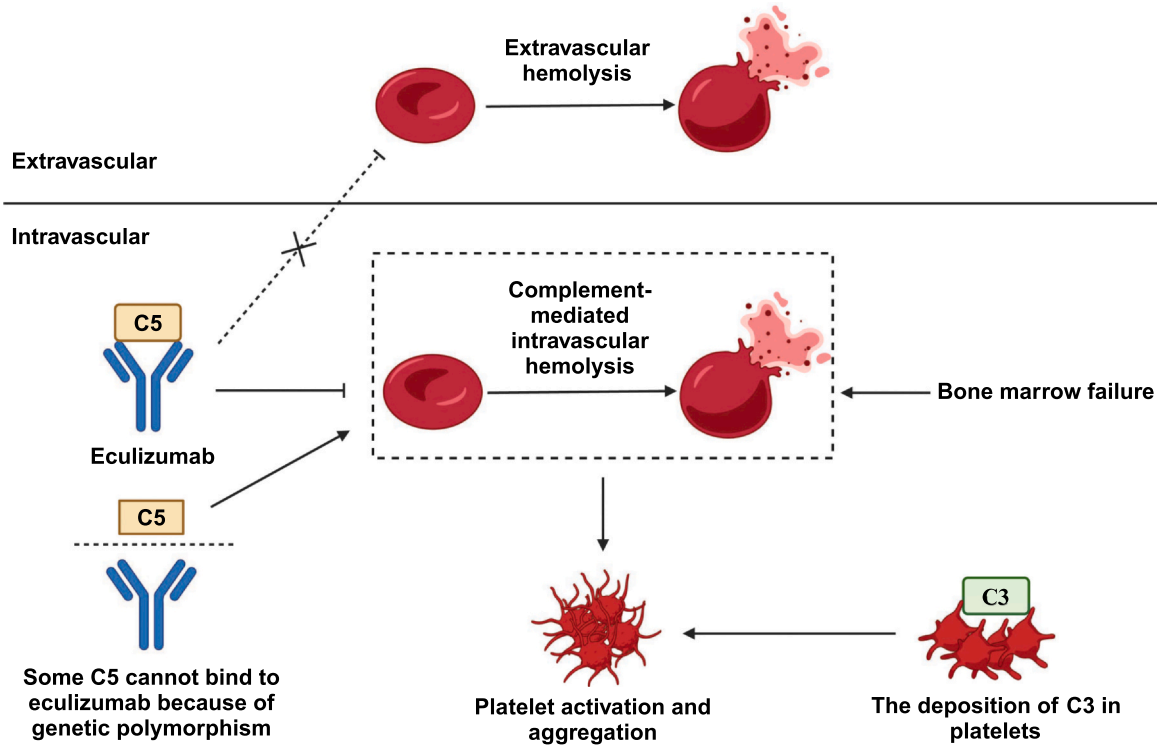

Fig. 3. Reasons for invalidity of eculizumab. (Created with BioRender.com).

hemoglobin levels without relying on blood transfusions,[20,21] and approximately 2%–4% of patients experience severe anemia when treatment with eculizumab is ineffective.[24] HSCT can eliminate abnormal red blood cells from peripheral blood, and more than 85% of patients with refractory anemia symptoms do not experience PNH symptoms after undergoing HSCT.[25] Due to the deposition of complement C3 in platelets or platelet activation and aggregation promoted by uncontrolled hemolysis (Fig. 3) (and some unexplained reasons including underdosing and PNH-unrelated causes),[45,46] thrombosis can occur, and 3.6% of patients treated with eculizumab experience persistent thrombosis.[47–50] However, the efficacy of HSCT for treating recurrent thrombosis is currently controversial,[25,51] and the mainstream view recommends performing HSCT when there are still recurrent life-threatening thromboembolic events after the end of drug treatment. Eculizumab, which mainly acts on peripheral blood, does not have enough therapeutic effect for bone marrow failure,[52] while HSCT can improve the occurrence of bone marrow failure by reconstructing the hematopoietic system. Current research indicates that HSCT is the only feasible option for treating PNH in these conditions.

Allo-HSCT as a treatment for PNH is currently indicated for patients with suitable donors who meet the following conditions[11,12,53,54]: (1) patients with severe cPNH who don't have access to complement inhibitors; (2) the treatment effect of complement inhibitors is poor or ineffective for cPNH patients, as indicated by unalleviated hemolytic anemia after continuous use or recurrent life-threatening thromboembolic events; (3) patients of PNH in the setting of another bone marrow failure, such as severe aplastic anemia (AA) and myelodysplastic syndrome (MDS); (4) PNH patients with evidence of clonal evolution to MDS and leukemia.

Additionally, it is worth noting that for patients with PNH combined with AA, the existence of PNH clone is a favorable predictor for efficacy of immunosuppressive therapy (IST).[55] The decision to IST or undergo an HSCT depends on whether the patient exhibits more pronounced symptoms of hemolysis and thrombosis or significant clinical manifestations of bone marrow failure.[6,56,57]

Additionally, clinical case reports suggest that allo-HSCT treatment can eliminate EVI1 gene abnormalities that may lead to the progression of MDS in PNH patients; therefore, choosing allo-HSCT for these patients may result in improved therapeutic efficacy.[58] Identifying PNH patients who can benefit from HSCT in clinical practice requires further research on the outcomes of different treatments.

Although PNH is rarer in children, the disease features are also present in children and children are more likely to develop bone marrow failure.[59–62] Therefore, HSCT may be an effective approach for children with PNH.

3. Outcomes of HSCT for the treatment of PNH

Multiple large-scale retrospective clinical studies have shown that the overall survival (OS) of patients who undergo allo-HSCT treatment for PNH through MRDs, HIDs or matched unrelated donors (MUDs) is 74%–85.9%, and failure-free survival (FFS) is 52.4%–77.3%, while treatment-related mortality (TRM) is only 14.1%–26.2%; in terms of major transplant-related complications, the incidence rate of Grade II–IV acute graft-versus-host disease (aGVHD) ranges from 15.9% to 28.81%, and the incidence rate of chronic graft-versus-host disease (cGVHD) ranges from 11.4% to 22.7%.[25,34,35,44,63–73] The incidence of infection and other complications varies greatly among different studies, possibly due to the inherent characteristics of retrospective studies (Fig. 4, Table 1). Most of the previous studies, including the studies listed in Table 1 were retrospective, and it is important to perform head-to-head comparison of HSCT and complement C5 inhibitors in patients with PNH.

Allo-HSCT in patients who did not respond to eculizumab treatment also showed good efficacy, with a response rate of 85.7% and an OS of 67.7% after transplantation.[25] However, studies on bridging transplantation are rare, and further research is needed to determine the prognosis.

At present, for PNH patients who meet the indications for transplantation, the use of first-line drugs before and after HSCT is a focus of clinical research. Relevant studies have shown that the use of eculizumab to control hemolysis and thrombosis symptoms before transplantation does not affect the efficacy of

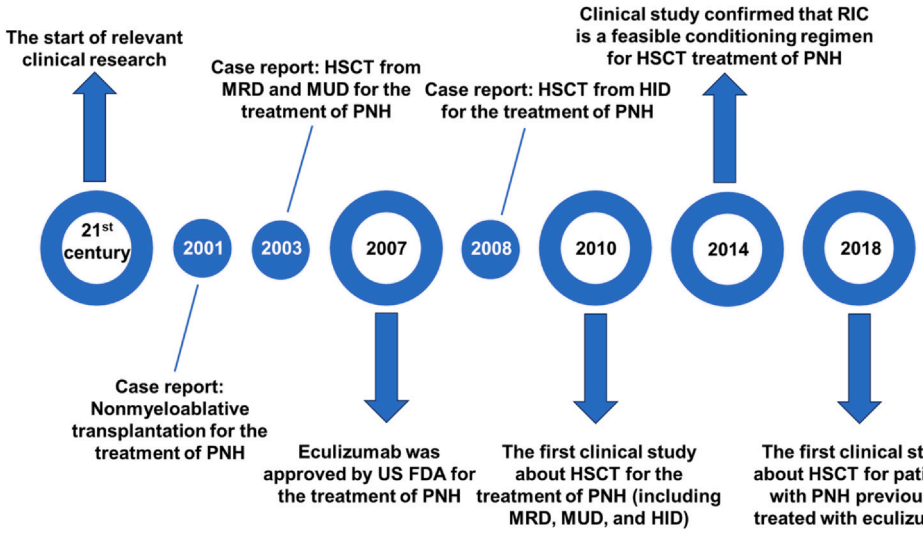

Fig. 4. Timeline of clinical progress in hematopoietic stem cell transplantation for paroxysmal nocturnal hemoglobinuria.[67–72] PNH, paroxysmal nocturnal hemoglobinuria; HSCT, hematopoietic stem cell transplantation; MRD, matched related donor; MUD, matched unrelated donor; US FDA, United States Food and Drug Administration; HID, haploidentical donor; RIC, reduced-intensity conditioning. (Created with BioRender.com).

hematopoietic stem cell implantation or the treatment effect of HSCT, does not increase the risk of complications, and may prevent GVHD[25,67]; however, its use after transplantation can reduce the recurrence of thrombosis and hemolysis and has the potential to reduce the incidence of GVHD, and no drug-related toxic reactions have been reported.[74,75] Some scholars believe that the deposition of complement factor P and complement C5b–C9 and microthrombus formation caused by complement activation are involved in the occurrence of GVHD, so the inhibition of complement by eculizumab helps to prevent GVHD.[76,77] In summary, the current research results suggest that eculizumab may assist HSCT in the treatment of PNH, but the specific therapeutic effects and timing of use still require further research.[8,67,74]

4. Factors influencing the outcome of HSCT treatment for PNH

4.1. PNH subtypes

cPNH can cause significant intravascular hemolysis, active bone marrow hyperplasia, or slight morphological abnormalities; PNH in the setting of another bone marrow failure presents with mild intravascular hemolysis accompanied by evidence of bone marrow failure, including PNH combined with AA and PNH combined with lower-risk MDS.[56,83–86]

According to the clinical studies conducted by Liu et al.[80] and Yilmaz et al.,[63] the OS and FFS of cPNH patients were 100%, 100%, 81.3%, and 79%, respectively, which were slightly greater than those of PNH patients with AA (85.7%, 78.7%, 79.9%, and 76%, respectively). Similarly, a clinical study conducted by Lee et al.[57] reported that the OS and GVHD-free and failure-free survival (GFFS) of PNH patients with AA were 92.3% and 63.5%, respectively, which were both greater than those of cPNH patients (71.4% and 42.9%, respectively). However, there were no statistically significant differences in the results of these three studies. In terms of transplant-related complications, the above three clinical studies showed that there was no difference in the incidence or severity of major complications, such as aGVHD, cGVHD, or infection after transplantation, between cPNH patients and PNH patients with AA. It is possible that most PNH patients with AA have a relatively smaller PNH clone population, and treatment usually focuses on potential bone marrow failure rather than intravascular hemolysis, so the prognosis improves after allo-HSCT manages bone marrow failure.[57]

Table 1
Clinical studies on hematopoietic stem cell transplantation treatment for paroxysmal nocturnal hemoglobinuria.

Studies, first author (year of publication)	Cases, *n* (male/female)	Age (years), median (range)	PNH subtypes (classical/with another bone marrow failure)	Donor, *n* (MRD/MUD/HID)	Conditioning regimen, *n* (MAC/RIC)	Main complications, *n* (aGVHD/cGVHD/infection)	Survival (%)
Lu et al. (2022)[34]	32 (20/12)	22 (6–48)	8/22	0/15/17	27/5	5/6/28	3 years OS 82.5 3 years FFS 76.7 TRM 15.2
Liu et al. (2022)[35]	151 (94/57)	NA	40/111	78/0/73	NA	0/2/8	3 years OS 84.1 3 years FFS 76.2 TRM 10.6
Khanikar et al. (2022)[78]	8 (3/5)	32 (15–38)	1/7	7/0/1	0/8	6/2/NA	26 months OS 87.5 TRM 12.5
Yilmaz et al. (2021)[63]	35 (19/16)	32 (18–51)	16/19	23/12/0	7/28	6/4/0	2 years OS 80.0 2 years FFS 77.1 TRM 17.1
Nakamura et al. (2021)[64]	42 (23/19)	32.5 (16–64)	NA	NA	7/32	9/7/3	6 years OS 74 TRM 26.2
Markiewicz et al. (2020)[65]	78	29 (12–65)	27/51	19/49/0	5/73	39/22/4	3 years OS 85.9 TRM 14.1
Liu et al. (2020)[66]	28 (14/14)	28 (6–54)	5/23	NA	NA	8/8/11	3 years OS 84.8 3 years GFFS 77.0 TRM 15.2
Mei et al. (2019)[74]	8 (6/2)	42 (25–63)	NA	4/4/0	0/8	4/5/2	TRM 37.5
Liu et al. (2019)[79]	40 (23/17)	NA	13/27	15/0/25	NA	11/11/12	3 years OS 90.0 3 years GFFS 85.0 TRM 10.0
Liu et al. (2019)[80]	46 (28/18)	NA	16/30	16/4/25	NA	12/13/17	3 years OS 91.3 3 years GFFS 87.0 TRM 8.7
Cooper et al. (2019)[75]	55 (18/37)	32.1 (14.0–66.9)	17/38	21/19/1	26/27	34/32/9	5 years OS 68
Vallet et al. (2018)[25]	21 (8/13)	30 (18–67)	9/12	10/6/1	3/18	7/NA/20	6 years OS 67.7 TRM 28.6

(*continued on next page*)

Table 1 (*continued*)

Studies, first author (year of publication)	Cases, *n* (male/female)	Age (years), median (range)	PNH subtypes (classical/with another bone marrow failure)	Donor, *n* (MRD/MUD/HID)	Conditioning regimen, *n* (MAC/RIC)	Main complications, *n* (aGVHD/cGVHD/infection)	Survival (%)
Lee et al. (2017)[57]	33 (21/12)	28.5 (6–54)	7/26	24/7/2	27/6	9/6/11	5 years OS 87.9 5 years GFFS 59.4 TRM 12.1
Kamranzadeh et al. (2017)[81]	13 (10/3)	27.5 (18–47)	13/0	NA	13/0	9/11/NA	13 years OS 74.1 TRM 23.08
Tian et al. (2016)[82]	18 (15/3)	25 (13–54)	14/4	5/3/10	18/0	9/10/5	20 months OS 94.4 TRM 5.6
Schcolnik-Cabrera et al. (2015)[52]	6 (4/2)	37 (25/48)	NA	6/0/0	0/6	1/2/NA	105 months OS 83.3 TRM 16.7
Pantin et al. (2014)[68]	17 (13/4)	31 (20–42)	11/6	17/0/0	0/17	8/11/NA	6 years OS 87.8 6 years FSS 87.8 TRM 5.9

PNH, paroxysmal nocturnal hemoglobinuria; MRD, matched related donor; MUD, matched unrelated donor; HID, haploidentical donor; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; OS, overall survival; FFS, failure-free survival; TRM, treatment-related mortality; GFFS, graft-versus-host disease-free and failure-free survival.

Therefore, the impact of clinical subtypes on the prognosis of HSCT in PNH patients remains controversial, further studies especially prospective studies are needed in this area.

4.2. Age

PNH can occur at any age, and the peak age of onset in China is between 20 and 40 years.[19] Clinical studies conducted by Nakamura et al. revealed that the OS (90%) of patients younger than 30 years was much greater than that of patients aged 30 years and older (59%).[64] However, perhaps due to the small span of the peak age of onset and the limited number of participants in clinical studies, most of the patients in the existing clinical studies have not been grouped according to age, so the conclusion that age affects prognosis still needs further confirmation.[87]

4.3. Blood transfusion rate and thrombosis history

Clinical research conducted by Nakamura et al.[64] showed that patients who received fewer than 20 concentrated red blood cell transfusions before transplantation had longer OS (90%) than those who received more transfusions (63%); the findings of Vallet et al.[25] may be related to the greater incidence of aGVHD. In addition, clinical studies conducted by Markiewicz et al.[65] revealed that when hemolysis occurs, PNH patients with another bone marrow failure syndrome have a longer OS (93.9%, compared to 62.9% when hemolysis does not occur). This is because in patients with bone marrow failure, the presence of PNH clones during hemolysis leads to better efficacy of immunotherapy.[88]

Clinical studies have shown that the OS of cPNH patients with a history of thrombosis is lower than that of patients without thrombosis,[51,65,81,89–93] and a younger age at thrombosis and a shorter interval of thrombosis after diagnosis of PNH are associated with a longer OS.[51] This difference may be related to mortality caused by thrombosis itself.[94–96]

For cPNH patients, a higher blood transfusion rate and a history of thrombosis are associated with poor prognosis,[97] and for PNH patients with another bone marrow failure syndrome, hemolysis is associated with better efficacy of immunotherapy. Therefore, the occurrence of hemolysis and thrombosis should be taken into consideration before transplantation, especially for patients with risk factors.[98–100] Some scholars recommend that patients with a history of blood transfusion undergo human leukocyte antigen (HLA) antibody level testing before HSCT to avoid the occurrence of complications.[82]

4.4. Donor selection

Due to the difficulty in obtaining hematopoietic stem cells, syngeneic transplantation, and autologous transplantation account for only approximately 0.9% of the HSCT procedures used for the treatment of PNH.[22] Basic studies suggest that syngeneic transplantation has a relatively lower risk of causing GVHD.[25,75,101] Hematopoietic stem cells derived from umbilical cord blood or skin fibroblasts may serve as sources of autologously transplanted stem cells in the future.[102,103]

Currently, MRDs are recommended for use in clinical practice.[104] Clinical trial results have confirmed that there is no significant difference in the efficacy of allo-HSCT for PNH between MRDs and MUDs[51,63]; therefore, MUDs are also a recommended source of donors. Shasheleva et al. reported a series of cases in which TCR α/β- and CD19-depleted hematopoietic cells were transplanted from MUDs and short-course eculizumab was used to treat young PNH patients, indicating that this transplantation method can also be used.[105]

In recent years, clinical studies have focused on HIDs as donors for allo-HSCT treatment of PNH. Clinical studies have confirmed that allo-HSCT via HIDs is a reasonable treatment method for PNH, with OS reaching 77.8%–84.8%.[66,106] Three clinical studies conducted by Liu et al.[35,79,107] used HIDs and MRDs as donors for allo-HSCT treatment of PNH and found no significant differences in key indicators for evaluating transplant efficacy, such as overall hematopoietic reconstruction time, incidence of

aGVHD, cGVHD, and infection, OS, FFS, TRM and other key indicators. A clinical study conducted by Lu et al.[34] revealed that there was no significant difference in various indicators between allo-HSCT using HIDs and MUDs as donors for the treatment of PNH.

MRDs, MUDs, and HIDs can all be used as donor sources for allo-HSCT treatment of PNH and overall do not affect treatment efficacy. Recently, the proportion of HID-treated patients receiving allo-HSCT for PNH has begun to increase.[22]

4.5. Conditioning regimen

The current commonly used conditioning regimens include the myeloablative conditioning (MAC) regimen and the reduced intensity conditioning (RIC) regimen. The MAC regimen is a high-intensity chemotherapy regimen,[108] and the recovery of hematopoietic function requires the support of hematopoietic stem cells to accelerate the reconstruction of hematopoietic function, which has greater potential toxicity. The RIC regimen is a regimen with low potential organ toxicity.[109–111]

Lee et al.[57] demonstrated through clinical studies that allo-HSCT after the RIC regimen could clear PNH clones. Subsequently, Pantin et al.[68] and Schcolnik-Cabrera et al.[52] found through clinical studies that allo-HSCT after the RIC regimen is an available option for treating PNH, with an OS of 83.3%–87.8%.

However, there is controversy about the impact of conditioning regimens on patient prognosis. The clinical studies conducted by Cooper et al.[75] and Tian et al.[82] both concluded that conditioning regimens did not affect patient prognosis, while Yilmaz et al.[63] suggested that RIC might be associated with a higher survival rate. In addition, a clinical study conducted by Santarone et al. revealed that patients receiving the MAC regimen had longer GFFS (73.3%, compared to 46.9% in patients receiving the RIC regimen).[69] A clinical study conducted by Lu et al.[34] reported in more detail that patients receiving the RIC regimen all had incomplete clearance of PNH clones, while patients who switched to or previously received the MAC regimen cleared all PNH clones under the premise of acceptable TRM (15.2%). These research results may be limited by the number of people included in the study.

Some scholars recommend the use of the MAC regimen to prevent PNH recurrence, but for patients with severe symptoms and poor tolerance, young patients with fertility needs, and older patients, the RIC regimen is recommended.[104] However, the impact of the conditioning regimen on the prognosis of patients needs to be further clarified.

Existing evidence suggests that factors affecting the prognosis of allo-HSCT treatment in PNH patients include age, occurrence of hemolysis and thrombosis, and conditioning regimen before transplantation.

5. Conclusion and prospects

In summary, although significant progress has been made in the treatment of PNH in recent years[23,112–114] (especially the continuous emergence and application of new drugs targeting complement similar to eculizumab,[17,115–118] including crovalimab[119] and iptacopan[120]), HSCT is still the only cure for PNH. When suitable donors are available, HSCT is recommended for patients in whom complement inhibitors, such as eculizumab, are ineffective or poorly effective and/or patients who are complicated with bone marrow failure. Before transplantation, it is necessary to consider the patient's age and history of hemolysis and thrombosis and to choose an appropriate conditioning regimen. Prospective studies involving more patients could be conducted in the future to specifically study the conditions that may affect the prognosis of patients, determine the characteristics of patients who will benefit from HSCT, and design a reasonable transplantation program to improve the efficacy of HSCT as a treatment for PNH.

CRediT authorship contribution statement

Zhixue Li: Investigation, Writing – Original Draft, Writing – Review & Editing, Visualization. **Defu Zeng:** Writing – Review & Editing. **Rong Fu:** Writing – Review & Editing, Supervision. **Xiaohui Zhang:** Conceptualization, Writing – Review & Editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

Xiaohui Zhang is an editorial board member for *Medicine Plus* and was not involved in the editorial review or the decision to publish this article. The authors declare that they have no conflict of interest.

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