VIA MEDICA

REVIEW ARTICLE

Acta Haematologica Polonica 2021
Number 4, Volume 52, pages 253–256
DOI: 10.5603/AHP.2021.0049
ISSN 0001–5814
e-ISSN 2300–7117

Allogeneic hematopoietic stem cell transplantation for paroxysmal nocturnal hemoglobinuria in the era of complement inhibition

Mirosław Markiewicz

Department of Hematology, Institute of Medical Sciences, College of Medical Sciences, University of Rzeszow, Rzeszow, Poland

Abstract

The only potentially curative treatment for paroxysmal nocturnal hemoglobinuria (PNH) is allogeneic hematopoietic stem cell transplantation (allo-HSCT).

However, its use has been largely abandoned following the introduction of efficient symptomatic treatment with complement inhibition. Nevertheless, the population of PNH patients is diverse, and some of them might still gain advantage from allo-HSCT, while anti-complement treatment would be the first choice for others. Both treatment modalities may be also sequentially applied in the same patient when needed.

This review aimed to present the current status of allo-HSCT in the treatment of patients with PNH, with special reference to Poland where the previous unavailability of anti-complement therapy enabled the acquisition of extensive experience in performing allo-HSCT for PNH, a treatment option currently restricted only to selected patients who are not candidates for eculizumab.

Key words: paroxysmal nocturnal hemoglobinuria, allogeneic hematopoietic stem cell transplantation, eculizumab

Acta Haematologica Polonica 2021; 52, 4: 253–256

Paroxysmal nocturnal hemoglobinuria (PNH) originates from acquired *PIGA* gene somatic mutation in hematopoietic stem cells, leading to deficiency in membrane proteins requiring glycosyl phosphatidyl inositol anchor [1]. The absence of these proteins, most importantly including natural complement inhibitors CD55 and CD59, is responsible for complement-mediated intravascular hemolysis, leading in classical hemolytic PNH to a wide spectrum of clinical symptoms mainly related to the presence of free hemoglobin, nitric oxide scavenging, and the increased occurrence of thrombosis. Patients with classical PNH nowadays are treated with a terminal complement protein C5 inhibitor, the monoclonal antibody eculizumab, which has been proved to be highly effective in reducing PNH-related morbidity (hemolytic anemia and thrombosis) and mortality [2]. Progress in anti-complement treatment has been achieved by substantial prolongation of half-life of a newer anti-C5 monoclonal antibody, ravulizumab, which instead of twice a month is given once every two months. However, access to this drug is restricted [3, 4]. Further progress in complement inhibition aims to overcome C5 polymorphisms responsible for resistance to eculizumab, and to reduce breakthrough episodes of hemolysis and extravascular hemolysis resulting from complement C3 opsonization. Moreover, other new monoclonal antibodies and complement inhibitors are currently in development, e.g. C1 esterase inhibitor [5], C3 inhibitors [6], and factor D inhibitors [7]. It is highly likely that they will improve response rates as well as quality of life. However, they inhibit the immune system which makes the organism more prone

Address for correspondence: Mirosław Markiewicz, Department of Hematology, Institute of Medical Sciences, College of Medical Sciences, University of Rzeszów, Szopena 2, 35–055 Rzeszów, Poland, e-mail: mir.markiewicz@wp.pl

Received: 28.04.2021 Accepted: 12.05.2021

Copyright © 2021
The Polish Society of Haematologists and Transfusiologists, Insitute of Haematology and Transfusion Medicine.
All rights reserved.

This article is available in open access under Creative Common Attribution-Non-Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) license, allowing to download articles and share them with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially.

to infectious complications [8]. Also, once started, they cannot be withdrawn and patients require life-long treatment with these drugs, which may negatively influence their quality of life. There are also reports indicating that only a minority of patients obtain complete, or at least major, hematological response [9, 10]. The main limitation of C5 inhibitors treatment however is that they are not curative, and they do not correct the underlying stem cell defect [11].

Therefore, despite the success of complement inhibitors in hemolytic PNH, there is still a continued need for allogeneic hematopoietic stem cell transplantation (allo-HSCT) in bone marrow failure-associated PNH, in which the presence of PNH clone overlaps with aplastic anemia, myelodysplastic syndrome, or both. PNH clone in this subtype is usually smaller than in classical PNH, however over the last decade progress has been achieved also in PNH diagnosis [12] through the introduction of high sensitivity flow cytometry which enables the detection of even very small PNH clones [13].

Allo-HSCT is indicated for PNH patients with very severe or severe aplastic anemia, high- or higherintermediate-risk myelodysplastic syndrome, or patients with severe hemolysis or thrombosis unresponsive to eculizumab [14], or those without access to it.

Allo-HSCT can cure the disease thanks to cytotoxicity of conditioning treatment and immunoreactivity of donor T-cells, leading to eradication of the PNH clone [15]. Allo-HSCT can be proposed after complement blocker therapy in the absence of alternative treatment and after careful assessment of the risk-benefit ratio, especially in transfused patients. Eculizumab did not change the risk of HSCT complications in PNH patients who sequentially received both treatment options. The optimal timing for the last eculizumab infusion before transplantation seems to be during the conditioning regimen [16]. Bridging therapy with eculizumab prior to allo-HSCT is safe, and does not negatively influence the engraftment of hematopoietic stem cells [17].

Identifying patients with PNH who may benefit from allo-HSCT is challenging. The low incidence of PNH, and the treatment of most patients with eculizumab, makes it practically impossible to conduct a randomized prospective trial. Thus, outcomes of allo-HSCT in PNH are generally obtained from observational studies and retrospective activity reports. Most of these have been based on low numbers of patients, except for a few registry or multicenter group studies.

The first large study was reported in 1999 from the International Bone Marrow Transplant Registry, which presented the results of 57 consecutive allo-HSCTs performed between 1978 and 1995. The two-year overall survival rate was 56%. The most common causes of treatment failure were graft failure and infection. Acute and chronic graft-versus-host disease (GvHD) occurred in 34% and 33%, respectively. Sustained engraftment was observed in 77% of patients [18].

Another long-term study of allo-HSCT in PNH was reported in 2010 by an Italian group. This included 26 patients transplanted between 1988 and 2006. Fifteen patients received myeloablative, and 11 were given reduced intensity, conditioning. Graft failure was 8%, and transplant-related mortality was 42% (26% and 63% following myeloablative or reduced intensity conditioning, respectively). The 10-year probability of disease-free survival was 57% for all patients, with better results after transplants from an identical donor (65%, 23 patients) and with myeloablative conditioning (73%, 15 patients) [19].

The largest study was reported in 2012 from European Society for Blood and Marrow Transplantation (EBMT): a retrospective analysis of 212 patients with PNH transplanted in 83 EBMT centers from 1978 to 2007 who were compared to 402 non-transplanted patients diagnosed during 55 years in French centers, and who were not treated with eculizumab. The overall survival at 5 years was 68% for the entire transplanted group. Overall mortality reached 30%, with an unacceptably higher risk of mortality in patients with a pre-transplant thrombosis history. Worse survival with allo-HSCT was reported in patients with thromboembolism (OS =54%, hazard ratio =10.0; p =0.007), but not in patients with aplastic anemia or with recurrent hemolytic anemia without thromboembolism (OS =69% and 86%, respectively) [20].

The obtained results have improved significantly in newer reports, which was recently confirmed by the Polish PALG group in a retrospective analysis of 78 patients, 27 with classical PNH and 51 with bone-marrow-failure-associated PNH (BMF/PNH), who underwent allo-HSCT in 11 Polish centers between 2002 and 2016, when eculizumab was not yet reimbursed in Poland. Treosulfan-based reduced toxicity conditioning was used in 66% of patients, classic myeloablative conditioning in 6%, and reduced intensity conditioning in 28%. Sustained engraftment was observed in 96% of patients. The 3-year overall survival for cPNH and BMF/PNH was 88.9% and 85.1%, respectively, and was highest in subgroups of patients with cPNH without thrombosis (92%) or with BMF/PNH with hemolysis (93.9%). Rate of acute GvHD II–IV was 23%; cumulative 1-year incidence of extensive chronic GvHD was 10.8% in BMF/PNH and 3.7% in cPNH [21].

In a retrospective analysis of 28 PNH patients, median age 28 (range 6–54) years, who received haplo-HSCT between 2010 and 2018 in China, despite one early failure due to septicemia, all evaluable patients achieved myeloid engraftment and complete chimerism. One secondary graft failure occurred, platelet recovery was delayed in three, and failed in one patient. Rate of acute GvHD II–IV was 14.82% and the cumulative incidence of moderate-severe chronic GvHD was 11.73%. The transplantation-related mortality

rate at 1 year was 15.25%, and the probability of 3-year overall survival was 84.8 ±7.1%. Haplo-HSCT has been recognized as a valuable option for PNH patients who lack HLA-matched donors [22].

The results of the presented registry or group studies, as well as of numerous single center reports not cited here, indicate that in patients with PNH who cannot be effectively treated with eculizumab for different reasons, allo-HSCT constitutes a valid therapeutic option with satisfactory overall survival and acceptable toxicity. These studies confirm that most patients with PNH can be definitively cured with allo-HSCT. The trends in allo-HSCT for PNH include the use of reduced toxicity conditioning to attain the graft versus PNH effect or the use of haploidentical donors. An interesting, although seldom implemented, approach involves the use of eculizumab immediately post-transplant as prophylaxis of thrombosis and hemolysis. This treatment was feasible and neither delayed engraftment nor increased infections [23]. Nevertheless, thrombosis or hemolysis were not reported as problematic post-transplant complications in the majority of other previously reported studies.

In summary, the indications for allo-HSCT in PNH have changed since the introduction of anti-complement therapy. Firstly, the risk of transplant-related mortality prevents the use of allo-HSCT as initial therapy in most patients with classical PNH, who can benefit more from complement inhibition, with exceptions in countries where the availability of eculizumab is a limiting factor. Allo-HSCT is a reasonable option for patients with classical PNH who do not respond well enough to eculizumab therapy.

Secondly, in patients with bone marrow failure (aplastic anemia or myelodysplastic syndrome)-associated PNH, allo-HSCT continues to be the preferred, and the only potentially curative, therapy.

Author's contributions

MM — sole author.

Conflict of interest

None.

Financial support

Author declares no competing financial interests in relation to this work.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

References

1. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. Hematology Am Soc Hematol Educ Program. 2016; 2016(1): 208–216, doi: 10.1182/asheducation-2016.1.208, indexed in Pubmed: 27913482.
2. Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006; 355(12): 1233–1243, doi: 10.1056/NEJMoa061648, indexed in Pubmed: 16990386.
3. Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood. 2019; 133(6): 530–539, doi: 10.1182/blood-2018-09-876136, indexed in Pubmed: 30510080.
4. Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood. 2019; 133(6): 540–549, doi: 10.1182/blood-2018-09-876805, indexed in Pubmed: 30510079.
5. DeZern AE, Uknis M, Yuan X, et al. Complement blockade with a C1 esterase inhibitor in paroxysmal nocturnal hemoglobinuria. Exp Hematol. 2014; 42(10): 857–861.e1, doi: 10.1016/j.exphem.2014.06.007, indexed in Pubmed: 25034232.
6. Risitano AM. Anti-complement treatment in paroxysmal nocturnal hemoglobinuria: where we stand and where we are going. Transl Med UniSa. 2014; 8: 43–52, indexed in Pubmed: 24778997.
7. Yuan X, Gavriilaki E, Thanassi JA, et al. Small-molecule factor D inhibitors selectively block the alternative pathway of complement in paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Haematologica. 2017; 102(3): 466–475, doi: 10.3324/haematol.2016.153312, indexed in Pubmed: 27810992.
8. Alfinito F, Ruggiero G, Sica M, et al. Eculizumab treatment modifies the immune profile of PNH patients. Immunobiology. 2012; 217(7): 698–703, doi: 10.1016/j.imbio.2011.11.009, indexed in Pubmed: 22206707.
9. Risitano AM, Notaro R, Marando L, et al. Complement fraction 3 binding on erythrocytes as additional mechanism of disease in paroxysmal nocturnal hemoglobinuria patients treated by eculizumab. Blood. 2009; 113(17): 4094–4100, doi: 10.1182/blood-2008-11-189944, indexed in Pubmed: 19179465.
10. Risitano AM, Marotta S, Ricci P, et al. Anti-complement treatment for paroxysmal nocturnal hemoglobinuria: time for proximal complement inhibition? A position paper from the SAAWP of the EBMT. Front Immunol. 2019; 10: 1157, doi: 10.3389/fimmu.2019.01157, indexed in Pubmed: 31258525.
11. Brodsky RA, Young NS, Antonioli E, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. Blood. 2008; 111(4): 1840–1847, doi: 10.1182/blood-2007-06-094136, indexed in Pubmed: 18055865.
12. Fattizzo B, Serpenti F, Giannotta JA, et al. Difficult cases of paroxysmal nocturnal hemoglobinuria: diagnosis and therapeutic novelties. J Clin Med. 2021; 10(5): 948, doi: 10.3390/jcm10050948, indexed in Pubmed: 33804461.
13. Donohue RE, Marcogliese AN, Sasa GS, et al. Standardized high-sensitivity flow cytometry testing for paroxysmal nocturnal hemoglobinuria in children with acquired bone marrow failure disorders: a single center US study. Cytometry B Clin Cytom. 2018; 94(4): 699–704, doi: 10.1002/cyto.b.21536, indexed in Pubmed: 28574201.

14. Brodsky RA. How I treat paroxysmal nocturnal hemoglobinuria. Blood. 2009; 113(26): 6522–6527, doi: 10.1182/blood-2009-03-195966.
15. Takahashi Y, McCoy JP, Carvallo C, et al. In vitro and in vivo evidence of PNH cell sensitivity to immune attack after nonmyeloablative allogeneic hematopoietic cell transplantation. Blood. 2004; 103(4): 1383–1390, doi: 10.1182/blood-2003-04-1281, indexed in Pubmed: 14525787.
16. Vallet N, de Fontbrune FS, Loschi M, et al. Société Francophone de Greffe de Moelle et Thérapie Cellulaire. 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(3): e103–e105, doi: 10.3324/haematol.2017.182360, indexed in Pubmed: 29269526.
17. DeZern AE, Jones RJ, Brodsky RA. Eculizumab bridging before bone marrow transplant for marrow failure disorders is safe and does not limit engraftment. Biol Blood Marrow Transplant. 2018; 24(12): e26–e30, doi: 10.1016/j.bbmt.2018.07.032, indexed in Pubmed: 30055352.
18. Saso R, Marsh J, Cevreska L, et al. Bone marrow transplants for paroxysmal nocturnal haemoglobinuria. Br J Haematol. 1999; 104(2): 392–396, doi: 10.1046/j.1365-2141.1999.01195.x, indexed in Pubmed: 10050724.
19. 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(6): 983–988, doi: 10.3324/haematol.2009.017269, indexed in Pubmed: 20007144.
20. Peffault de Latour R, Schrezenmeier H, Bacigalupo A, et al. Allogeneic stem cell transplantation in paroxysmal nocturnal hemoglobinuria. Haematologica. 2012; 97(11): 1666–1673, doi: 10.3324/haematol.2012.062828, indexed in Pubmed: 22689687.
21. Markiewicz M, Drozd-Sokolowska J, Biecek P, et al. Allogeneic hematopoietic stem cell transplantation for paroxysmal nocturnal hemoglobinuria: multicenter analysis by the Polish Adult Leukemia Group. Biol Blood Marrow Transplant. 2020; 26(10): 1833–1839, doi: 10.1016/j.bbmt.2020.05.024, indexed in Pubmed: 32512214.
22. Liu L, Zhou H, Miao M, et al. Outcomes of haploidentical haematopoietic stem cell transplantation for paroxysmal nocturnal haemoglobinuria. Blood. 2019; 134(Suppl 1): 5730, doi: 10.1182/blood-2019-131808.
23. Mei M, Gupta R, O'Donnell M, et al. Post-allogeneic hematopoietic stem cell transplantation eculizumab as prophylaxis against hemolysis and thrombosis for patients with hematologic disorders associated with paroxysmal nocturnal hemoglobinuria clones. Biol Blood Marrow Transplant. 2019; 25(5): e183–e185, doi: 10.1016/j.bbmt.2019.01.025, indexed in Pubmed: 30708188.