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HSCT FOR ACQUIRED BONE MARROW FAILURE SYNDROMES

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ABSTRACT

Severe aplastic anemia (SAA) is a potentially fatal disease in the absence of adequate treatment. Allogeneic hematopoietic stem cell transplantation (HSCT) is considered as first-line treatment for patients up to 40 years with an HLA-identical related donor and those up to 18 years with an HLA-identical unrelated donor. HSCT with an HLA identical donor, related or unrelated, should also be considered for patients who were refractory to first-line immunosuppression. Salvage haploidentical HSCT may be considered for younger patients without an HLA-identical donor. Recently a consensus document was established on behalf of the Brazilian Society of Bone Marrow Transplantation (SBTMO) to discuss HSCT in the setting of SAA. Recommendations from this expert panel are presented in this report.

Keywords: Severe Aplastic Anemia, Paroxysmal nocturnal hemoglobinuria, and Hematopoietic Stem Cell Transplantation

INTRODUCTION

Aplastic anemia (AA) is characterized by bone marrow failure associated with bone marrow hypoplasia/aplasia. AA can be hereditary or acquired, an important distinction, given that hereditary presentations do not respond to immunosuppression [1]. Most cases are acquired and without an etiologic trigger, in which an autoimmune pathophysiology is inferred [2]. Acquired AA is a rare disease with an incidence of 2 to 3 cases per million and with two incidence peaks, the highest around 20-30 years and the second after 60 years [3]. AA is defined as severe (SAA) when bone marrow biopsy has a cellularity <30% associated with at least two hematological criteria of severity: neutrophil count <500/µL, platelets <20,000/µL, and reticulocyte count <60,000/µL [4]. SAA is a potentially fatal disease in the absence of adequate treatment, with death related to infections or severe bleeding in most cases.

FIRST-LINE TREATMENT OF ACQUIRED SAA

First-line treatment of acquired SAA depends on the patient's age, the availability of an HLA-identical donor, and the absence of contraindications for hematopoietic stem cell transplantation (HSCT) [5]. Patients up to 40 years with an HLA-identical related donor and those up to 18 years with an HLA-identical unrelated donor should undergo HSCT as their first-line treatment (*level of evidence 2C*) [5]. If a matched unrelated donor HSCT cannot be performed in less than 2 months, immunosuppression should be applied. Those not eligible for upfront transplant due to age or lack of a histocompatible donor should receive treatment with horse antithymocyte globulin (ATG), cyclosporine (CSA), and eltrombopag (*level of evidence 1B*) [5]. The combination of these three drugs results in an overall hematological response rate of 94%, surpassing the historical results of 61% obtained after the combination of horse ATG and CSA [5,6]. Due to the unavailability of horse ATG in Brazil, rabbit ATG is used for first-line treatment in association with CSA, despite the lower response rate observed with this ATG preparation in comparison with horse ATG [7,8]. The results of the combination of rabbit ATG, CSA, and eltrombopag for the first-line treatment of acquired SAA are still unknown.

SECOND-LINE TREATMENT OF ACQUIRED SAA

Patients who do not respond to first-line immunosuppressive treatment must undergo bone marrow reassessment to exclude clonal evolution. Eligibility for HSCT should be reevaluated and considered as salvage for those eligible. An HLA identical donor, related or unrelated, should be preferred. In younger patients without a histocompatible related or unrelated donor, a haploidentical HSCT may be considered (*level of evidence 2C*) [5]. Patients without a donor or with a contraindication to HSCT should undergo a second-line drug treatment.

HLA-IDENTICAL RELATED ALLOGENEIC TRANSPLANT FOR ACQUIRED SAA

Related HSCT is the first-line treatment in acquired SAA for patients up to 40 years who have an HLA-identical related donor *(level of evidence 2C)* [5]. An EBMT registry study did not demonstrate an improvement in 5-year overall survival (OS) in patients over 40 years transplanted in different periods: 61% from 2001 to 2009 *versus* 58% from 2010 to 2018 (P=0.7), despite the improvement in supportive care recently [9]. In recent years, another study from EBMT and CIBMTR with 499 patients with SAA older than 50 years undergoing HSCT did not identify age as an independent variable associated with death, but found worse OS in patients with performance status <90% [10].

When HSCT is indicated as a first-line treatment for acquired SAA, it should be performed as soon as possible. The delay in performing HSCT is independently associated with the risk of death after the procedure [11,12]. Thus, any patient with newly diagnosed SAA who is a candidate for HSCT should be subjected to HLA typing together with all of his/her siblings. Immunosuppressive treatment should be discouraged in the weeks when results of HLA typing is pending.

The source of HSC for HSCT in SAA should always be bone marrow *(level of evidence 2C)*. An EBMT registry study with 1886 patients with SAA who underwent HLA-identical related HSCT observed an OS advantage for patients who received bone marrow compared to peripheral blood in all age groups: 1-19 years (90% *versus* 76%, P<0.00001), over 20 years (74% *versus* 64%, P=0.001), and over 50 years (69% *versus* 39%, P=0.01). The incidence of graft-versus-host disease (GVHD) was higher in the group that received peripheral blood as a source of HSC: 17% versus 11% (P=0.001) and 22% versus 11% (P=0.0004) for acute and chronic GVHD, respectively [11]. Another EBMT registry study demonstrated that the use of peripheral blood HSC is the independent variable that most increases the risk of death after HSCT: *hazard ratio* (HR) of 1.66, P<0.001 [12].

Rabbit ATG should always be used in the conditioning regime for related HSCT *(level of evidence 2C)* [13,14]. A CIBMTR registry study demonstrated a protective effect of rabbit ATG against acute and chronic GVHD in related HSCT: 17% *versus* 6% (P<0.001) and 20% *versus* 9% (P<0.001), respectively [14]. In unrelated HSCT, rabbit ATG protected against acute GVHD (42% *versus* 23%, P<0.001) and was independently associated with better OS (83% *versus* 75%, P= 0.02) [14]. EBMT registry studies also showed that the use of rabbit ATG is an independent variable associated with better OS after HSCT [11,12].

The conditioning regime in SAA must be non-myeloablative due to the absence of malignant cells, therefore preserving fertility in young patients and reducing the long-term sequelae after HSCT *(level of evidence 2C)*. One of the conditioning regimens used for this purpose is the combination of high-dose cyclophosphamide (CY) (200 mg/kg) with rabbit ATG. A series of 61 consecutive transplants conditioned with CY 200 mg/kg associated with rabbit ATG 2.5 mg/kg for 5 days (Thymoglobulin©) demonstrated an incidence of acute GVHD grades II-IV of 23%, chronic GVHD of 32%, primary rejection in only two patients, and an 6-year OS of 87% [15]. One of the main limitations of this conditioning regimen is a higher mortality rate in patients over 20 years, HR of 2.0 and P<0.00001 in multivariate analysis [11]. Trying to circumvent this problem, the EBMT conducted a study in which patients with SAA older than 30 years were conditioned with fludarabine (Flu) 30 mg/m^2/day for four days, CY 300 mg/m^2/day for four days, and rabbit ATG 3.75 mg/kg/day for four days (Thymoglobulin©) and compared with a historical control of patients conditioned with CY 200 mg/kg and rabbit ATG [16]. A lower graft rejection rate (0% *versus* 11%, P=0.09) and a better OS were observed in the group that received Flu (HR 0.44, P= 0.04) [16]. A recent CIBMTR study analyzed 955 patients with SAA who underwent related HSCT between 2000 and 2014 [17]. The 5-year OS after conditioning with Flu/CY/ATG, CT/ATG, CY ± Flu, and busulfan (Bu)/CY were 91%, 91%, 80%, and 84%; P=0.001 [17]. Conditioning with Bu/CY was associated with a higher risk of death, HR of 2.44, P=0.03 [17]. Thus, the recommended condition regimens for HLA related HSCT are *(evidence level 2C)*:

CY 200 mg/kg + rabbit ATG 5 - 7.5 mg/kg;

Flu 120mg/m^2 + CY 120 mg/kg + Rabbit ATG 5 - 7.5 mg/kg. Recommended for patients over 30 years, polytransfused, or with comorbidities;

regimens containing Bu should only be used in special situations.

The ideal immunosuppression regimen after HLA-identical related HSCT in SAA consists in combination of a calcineurin inhibitor (tacrolimus or cyclosporine A) with methotrexate *(level of evidence 1B)* [18,19]. The calcineurin inhibitor must be started on day -1 and must be maintained for at least one year after HSCT with a slow withdrawal afterwards. Methotrexate should be used on the short-course regimen (15 mg/m^2 on day +1 and 10 mg/m^2 on day +3, day +6, and day +11).

UNRELATED ALLOGENEIC TRANSPLANTATION FOR ACQUIRED AAS

All patients up to 60 years without an HLA-identical related donor must be registered for unrelated donor search. Second-line unrelated HSCT should be considered in younger patients, less than 40 years, and refractory to first-line immunosuppressive treatment *(level of evidence 2C)* [20]. Salvage unrelated HSCT may be considered in those aged between 40 and 60 years, with a good *performance status*, in the absence of significant comorbidities, and with the availability of a 10:10 compatible donor in high-resolution HLA typing.

A study conducted in Europe compared the outcomes of unrelated HSCT in the upfront setting with a historical control of related HSCT, and immunosuppression in children with SAA [21]. There was no difference in OS between the three groups, but the event-free survival was higher in patients undergoing related (87%) and unrelated (92%) HSCT compared to those treated with immunosuppression (40%). Thus, patients up to 18 years without an identical HLA-related donor can be submitted to upfront unrelated HSCT as long as the donor search and the procedures for carrying it out does not take more than 2 months given the risks of persistent severe pancytopenia *(level evidence 3B)* [21,22].

The ideal unrelated donor must be identical in HLA high-resolution typing for *locus*: HLA-A, -B, -C, -DRB1, and -DQB1 (compatibility 10:10) *(evidence level 2C)*. Unrelated HSCT with donors with one or more allelic incompatibility have an increased risk of primary graft failure, post-HSCT complications, and mortality [23].

As recommended for related HSCT, bone marrow is the preferred source of HSC for unrelated HSCT *(level of evidence 2C)* [12]. Peripheral blood HSC may be used only when bone marrow collection is not feasible [24,25].

The recommended conditioning regimens for unrelated HSCT are *(evidence level 2C)*:

Flu 120mg/m^2 + CY 120 mg/kg + rabbit ATG 5 - 7.5 mg/kg $\pm$ TBI 200 cGy. The addition of TBI at a dose of 200 cGy reduces the incidence of primary failure, especially in adult and/or polytransfused patients [26].

Similarly to HLA-identical related HSCT, the ideal post-HSCT immunosuppression regimen consists in the association of a calcineurin inhibitor with short-course methotrexate *(level of evidence 1B)*. The calcineurin inhibitor should be started on day -1, being maintained for at least during the first year after HSCT and with slow tapper afterwards. Methotrexate should be used on the short-course schedule (15 mg/m^2 on day +1 and 10 mg/m^2 on day +3, day +6, and day +11).

The haploidentical HSCT platform with post-CY can be a conditioning option for unrelated HSCT, especially in the presence of HLA incompatibility *(level of evidence 4)* [27].

HAPLOIDENTICAL TRANSPLANTATION FOR ACQUIRED AAS

Haploidentical HSCT should be considered as a rescue treatment for patients who are younger (< 40 years) and fail immunosuppressive treatment and who do not have an identical HLA donor (related or unrelated) (level of evidence 4) [28].

The choice between an unrelated donor with an HLA incompatibility or a haploidentical related donor must be made individually. The main issues that must be evaluated in making this decision are: the urgency of the transplant, neutrophil count, age of the recipient, the donor's characteristics (age, gender, and ABO/CMV agreement), and the presence of donor-specific antibodies against HLA (DSA).

The donor and recipient should be identical on at least one allele in high resolution typing for *locus*: HLA-A, -B, -C, and -DRB1, and the best donor is the one with fewer incompatibilities. In the case of more than one donor with the same degree of compatibility, the selection of the most suitable donor should prioritize: the absence of incompatibility in the *host-versus-graft direction*, ABO isogroup, serostatus for CMV, younger donors, donor weight, and gender

[29,30]. The search of DSA is mandatory and the presence of a high titer of DSA practically excludes this donor, due to the risk of rejection. In cases where there is no possibility of selecting another donor, desensitization protocols can be performed [31].

Based on national experience, the recommended conditioning regimen for haploidentical HSCT consists in the association of *(evidence level 4)*:

Flu 150 mg/m^2 + CY 29 mg/kg + TBI 400 cGy single dose [32]. The use of increased doses of TBI was associated with a reduction in the primary graft rejection rate, 27% versus 7% (P=0.02) and a higher 2-year event-free survival, 88% versus 60 % (P=0.01). The role of rabbit ATG in conditioning for haploidentical HSCT remains controversial and can be considered mainly for patients with less exposure to prior immunosuppression [30,32].

The source of HSC must be the bone marrow (level of evidence 4) [30,33,34]. The use of peripheral blood as a HSC source after stimulation with G-CSF is only recommended when bone marrow collection is not possible. GVHD prophylaxis consists on the association of CY 50 mg/kg/day on days +3 and +4, mycophenolate mofetil from day +5 to +35, and calcineurin inhibitor from day +5 to +365 with slow withdrawal after this period (level of evidence 4) [30,33,34].

Although promising, haploidentical transplantation is still not recommended in the upfront treatment of AAS until the results of prospective studies (NCT02833805).

ALLOGENEIC TRANSPLANT FOR PNH

Paroxysmal nocturnal hemoglobinuria (PNH) is a disorder caused by a somatic mutation in the phosphatidylinositol glycan A (PIGA) gene, an enzyme responsible for anchoring different proteins in the cell membrane. This enzyme deficiency results in reduced or absent expression of CD55 and CD59 proteins on the surface of red blood cells, making them susceptible to attack by the complement system [35]. Clinically, PNH can manifest itself through the occurrence of intravascular hemolysis, thromboembolic manifestations, and bone marrow failure syndrome [36]. The use of complement inhibitors, such as eculizumab, has allowed PNH patients with significant hemolysis (LDH above 1.5 times the upper limit of normality associated with target organ damage) to experience symptomatic improvement and reduced risk of death [36,37]. The largest series of HSCT in PNH reports the outcomes of 211 patients with PNH transplanted between 1978 and 2007, observing worse overall survival in those with previous episodes of venous thromboembolism [38]. Thus, the indication of allogeneic transplantation in PNH is now restricted to patients with significant bone marrow failure syndrome or clonal evolution to myelodysplastic syndrome/acute myelogenous leukemia *(level of evidence 2C)*. The ideal conditioning regime for HSCT in PNH with bone marrow failure is of reduced intensity, and the conditioning platforms mentioned above for SAA can be adopted *(level of evidence 2C)*. Patients who were using eculizumab apparently can continue to use it until the beginning of conditioning without the occurrence of unexpected adverse events *(level of evidence 4)* [39].

REFERENCES

1. Boddu PC, Kadia TM. Updates on the pathophysiology and treatment of aplastic anemia: a comprehensive review. *Expert Rev Hematol.* v.10, n.5, p. 433-48, may 2017.
2. Young NS, Scheinberg P, Calado RT. Aplastic anemia. *Curr Opin Hematol.* v. 15, n.3, p. 162-8, may 2008.
3. Young NS, Kaufman DW. The epidemiology of acquired aplastic anemia. *Haematologica.* 2 it. v.93, n.4, p. 489-92, apr. 2008.
4. Brodsky RA, Jones RJ. Aplastic anaemia. *Lancet.* v. 365, n.9471, p.1647-56, may 2005..
5. Young NS. Aplastic Anemia. *N Engl J Med.* v. 379, n.17, p.1643-56, 25 oct. 2018.
6. Townsley DM, Scheinberg P, Winkler T, Desmond R, Dumitriu B, Rios O, *et al*. Eltrombopag Added to Standard Immunosuppression for Aplastic Anemia. *N Engl J Med.* v.376, n.16, p.1540-50, 20 apr. 2017.
7. Atta EH, de Sousa AM, Schirmer MR, Bouzas LF, Nucci M, Abdelhay E. Different outcomes between cyclophosphamide plus horse or rabbit antithymocyte globulin for HLA-identical sibling bone marrow transplant in severe aplastic anemia. *Biol Blood Marrow Transplant.* v.18, n.12, p.1876-82, dec. 2012.

8. Scheinberg P, Nunez O, Weinstein B, Scheinberg P, Biancotto A, Wu CO, *et al*. Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. *N Engl J Med.* v.365, n.5, p. 430-8, aug. 2011.

9. Giammarco S, Peffault de Latour R, Sica S, Dufour C, Socie G, Passweg J, *et al*. Transplant outcome for patients with acquired aplastic anemia over the age of 40: has the outcome improved? *Blood*. v.131, n.17, p. 1989-92, apr.2018.

10. Rice C, Eikema D-J, Marsh JCW, Knol C, Hebert K, Putter H, *et al*. Allogeneic Hematopoietic Cell Transplantation in Patients Aged 50Years or Older with Severe Aplastic Anemia. *Biol Blood Marrow Transplant*. v.25, n.3, p. 488-95, mar. 2019.

11. Bacigalupo A, Socié G, Schrezenmeier H, Tichelli A, Locasciulli A, Fuehrer M, *et al*. Bone marrow versus peripheral blood as the stem cell source for sibling transplants in acquired aplastic anemia: survival advantage for bone marrow in all age groups. *Haematologica*. v. 97, n.8, p. 1142-8, aug. 2012.

12. Bacigalupo A, Socié G, Hamladji RM, Aljurf M, Maschan A, Kyrcz-Krzemien S, *et al*. Current outcome of HLA identical sibling versus unrelated donor transplants in severe aplastic anemia: an EBMT analysis. *Haematologica*. v.100, n.5, p. 696-702, may 2015.

13. Atta EH, de Oliveira DCM, Bouzas LF, Nucci M, Abdelhay E. Less graft-versus-host disease after rabbit antithymocyte globulin conditioning in unrelated bone marrow transplantation for leukemia and myelodysplasia: comparison with matched related bone marrow transplantation. *PLoS One*. v.9, n.9, p. 107-155, 4sep 2014.

14. Kekre N, Zhang Y, Zhang M-J, Carreras J, Ahmed P, Anderlini P, *et al*. Effect of antithymocyte globulin source on outcomes of bone marrow transplantation for severe aplastic anemia. *Haematologica*. v.102, n.7, p. 1291-8, jul. 2017.

15. Konopacki J, Porcher R, Robin M, Bieri S, Cayuela J-M, Larghero J, *et al*. Long-term follow up after allogeneic stem cell transplantation in patients with severe aplastic anemia after cyclophosphamide plus antithymocyte globulin conditioning. *Haematologica*. v.97, n.5, p. 710-6, may 2012.

16. Maury S, Bacigalupo A, Anderlini P, Aljurf M, Marsh J, Socié G, *et al*. Improved outcome of patients older than 30 years receiving HLA-identical sibling hematopoietic stem cell transplantation for severe acquired aplastic anemia using fludarabine-based conditioning: a comparison with conventional conditioning regimen. *Haematologica*. v.94, n.9, p. 1312-5, sep. 2009.

17. Bejanyan N, Kim S, Hebert KM, Kekre N, Abdel-Azim H, Ahmed I, *et al*. Choice of conditioning regimens for bone marrow transplantation in severe aplastic anemia. *Blood Adv.* v 3, n.20, p. 3123-31, 22 out.,2019.

18. Storb R, Deeg HJ, Farewell V, Doney K, Appelbaum F, Beatty P, *et al*. Marrow transplantation for severe aplastic anemia: methotrexate alone compared with a combination of methotrexate and cyclosporine for prevention of acute graft-versus-host disease. *Blood*. v.68, n.1, p. 119-25, jul. 1996.

19. Locatelli F, Bruno B, Zecca M, Van-Lint MT, McCann S, Arcese W, *et al*. Cyclosporin A and short-term methotrexate versus cyclosporin A as graft versus host disease prophylaxis in patients with severe aplastic anemia given allogeneic bone marrow transplantation from an HLA-identical sibling: results of a GITMO/EBMT randomized trial. *Blood*. v.96, n.5, p. 1690-7, 1 set. 2000.

20. Bacigalupo A, Giammarco S. Stem cell transplantation in aplastic anemia [Internet]. Vol. 3, *HemaSphere*. v.3, p. 15-7, 2019. Available from: http://dx.doi.org/10.1097/hs9.0000000000000249

21. Dufour C, Veys P, Carraro E, Bhatnagar N, Pillon M, Wynn R, *et al*. Similar outcome of upfront-unrelated and matched sibling stem cell transplantation in idiopathic paediatric aplastic anaemia. A study on behalf of the UK Paediatric BMT Working Party, Paediatric Diseases Working Party and Severe Aplastic Anaemia Working Party of EBMT. *Br J Haematol*. v. 171, n.4, p. 585-94, nov. 2015.

22. Georges GE, Doney K, Storb R. Severe aplastic anemia: allogeneic bone marrow transplantation as first-line treatment. *Blood Adv.* v. 2, n.15, p. 2020-2028, 14 aug. 2018.

23. Horan J, Wang T, Haagenson M, Spellman SR, Dehn J, Eapen M, *et al*. Evaluation of HLA matching in unrelated hematopoietic stem cell transplantation for nonmalignant disorders. *Blood*. v.120, n.14, p. 2918-24, 4 oct. 2012.

24. Bacigalupo A. How I treat acquired aplastic anemia [Internet]. *Blood*. v.129, p. 1428-36, 2017. Available from: http://dx.doi.org/10.1182/blood-2016-08-693481

25. Kumar R, Kimura F, Ahn KW, Hu Z-H, Kuwatsuka Y, Klein JP, *et al*. Comparing Outcomes with Bone Marrow or Peripheral Blood Stem Cells as Graft Source for Matched Sibling Transplants in Severe Aplastic Anemia across Different Economic Regions [Internet]. Vol. 22, *Biology of Blood and Marrow Transplantation*. v. 22, p. 932-40, 2026. Available from: http://dx.doi.org/10.1016/j.bbmt.2016.01.012

26. Bacigalupo A. Alternative donor transplants for severe aplastic anemia. *Hematology Am Soc Hematol Educ Program*. n.1, p. 467-73, 30 nov. 2018.

27. Arcuri LJ, Nabhan SK, Loth G, Atta EH, Oliveira M, Nichele S, *et al*. A Case Series of Post-Transplantation Cyclophosphamide in Unrelated Donor Hematopoietic Cell Transplantation for Aplastic Anemia. *Biol Blood Marrow Transplant* [Internet]. 3 jun. 2020.; Available from: http://dx.doi.org/10.1016/j.bbmt.2020.05.023

28. DeZern AE, Brodsky RA. Haploidentical Donor Bone Marrow Transplantation for Severe Aplastic Anemia. *Hematol Oncol Clin North Am*. v.32, n.4, p. 629-42, aug. 2018.

29. Ciurea SO, Al Malki MM, Kongtim P, Fuchs EJ, Luznik L, Huang X-J, *et al*. The European Society for Blood and Marrow Transplantation (EBMT) consensus recommendations for donor selection in haploidentical hematopoietic cell transplantation. *Bone Marrow Transplant*. v.55, n.1, p. 12-24, jan. 2020.

30. DeZern AE, Zahurak ML, Symons HJ, Cooke KR, Rosner GL, Gladstone DE, *et al*. Haploidentical BMT for severe aplastic anemia with intensive GVHD prophylaxis including posttransplant cyclophosphamide. *Blood Adv*. v.4, n.8, p. 1770-9, apr. 2020.

31. Gladstone DE, Bettinotti MP. HLA donor-specific antibodies in allogeneic hematopoietic stem cell transplantation: challenges and opportunities. *Hematology Am Soc Hematol Educ Program*. n.1, p. 645-50, 8 dec. 2017.

32. Arcuri LJ, Nabhan SK, Cunha R, Nichele S, Ribeiro AAF, Fernandes JF, *et al*. Impact of CD34 Cell Dose and Conditioning Regimen on Outcomes after Haploidentical Donor Hematopoietic Stem Cell Transplantation with Post-Transplantation Cyclophosphamide for Relapsed/Refractory Severe Aplastic Anemia [Internet]. *Biology of Blood and Marrow Transplantation*. 2020. Available from: http://dx.doi.org/10.1016/j.bbmt.2020.09.007

33. Esteves I, Bonfim C, Pasquini R, Funke V, Pereira NF, Rocha V, *et al*. Haploidentical BMT and post-transplant Cy for severe aplastic anemia: a multicenter retrospective study. *Bone Marrow Transplant*. v.50, n.5, p. 685-9, may 2015.

34. Prata PH, Eikema D-J, Afansyev B, Bosman P, Smiers F, Diez-Martin JL, *et al*. Haploidentical transplantation and posttransplant cyclophosphamide for treating aplastic anemia patients: a report from the EBMT Severe Aplastic Anemia Working Party. *Bone Marrow Transplant*. v.55, n.6, p. 1050-8, jun. 2020.

35. Rosse WF. Paroxysmal Nocturnal Hemoglobinuria as a Molecular Disease [Internet]. Vol. 76, *Medicine*. v.76, p. 63-93, 1997. Available from: http://dx.doi.org/10.1097/00005792-199703000-00001

36. Hill A, DeZern AE, Kinoshita T, Brodsky RA. Paroxysmal nocturnal haemoglobinuria. *Nat Rev Dis Primers*. 2017 May 18;3:17028.

37. Hillmen P, Muus P, Röth A, Elebute MO, Risitano AM, Schrezenmeier H, *et al*. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol*. v.162, n.1, p. 62-73, jul. 2013.

38. Peffault de Latour R, Schrezenmeier H, Bacigalupo A, Blaise D, de Souza CA, Vigouroux S, *et al*. Allogeneic stem cell transplantation in paroxysmal nocturnal hemoglobinuria. *Haematologica*. v. 97, n.11, p. 1666-73, nov. 2012.

39. 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*. v.24, n.12, p.26-30, dec. 2018.