DOI: 10.46765/2675-374X.2021v4n1p39-43

HSCT FOR INHERITED BONE MARROW FAILURE SYNDROMES

Luiz Guilherme Darrigo Junior [1], Phillip Scheinberg [2], Elias Hallack Atta [3], and Carmem Bonfim [4,5,6]

1 - Hospital de Clínicas da Faculdade de Medicina da Universidade de São Paulo - Ribeirão Preto - 2 - Hospital A Beneficência Portuguesa de São Paulo - 3 - Instituto Nacional do Cancer - INCA - 4 - Hospital de Clínicas da Universidade Federal do Paraná - 5 - Hospital Infantil Pequeno Príncipe - 6 - Hospital Nossa Senhora das Graças

Correspondence to: Luiz Guilherme Darrigo Junior- E-mail: darrigo.jr@gmail.com

ABSTRACT

The inherited bone marrow failure syndromes (IBMFS) are a heterogeneous group of genetic disorders characterized by the inadequate production of one or more hematopoietic lineages, leading to cytopenias' development. Allogeneic hematopoietic stem cell transplantation (HSCT) offers the potential to cure patients with an IBMFS. However, the procedure corrects only the hematological manifestations of the disease, and long-term follow-up should be provided for all patients. Recently a consensus document was established on behalf of the Brazilian Society of Bone Marrow Transplantation (SBTMO) to discuss HSCT in the setting of IBMFS. Recommendations from this expert panel are presented in this report.

Keywords: Anemia, Diamond-Blackfan, Fanconi Anemia, Shwachman, Telomere Diamond Syndrome, Bone Marrow Transplantation and Hematopoietic Stem Cells

INTRODUCTION

Inherited bone marrow failure syndromes (IBMFS) constitute a heterogeneous group of genetic disorders characterized by the inadequate production of one or more hematopoietic lineages leading to the development of cytopenias [1,2]. Distinct biological mechanisms underly the pathophysiology in IBMFS, such as repair pathways in Fanconi anemia (FA), telomere maintenance in dyskeratosis congenita (DKC), and ribossomopathy in Shwachman Diamond syndrome (SDS) and Diamond Blackfan anemia (DBA) [3]. These disorders are generally associated with the presence of congenital malformations and an increased risk of cancer, especially hematological and gynecological, as well as squamous cell carcinomas [4]. Although the diagnosis usually occurs in childhood, adults with a history suggestive of a hereditary bone marrow failure syndrome should be investigated [2]. Currently, hematopoietic stem cell transplantation (HSCT) is the only curative option for hematological complications related to IBMFS [1,2]. It is essential to highlight that these patients must be monitored throughout their lives, given the risk of developing non-hematopoietic neoplasias, which have a better prognosis if detected early [5].

GENERAL RECOMMENDATIONS

Donor selection: All siblings should be tested for IBMFS before being considered as potential donors for HSCT [6]

HLA Compatibility: The ideal unrelated donor must be HLA identical in high resolution typing for the HLA-A, -B, -C, -DRB1, and -DQB1 locus, that is, 10:10 compatibility. Donors with one or more allelic incompatibility are at increased risk of primary graft failure, HSCT complications, and mortality [7]. We recommend testing DP locus as incompatibilities in DPB1 are associated with an increased risk of GVHD and transplant-related mortality [8].

Cell source: Bone marrow is the preferred source of stem cells. The use of cord blood is recommended only when matched unaffected siblings are available, and outcomes are excellent [9,10]. Unrelated umbilical cord blood transplantation is usually associate with high rejection and GVHD rates and should be performed with caution in this group of patients [9,11].

FANCONI ANEMIA

Recommendation:
Indications for transplant include marrow failure or clonal evolution (myelodysplastic syndrome - MDS or acute myeloid leukemia - AML). In an ideal scenario, HSCT should be performed before blood transfusions, serious infections, or the development of clonal disease [6,12,13].

Conditioning:

Patient in aplasia with an identical related donor (14)
• Cy 60 mg / kg (divided into 4 days: D -6, -5, -4, -3);

• Mesna, 160% of the Cy dose, divided into five doses (0, 3, 6, 9, and 12 hours after Cy);

• Rabbit ATG at a dose of 5 mg/kg (divided into three days: D-3, D-2, and D-1), in patients aged 11 years and older, to reduce the incidence and severity of GVHD.

Patient in aplasia with unrelated matched donor (6,13,15)
• Cy 60 mg / kg (divided into four days: D -6, D-5, D-4, D-3);

• Mesna, 160% of the Cy dose, divided into 5 doses (0, 3, 6, 9 and 12 hours after Cy);

• Fludarabine 150 mg / m^2 (divided into 5 days: D -6, D-5, D-4, D-3 D-2);

• Rabbit ATG 5 mg / kg (divided into three days: D -3, D-2 and D-1).

Patients progressing to MDS and/or AML with matched related or unrelated donors The preparatory regimen will depend on the clinical conditions and the disease stage. These patients may be referred for transplantation without prior chemotherapy. Patients with refractory cytopenia or MDS with less than 10% blasts (RAEB-1) should be treated according to the recommended protocol for Fanconi's anemia in the aplastic phase. In patients with 10% or more blasts in the bone marrow and good clinical condition, the FLAG protocol (fludarabine, cytarabine, and G-CSF) is recommended, followed by related or unrelated HSCT approximately two weeks after the beginning of the chemotherapy. This scheme should be performed only on patients with a related or unrelated donor available and a confirmed transplant schedule [12].

Patients in the aplastic phase or clonal evolution lacking a matched related or unrelated donor:
• It is recommended that the decision to proceed to transplant should be discussed with the experts to define the best time to perform this procedure and the best conditioning/prophylaxis regimen for GVHD.

• These patients can benefit from haploidentical transplantation using a modified dose of post transplantation cyclophosphamide. However, we recommend that this transplant should be performed only in centers with experience in this type of patient [16].

TELOMERE BIOLOGY DISEASE

Recommendation:
The indication for transplant includes patients in aplastic phase, myelodysplasia, or acute leukemia. In the ideal scenario, HSCT should be performed before transfusions, serious infections, or clonal evolution [13]. The prototype of telomeric biology disease (TBD) is DKC; however, we recommend that transplant also be performed in patients with severe aplasia and very short telomeres (<1%), even in the absence of classic symptoms of DKC.

Conditioning:
Patients with matched related or unrelated donors [13,17]

• Cy 60 mg / kg (divided into 4 days: D -6, D-5, D-4, D-3);

• Mesna, 160% of the Cy dose, divided into 5 doses (0, 3, 6, 9 and 12 hours after Cy);

• Fludarabine 150 mg / m^2 (divided into 5 days: D -6, D-5, D-4, D-3 D-2);

• Rabbit ATG 5 mg / kg (divided into three days: D -3, D-2 and D-1).

BLACKFAN-DIAMOND ANEMIA

Recommendation [13,18]:
• Non-response to steroids, steroid dependency at a dose of ≥ 0.3 mg/kg/day, unacceptable steroid toxicity

• Dependence on transfusions and/or alloimmunization.

• Pancytopenia or with progression to MDS /AML.

Conditioning:
Patients with matched related or unrelated donors (19)

• Busulfan 16 - 20 mg/kg EV + Fludarabine 160 mg / m^2 + rabbit ATG 5 mg/kg;

• Rabbit ATG 5 mg/kg (divided into three days: D -3, D-2 and D-1).

Comments:
Transplantation should be performed in patients under ten years of age, preferably before five years of age [19,20]. The dose of busulfan should be myeloablative and based on the patient's weight and preferrable with pharmacokinetics.

Body-weight	mg/kg/day
3 to 15kg	5.1
15 to 25kg	4.9
25 to 50kg	4.1
50 to 75kg	3.3
75 to 100kg	2.7

Adaptado de (21)

SHWACHMAN-DIAMOND SYNDROME

Recommendation [13,22]:
• Progressive cytopenias or pancytopenia.
• Dependence on blood transfusions.
• Progression to MDS / LMA.

Conditioning:
Patients with matched related or unrelated donors [13,22]
• Cy 120 mg / kg + Fludarabine 150 mg/m^2;

• Mesna, 160% of the Cy dose, divided into 5 doses (0, 3, 6, 9 and 12 hours after Cy);

• Rabbit ATG 5 mg/kg (divided into three days: D-3, D-2 and D-1).

Comments:
The best results are obtained in patients receiving a reduced-intensity conditioning regimen using a matched related or unrelated donor [13,22]

Congenital Amegakaryocytic Thrombocytopenic Purpura

Recommendation [23,24]
• Severe thrombocytopenia and transfusion-dependent patients.
• Pancytopenia or evolution to MDS / AML.

Conditioning:
Patients with matched related or unrelated donors [24,25]:
• Busulfan 16 - 20 mg/kg EV + Fludarabine 160 mg/m^2.
• Rabbit ATG 5 mg/kg (divided into three days: D -3, D -2 and D -1).
The busulfan dose should be myeloablative and based on the patient's weight and preferrable with pharmacokinetics, as mentioned before.

CONCLUSION

• HSCT is currently the only curative option for the hematological complications related to the different IBMFS [1,10,26]

• All family donors should be screened before considered as potential donors.

• Patients and their families should be informed that HSCT corrects only the hematological manifestations of the disease

• We advise that all transplant patients be followed up for a lifetime with the aim of preventing or detecting early changes resulting not only from HSCT but also from the underlying genetic disorder [5]

• Particular attention should be paid to the appearance of hematological and non-hematological malignancies [4,5]

REFERENCE

1. Dokal I, Vulliamy T. Inherited bone marrow failure syndromes. *Haematologica*; v.95, n. 8, p. 2010

2. Alter BP. Diagnosis, Genetics, and Management of Inherited Bone Marrow Failure Syndromes. *Hematology*; v. 1, p. 29-39, 2007.

3. Shimamura A, Alter BP. Pathophysiology and management of inherited bone marrow failure syndromes. *Blood Rev*; v.24, n.3, p. 101-122, 24 may 2010.

4. Alter BP, Giri N, Savage SA, Rosenberg PS. Cancer in the National Cancer Institute inherited bone marrow failure syndrome cohort after fifteen years of follow-up. *Haematologica*; v.103, n. 1, p.30-39, 2018.

5. Dietz AC, Savage SA, Vlachos A, Mehta PA, Bresters D, Tolar J, et al. Late Effects Screening Guidelines after Hematopoietic Cell Transplantation for Inherited Bone Marrow Failure Syndromes: Consensus Statement From the Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects After Pediatric HCT. *Biol Blood Marrow Transplant*; v.23, n. 9, p. 1422-1428, 2017.

6. Dufour C. How I manage patients with Fanconi anaemia. *Br J Haematol*; v.178, n.1, p. 32-47, 2017.

7. 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, 2924, 2012.

8. Petersdorf EW, Bengtsson M, De Santis D, Dubois V, Fleischhauer K, Gooley T, et al. Role of HLA-DP Expression in Graft-Versus-Host Disease After Unrelated Donor Transplantation. *J Clin Oncol Off J Am Soc Clin Oncol*; v. 38, n. 24, p.2712-2718, 2020.

9. Bizzetto R, Bonfim C, Rocha V, Socie G, Locatelli F, Chan K, et al. Outcomes after related and unrelated umbilical cord blood transplantation for hereditary bone marrow failure syndromes other than Fanconi anemia. *Haematologica*; v. 96, n. 1. p. 134-141, 2011.

10. Dokal I, Vulliamy T. Inherited aplastic anaemias/ bone marrow failure syndromes. *Blood Rev*; v. 22, n. 3, p. 2008.

11. Pagliuca S, Ruggeri A, Peffault de Latour R. Cord blood transplantation for bone marrow failure syndromes: state of art. Stem Cell Investig. 2019;6:39.

12. Peffault de Latour R, Soulier J. How I treat MDS and AML in Fanconi anemia. *Blood*; v. 127, n. 24, p. 2971-2979, 2016.

13. Dalle J-H, de Latour RP. Allogeneic hematopoietic stem cell transplantation for inherited bone marrow failure syndromes. *Int J Hematol*; v. 103, n. 4, p. 373-379, 2016.

14. Bonfim CM, de Medeiros CR, Bitencourt MA, Zanis-Neto J, Funke VAM, Setubal DC, et al. HLA-Matched Related Donor Hematopoietic Cell Transplantation in 43 Patients with Fanconi Anemia Conditioned with 60 mg/kg of Cyclophosphamide. *Biol Blood Marrow Transplant*; v. 13, n. 12, p. 1455-1460, 2007.

15.Bonfim C, Ribeiro L, Nichele S, Bitencourt M, Loth G, Koliski A, et al. Long-term Survival, Organ Function, and Malignancy after Hematopoietic Stem Cell Transplantation for Fanconi Anemia. *Biol Blood Marrow Transplant*; v. 22, n. 7, p.1257-1263, 2016.

16. Bonfim C, Ribeiro L, Nichele S, Loth G, Bitencourt M, Koliski A, et al. Haploidentical Bone Marrow Transplantation with Post-Transplant Cyclophosphamide for Children and Adolescents with Fanconi Anemia. *Biol Blood Marrow Transplant*; v. 23, n. 4, p. 2017.

17. Fioredda F, Iacobelli S, Korthof ET, Knol C, van Biezen A, Bresters D, et al. Outcome of haematopoietic stem cell transplantation in dyskeratosis congenita. *Br J Haematol*; v. 183, n. 1, p. 110-118, 2018.

18. Bartels M, Bierings M. How I manage children with Diamond-Blackfan anaemia. *Br J Haematol*; v. 184, n. 2, p. 123-133, 2019.

19. Darrigo LG, Loth G, Kuwahara C, Vieira A, Colturato V, Rodrigues AL, et al. Hematopoietic cell transplantation for Diamond Blackfan anemia: A report from the Pediatric Group of the Brazilian Bone Marrow Transplantation Society. *Eur J Haematol*. 2020 Jul 2;ejh.13463.

20. Strahm B, Loewecke F, Niemeyer CM, Albert M, Ansari M, Bader P, et al. Favorable outcomes of hematopoietic stem cell transplantation in children and adolescents with Diamond-Blackfan anemia. *Blood Adv*; v. 4, n.8, p.1760-1769, 2020.

21. Bartelink IH, Boelens JJ, Bredius RGM, Egberts

ACG, Wang C, Bierings MB, et al. Body weight-dependent pharmacokinetics of busulfan in paediatric haematopoietic stem cell transplantation patients: towards individualized dosing. *Clin Pharmacokinet*; v.51, n. 5, p. 331-345, 2012.

22. Cesaro S, Pillon M, Sauer M, Smiers F, Faraci M, de Heredia CD, et al. Long-term outcome after allogeneic hematopoietic stem cell transplantation for Shwachman–Diamond syndrome: a retrospective analysis and a review of the literature by the Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation (SAAWP-EBMT). *Bone Marrow Transplant*. 19 mar. 2020.

23. Ballmaier M, Germeshausen M. Congenital Amegakaryocytic Thrombocytopenia: Clinical Presentation, Diagnosis, and Treatment. *Semin Thromb Hemost*; v. 37, n. 6, p. 2011.

24. Al-Ahmari A, Ayas M, Al-Jefri A, Al-Mahr M, Rifai S, Solh HE. Allogeneic stem cell transplantation for patients with congenital amegakaryocytic thrombocytopenia (CAT). *Bone Marrow Transplant*; v. 33, n. 8, p. 829-831, 2004.

25. Mahadeo KM, Tewari P, Parikh SH, Driscoll TA, Page K, Martin PL, et al. Durable engraftment and correction of hematological abnormalities in children with congenital amegakaryocytic thrombocytopenia following myeloablative umbilical cord blood transplantation. *Pediatr Transplant*; v. 19, n.7, p. 2015

26. Alter BP. Inherited bone marrow failure syndromes: considerations pre- and posttransplant. *Blood;* v. 23, n. 130, p. 2257-2264, 2017.