**Haploidentical transplantation of hematopoietic stem cells**

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**SUMMARY**

**Objective:** To review and discuss the literature on hematopoietic stem cell transplantation (HSCT) with haploidentical donors in Brazil.

**Method:** Literature review.

**Results:** The haploidentical hematopoietic stem cell transplantations have become a safe option in hematology since the 80s, with the possibility of ex-vivo T-cell depletion. However, its broad use worldwide occurred with the advent of haploidentical non-myeloablative transplants using in vivo T-cell depletion with the administration of post-transplant cyclophosphamide. The results were encouraging, despite the increased risk of infection and post-transplantation recurrence. Recent publications on acute myeloid leukemia, myelodysplastic syndrome and Hodgkin’s lymphoma have shown similar results among haploidentical, unrelated and related full-match transplants. Obviously, these findings of retrospective studies should be confirmed by clinical trials.

**Conclusions:** Transplantation with haploidentical donor has shown to be feasible in Brazil and the first publications and results are showing encouraging results.

**Keywords:** Bone Marrow Transplantation. Stem cells. Transplants.

**INTRODUCTION**

The haploidentical transplantation initiatives in the 1970s were catastrophic and prohibitive, with an incidence of graft-versus-host-disease (GVHD) >70% and grafting failure of 20%.1 In the 1980s, with the use of T-cell depletion with sheep erythrocytes, the methodology started to show greater acceptance.1

In 1994, the Italian group with the CD34 cell selection equipment, demonstrated decreased risk of rejection using high doses of cells (“mega dose”: 13.8 x 10⁶ CD34 with 1x10⁴ CD3).2 The initiatives of Chinese researchers with stringent conditioning have shown excellent results since 2006.3 In 2007, the Duke University group led by Nelson Chao presented a protocol without selection of CD34+ cells in vitro and in vivo depletion using Campath (alemtuzumab) in the conditioning regimen.4 However, a major breakthrough occurred in 2008 when the group of Baltimore, led by Ephraim Fuchs, consolidated the use of post-transplant cyclophosphamide on days +3 and +4 post-transplantation, also with depletion of T cells in vivo.5 The authors published results using this type of regimen in several types of malignant diseases, such acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplasia and non-Hodgkin and Hodgkin’s lymphoma, with an overall survival >50% in Hodgkin’s lymphoma, reaching 76%. From that point onward, what we saw was a constant search for methodologies that would further improve the results of haploidentical transplants.5-7

The advantages of using this type of transplant is the immediate donor availability, instant access to the donor for cell therapy after transplantation and the possibility of selecting several family members according to clinical characteristics and alloreactivity of NK (natural killer) cells. As disadvantages, we can mention the higher potential risk of GVHD, the need for depletion of T cells in vivo or ex vivo, leading to a higher incidence of infection due to the slow immuno-reconstitution and high incidence of recurrence.6,7

But undoubtedly, the great advantage is that, considering that 40-50% of patients have no related or unrelated compatible donors, HLA “mismatch” or haploidentical transplants of first-degree relatives can be found in over 95% of patients.7,9

In Brazil, the use of post-transplantation cyclophosphamide is the one most often used to perform haploidentical transplants. This choice is not made by chance.
First, it results from the high cost of processing, which is restricted to a few treatment centers that have specific protocols to be used in, for instance, congenital immunodeficiencies. Secondly, literature reports indicate that the results tend to be better, since only alloreactive lymphocytes are affected.\textsuperscript{5,8,9,10}

Initial studies seeking to compare the haploidentical transplantation with other alternatives, such as the umbilical cord or unrelated mismatch transplants, have not shown great superiority between one form or another of transplanting. Given that factors such as mismatch, presence of anti-HLA antibodies, KIR reactivity, NIMA and HLA C in umbilical cord can help in the decision-making, Table 1 has been widely used as a guide.\textsuperscript{11-15}

Recently, the MD Anderson group, led by Dr. Stefan Ciurea, showed comparable results between haploidentical and unrelated transplants, even fully compatible. This fact opens the possibility of using the haploidentical transplant primarily when compatible related donor cannot be found and when it takes longer to find unrelated donors due to genetic or operational difficulties. This finding, which has been demonstrated by other groups, will obviously change – if confirmed by clinical studies – the way we choose the best donor for hematopoietic cell transplantation, significantly modifying Table 1 and establishing the haploidentical transplant option or unrelated transplant as fully compatible for most clinical situations\textsuperscript{16,17}.

**ADVANTAGES AND DISADVANTAGES OF USING HAPLOIDENTICAL DONORS**

Compared to other sources of donors, the main advantages of using haploidentical transplants are\textsuperscript{5,7,9}

a) Availability: it is estimated that a patient has 2.7 potential haploidentical donors among their first-degree relatives. This number is compared to a 25 to 30% chance of an HLA-identical family donor and the variable chances between 16% and 75% of a fully compatible donor (8 x 8) in a donor registry, depending on the genetic difficulty of each case.

b) Immediate availability: in urgent cases, when compatible family donors cannot be found, a haploidentical donor will be selected quickly, compared with the mean time for search and confirmation of an unrelated donor, which is around three to four months.

**CHART 1.** Decision process between alternative transplants
c) Low cost: compared with unrelated donors and umbilical cord blood, the costs are significantly lower in the search for haploidentical donors.

d) Possibility of using the donor cells for immunotherapy (lymphocyte infusion): this strategy is impossible in the case of umbilical cords.

However, the use of methods that target T-cell depletion decreases the incidence of GVHD, but increases the risk of rejection, infection and reduces graft-versus-leukemia reaction.11-13

**Main current strategies for haploidentical transplants**

a) *In vitro* T-cell depletion: This methodology employs megadoses of CD34 and is used by the Perugia group.1,2,12,13

b) GIAC: uses G-CSF (G) granulocyte colony stimulating factor to stimulate the donor and extensive post-transplantation immunosuppression (I), using ATG (A) (antithymocyte globulin) and the combined use (C) of bone marrow and peripheral blood. This methodology is used almost exclusively in China, where there is extensive experience in haploidentical transplants.13

c) Post-transplantation cyclophosphamide: this is the main form of T-cell depletion used worldwide, with adaptations to the first works with non-myeloablative transplants using fludarabine, low-dose (200 Gy) total body irradiation and cyclophosphamide. Cyclophosphamide 50 mg/kg is used on days +3 and +4 and the prophylaxis of graft-versus-host disease is made with MMF and tacrolimus.4,16,18

d) Choice of the best donor: According to a study published by the Chinese group, the best donor is young and male.19 The father has precedence over the mother. It is also important to assess the blood group, perform serology for cytomegalovirus, assess the presence of HLA donor-specific antibodies, NIMA (non-inherited maternal antigens) and KIR reactivity.20 These data have not been reproduced by others and we do not know whether their use is valid for other conditioning regimens. The most important factor in all the works and for any type of methodology, is the assessment of the presence of anti-donor specific antibodies.

**Brazilian experience with haploidentical transplantation**

The number of haploidentical transplants have been increasing in Brazilian centers. Until mid-2013, 85 transplants had been performed. From that date until mid-2015, over 100 transplants were performed, totaling 185 cases and this number is increasing.21 Most were performed in cases of acute leukemia (90 patients), severe aplastic anemia (24 patients) and Hodgkin’s lymphoma (20 patients), with the remaining patients scattered among other indications of malignant and nonmalignant diseases. The overall survival of these patients can be seen in Graph 1. The presence of hepatic veno-occlusive disease was the only factor that had an impact on survival in the multivariate analysis of Brazilian cases as shown in Table 1.21

Regarding specific initiatives, the Brazilian group published a series of severe aplastic anemia cases (16 patients) with interesting results (Graph 2) and presented the results of 20 patients with Hodgkin’s lymphoma...
(Figure 3) at the Congress of the Brazilian Association of Hematology (ABHH) in 2015.22,23 The main initiatives in haploidentical transplants of the Brazilian Society of Bone Marrow Transplantation (SBTMO) were established at the society meetings, with members interested in the area and the creation of uniform protocols for the following situations: acute myeloid leukemia and myelodysplasia, acute lymphocytic leukemia, Hodgkin’s lymphoma and severe aplastic anemia.24

CONCLUSION

The haploidentical transplantation is a type of procedure that has become more and more popular among specialists in the area. The use of post-transplant cyclophosphamide has popularized its use. In some pathologies, the results are as good as in related and unrelated transplants. In Brazil, its use has gained much acceptance.

RESUMO Transplantes haploidênticos de células-tronco hematopoiéticas

Objetivo: Revisar e discutir a literatura sobre transplantes de células-tronco hematopoiéticas (TCTH) com doador haploidêntico no Brasil.

Métodos: Revisão da literatura médica.

Resultados: Os transplantes haploidênticos de células-tronco hematopoiéticas tornaram-se uma opção segura na hematologia a partir dos anos 1980, com a possibilidade de depleção de células T ex-vivo. No entanto, sua ampla utilização em todo mundo ocorreu após os trabalhos com os transplantes haploidênticos não mieloablativos, com depleção de células T in-vivo, utilizando ciclofosfamida pós-transplante. Os resultados se mostraram encorajadores, apesar do maior risco de infecções e recidiva pós-transplante. Estudos em determinadas patologias, principalmente na leucemia mieloide aguda, mielodisplasia e linfoma de Hodgkin, mostram resultados semelhantes entre transplantes haploidênticos e não aparentados e aparentados totalmente compatíveis. Logicamente, esses achados de estudos retrospectivos precisam ser confirmados por estudos clínicos.

Conclusões: No Brasil, a modalidade de transplante com doador haploidêntico se mostrou factível e as primeiras publicações e resultados mostram resultados animadores.


REFERENCES


