

HAPLOIDENTICAL STEM CELL TRANSPLANTATION

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DEFINITION

A haploidentical donor is one who divides, by common genetic inheritance, exactly one haplotype with the recipient and presents mismatch in a variable number of genes in the non-shared haplotype. Potential haploidentical donors include biological parents, children, siblings, uncles, aunts, cousins, nephews, or grandchildren.

INTRODUCTION

As matched related donors can be found in only 30% of cases, alternative donors such as unrelated matched transplants, cord transplantation, partially compatible transplantation, and haploidentical transplantation are important alternatives. Due to important improvements in techniques for performing haploidentical transplantation and as first-degree haploidentical donors can be found in more than 95% of patients, this type of transplantation has been growing in recent years [1-3].

The advantages of using this type of transplant are the immediate availability of the donor, the immediate access to the donor for cell therapy in the post-BMT, and the possibility of selecting several family members according to clinical characteristics and NK alloreactivity. The biggest challenge is the intense bidirectional alloreactivity with increased risk of graft-versus-host disease (GVHD) and rejection, leading to the need for depletion of T cells *in vivo* or *ex vivo* and a greater incidence of infection by slow immunoreconstitution and high incidence of relapse [4].

HISTORICAL ASPECTS

The haploidentical stem cell transplant initiatives in the 1970s were catastrophic and prohibitive, with graft vs host disease incidence above 70% and grafting failure of 20% (5). In the 1980s, with the use of depletion of T cells with sheep red blood cells, the methodology started to be accepted [5].

In 1994, the Italian group demonstrated a reduction in the risk of rejection using high doses of cells ("mega dose": 13.8×10^6 CD34 with 1×10^4 CD3) with CD34 cell selection (6). In 2007, the Duke University group, led by Nelson Chao, presented a protocol with depletion "in vivo" with Campath in the conditioning regime, without selecting CD34 cells "in vitro" [7]. But a breakthrough was in 2008 when the Baltimore group led by Efraim Fuchs consolidated the use of cyclophosphamide on days +3 and +4 post-transplant, also with depletion "in vivo" [8]. From that moment on, what is seen is a constant search for methodologies that further improve the results of haploidentical transplants [4, 9].

Post-transplantation cyclophosphamide is the most frequently used immunosuppression to perform haploidentical transplants. The reasons are the high cost of a column to select CD34+ cells and the encouraging results with the use of post-transplant cyclophosphamide [2, 3, 8].

TRANSPLANTATION STRATEGIES

The main haploidentical transplant strategies are:

- a) "In vitro" T cell depletion: in this methodology, it is used mega doses of CD34 and is most used by the Perugia group [5, 6, 10, 11]
- b) GIAC: in this protocol, it is used GCSF (G) to stimulate the donor, an intensified immunosuppression after transplantation (I), ATG in the conditioning (A), and combined (C) use of bone marrow and peripheral blood. This methodology is used almost exclusively in China, where there is extensive experience in haploidentical transplants [11]
- c) Post-transplant cyclophosphamide: this is the main strategy of T cell depletion used worldwide. It was first described with a non-myeloablative protocol using Fludarabine, low-dose total body irradiation

ation (200 Gy), and cyclophosphamide. Cyclophosphamide 50 mg/kg is used on days + 3 and +4 and the graft vs host disease prophylaxis is done with mycophenolate mofetil and tacrolimus [8, 12, 13].

CHOOSING THE DONOR:

The studies comparing haploidentical transplantation with post-transplantation cyclophosphamide to unrelated matched transplant did not demonstrate great superiority for one or other donors. Registry studies have shown that overall survival (OS) was not significantly different between patients with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) receiving haploidentical or unrelated grafts (reduced intensity or myeloablative conditioning) [12, 14]. Similarly, in recipients with lymphoma, OS, non-relapse-related mortality and progression-free survival were comparable between these two types of donors, although the incidence of acute GVHD grades III-IV and chronic GVHD was lower in haploidentical transplantation [15]. In aplastic anemia, haploidentical transplantation has also been associated with satisfactory experiences [16].

Registry studies comparing haploidentical transplant and umbilical cord transplantation have shown superior outcomes with haploidentical transplantation compared to cord transplantation [17-19]. The BMT CTN 1101 phase 3 randomized trial recently demonstrated superior OS in haploidentical transplant recipients compared to cord transplantation [20]. In the future, studies may compare better-selected cord transplantations (eg, higher cell dose, grafts with fewer HLA mismatches, and others) to haploidentical transplantation [6, 10, 11, 21, 22].

CHOOSING THE BEST HAPLOIDENTICAL DONOR:

The main factor in the donor choice is the presence of donor-specific antibodies (DSA), which is present, more frequently, in women with children, but can also occur due to a history of transfusions. The donor chosen should be preferably the one for whom the patient does not have antibodies. Besides, the specific antibody titer is also an important factor, since mean fluorescence intensity (MFI) > 1500 (23) may be associated with graft dysfunction, MFI > 5000 with graft failure, and > 10,000 (24) with a high incidence of graft failure [23]. MFI values may vary between laboratories and each institution must establish its cut-off value for graft failure risk. As high MFI values are usually more frequent in family donors, the search for an unrelated donor should be done. If an-

other donor cannot be identified, desensitization to reduce antibody concentration can be considered in centers with expertise. Desensitization schemes generally include immunosuppressants, plasmapheresis, "buffy coat", among others, and the protocol must be established at the institution.

Another important factor to be considered is donor age, with preference for the younger donor. Donors who are the recipient's children or siblings are preferred over parents [25]. Blood group, donor gender, serology for cytomegalovirus, non-inherited maternal HLA antigen (NIMA), the disparity in specific HLA alleles, and mismatching KIR are still controversial factors that need further study at this time.

GRAFT SOURCE

Bone marrow and peripheral blood are possible stem cell sources for haploidentical transplantation, and the choice is generally based on the institution's expertise and preferences. Studies comparing both graft sources have shown no difference in overall survival, but there may be a difference in transplant-related mortality, relapse, GVHD, and cytokine release syndrome.

In a multicenter study, bone marrow was associated with a lower risk of acute GVHD grades II to IV and chronic GVHD and a higher risk of relapse in patients with acute leukemia, but not in lymphomas, with no difference in overall survival and transplant-related mortality [26]. In another study, bone marrow was associated with a lower risk of acute GVHD, but the source did not affect the risk of chronic GVHD, relapse, and non-relapse mortality [27]. Some studies have shown a higher incidence of \geq grade 2 cytokine release syndrome using a peripheral source [28, 29]. If bone marrow source is used in haploidentical transplantation with post-transplant cyclophosphamide, the higher nucleated cell count is associated with increased progression-free survival and overall survival [30].

CYTOKINE RELEASE SYNDROME

Fever of noninfectious origin occurs in 80-90% of the cases after haploidentical transplantation, usually between days 0 and 6, with resolution after post-transplant cyclophosphamide. This fever is related to a mismatch in HLA class II and high doses of CD3 + lymphocytes in the infused product. In most cases, there is no need for steroid treatment. Treatment is based on supportive measures that include blood culture collection, antipyretics, and

broad-spectrum antibiotic therapy according to institutional protocol due to the difficulty of differentiating with septic conditions. Grade III and IV cytokine release syndrome may be related to increased transplant-related mortality. Some authors have shown benefit of using tocilizumab in this situation or, if not available, steroids. Routine administration of steroids before post-transplant cyclophosphamide is generally avoided until 24 hours after the last dose of cyclophosphamide since the mechanism of action of cyclophosphamide involves the proliferation of alloreactive lymphocytes [31].

CONDITIONING REGIMEN

Most of the data on conditioning regimen in haploidentical transplantation came from non-myeloablative or reduced-intensity conditioning, especially the protocol with cyclophosphamide, fludarabine, and a low dose of TBI. A study that compared myeloablative regimen with reduced intensity, showed a lower incidence of relapse with myeloablative regimens, but at the expense of increased transplant-related mortality, with no difference in overall survival or disease-free survival [32]. In patients over 60 years of age, a retrospective study demonstrated that there was no difference between myeloablative regimens or reduced-intensity regarding non-relapse mortality, relapse, overall survival, and progression-free survival [33]. A recent CIBMTR study comparing myeloablative and reduced-intensity regimens demonstrated greater disease-free survival with the myeloablative regimen in young patients, but not in patients aged 55 to 70 years [34].

POST-TRANSPLANT RELAPSE

In the case of post haploidentical transplant relapse, it is important to evaluate if the incompatible HLA haplotype is maintained or lost (HLA lost). Donor lymphocyte infusions (initial dose of 1 million CD3 + T cells/kg of recipient weight) are capable of inducing sustained remissions if the incompatible HLA haplotype is maintained. Cases that have lost expression of the incompatible HLA haplotype are candidates for a second haploidentical transplant from a relative who has HLA incompatibility with the original donor [35-37].

RECOMMENDATIONS:

- Haploidentical and unrelated transplants show comparable results in recent studies (2B). Haploidentical transplantation has been associated with superior overall survival compared to cord transplantation (1B). In malignant diseases, particularly in acute

myeloid leukemias and lymphomas, haploidentical transplantation presents results comparable to unrelated matched transplants (2B). In patients with severe aplastic anemia previously immunosuppressed, haploidentical transplantation is an alternative (2C) and randomized studies will show the real role of this type of transplantation.

Thus, haploidentical transplantation can be used in patients without a matched related donor readily available or when there is a delay in unrelated donors search (grade of recommendation B; level of evidence 2B)

- Post-transplant cyclophosphamide (50mg/Kg days +3 and +4) is the main strategy for T cell depletion, associated with mycophenolate mofetil and tacrolimus or cyclosporine (grade of recommendation B; level of evidence 2B)

- The main factor in the donor choice is the presence of donor antibodies (DSA), with preference to the donor for whom the patient does not have antibodies. Besides, young donors (siblings and children) are preferable (grade of recommendation B, level of evidence 2C)

- Bone marrow and peripheral blood are possible graft sources. The choice should be based on the institution's expertise and preferences (grade of recommendation B; level of evidence 2B)

- Cytokine release syndrome in haploidentical transplantation must be treated with supportive measures that include blood culture collection, antipyretics, and broad-spectrum antibiotic therapy according to the institutional protocol (grade of recommendation B; a level of evidence 2B). Grade III and IV cytokine release syndrome can be treated with corticosteroids or tocilizumab (grade of recommendation C; level of evidence 4)

- Non-myeloablative, reduced intensity, and myeloablative conditioning schemes can be used, however, there is a lack of randomized studies comparing the types of conditioning (grade of recommendation B; level of evidence 2C)

- Donor lymphocyte infusions (initial dose of 1 million CD3 + T cells/kg of recipient weight) can be used in relapses after haploidentical transplantation if the incompatible HLA haplotype is maintained. Cases that have lost expression of the incompatible HLA haplotype are candidates for a second haploidentical transplant from a relative who has HLA incompatibility with the original donor (grade of recommendation B; level of evidence 2C).

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