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REVIEW ARTICLE

# The European Society for Blood and Marrow Transplantation (EBMT) consensus recommendations for donor selection in haploidentical hematopoietic cell transplantation

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## Abstract

The number of HLA-haploidentical hematopoietic cell transplants continues to increase worldwide due to recent improvements in outcomes, allowing more patients with hematological malignancies and non-malignant disorders to benefit from this procedure and have a chance to cure their disease. Despite these encouraging results, questions remain as multiple donors are usually available for transplantation, and choosing the best HLA-haploidentical donor for transplantation remains a challenge. Several approaches to haploidentical transplantation have been developed over time and, based on the graft received, can be grouped as follows: T-cell depleted haploidentical transplants, either complete or partial, or with T-cell replete grafts, performed with post-transplant cyclophosphamide-based graft-versus-host disease (GVHD) prophylaxis, or G-CSF-primed bone marrow graft and enhanced GVHD prophylaxis. Carefully selecting the donor can help optimize transplant outcomes for recipients of haploidentical donor transplants. Variables usually considered in the donor selection include presence of donor-specific antibodies in the recipient, donor age, donor/recipient gender and ABO combinations, and immunogenic variables, such as natural killer cell alloreactivity or KIR haplotype. Here we provide a comprehensive review of available evidence for selecting haploidentical donors for transplantation, and summarize the recommendations from the European Society for Blood and Marrow Transplantation (EBMT) on donor selection for different transplant platforms.

## Introduction

HLA-haploidentical donors are now largely employed for allogeneic hematopoietic cell transplantation (AHCT) for those patients who lack of an HLA-matched donor or need an urgent allograft. The field of haploidentical hematopoietic cell transplantation (HHCT) has grown significantly over the past decade [1, 2]. According to the 2015 European Society for Blood and Marrow Transplant (EBMT) activity survey report, the use of haploidentical donors has dramatically surged by almost 300% since the year 2005 [2]. This significant growth is primarily the result of the successful development of several novel methods to overcome the alloreactivity generated by major donor–recipient human leukocyte antigen (HLA)-disparity, and improvements in prevention and treatment of post-transplant complications, such as primary graft failure, delayed immunologic recovery or graft-versus-host disease (GVHD). Several platforms have been developed over time using either a T-cell depleted (TCD) graft (complete or partial elimination of donor T lymphocytes) [3–6], or T-cell replete (TCR) graft and effective GVHD prevention [using post-transplantation cyclophosphamide (PTCy) or G-CSF-primed bone marrow graft and enhanced GVHD prophylaxis] [7, 8]. Following these advances, recent results from multiple studies have shown that HHCT can provide long-term survival benefit equivalent to that of HLA-matched donor transplantation [7, 9–19]. Haploidentical donors can be identified for nearly all patients who require a transplant [20]. Based on data from the Johns Hopkins, at least 1 HLA-haploidentical first-degree relative can be identified in more than 95% of patients, and the average number of haploidentical donors per patient is two or more. In addition, second degree related donors with a full haplotype match with the recipient, have been successfully used for transplantation [20]. Consequently, with more than one haploidentical donor usually available for transplantation, a

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crucial question is which donor can lead to the best transplant outcomes.

In this review, a panel of members of the European Society for Blood and Marrow Transplantation (EBMT) and affiliates provide a comprehensive analysis of available data regarding outcomes of haploidentical transplants based on different donor characteristics and summarize recommendations regarding selection of best HLA-haploidentical donors for different haploidentical transplant platforms.

## Haploidentical donor transplant platforms

To date, several methods have been developed and successfully used to control bi-directional alloreactivity from a major HLA-disparity between the donor and the recipient in HHCT, such as multiple approaches using ex vivo T-cell depletion [3–6, 21–23], either complete or partial, with or without T cell addback, as well as TCR (unmanipulated) haploidentical transplants with post-transplant high-dose cyclophosphamide [9, 24, 25], or G-CSF/anti-thymocyte globulin (ATG)-based GVHD prevention [7, 8, 15–17, 26–28].

### T cell depleted haploidentical transplantation

T-cell depletion has been used to minimize morbidity and mortality associated with GVHD. Unfortunately, the complete removal of T cells from the graft has been shown to be associated with an increased risk of graft failure, delay in immunologic reconstitution post-transplant, and, in most studies, disease relapse [3, 23, 29–32]. Consequently, several novel graft manipulation techniques have been developed to compensate for these limitations and improve immune reconstitution and graft-versus-tumor (GVT) effect, while limiting the development of GVHD.

#### Ex vivo T cell depleted haploidentical transplant with T cell addback

To facilitate engraftment and immune reconstitution T-cell addback has been used by several groups. Infusion of conventional T cells along with regulatory cells (Tregs) [4] or of donor T cells genetically modified with a suicide gene has been shown to partially compensate for the limitations associated with complete T-cell depletion [21, 33, 34]. Infusion of sufficient donor T cells may contribute to antiviral and anti-tumor responses, while GVHD was prevented by either Tregs [4] or photo-depletion of alloreactive T cells [6] or regulated by activation of a suicide gene included in engineered donor lymphocytes [35].

#### Selective alpha-beta T cells depletion

The αβ T-cell receptor-positive T cells has been recognized as the T cell subset mainly responsible for the occurrence of GVHD [36], while innate-like γδ T cells may provide an important contribution to control opportunistic infections and to exert an anti-tumor effect, without inducing GVHD. Therefore, selective depletion of αβ T-cell receptor-positive T cells, in combination with removal of CD19 + B cells from the graft for reducing the incidence of EBV-related post-transplant lymphoproliferative disorders (EBV-PTLD) was found to prevent GVHD. This method, primarily used in pediatric population, spares γδ T-cell receptor-positive T cells and natural killer (NK) cells, is providing anti-tumor immunity and may help facilitate immune reconstitution post-transplant [5, 37]. Bertaina and colleagues recently reported updated data in pediatric patients with acute leukemia and showed that αβ TCD HHCT was associated with a low incidence of acute and chronic GVHD, as well as better survival compared with unrelated donor transplants, in particular when the donor showed 1 or more HLA-disparity with the recipient [38].

### TCR (unmanipulated) haploidentical transplantation

To avoid complexity and cost associated with an ex vivo manipulation of T cells, several platforms of HHCT using TCR graft with intensified post-transplant immunosuppression have been developed with promising results. These are widely adopted as TCR HHCT platforms.

#### Post-transplantation cyclophosphamide

Since the initial reports suggesting that high-dose cyclophosphamide given after AHCT could induce immunologic tolerance and suppress GVHD without causing global immunosuppression or graft failure [7, 39–42], several groups have successfully translated this approach into clinical practice [43, 44]. The main mechanism by which PTCy can induce immune tolerance lays on the selective elimination of host and donor alloreactive T cells, while sparing hematopoietic progenitor cells and regulatory T cells. The use of PTCy overcomes the need for extensive host and donor T-cell depletion to achieve sustained engraftment and effectively control GVHD, respectively, in HLA-partially mismatched AHCT, and has become the most common method used for GVHD prophylaxis in TCR HHCT [7].

### GCSF-primed bone marrow and enhanced ATG-based GVHD prophylaxis

The group from Peking University first established HHCT based on G-CSF-primed bone marrow and peripheral blood graft and intensified, ATG-based GVHD prophylaxis with cyclosporine, mycophenolate mofetil, methotrexate and ATG [8, 15–17, 26–28]. Results obtained in both benign diseases and hematologic malignancies showed that the Beijing Protocol can provide comparable outcomes to those of HLA-identical sibling donor or unrelated donor transplantation [15–17, 26], suggesting a strong graft-versus-leukemia effect, while a higher incidence of chronic GVHD has been observed. Although primarily used in China, other centers in Asia and Europe have adopted this approach [45, 46].

All these HHCT platforms have been shown to be associated with very good outcomes and allow HHCT to be safely performed. However, differences in outcomes have been observed based on various donor types and careful selecting donors may further improve these outcomes. In addition, differences in the cost associated with different platforms and resource utilization remains the area unmet need and will need to be explored in the future.

## Donor characteristics influencing outcomes of haploidentical stem cell transplantation

### Donor-specific anti-HLA antibodies

Several studies have clearly confirmed the association of preformed donor-specific anti-HLA antibodies (DSAs) and the occurrence of primary graft failure in patients receiving AHCT, in particular in HLA-mismatched transplantation [47–50]. In HHCT, this issue can be more challenging especially in the child donor to mother recipient setting, since the recipient might be allosensitized and form antibodies against the non-shared donor's HLA antigens during pregnancy [48]. The incidence of DSAs in HHCT ranges between ~10–21%, being higher in females compared with male recipients [47–50]. A study from MD Anderson Cancer Center (MDACC) reported outcomes of 122 patients treated with both TCD and TCR HHCT, and showed a high incidence of DSAs (18%) and a strong association with primary graft failure. Moreover, the time to engraftment was significantly delayed in patients with DSAs [48]. Likewise, Yoshihara and colleagues revealed that a high level of DSAs (>5000 MFI) was the only significant risk factor for graft failure in recipients of unmanipulated HHCT [49]. Beside primary graft failure and delayed engraftment, the development of DSAs was also found to be associated with primary poor graft function [50], and has negative impact survival post-transplant, not only in HHCT but also in other alternative donor transplants [47–57]. The ability of DSAs to cause primary graft failure seems to depend on both antibody levels and activation of the complement system. The MDACC group demonstrated that DSAs that activate the complement system, detected by the c1q assay, associate with high antibody levels and a very high likelihood of developing graft rejection, underlining the importance of antibody detection prior to HHCT [48]. Considering these evidences, EBMT now recommends routine testing for DSAs before choosing haploidentical donors for transplantation. Using hematopoietic stem cells from a donor without the corresponding HLA antigens is an ideal option for a recipient with HLA antibodies. However, if there are no such donors available, recipients with DSAs should undergo desensitization treatment prior to transplantation to prevent graft failure. Current approaches have been detailed recently in the recent EBMT consensus guidelines for detection and treatment of patients with DSAs in HHCT [58].

### Donor age

Although donor age does not appear to be a limitation for the AHCT in HLA-matched transplants, transplantation using stem cells from a younger donor is strongly associated with a lower incidence of both acute and chronic GVHD, as well as with better survival [59–61]. The benefit of using a younger donor has been confirmed both in TCD and TCR HHCT. González-Vicent et al. showed an improved immune recovery, less acute GVHD, lower non-relapse mortality (NRM) and better disease-free survival (DFS) when using younger donors for pediatric patients with high-risk leukemia receiving CD3/CD19 and TCRαb+/CD19 TCD HHCT [62]. In TCR HHCT, donor age has also been shown to influence outcomes of transplantation. Using the Beijing protocol, Wang et al. [27] found that donors younger than 30 years were significantly associated with lower NRM and better survival compared with older donors. The impact of donor age seems to be more relevant in older than in younger HHCT recipients. The most recent report on acute leukemia patients receiving TCR HHCT conducted by the Acute Leukemia Working Party (ALWP) of the EBMT demonstrated an increased NRM, inferior leukemia-free survival (LFS), overall survival (OS) and GVHD-free, relapse-free survival (GRFS) when patients over the age of 40 were transplanted using stem cells from an older donor, whereas donor age did not predict transplant outcomes in recipients younger than 40 years [63]. Likewise, Ciurea et al. found that younger donor age (</=40 years) was an independent predictor for better OS in older patients (>/=55 years) with AML and MDS receiving HHCT using PTCy for GVHD prophylaxis [64].

Although results from two other retrospective studies of HHCT with PTCy platform did not show a significant

impact of donor age on transplant outcomes [65, 66], using a younger donor might provide additional benefits, including better CD34+ cell yield especially with a BM graft [67] and lower likelihood of clonal hematopoiesis, which can increase the risk of developing hematologic malignancies later in life in recipients of stem cells from older donors [68]. Moreover, younger donors are more likely to be physically fit and better tolerate the stem cell collection procedure and ensure that the procedure is perfectly safe for the donor.

### Donor gender

It has been hypothesized that minor histocompatibility antigens (mHAgs) encoded on Y chromosome (H-Y) can be recognized by female donor T lymphocytes and may be responsible to an increased risk of GVHD and NRM in a setting of female donor to male recipient transplantation. However, this risk can be counterbalanced by the benefit of increasing graft-versus-tumor effect and a lower risk of relapse, since H-Y antigen can also be expressed on tumor cells. This is particularly important in HLA-matched transplantation when minor HLAs are the main target of donor alloreactive T cells [69–71]. However, an adverse impact of using a female donor to a male recipient seems to be more pronounced in HLA-haplotype matched transplants. Kasamon et al. found that transplantation using a female donor to a male recipient resulted in lower survival after TCR HHCT using PTCy for GVHD prophylaxis. Although the negative impact on survival was not entirely accounted for by a significantly increased risk of GVHD, this finding still suggests that a male donor should be a preferred choice when selecting haploidentical donor for a male recipient, at least in a HHCT with PTCy platform [44].

The effect of donor gender on HHCT outcomes has also been explored outside the female to male transplant setting. Using the Beijing protocol of unmanipulated HHCT, Wang et al. showed that transplantation using a female donor was associated with a higher rate of severe acute GVHD, NRM and inferior survival. However, this negative impact was lost when mother donors were excluded from the analysis [27]. Mothers seem to be a poor donor choice for child recipients when using the Beijing protocol of HHCT as it was shown to be associated with higher rate of GVHD, NRM, and poor survival. In contrast, Stern et al. found that relapse rate and NRM were lower, resulting into better EFS in acute leukemia young patients who received TCD HHCT from a mother than from a father donor. The protective effect from using a mother donor was seen in both female and male recipients, while in a control cohort of patients who received transplants from haploidentical siblings, donor sex had no influence on outcome [72]. These apparently conflicting results suggest that perhaps donor relationship (mother donor) rather than donor gender has a stronger influence on transplant outcomes.

### Donor relationship and non-inherited maternal and paternal antigens (NIMA/NIPA)

The effects of donor relationship on HHCT outcomes have been investigated in several studies [27, 65, 66, 73]. Focusing on TCR HHCT with PTCy, Solomon et al. [65] found that a parent donor (either maternal or paternal) resulted into a significantly higher risk of relapse and lower survival compared with a sibling or child donor, and the impact of donor relationship on outcomes persisted after adjusting for donor age. Moreover, a recent study by McCurdy and colleagues revealed a significantly higher risk of graft failure in patients who received haploidentical grafts from their parent, while graft failure risk was not different between sibling and offspring donors [66]. Taken together, these data suggest that an offspring or sibling donor is preferred over a parent donor for HHCT. However, conflicting results were seen when comparing outcomes with different parental donors.

It has been speculated that the benefit of mother-to-child transplantation may be the result of the maternal immune system exposure to paternal antigens from fetus during pregnancy, which can enhance graft-versus-tumor effect in a mother graft [69]. Moreover, child exposure to maternal antigens during in utero development or nursing can lead to a lifelong immunologic tolerance, preventing alloimmunization against maternal HLA antigens that the patient did not inherit such as in a setting of mother to child or non-inherited maternal antigens (NIMA) mismatched sibling donor transplants [74, 75]. This evidence was first observed in kidney transplants; indeed kidney graft from haploidentical sibling mismatched for NIMA had similar graft survival with graft from an HLA-identical sibling donor [76]. In TCR HHCT, some studies have shown a lower risk of GVHD and TRM in patients receiving stem cell graft from a NIMA mismatched sibling donor than from a non-inherited paternal antigens (NIPA) mismatched sibling [27, 73, 77, 78]. The Chinese group found that NIMA mismatched sibling donor was associated with less acute GVHD when compared with NIPA mismatched sibling. Althogh NRM and survival were not influenced by NIMA/NIPA mismatching, NIMA mismatched siblings may be preferred over NIPA mismatched ones when using the Beijing protocol, at least to avoid the higher risk of acute GVHD [27]. However, whether this immunologic tolerance is associated with better outcomes in TCD and TCR HHCT using PTCy remains unclear.

Another aspect is the use of one-haplotype match second-degree related donors, especially younger donors, if

no first degree related donor exists or the donor is too old or too young for donation. The Hopkins group has recently showed feasibility of using second-degree related donors with their non-myeloablative PTCy-based protocol [79]. Correspondingly, the Chinese group reported comparable survival outcome among recipients of a collateral and immediate haploidentical family donor using their transplant platform [80].

### ABO compatibility

The impact of donor–recipient ABO compatibility on transplant outcomes has been evaluated in different transplant settings, and has shown different results [81–84]. In HLA matched related donor transplants, results from a meta-analysis revealed that ABO mismatched transplantation did not impact overall survival. However, minor and bi-directional ABO mismatched graft was associated with poor overall survival in patients receiving unrelated AHCT [81]. Additionally, the impact of ABO mismatch on transplant outcomes appears to be different in some studies, when using peripheral blood or bone marrow stem cell source. Logan et al., using data from Stanford University and the Center for International Blood and Marrow Transplant Research (CIBMTR), showed that ABO minor mismatched transplantation was associated with higher NRM and negatively affected survival only in patients receiving bone marrow but not peripheral blood stem cell grafts [85].

In HHCT setting, a large retrospective study from the ALWP of the EBMT demonstrated inferior engraftment rate in HHCT recipients who received a major ABO mismatch graft compared with ABO matched HHCT, whereas bi-directional ABO mismatching was found to be associated with a significantly increased risk of grade II–IV acute GVHD. Patients with major ABO mismatched grafts had decreased OS only when bone marrow-derived stem cell grafts were used, while ABO compatibility had no impact in patients who received peripheral blood grafts [86], in agreement with findings from the above-mentioned study by Logan et al. [85]. These results suggest that, at least in TCR HHCT with PTCy, patients with major ABO mismatched grafts should receive PB stem cells.

In addition to an adverse effect on survival, major ABO mismatch can also lead to hemolytic anemia, delayed red cell engraftment as well as pure red cell aplasia. Therefore a major ABO mismatched graft requires graft manipulation to decrease the amount of incompatible RBCs and to prevent hemolytic complications. This process could reduce the number of mononuclear cells, CD34+ and total nucleated cells in a bone marrow graft and perhaps negatively affect transplant outcomes [87].

In summary, the available evidence supports the use of an ABO compatible over a minor and/or a major ABO mismatched graft for TCR haploidentical donor transplants with PTCy. A peripheral blood graft is preferred in case of transplant from a major ABO incompatible donor when other donors are not available.

### NK cell alloreactivity

NK cells are an important component of human innate immunity, recover early post-transplant and provide antitumor and antiviral effects during the period of severe lymphopenia. NK cell alloreactivity can potentially provide better antitumor effect, as documented by lower relapse rates and better survival in patients with higher NK cell numbers early post-transplant [88, 89]. Cytotoxic activity of NK cells is mediated primarily by a balance between inhibitory and activating receptors expressed on the cell surface, the former being mainly accounted by killer-cell immunoglobulin-like receptors (KIRs) that recognize HLA class I molecules on surface of target cells. However, understanding of the biological determinants of anti-tumor effects of NK cells remains incomplete and conflicting evidence exists in the transplantation literature. Several models of donor–recipient NK cell alloreactivity have been proposed and studied in different settings of AHCT especially in HHCT, which may explain, at least in part, different results. The KIR ligand incompatibility (ligand–ligand) model, in which NK cells will react and kill host cells that lack the HLA class I ligand(s) for inhibitory KIR, was first proposed by the Perugia group [90]. Using this model in a clinical study of TCD HHCT, Ruggeri et al. [91] found that alloreactive NK cells in the graft-versus-host direction helped promote engraftment and graft-versus-tumor effect, resulted in reduced risk of leukemia relapse and better survival in adults with acute myeloid leukemia (AML) without increasing the rate of GVHD. Leung et al. proposed an alternative model called the receptor-ligand or missing-self model, according to which NK cells will react if at least one KIR gene expressed in the donor's NK cell repertoire does not recognize any of the HLA molecules in the recipient's ligand repertoire. In a study of pediatric patients with high-risk leukemia given CD34+ selected haploidentical graft, the authors found that NK alloreactivity based on this model more accurately predicted the lower risk of leukemia relapse than the ligand–ligand model [92].

KIR genes are organized in haplotypes and, although more than 80 different KIR haplotypes have been reported, two distinct groups (termed A and B) have been identified. The A haplotypes (found in around 20–25% of subjects) are characterized by a fixed number of KIR genes including several inhibitory KIR (KIR3DL3, KIR2DL3, KIR2DL1, KIR2DL4, KIR3DL1, and KIR3DL2), only one activating KIR (KIR2DS4), and the two pseudogenes (KIR2DP1 and KIR3DP1). In contrast, B haplotypes have variable and greater gene content, and are characterized by the presence

of at least one of the following genes: KIR2DS2, KIR2DL2, KIR2DL5B, KIR3DS1, KIR2DL5A, KIR2DS3, KIR2DS5, and KIR2DS1. All individuals can be categorized as having 1 of 2 KIR genotypes: homozygous group A KIR haplotype (A/A) or having at least one group B haplotype (B/x). Michealis et al. [93] demonstrated a significantly reduced incidence of relapse in recipients of TCD HHCT receiving stem cell graft from a KIR haplotype Bx donor when compared with haplotype AA donor. A similar result was reported in a study of TCD HHCT for pediatric patients with ALL, confirming the survival benefit of using donor with KIR B haplotype [94, 95]. Mancusi and colleagues also showed a reduction of NRM in patients transplanted using a KIR B haplotype donor in comparison to those given a KIR A haplotype donor HHCT [92]. All above-mentioned studies showing the benefit of NK alloreactivity using different models and of KIR B haplotype donors were conducted in TCD HHCT platforms, where donor T cells do not obscure the importance of the role played by NK cells, whereas the benefit of donor–recipient NK alloreactivity in TCR HHCT setting remains unclear since conflicting results have been recently reported. Solomon and colleagues showed that KIR mismatch using receptor-ligand model and group B KIR haplotype with the presence of *KIR2DS2* were associated with reduced relapse rate and improvements in survival post-transplant [65]. Likewise, another recent study by Wanquet et al. revealed that the presence of donor-recipient KIR-ligand mismatch was associated with a lower incidence of relapse, which led to a significantly improved progression-free survival (PFS) and a trend for improved OS, while rate of acute and chronic GVHD did not significantly increase. However, this benefit was seen only in a subgroup of patients with active disease, but not in patients who were in remission at time of transplant [96]. Also, Symons et al. showed that recipients of inhibitory KIR gene-mismatched grafts had an improved OS, EFS and relapse rate in TCR HHCT with PTCy. Moreover, the authors also found that patients homozygous for the KIR A haplotype had an improved OS, EFS, and NRM if their donor expressed at least one KIR B haplotype [97]. Collectively, results from these studies revealed beneficial effects of NK cell alloreactivity, suggesting that selection of donors based upon NK cell alloreactivity may be warranted. On the contrary, a study by the EBMT group demonstrated that KIR ligand mismatching described by "the ligand-ligand" model was associated with a trend for higher relapse and significantly lower OS in recipients of TCR HHCT [98]. In accordance with these findings, Huang et al. [99] demonstrated that use of donors with KIR match rather than mismatch was associated with an improved NK-cell reconstitution quantitatively and functionally, resulting in a lower incidence of GVHD, relapse rate and a better survival in the setting of HHCT using the Beijing protocol. In addition, the Japanese group reported a similar relapse rate, NRM and OS between TCR HHCT patients receiving graft from either a KIR haplotype A/A or B/x donor, while using a donor with KIR haplotype B/x was associated with a higher incidence of severe acute GVHD [100]. The reasons for these conflicting results perhaps come from the heterogeneity in transplant protocols employed and differences in inclusion criteria, as well as model used to describe NK cell alloreactivity.

However, taken together, a donor with alloreactive NK cells appears to be a preferred choice for patients receiving TCD HHCT, while more studies are needed to clarify this issue in TCR HHCT, especially when PTCy-based GVHD prophylaxis is employed. Recent work by Russo et al. [88] suggests that the majority of mature NK cells infused with unmanipulated grafts are lost upon PTCy administration likely resulting in the blunting NK cell alloreactivity in this setting.

### Donor–recipient CMV serostatus

CMV infection/reactivation is a common complication after AHCT, which sometimes can be fatal and may negatively influence post-transplant outcomes [101]. Although the incidence of symptomatic CMV diseases has decreased significantly because of preemptive therapy [102–104], this infectious complication still develops in a significant proportion of all AHCT recipients, and it is influenced partly by the mismatch between donor and recipient CMV serostatus [105]. This issue may be more concerning in HHCT as more patients reactivate CMV in the setting of an HLA-disparate donor transplant, and more potent immunosuppression is needed to overcome the HLA barrier. Interestingly, the use of a CMV positive donor in AHCT has been shown to prevent CMV reactivation and improve outcome when administered to a CMV positive recipient [101, 106]. This donor–recipient combination may be particularly important when used in the context of transplant strategies to eliminate T cells as encountered in TCD HHCT. Indeed, the immediate availability of T cells with anti-CMV reactivity may be useful to overcome CMV viral load early post-transplant when T cells are only present in low numbers.

However, conflicting results on the impact of donor–recipient CMV serostatus match on TCR HHCT outcomes have been reported to date. In a recent study, Solomon et al. [65] found that donor CMV-negative serostatus was associated with inferior survival, while a protective effect of a CMV-seropositive donor was limited to CMV-seropositive recipients. On the contrary, two retrospective studies failed to demonstrate any significant clinical impact of donor CMV serostatus after TCR HHCT [66, 107]. Moreover, a report restricted to 983 CMV seropositive recipients of TCR

HHCT with PTCy from the EBMT group revealed that donor CMV serostatus did not influence NRM or OS [108]. Due to these conflicting results, it is difficult to conclude and make recommendations on TCR haploidentical donor selection based on donor–recipient CMV serostatus.

### Degree of HLA-mismatch

Higher degree of HLA-mismatch between donor and recipient has been associated with a significantly increased TRM and poor survival after AHCT from both related and unrelated donors using conventional GVHD prophylaxis [109–111]. However, the adverse effect of donor–recipient HLA disparity appears to be reduced with the new approaches used for GVHD prophylaxis in HHCT. Kasamon and colleagues found that, in TCR HHCT using non-myeloablative conditioning with PTCy for GVHD prophylaxis, the presence of a greater number of HLA mismatches at either the antigen or allele level did not worsen overall outcomes with regards to GVHD, relapse and NRM. Besides that, having three or more HLA-mismatches in the host-versus-graft (HVG) direction was associated with superior EFS [44]. These results suggest that greater HLA mismatch between the donor and the recipient is not associated with worse outcomes in HHCT. Similar findings were also reported in other studies of TCR HHCT using both PTCy and with the Beijing protocol. In these studies, the total number of HLA mismatches either bidirectional or in the GVH/HVG direction did not influence transplant outcomes [27, 65, 112–114]. Regarding the specific HLA allele and antigen mismatch, the most recent data from the EBMT demonstrated that an antigenic but not allelic mismatch at the HLA-DRB1 locus was an independent risk factor for severe acute GVHD in PTCy, but not in ATG regimens, suggesting that the role of HLA matching in HHCT might be modulated by GVHD prophylaxis [113]. Other studies found that the presence of an HLA-DRB1 mismatch in the graft-versus-host direction and HLA-DPB1 non-permissive mismatch were associated with an improvement in survival [65].

Taken together, these data do not support selection of haploidentical donors based on the degree of HLA mismatch. More data are needed to clarify the impact of specific HLA antigens/alleles on outcomes of HHCT as conflicting results have been reported to date.

## Special considerations regarding using minors as donors for haploidentical transplantation—Psychological aspects and potential conflict of interest

It is clear that the increasing use of haploidentical donors will have to be accompanied by a strengthening of the psychological evaluation and will necessitate an increased training of caregiver teams. With the shift from unrelated to family donors, family dynamics and dormant tensions may be reactivated. Indeed, the transplant is very often experienced by the patient as an upheaval, not just in his or her own body, but also in relation to others, especially the nuclear family. From the donor's point of view, giving is a gift of self and an investment, especially in time but also symbolically. The challenge of choosing between several potential haploidentical related donors—mother, father, brother, sister or cousin, niece, nephew—will open up particularly complex elaborations and exchanges: teams will have to explain their choice and justify them. It will be important for the transplant team to establish a personal relationship with the donor and carefully/cautiously manage the psychological repercussions of complications occurring either during or after the transplant, especially in case of failure. Children who die of complications of a transplant of stem cells from their mother or a father, or patients who must live with chronic GVHD after a transplant of their child's cells might become common but new situations and inevitably, Oedipal updates will insistently color the dynamics of this type of transplant.

One of the major aspects regarding a minor donor for parents or siblings as recipients is the potential conflict of interest related to such donation. In this circumstance, several ethical challenging questions arise such as "are parents capable to make fair decisions regarding the donation in the best interests of their donor child, and not determined by interests of themselves or other family members?" or "should mature and immature children be treated differently regarding consent or assent to donate?" While regulations regarding minor donors differ between countries and regions, it is fundamental that practice recommendations and standards focusing on medical and psychological assessments and follow-up care for the donors are established by multi-disciplinary teams to ensure that donor's best interests in case of children are fully considered and acted upon. According to the FACT-JACIE international standards, a donor advocate different from the transplant recipient's primary treating physician should be available to represent allogeneic donors who are minors or who are mentally incapacitated, to help the donor understand the risks and benefits of donation, ensure that the consent is made without time pressure and with full information, and to aid in the resolution of subsequent problems both physically and psychologically [115]. In cases of using children as donors, in addition to evaluation by a Pediatrician, a medical ethicist should probably be involved to provide an unbiased assessment and help facilitation the donation.

**Table 1** Summary of characteristics considered in selecting donors for haploidentical hematopoietic cell transplantation

| T cell depleted haploidentical transplants | T cell replete haploidentical transplants |
|---|---|
| -No DSAs (MFI < 1000) | -No DSAs (MFI < 1000) |
| -NK cell alloreactive donor | -Younger donor over older donor |
| -Younger donor over older donor | -Male donor for a male recipient |
| -Male donor for a male recipient | -Sibling or offspring donor over parent donor |
| -First degree relative over second degree HLA half-matched donor | -Between parent donors, father is preferred over mother donor |
| -Between parent donors, mother is preferred over father | -ABO matched is preferred to minor ABO mismatch to major ABO mismatched donor |
| -ABO matched donor | -Donor with KIR ligand match for a recipient of HHCT[a] |
| -CMV seropositive donor for CMV seropositive recipients | -First degree relative over second degree HLA half-matched donor[a] |
| | -Donor with NIMA mismatch over NIPA mismatch for a recipient of HHCT[a] |

*DSA* donor-specific anti-HLA antibodies, *NK* natural killer cells, *HHCT* haploidentical hematopoietic cell transplantation, *NIMA* non-inherited maternal antigens, *ABO* blood group

[a]Conclusive data available for the TCR Haploidentical transplants with GCSF-primed bone marrow and enhanced GVHD prophylaxis (Beijing protocol)

## Conclusions and summary recommendations

It is now clear that HHCT can provide the chance of a cure for many patients who lack an HLA-matched donor, including especially ethnic minorities, with similar results to those reported using an HLA-matched donor. This development has become one of the most important success stories in transplantation and probably in modern medicine. Among several factors responsible for the success of HHCT, donor considerations are particularly important when more than one potential HLA-haploidentical donor might be available for transplantation, and multiple donor factors can impact transplant outcomes. Therefore, the EBMT has formed an expert panel charged to summarize the recommendations for selection of a haploidentical donors based on available published data for all HHCT platforms used in clinical practice (Table 1). Although it is likely that this field will further evolve in the future, enough work has been done to date to provide a comprehensive overview of this topic right now. Below we have summarized our recommendations in a still preliminary order of importance.

## Summary of preferred donor characteristics for T-cell depleted haploidentical transplants

1. For a recipient with DSAs, a donor without corresponding HLA antigen is preferred
2. NK cell alloreactive donor if available
3. Younger donor over older donor
4. A male donor for a male recipient
5. First degree relative over second degree HLA half-matched donor
6. Between parent donors, mother is preferred over father
7. ABO matched donor
8. CMV seropositive donor for CMV seropositive recipients

## Summary of preferred donor characteristics for T cell replete haploidentical transplants

1. For a recipient with DSAs, a donor without corresponding HLA antigen is preferred
2. Younger donor over older donor
3. A male donor for a male recipient
4. Sibling or offspring donor over parent donor
5. Between parent donors, father is preferred over mother donor
6. ABO matched to minor ABO mismatch to major ABO mismatched donor
7. First degree relative over second degree HLA half-matched donor (Beijing protocol)
8. Donor with KIR ligand match for a recipient of HHCT (Beijing protocol)
9. Donor with NIMA mismatch over NIPA mismatch for a recipient of HHCT (Beijing protocol)

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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