Selecting the best haploidentical donor

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ABSTRACT

The substantial evidence of the safety of human leukocyte antigen (HLA)-haploidentical (haplo) blood or marrow transplantation (BMT) with modern transplant approaches, such as post-transplantation cyclophosphamide (PTCy), has led to its increasing utilization. When prioritizing HLA-matched grafts, patients frequently have few or no donors from whom to choose. However, a given patient may have multiple suitable haplo donors. Therefore factors other than HLA-match become critical for selecting the best donor. We recommend a donor selection algorithm based on the donor-specific antibodies, ABO match, donor age, donor sex, and cytomegalovirus (CMV) serostatus match. Despite provocative initial evidence, further studies are warranted to determine whether there is any benefit to selecting a haplo donor based on the number of HLA-mismatches, natural killer cell alloreactivity, or the presence of non-inherited maternal HLA antigens.

1. Introduction

The improved safety of HLA-haploidentical (haplo) blood or marrow transplantation (BMT) with modern transplant approaches, such as post-transplantation cyclophosphamide (PTCy), has led to the increasing utilization of haplo donors. For a given patient, multiple haplo donors (parents, siblings, children, aunts, uncles, nieces, nephews, cousins, and grandchildren) are often available. Therefore, factors other than HLA-match become prominent in donor selection. The most important factor when selecting a haplo donor is to ensure that he or she is medically, socially, and psychologically capable of donating. This not only minimizes the donor’s risk, but also reduces the likelihood that they become unavailable for donation after the recipient has started transplantation conditioning. Further, should the recipient relapse, a fit donor is more likely to be available to donate lymphocytes. Here we review the data for relevant donor–recipient factors and summarize our selection algorithm for the preferred haplo donor.

2. Degree of HLA-mismatch

Historically, the degree of HLA-mismatching has been associated with the incidence of graft-versus-host disease (GVHD) and non-relapse mortality (NRM) after alloBMT [1–3]. However, modern transplant techniques, such as haplo BMT with high-dose PTCy on days +3 and +4, have reduced the incidence of acute GVHD [4–8] to levels consistent with, and chronic GVHD [4,5,7–10] to levels below that of HLA-matched transplantation with standard immunosuppression incorporating a calcineurin inhibitor [11]. Concomitantly, NRM after haplo BMT with PTCy declined to a level comparable to HLA-matched transplantation [4,6,8,12,13].

Despite the substantial recent evidence supporting the similar survival after haplo and HLA-matched BMT, there are less data comparing outcomes within haplo BMT by the degree of HLA-mismatch. Using the Hopkins PTCy approach, Kasamon et al found that greater HLA disparity between donor and recipient was not associated with higher incidence of acute GVHD or worse survival. Interestingly, compared with fewer mismatches, there was a significantly decreased risk of relapse and improved event-free survival (EFS) with three or four mismatches in the host-versus-graft (HVG) direction but not the graft-versus-host (GVH) direction. Neither number of HVG nor GVH mismatches were associated with increased GVHD risk in this study. While GVHD occurrence has been associated with reduced relapse in numerous studies, the association of HVG mismatches with relapse reduction is unclear and it is possible that these findings were due to chance. Regardless, EFS and relapse with higher number of donor–recipient mismatches was, if not improved, at a minimum comparable to that with fewer mismatches. Confirming these results in an alternative platform, Wang et al also found no association of degree of HLA disparity with NRM, GVHD, or overall survival (OS) after a haplo BMT platform that incorporates anti-thymocyte globulin into their GVHD prophylaxis [14]. Despite the provocative results from the Hopkins group suggesting a potential beneficial effect from higher mismatch number, at the
present time the data do not support donor selection based on the degree of HLA-disparity.

3. Donor-specific antibodies

HLA-mismatch was also historically associated with graft failure, with rates of 12% and 2% after HLA-mismatched and HLA-matched related donor (MRD) allografting, respectively [15]. That same study showed that the presence of anti-donor lympho-cytotoxic antibodies on crossmatch was associated with a 39% graft failure rate compared with 10% in patients with a negative crossmatch. In haplo BMT with PTCy, Ciurea et al found that graft failure occurred in 75% of recipients with donor-specific antibodies (DSA) compared with 5% of recipients without DSA \((P = .008)\) and that antibodies to HLA-DRB1 were most frequent [16]. Also in haplo BMT with PTCy, Gladstone et al found that HLA-directed DSA occurred in 14.5% of all patients and 42% of women undergoing haplo transplant evaluation [17]. Women most frequently had antibodies directed against their children. DSA can be quantified by the solid phase immunooassay (SPI) using fluorescent beads coated with single phenotype and single HLA antigens. SPI results can be correlated with cross-matching by flow cytometry or complement-dependent cytotoxicity assays and can be used as a “virtual crossmatch” [18]. In subsequent analyses from Ciurea and colleagues, the overall incidence of DSA in haplo BMT assessments was 18%, 86% of whom were women [19]. Thirty-two percent of patients with DSA rejected their grafts. Median DSA mean fluorescence intensity (MFI) was 10,055 for patients who rejected versus 2,065 for those who engrafted. In their study, graft failure was associated with a complement assay that detects C1q binding DSA, with only one C1q-negative patient (who had a MFI of 6,265) failing to engraft. Patients with C1q binding DSA also had a higher median MFI of 15,279 versus 2,471 for C1q-negative patients. All male patients were C1q-negative and their median MFI levels were much lower. Pregnancy was associated with a much higher risk of developing DSA than transfusion of blood products.

In patients without alternative available donors, Gladstone et al found that plasmapheresis combined with anti-cytomegalovirus (CMV) intravenous immunoglobulin, tacrolimus, and mycophenolate mofetil (MMF) starting 1–2 weeks prior to conditioning, depending on the level of DSA, was associated a 64.4% mean reduction in DSA levels [17,19]. Fifteen patients received this treatment and the 14 patients who achieved DSA reduction to negative or weak levels underwent transplantation and engrafted. Ciurea et al proposed an alternative desensitization method of plasma exchange, rituximab, and intravenous immunoglobulin, which they found to be only partially effective [19]. However, combining the above regimen with the infusion of donor HLA antigens via auffy coat 24 hours prior to stem cell transplant was highly effective. They also reported that clearing of DSA may be unnecessary, with reduction to non-complement binding levels sufficient to achieve engraftment.

4. ABO compatibility

ABO compatibility may also affect outcomes after BMT. Major ABO mismatches lead to anti-donor isoagglutinins, which are associated with delayed RBC engraftment, pure red cell aplasia, and hemolytic anemia in the HLA-matched setting [21,22]. Minor ABO mismatches lead to anti-host isoagglutinins and are associated with acute hemolysis from donor plasma and delayed hemolytic reactions via passenger lymphocytes [18,19]. Kanda et al found that major ABO mismatches were not associated with survival after HLA-matched transplant. Minor and bidirectional mismatches were associated with non-significant differences in survival \((P = .10)\) [23]. However, to prevent acute hemolytic reactions from major ABO mismatches, the graft must be depleted of red blood cells through differential centrifugation [24]. This process reduces the mononuclear content of the graft as well as the CD34+ and total nucleated cell (TNC) dose administered [25]. While the ABO mismatches themselves may not be associated with survival, several studies have associated higher graft cell dose with improved leukemia-free survival and engraftment, concluding that the targeted cell dose should be between 3 x 108 and 4 x 108 TNCs/kg for HLA-matched transplantation [26]. Given the heightened risk of graft failure, many transplant centers have extrapolated the results in HLA-matched BMT and recommend a target cell dose of 4 x 108 TNCs/kg for haplo BMT. However, Zhang et al showed that there was no association with graft cell dose and engraftment in a haplo BMT protocol that combined administration of granulocyte colony-stimulating factor peripheral blood and bone marrow stem cells [27]. Furthermore, there was no association with ABO major or minor mismatch on neutrophil or platelet engraftment. Despite the absence of data in haplo BMT, engraftment in haplo BMT platforms is likely impacted by graft cell dose. Therefore avoidance of major ABO mismatches with their risks of pure red cell aplasia, delayed red blood cell engraftment, and requirement for differential centrifugation has merit.

5. Cytomegalovirus serostatus matching

Recipient and donor CMV serology mismatching has been associated with CMV disease in many studies of HLA-matched transplantation. In one analysis, CMV disease was evident in 0% of recipient-seronegative/donor-seronegative allografts, 9% of recipient-seropositive/donor-seropositive allografts, 7% of recipient-seronegative/donor-seropositive allografts, and 57% of recipient-seropositive/donor-seronegative allografts [28]. CMV disease also increases the risk of non-viral opportunistic infections [29]. Furthermore, CMV serostatus matching has also been associated with improved OS, treatment-related mortality (TRM), and EFS in CMV-seropositive recipients treated with HLA-matched unrelated donor (MUD) BMT [30]. While none of the above studies evaluated haplo BMT, data suggest that there is an increased rate of CMV reactivation after haplo compared with HLA-matched BMT [4,31]. Therefore, reducing the risk of CMV may be particularly important with haplo platforms.

6. Donor relationship

Since the early days of BMT, donor relationship has been speculated to affect outcomes by two major mechanisms. The first theorizes that children acquire tolerance of non-inherited maternal HLA antigens (NIMAs) during the in utero period. In support of this, Claas et al found that half of patients receiving blood transfusions had less alloreactivity against NIMAs, than against non-inherited paternal HLA antigens (NIPAs) [32]. Whether carrying a child tolerizes the mother to paternal antigens or primes her lymphocytes against them is a matter of debate and it is possible that either may occur depending on the pregnancy. The second mechanism is based on the discovery of decades-long persistence of microchimerism of the child’s cells in the mother’s peripheral blood [33,34] and the mother’s cells in the child’s peripheral blood [35,36]. Persistent microchimerism was hypothesized to persist, long after delivery with tolerance of the mother to paternal antigens (PA) inherited by the child and the child to NIMAs. These theories led to the early selection of haplo donors based on their relationship, with reports showing low rates of severe GVHD in
children receiving unmanipulated maternal grafts [37,38]. Several [39–41], but not all [14,42], studies have shown either improved survival or reduced GVHD with maternal grafts compared with haplo sibling or paternal grafts. Selection of sibling haplo donors based on NIMA, rather than NIPA, mismatches has also been associated with reduced GVHD [37,39,40] and improved survival [14] in some, but not all [41], studies.

7. Donor sex

In HLA-matched BMT increased risk of acute GVHD with female donors for male recipients has been demonstrated in multiple analyses [43–49]. However, this relationship has not been quite as clear-cut in haplo transplantation. In the several reports mentioned above [39–41], maternal donors were associated with reduced GVHD and improved survival. For example, in Stern et al, maternal donors were preferred for both sons and daughters [41]. In contrast, Wang et al found that maternal donors were associated with higher NRM for sons but not for daughters. They also found female donors older than 30 were associated with higher NRM and worse OS compared with paternal donors, especially when the recipient was a brother. The same mechanism proposed in HLA-matched transplantation (alloreactivity to male-specific histocompatibility antigen, H-Y) may predispose male recipients of female grafts to GVHD after haplo BMT. However, it is possible that this alloreactivity may be offset by the tolerizing effect of carrying a child. Furthermore, a male may have less GVHD after receiving a stem cell graft from a NIMA-mismatched sister as compared to a NIPA-mismatched brother, in which case the influence of Y antigens is outweighed by tolerization to unshared maternal antigens.

8. Donor age

In HLA-matched BMT, younger patient age has been associated with a reduction in risk of GVHD in many studies [43,44,47,49–52]. Younger donor age has also, but less frequently, been reported to reduce GVHD after HLA-matched BMT [47,50,53,54]. In one analysis of MUD BMT, donor age younger than 30 was associated with a 30% incidence of acute GVHD compared with 34% in patients with donors over 30 (P = .005) [53]. Improved survival was also seen with younger donors with age 18–30, 31–45, and > 45 being associated with 5-year OS rates of 33%, 29%, and 25%, respectively (P = .0002) [53]. A recent study of largely HLA-matched BMT suggested that donor age affected outcomes more than receiving related or unrelated donor grafts. Sibling donors over 50 were associated with a 3-year OS of 54% compared with 72% in unrelated donors younger than 50 (P < .0001). TRM and relapse occurred in 20% and 39% of transplants from donors >50, compared with 8% and 28%, respectively, after younger donor transplantation (P values = .03) [55]. In addition to possible GVHD and survival benefits, younger donors have been associated with higher graft cell doses, improved immune reconstitution [56], and increased ease of harvesting. Furthermore clonal hematopoietic disorders and donor-derived leukemia, while rare after BMT, are likely to be more frequent with older donors, presenting another benefit for the utilization of younger donors when available.

9. Natural killer cell alloreactivity

The natural killer (NK) cell killer immunoglobulin-like-receptor (KIR) gene complex is encoded on chromosome 19q13.4, which is the second most polymorphic gene locus in humans, next to HLA. KIRs with long cytoplasmic tails deliver signals that inhibit NK cell activation, whereas KIRs with short cytoplasmic tails deliver stimulatory signals. HLA class I molecules are the natural ligands for both inhibitory and stimulatory KIRs, and the outcome of NK cell interactions with a target cell depends upon the balance of inhibitory versus activating signals. However, since HLA and KIR molecules are inherited separately, a KIR may be inherited for which there is no corresponding HLA ligand. Cells expressing these KIRs cells are believed to become non-functional because of the absence of a class I–dependent maturation process termed licensing [57,58]. However, NK cell tolerance can be broken by inflammatory processes, such as transplantation or infection, and may lead to tumor directed killing [59–61]. There are four models to predict NK cell reactivity after BMT: (1) KIR ligand incompatibility (ligand–ligand) model; (2) the missing HLA ligand model; (3) the KIR receptor-HLA ligand model; and (4) the KIR gene–gene model.

Ruggeri and colleagues first developed the KIR ligand incompatibility model, which predicts that donor mature NK cells will react to recipient cells that lack the appropriate HLA ligand for an inhibitory KIR. This model predicts both graft-versus-leukemia (GVL) effects, but also decreased graft rejection and GVHD due to killing of host T cells and antigen-presenting cells, respectively. Ruggeri et al showed evidence of the GVL effect in T-cell–depleted haplo BMT where KIR ligand incompatibility was associated with a reduction in acute myeloid leukemia (AML) and pediatric acute lymphoblastic leukemia (ALL) relapse [62]. However, their data have not supported a reduction in graft failure or GVHD with the KIR ligand incompatibility model [63].

Work by Leung and colleagues led to the receptor–ligand model, which anticipates NK cell alloreactivity when the recipient lacks expression of an HLA ligand for a verified donor inhibitory KIR. In contrast to the KIR ligand incompatibility model, this model allows for alloreactivity to missing recipient ligands even when the donor does not express that ligand. This is largely due to belief that donor NK cells can be activated during the inflammation seen post-transplant. Leung et al demonstrated that this model of NK incompatibility was associated with reduced AML and pediatric ALL relapse in HLA-mismatched BMT and was a better predictor of outcomes than the KIR ligand incompatibility model [64]. The missing ligand model is a slight modification of the above, predicting NK alloreactivity when the recipient is missing one or more of the major classes of HLA ligands, but unlike the receptor–ligand model it does not require flow cytometry of donor cells to determine expression patterns.

Finally, the KIR gene–gene model characterizes the KIR genotype by A or B haplotypes. No KIR genes are unique to the A haplotype, therefore any expression of the B haplotype leads to greater KIR diversity. Using this last model Symons et al showed that recipients homozygous for A had improved OS, EFS, and NRM if they were transplanted from donors with at least one B haplotype. Furthermore, they found that any inhibitory KIR gene mismatch was associated with an improved OS, EFS, and reduced relapse compared with identical KIR gene content between recipient and donor [65]. Importantly, this study was conducted in T-cell–replete haplo transplant, whereas the majority of the other analyses of NK alloreactivity were in T-cell–depleted platforms in which graft T cells do not impair NK cell reconstitution. Subsequently, Micahelis et al and Oevermann et al found that in the T-cell–depleted haplo setting relapse was lower when donors with KIR B haplotypes were utilized [66,67].

10. Donor selection algorithm (in decreasing order of priority)

1. Donor must be medically and psychologically fit to donate
2. No anti-donor HLA antibody at a level of cytotoxic crossmatch
3. HLA-matched sibling over HLA-haploidentical donor
11. Conclusion

One of the benefits of haplo BMT is the frequent availability of multiple potential donors. This can make selecting the best haplo donor a complicated process (Fig. 1). When choosing from medically, socially, and psychologically fit donors, we recommend first avoiding donors to which the recipient has anti-donor HLA antibodies, particularly for levels compatible with a positive complement dependent cytotoxicity or flow cytometric crossmatch. If no other donors are available, desensitization techniques can be highly effective, such as the use of alternate-day, single-volume plasmapheresis, followed by intravenous immunoglobulin (100 mg/kg), tacrolimus (1 mg intravenously per day), and MMF (1,000 mg twice daily) starting 1–2 weeks before BMT conditioning initiation. Next we advise first-degree relative haplo donors over second-degree relative haplo donors. Then, we suggest avoiding major ABO incompatibility because of the risks of depleting the graft cell count, delayed red cell engraftment, and red cell aplasia. Younger donors, ideally younger than 45 years old, are preferred in order to reduce the chance of donor derived malignancy, lower graft cell dose, and potentially to reduce GVHD and improve survival. We advise male donors for male recipients, followed by nonparous females, then parous female donors. Lastly, we advocate CMV matching, with CMV-seronegative recipients receiving CMV-seronegative donors, and CMV-seropositive recipients receiving CMV-seropositive donors. The most critical of these is to ensure that a CMV-seropositive recipient receives a seropositive donor graft, which will dramatically reduce the chance of CMV disease and may have benefits in terms of survival. Given the preliminary and, at times, conflicting data of NIMA and KIR alloseactivity and degree of HLA-disparity, more studies are needed to clarify their influence and we do not routinely include these in donor selection algorithms at present. It should be emphasized that only the first two criteria in the donor selection algorithm are absolute exclusions for selection, and the order of the remainder may vary by physician or patient preference, or by unique circumstances.

Conflicts of interest

The authors declare that they have no conflicts of interest or competing financial or personal relationships that could inappropriately influence the content of this article.

References


