Hematopoietic Stem Cell Transplantation Donor Sources in the 21st Century: Choosing the ideal donor when a perfect match doesn’t exist

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Abstract

Most patients who require allogeneic stem cell transplantation do not have a matched sibling donor, and many patients do not have a matched unrelated donor. In an effort to increase the applicability of transplantation, alternative donors such as mismatched adult unrelated donors, haploidentical related donors, and umbilical cord blood stem cell products are frequently used when a well matched donor is unavailable. We do not yet have the benefit of randomized trials comparing alternative donor stem cell sources to inform the choice of donor; however, data exist to allow some inferences based on existing observational and phase II studies. All three alternative donor sources can provide effective lymphohematopoietic reconstitution, but time to engraftment, graft failure rate, graft versus host disease, transplant-related mortality, and relapse risk vary by donor source. These factors all contribute to survival outcomes and an understanding of them should help guide clinicians when choosing amongst alternative donor sources when a matched related or matched unrelated donor is not available.
Introduction

The ability to perform hematopoietic stem cell transplantation (HSCT) hinges on the availability of a suitable donor. The best donor for HSCT is an HLA matched sibling or unrelated donor. Unfortunately, based on average family size, less than 30% of patients will have a matched sibling donor.¹ As ethnic diversity increases in Europe and North America, it is imperative to have a strategy to identify an alternative stem cell source when an adult matched unrelated donor cannot be identified. At present there are three alternative donor options: a partially HLA mismatched unrelated donor (MMURD), a haploidentical related donor, and an umbilical cord blood (UCB) stem cell product.

The heterogeneity of subjects in observational studies in the literature does not lend itself to direct comparisons of alternative donor sources. Until such studies as the Blood and Marrow Transplantation Clinical Trials Network randomized comparison of UCB and haploidentical transplantation (BMT-CTN 1101, NCT01597778) are complete, physicians are left to cautiously interpret the existing data in making these important decisions. There are patient-related, disease-related, and transplant protocol-related factors that together uniquely affect the clinical outcomes of an individual patient. Here we summarize the existing body of evidence in an effort to guide clinicians in utilizing the current literature in making a decision on donor source for an individual patient when a matched related donor (MRD) or matched unrelated donor (MUD) are unavailable.

Defining Stem Cell Sources

**MMURD Transplantation:** In this analysis MMURD refers to an adult unrelated donor mismatched in at least one antigen or allele at HLA-A, B, C, or DR. Mismatched related donor transplants are not included in this analysis. Older studies evaluated HLA compatibility on the
basis of *antigen* matching, that is, by the use of anti-HLA antibodies or by low resolution molecular typing. HLA typing precision improved to high resolution molecular typing of the HLA locus, termed HLA *allele* matching, which became available over the last 2 decades. It is clear that allele level typing gives more reliable results than antigen level typing, so earlier observational studies using antigen level testing need to be interpreted cautiously. There is growing evidence that not all HLA mismatches are created equal. Permissive HLA mismatches seem to confer similar transplant-related outcomes when compared with matched donor sources, presumably reflecting both the inability of the T cell to recognize an intrinsic HLA sequence difference,\(^2\) as well as the tendency of the mismatched HLA molecules to present similar minor histocompatibility proteins to the immune system. A non-permissive HLA allele mismatch combination leads to poorer outcomes.\(^2\)\(^-\)\(^6\) Mismatched unrelated donor transplants increase donor availability but take time to organize due to donor screening and graft retrieval.

**Haploidentical Transplantation:** In this review, haploidentical refers to a complete half mismatch (generally 3 out of 6 or 4 out of 8) from a related donor. These transplants have the advantage of speed since relatives are usually easy to contact for stem cell collection. The cost of collection is generally lower than in MMURD and UCB products. The major disadvantage of haploidentical donors is the HLA disparity. In T cell depleted haploidentical grafts, selection of a maternal over a paternal donor has been shown to result in better survival, as the maternal immune system is tolerized to fetal antigens during pregnancy.\(^7\) The benefit of maternal versus paternal donor is not as clear in T cell replete grafts.\(^8\) The use of a haploidentical sibling with non-inherited maternal antigens has been associated with lower transplant-related mortality and better GVHD outcomes when compared with haploidentical sibling donors with non-inherited paternal antigens.\(^8\)
UCB Transplantation: Umbilical cord blood stem cell products are cryopreserved and stored so they are available very quickly. The minimal number of T cells in an UCB product allows it to be used across HLA barriers. Typically UCB stem cell products are HLA mismatched at 1 to 6 antigens or alleles. The disadvantage is the small size of the product, which limits the stem cell dose in adults and often requires the use of a second UCB product. UCB units are also expensive since each unit must be bought from a bank that needs to recoup the costs of typing, cryopreservation, and storage.

Engraftment failure

When comparable conditioning regimens and cellular products are utilized, total nucleated cell dose (TNC), engraftment time and reliability with MMURD, MRD, MUD, and haploidentical donors are similar. Umbilical cord blood products have the lowest effective cell dose based on the amount collected and losses incurred during cryopreservation and thawing. The median TNC and CD34+ cells infused from a single UCB product are between 1.0-3.3 × 10^7/kg and 0.74-1.2 × 10^5/kg respectively. This is 10-fold fewer stem cells compared with adult donor stem cell products. In situations where body size is large, a strategy to increase the effective stem cell dose by the use of two UCB products is generally adopted. This increases the TNC and CD34+ cell dose infused and reduces the duration of cytopenias in adults, but still results in slower count recovery than anticipated in MMURD and haploidentical transplant recipients. One may reasonably anticipate at least a 7 day prolongation in time to neutrophil recovery in adults receiving a double UCB transplant when compared with peripheral blood reduced intensity conditioning (RIC) MUD transplants (21.5 days versus 13 days). Platelet recovery time is delayed from a median of 19 days in MUD to 41 days in UCB recipients.
Research to expand stem cells in UCB units has demonstrated an improved engraftment time with these strategies,\textsuperscript{23,24} but this remains experimental.

Graft failure can be mediated by cellular or humoral immunity or it may reflect insufficient or damaged stem cells. Immunologically mediated rejection can be caused by sensitization of the recipient to non-shared HLA antigens. For instance, in all three alternative donor sources, the risk of graft failure is higher in transplant recipients who have donor specific anti-HLA antibodies.\textsuperscript{25-27}

**MMURD Transplantation:** There is about a 10% graft failure rate in MMURD transplants, significantly higher than that observed in MRD and MUD transplants.\textsuperscript{28-31} Similar to MUD transplants, the risk of graft failure is higher with bone marrow (BM) than with peripheral blood stem cells (PBSC) as a graft source in MMURD transplants (16% with BM versus 3% with PBSC).\textsuperscript{32,33} The direction or vector of the HLA mismatch may also be important. In patients with an HLA non-permissive mismatch in the host versus graft vector, the risk of graft failure is increased when compared with permissive or MUD transplants.\textsuperscript{6}

**Haploidentical Transplantation:** Graft failure rates have been reduced by the Perugia group by increasing the CD34+ cell dose (so-called “mega-dose”) with a CD34+ selected PBSC graft, in which the median CD34+ cell dose was $13.8 \times 10^6$/kg (range, 5.1 to $29.7 \times 10^6$/kg).\textsuperscript{34} This results in a primary engraftment failure rate of 9%. Rizzieri et al observed a 6% graft failure rate in RIC haploidentical transplantation by infusing similarly large CD34+ cell doses (median $13.5 \times 10^6$/kg), but in contrast to the Perugia regimen, used in vivo T cell depletion with alemtuzumab. Huang et al used a combination of T cell replete BM and G-CSF primed PBSC with an augmented MA conditioning regimen that included ATG which resulted in almost no primary engraftment failures.\textsuperscript{35} Drobyski et al also observed a low graft failure rate of 4% using
augmented conditioning with an ex-vivo T cell depleted BM graft. In patients receiving the Hopkins strategy of post-transplant cyclophosphamide with a T cell replete graft, the graft failure rate is 10% in MA and 13% in RIC transplants.

**UCB Transplantation:** In UCB transplantation, there are few passively transferred T cells from the donor to protect against graft rejection and this may be more problematic because of the low TNC and CD34+ cell doses. Graft failure is close to 10% in RIC UCB transplantation and as high as 20% in MA UCB transplantation. If engraftment failure follows UCB transplant, there is no opportunity to return to the donor for more stem cells. Thus, either additional UCB needs to be used and the recipient must survive the additional period of cytopenias, or a haploidentical donor transplant may be attempted. Salvage RIC haploidentical transplantation has been used with some success after graft failure from UCB transplantation.

**Conclusion:** UCB transplant is associated with the highest engraftment failure rate. Furthermore, options after UCB infusion for graft failure are limited since returning to the donor is not an option. Small studies have shown that haploidentical stem cells can be infused at the time of UCB transplant or at evidence of graft failure to promote engraftment. In recent years the graft failure rate in haploidentical transplantation has improved to levels comparable to MUD, MRD, and MMUD levels. If graft rejection does occur after haploidentical transplantation, it is also difficult to re-transplant patients who have become sensitized to unshared alleles or antigens. Graft failure rates for alternative donor transplants are summarized in Tables 1 and 2.

**Graft versus Host Disease**

**MMURD Transplantation:** The HLA disparity that results in high engraftment failure rates with alternative donors also results in a higher rate of GVHD. Woolfrey et al examined
MMURD with PBSC as a graft source and found an increased risk of acute grade III/IV GVHD with single allele MMURD when compared with matched transplants (RR=1.59, 95% CI: 1.20-2.09), but no difference in chronic GVHD. A similar study by Lee et al in patients receiving a BM graft showed that one allele MMURD transplants had more grade III/IV acute GVHD (RR=1.34, 95% CI: 1.12-1.61) than MUD transplants. The majority of patients in these studies received MA conditioning, but a similar increase in acute GVHD and not chronic GVHD has been observed with RIC MMURD when compared with MUD transplants.

In myeloablative PBSC or marrow MMURD transplants, adding ATG to calcineurin inhibitors (CNI) for GVHD prophylaxis results in a rate of grade II-IV acute GVHD of 30 - 40%. In contrast, CNI based GVHD prophylaxis without ATG in MMURD transplants results in acute GVHD rates of 50 - 80%.

Class I HLA allele mismatched as well as HLA-DRB1 allele mismatched transplants are associated with higher rates of acute GVHD when compared with MUD transplants. The difference in chronic GVHD between MMURD and MUD transplants is not as clear, but some reports do show a higher risk of chronic GVHD with HLA class I mismatched transplants. In contrast, HLA-DQ and HLA-DP mismatches have not always shown to worsen clinical outcomes when compared with matched donor recipients. In patients who are otherwise matched at HLA-A, -B, -C and –DRB1, there is no survival difference if there is an HLA-DQ mismatch, but HLA-DQ mismatch may worsen outcomes in patients who already have a 1 or 2 HLA allele mismatch. HLA-DPB1 mismatches are associated with lower relapse rates, but with an associated increase in GVHD and TRM. HLA-C mismatch has been associated with worse survival when compared with HLA-C matched donor transplants, likely due to more severe acute GVHD.
**Haploidentical Transplantation:** In studies using high-intensity conditioning by adding cytarabine and semustine to cyclophosphamide and busulfan or total body irradiation, graft failure rates have been low, but acute GVHD has been 40-60%, despite the use of ATG.\(^{11,35,59}\) An alternative approach from Perugia using “mega-doses” of CD34+ selected stem cells, ATG for GVHD prophylaxis, and standard MA conditioning demonstrated low rates of acute and chronic GVHD (8% and 3% respectively), but with higher graft failure rates\(^ {34}\) as described in the above graft failure section. Both approaches continue to have drawbacks: slow post-transplant immune reconstitution in patients who receive T cell depleted transplants and acute and chronic GVHD in those who receive T cell replete grafts.\(^{60}\) In RIC haploidentical transplantation, the Johns Hopkins group pioneered the use of post-transplant cyclophosphamide in an effort to reduce GVHD rates. This approach has proven to be very effective requiring no stem cell manipulation, a simple marrow collection, and well-tolerated conditioning with modest toxicity. The rate of acute grade II-IV, acute grade III/IV and chronic GVHD was 34%, 6% and 5% respectively.\(^ {37}\)

**UCB Transplantation:** The less stringent HLA matching needed when selecting an UCB unit for transplantation is not associated with an increased risk of GVHD-related mortality. The risk of acute GVHD appears to be slightly lower with the use of ATG with MA conditioning, but this difference is not as appreciable with RIC UCB transplants (see tables 1 and 2).

Grade II-IV acute GVHD was significantly higher in MMURD (85%) compared with UCB transplants (53%) at 100 days after HSCT for hematologic malignancies, but grade III/IV acute GVHD was not significantly different.\(^ {51}\) Similarly, chronic GVHD rates at 2 years after HSCT were significantly higher for MMURD transplantation when compared with UCB.
transplants (48% versus 26% respectively). Smaller studies have not been able to show an appreciable difference in GVHD rates after UCB or MMURD transplantation.\textsuperscript{61,62}

In parallel phase II trials of UCB or haploidentical transplantation using post-transplantation cyclophosphamide conducted by the BMT-CTN, the grade II-IV GVHD rate was 40% for UCB transplants recipients and 32% for haploidentical transplant recipients. The grade III/IV acute GVHD rates were 21% and 0 for UCB and haploidentical transplants respectively. Chronic GVHD was also higher in UCB transplants; 25% compared with 13% at 1 year after transplant.\textsuperscript{39}

**Conclusion:** Graft versus host disease is most frequent in MMURD transplants, and comparable between UCB and haploidentical transplants when post-transplant cyclophosphamide is utilized for the latter. Studies in alternative donor transplants employ a variety of GVHD prophylaxis strategies which complicates a comparative analysis. With the high degree of HLA mismatch in haploidentical transplants, novel techniques to reduce GVHD are necessary. This includes high stem cell doses, \textit{in vivo} or \textit{ex-vivo} T cell depletion, and post-transplant cyclophosphamide. None of these strategies have been compared directly to each other, and the risk of graft failure needs to be weighed against the benefit of GVHD in each of these strategies. Tables 1 and 2 summarize GVHD rates in alternative donor transplants.

**Transplant-related mortality**

The reported transplant related mortality (TRM) is highly variable and likely accounted for by the diversity in conditioning regimens, underlying disease, use of PBSC or BM, and co-morbidities at time of transplantation. Most studies do not account for these differences when reporting an overall TRM.
**MMURD Transplantation:** Multiple studies have demonstrated that the long term non-relapse mortality is significantly higher in MMURD when compared with MUD transplants. In a large CIBMTR study of over 4000 patients receiving a transplant for CML in chronic phase, the 5 year TRM was 31% in MRD, 38% in MUD, 50% in one HLA Class I MMURD, and 48% in one HLA-Class II MMURD.\(^{53}\) In another large retrospective study of 1800 patients, the relative risk of an allele MMURD was 1.4 (95% CI, 1.09-1.81) when compared with HLA allele-matched unrelated donors,\(^ {44}\) and this observation is consistent among other studies.\(^ {29,45,50}\)

**Haploidentical Transplantation:** In a study of patients receiving MA conditioning for a haploidentical transplant with *ex-vivo* T cell depleted BM, the 2 year TRM in haploidentical transplants was 42%, which was not significantly different from MMURD (45%) but significantly higher than MUD transplants (23%).\(^ {11}\) In a more recent analysis by Wang et al in which patients with AML or ALL received MA conditioning with ATG as part of GVHD prophylaxis, there was no appreciable difference in TRM between haploidentical (34%) and MRD transplant recipients (38%) at 2 years after transplant.\(^ {12}\) Another study examined the impact of T cell depletion with ATG on transplant outcomes and found that the use of ATG increased the TRM significantly from 16% to 42%.\(^ {63}\) In patients receiving the Perugia regimen the TRM was 36.5%,\(^ {34}\) mostly due to infection, which reflected impaired T cell immune reconstitution. In patients receiving post-transplant cyclophosphamide without ATG to prevent GVHD, the TRM has been reported as 16% at 100 days after transplant.\(^ {36}\)

In heavily pre-treated Hodgkin’s disease patients, the TRM with RIC haploidentical transplant was 8% at 2 years, significantly better than MUD and MRD transplants in this study.\(^ {64}\) Low TRM has also been reported in RIC haploidentical transplants for patients receiving post-transplant cyclophosphamide (4 to 6%).\(^ {37,39}\) A small study in high risk AML patients receiving
RIC haploidentical transplantation did not demonstrate a difference in TRM when compared with MMURD transplants (10.1 versus 17.9% respectively).\textsuperscript{10}

\textit{UCB Transplantation:} Long term TRM of UCB transplants has been comparable to MUD and MRD transplants in some studies,\textsuperscript{13,40,65} but the upfront mortality associated with UCB transplants is higher.\textsuperscript{66,67} Small studies that have compared TRM of UCB to MMURD could not demonstrate a significant difference, but these are small studies that were likely underpowered.\textsuperscript{51,62}

The TRM in RIC UCB transplant recipients is reportedly higher than that observed in MUD and haploidentical transplants. In a study of two phase II parallel trials, the 2 year TRM with UCB was 24% as compared with 7% in haploidentical transplant recipients.\textsuperscript{39} It is difficult to compare stem cell sources here as this was not a randomized trial and post-transplant immune suppression differed by stem cell source. Nevertheless, the data do suggest that early TRM with UCB is higher than that of haploidentical transplants. This is likely due to the slower UCB transplant lymphohematopoietic reconstitution.\textsuperscript{68} This higher rate of TRM in UCB is also observed when compared with MUD transplants.\textsuperscript{21,22,38,40,69}

\textit{Conclusion:} In all alternative donor transplants, the TRM is generally higher than that observed in matched donor transplants, when similar conditioning regimens are used. In the MA setting, the TRM from haploidentical and UCB transplants is comparable with MMURD transplants. Reduced intensity conditioning reduces the risk of TRM in haploidentical and UCB transplants. Comparing RIC haploidentical and UCB transplants suggests that UCB has a higher TRM than haploidentical transplants, likely related to the slower engraftment and risk of infection related fatality with UCB. Tables 3 and 4 summarize TRM rates in alternative donor transplants.
Relapse Rates

**MMURD Transplantation:** In MMURD, regardless of the indication for transplant and the conditioning regimen, patients generally have comparable relapse rates to MUD and MRD transplant recipients. A large retrospective CIBMTR analysis compared 521 patients who received a 1 or more allele MMURD to 3514 patients who received a MRD transplant. Relapse rates at 5 years were 14% in MRD, 12% in MUD, 11% in single class I mismatch and 9% in single class II mismatched donors and these were not significantly different in multivariate analysis.\(^{53}\)

**Haploidentical Transplantation:** Relapse in haploidentical transplants is highly variable based on GVHD and graft failure strategies utilized. In patients receiving a RIC haploidentical transplant with post-transplant cyclophosphamide to reduce GVHD, the relapse rate was 45% at 1 year after transplant.\(^{39}\) The relapse rate for MA haploidentical transplant with post-transplant cyclophosphamide is 22% at a median follow up of about 11 months, suggesting that the higher intensity conditioning can improve relapse rates in patients receiving post-transplant cyclophosphamide. In patients receiving the Perugia regimen, the cumulative incidence of relapse at 6 months was 25% for all patients, but was significantly higher in patients transplanted in relapse (51%) when compared with those transplanted in remission (16%).\(^{34}\)

**UCB Transplantation:** Patients receiving MA UCB transplants are associated with a lower risk of relapse (16%) when compared with matched and mismatched transplants (37-52%).\(^{51}\) In patients receiving a RIC double UCB transplant, the one year relapse incidence was 31%. This appeared to be lower than the 45% observed in the parallel haploidentical transplant study,\(^{39}\) however, patients who received UCB had a higher TRM. Therefore the relapse rates are not directly comparable, since more haploidentical patients were at risk for relapse.
Conclusion: Disease risk stratification and status at time of transplantation is ultimately very important in determining risk of relapse or progression after transplant and it is difficult to compensate for these issues in non-comparative trials.

Overall Survival

**MMURD Transplantation:** A large retrospective study of about 1300 patients receiving a HSCT for malignant hematologic diseases showed a 3 year survival of 40% in MMURD, a 20% disadvantage when compared with MUD transplants.\(^{50}\) This relationship has been observed in multiple other studies of MMURD compared with matched donor sources (Tables 3 and 4). When comparing MA and RIC conditioning regimens, Woolfrey et al were not able to demonstrate a difference in survival based on regimen intensity.\(^{44}\) Woolfrey et al went on to compare the results of their study with PBSC MMURD with the results reported by Lee et al\(^{45}\) in which patients had a similar MMURD transplant, but with a BM graft. No difference in OS was observed in one antigen MMURD transplants with PBSC when compared with one antigen MMURD with BM (RR 1.13; 95% CI, 0.93-1.40).

In RIC MMURD transplants, the OS difference when compared with matched donor sources is not as clear. Koreth et al recently reported a large retrospective analysis of the CIBMTR in which a 3 year OS of 30.9% for RIC allele MMURD was seen, significantly lower than that observed in MUD transplants (37.4%).\(^{46}\) In a CIBMTR analysis of patients with non-Hodgkin’s lymphoma receiving RIC MMURD transplant showed that older age, shorter time from diagnosis to transplant, non-TBI conditioning regimen, ex-vivo T cell depletion and HLA mismatch were associated with mortality.\(^{70}\)

**Haploidentical Transplantation:** The largest analysis to date in 756 adults receiving a MA haploidentical transplant for AML, CML or ALL had an excellent 3 year OS of 67%.\(^{59}\) In
patients with intermediate or high risk AML in first complete remission, 4 year OS was 77.5% and was significantly better than patients receiving chemotherapy alone. Other studies have demonstrated similar survival outcomes with MA haploidentical transplants (Tables 3 and 4). When compared with MUD and MMURD transplants, patients receiving a haploidentical transplant with an \textit{ex-vivo} T cell depleted BM graft had an OS at 2 years of 21%, significantly lower than both MUD (58%) and one antigen MMURD (34%), indicating that GVHD prevention strategy is an important variable.

In 83 patients with AML or MDS who received RIC haploidentical transplants with busulfan and fludarabine, including ATG as part of GVHD prophylaxis, OS at a median follow up of 26 months was 60% in leukemia in CR1, 53% in CR2/CR3 and 53% in MDS. Patients with refractory leukemia had a significantly lower OS at 9%. In high risk AML patients who received RIC haploidentical transplants and ATG for GVHD prophylaxis, 3 year OS was 65.7%. This was comparable to patients receiving a well matched or partially matched myeloablative HSCT in this study. In refractory or relapsed Hodgkin’s disease patients, most of whom had failed a previous autologous transplant, no difference in OS at 2 years was observed in MRD, MUD or haploidentical transplants with reduced intensity conditioning. Table 4 summarizes the reported OS rates in RIC haploidentical transplants.

\textit{UCB Transplantation:} In two studies of patients receiving myeloablative UCB transplants compared with MMURD transplants, the 3 year OS was 66% for UCB, significantly higher than that of MMURD transplants. In both studies, the TRM was lower and PFS was higher with UCB compared with MMURD. A CIBMTR observational analysis was not able to show a significant OS difference between UCB and MMURD transplants receiving MA conditioning. In another study of UCB myeloablative conditioning including over 500 patients,
a one year OS of 37% was observed. Other studies to report OS in myeloablative UCB HSCT are summarized in Table 3. As in MMURD, the direction of HLA mismatch may be important in UCB transplantation. Unidirectional mismatch in the graft versus host direction alone may result in better TRM and OS when compared with host versus graft unidirectional mismatches and bidirectional mismatches.

Overall survival in patients receiving RIC UCB is between 34% and 63% in patients with hematologic malignancies. In the BMT-CTN phase II parallel studies of UCB and haploidentical transplants, UCB appeared to have higher TRM, 24% versus 7% with comparable DFS rates, resulting in an apparent OS benefit with haploidentical transplants (62% versus 54% with UCB transplants) at one year after transplantation. More TRM has also been observed with UCB transplants compared with MUD transplants, but similar DFS and OS rates were observed.

Conclusions: Overall survival is a compound outcome of transplant related complications and disease relapse. Patients receiving a MMURD have a higher rate of TRM than matched donor transplants, resulting in an overall lower OS. The range of OS rates after haploidentical transplants likely relates to the differences in transplant indication, severity of disease and GVHD prophylaxis strategies. Compared with haploidentical and MMURD transplants, UCB transplantation results in higher TRM but similar PFS and OS rates. Tables 3 and 4 summarize survival outcomes in alternative donor transplants.

Making a Decision

Despite the large number of phase II and observational studies in the literature, the dearth of randomized trials makes the prioritization of an alternative donor difficult. Clearly, the decision may in part reflect the research agenda of the transplant center since no one stem cell
source is clearly superior to another. The anticipated outcomes of alternative donor transplantation are relatively predictable, and they are similar enough that randomized controlled trials will be critical to resolve the remaining issues. However, the large number of variables influencing outcomes makes it unrealistic to expect such trials to be conducted quickly enough or in large enough numbers to provide definitive recommendations. Nevertheless there are themes that can be inferred by the current data to inform a decision.

If a donor is required quickly, UCB and haploidentical transplantation have the advantage over adult volunteer MMURD. In general, UCB products can be obtained promptly because they are cryopreserved and in inventory. Haploidentical family members are usually evaluated and scheduled for stem cell collection more promptly than unrelated donors. If upfront cost is a major concern, haploidentical donors have a clear advantage over both UCB products and MMURD. For patients who have had problems with EBV, CMV or other infections, UCB may be less desirable because of both the delay in hematopoietic recovery and the lack of passively transferred cellular immunity. Strategies to speed hematopoietic recovery in UCB transplantation are very interesting, but they are unlikely to improve immunologic function and they are likely to be quite expensive.

All MMURD transplants are not equal. While in general there is a higher risk of GVHD and similar outcomes to UCB and haploidentical transplantation, the ability to recognize permissive and non-permissive mismatches and choosing donors with mismatches in the graft rejection direction rather than the GVHD direction may allow for graft versus leukemia effect with a similar risk of GVHD as observed using matched donors.

Physicians are left with the current evidence to decide on what transplant would be best for their patient. Diagnosis, disease severity, disease status at time of transplant, conditioning
regimens, graft source and GVHD prophylaxis strategies are the factors that together influence clinical outcomes after transplantation. The outcomes have significantly improved with alternative donor transplantation, but much work remains to be done until they are proven to be non-inferior to matched related and unrelated donor transplants.

Authorship

NK and JA performed the literature review, writing and editing of the manuscript.

The authors have no conflicts of interest to disclose.
Reference List


Table 1. Transplant-related outcomes with MA conditioning

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<td>NR</td>
<td>54%</td>
<td>24%</td>
<td>NR</td>
<td>60%</td>
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<tr>
<td>Hasegawa</td>
<td>60</td>
<td>PB or BM</td>
<td>CsA, Mtx</td>
<td>13%</td>
<td>70%</td>
<td>NR</td>
<td>60%</td>
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<tr>
<td>Greinix</td>
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<td>70% BM</td>
<td>CsA, Mtx</td>
<td>5%</td>
<td>57%</td>
<td>NR</td>
<td>37%</td>
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<tr>
<td>Laughlin</td>
<td>83</td>
<td>BM</td>
<td>CNI based</td>
<td>NR</td>
<td>52%</td>
<td>NR</td>
<td>40%</td>
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**HAPLOIDENTICAL**

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<th>TCD</th>
<th>TCD PROPHYLAXIS</th>
<th>GF</th>
<th>aGVHD II-IV</th>
<th>aGVHD III/IV</th>
<th>cGVHD</th>
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<tr>
<td>Di Bartolomeo</td>
<td>78</td>
<td>80</td>
<td>BM</td>
<td>ATG</td>
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<td>24%</td>
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<td>Tac, MMF, Cy</td>
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<td>NR</td>
<td>7%</td>
<td>16%</td>
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<td>BM</td>
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<td>CsA</td>
<td>4%</td>
<td>42%</td>
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<tr>
<td>Huang</td>
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<td>13%</td>
<td>52%</td>
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<tr>
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<td>PBSC or BM</td>
<td>ATG</td>
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<td>NR</td>
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<td>2%</td>
<td>55%</td>
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<tr>
<td>Aversa</td>
<td>104</td>
<td>PBSC</td>
<td>ATG</td>
<td>none</td>
<td>9%</td>
<td>8%</td>
<td>2%</td>
<td>3%</td>
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<tr>
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<td>756</td>
<td>BM + PBSC</td>
<td>CsA, Mtx, MMF</td>
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<td>43%</td>
<td>14%</td>
<td>53%</td>
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</tr>
<tr>
<td>Raiola</td>
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<td>BM</td>
<td>CsA, MMF, Cy</td>
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<td>12%</td>
<td>NR</td>
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</tr>
<tr>
<td>Solomon</td>
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<td>PBSC</td>
<td>Tac, MMF</td>
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<td>30%</td>
<td>10%</td>
<td>35%</td>
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**UMBILICAL CORD BLOOD**

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<th>TCD PROPHYLAXIS</th>
<th>GF</th>
<th>aGVHD II-IV</th>
<th>aGVHD III/IV</th>
<th>cGVHD</th>
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<tr>
<td>Rocha</td>
<td>98</td>
<td>Single</td>
<td>ATG</td>
<td>CsA, steroid</td>
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<td>26%</td>
<td>13%</td>
<td>30%</td>
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<td>NR</td>
<td>21%</td>
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<td>Sanz</td>
<td>49</td>
<td>Single</td>
<td>ATG</td>
<td>CsA, (MMF or steroid)</td>
<td>4%</td>
<td>26%</td>
<td>15%</td>
<td>30%</td>
<td></td>
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<td>van Heeckeren</td>
<td>31</td>
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<td>17%</td>
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<td>Cohen</td>
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<td>NR</td>
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<td>36%</td>
<td>NR</td>
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<td>Ooi</td>
<td>77</td>
<td>Single</td>
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<td>82%</td>
<td>25%</td>
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<td>NR</td>
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<td>22%</td>
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<td>23%</td>
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MMURD=mismatched unrelated donor, PB=peripheral blood stem cells, BM=bone marrow, TCD=T cell depletion, ATG=anti-thymocyte globulin, GF=graft failure, aGVHD=acute graft versus host disease, cGVHD=chronic GVHD, CsA=cyclosporine A, Mtx=methotrexate, CNI=calcineurin inhibitor, MMF=mycophenolate mofetil, Cy=cyclophosphamide, Tac=tacrolimus, NR=not reported
Table 2. Transplant-related outcomes with RIC conditioning

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<th>REFERENCE</th>
<th>N</th>
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<td>Nakamae82</td>
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<td>PBSC</td>
<td>Campath</td>
<td>CsA, MMF</td>
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<td>69%</td>
<td>26%</td>
<td>41%</td>
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<tr>
<td>Koreth83</td>
<td>45</td>
<td>PBSC</td>
<td>Tac., Mtx, Velcade</td>
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<td>29%</td>
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<td>Rizzieri84</td>
<td>49</td>
<td>PBSC</td>
<td>Campath</td>
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<td>ATG</td>
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<td>40%</td>
<td>NR</td>
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<tr>
<td>Federmann86</td>
<td>61</td>
<td>PBSC</td>
<td>OKT-3, TCD</td>
<td>MMF</td>
<td>8%</td>
<td>46%</td>
<td>NR</td>
<td>18%</td>
</tr>
<tr>
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<td>83</td>
<td>PBSC</td>
<td>ATG</td>
<td>CsA, Mtx</td>
<td>5%</td>
<td>20%</td>
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<td>34%</td>
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<td>NR</td>
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<td>33%</td>
</tr>
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<td>Guo88</td>
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<td>BM + PBSC</td>
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<td>31%</td>
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<td>ATG</td>
<td>Tac, MMF, Cy</td>
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<td>NR</td>
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<td>NR</td>
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<td>34%</td>
<td>6%</td>
<td>25%</td>
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<tr>
<td>Brunstein39</td>
<td>50</td>
<td>BM</td>
<td>Tac, MMF, Cy</td>
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<td>13%</td>
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<td>Bashey39</td>
<td>53</td>
<td>60% BM</td>
<td>Tac, MMF</td>
<td>2%</td>
<td>30%</td>
<td>11%</td>
<td>38%</td>
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<tr>
<td>Chen22</td>
<td>64</td>
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<td>Tac based</td>
<td>NR</td>
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<td>22%</td>
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<td>Cutler79</td>
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<td>ATG</td>
<td>Siro, Tac</td>
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<td>9%</td>
<td>3%</td>
<td>13%</td>
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<td>CsA, MMF</td>
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<td>Majhail40</td>
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<td>ATG</td>
<td>CsA, MMF</td>
<td>11%</td>
<td>49%</td>
<td>NR</td>
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<td>ATG</td>
<td>CsA, MMF</td>
<td>6%</td>
<td>59%</td>
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<td>23%</td>
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<td>Ballen21</td>
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<td>CsA, MMF</td>
<td>10%</td>
<td>40%</td>
<td>5%</td>
<td>31%</td>
</tr>
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<td>Rodrigues90</td>
<td>104</td>
<td>75% Single</td>
<td>46% ATG</td>
<td>CsA based</td>
<td>NR</td>
<td>24%</td>
<td>8%</td>
<td>18%</td>
</tr>
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<td>40%</td>
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<td>25%</td>
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<td>7%</td>
<td>27%</td>
<td>23%</td>
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<tr>
<td>Narimatsu75</td>
<td>1072</td>
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<td>NR</td>
<td>NR</td>
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<td>NR</td>
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<td>Oran15</td>
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<td>CsA, MMF</td>
<td>NR</td>
<td>RIC=47%, MA=67%</td>
<td>RIC=16%, MA=31%</td>
<td>RIC=30%, MA=34%</td>
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</tr>
</tbody>
</table>

MMURD=mismatched unrelated donor, PB=peripheral blood stem cells, BM=bone marrow, TCD=T cell depletion, ATG=anti-thymocyte globulin, GF=graft failure, aGVHD=acute graft versus host disease, cGVHD=chronic GVHD, CsA=cyclosporine A, Mtx=methotrexate, CNI=calcineurin inhibitor, MMF=mycophenolate mofetil, Cy=cyclophosphamide, Tac=tacrolimus, Siro=sirolimus, NR=not reported
Table 3. Survival outcomes with MA conditioning

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<th>REFERENCE</th>
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<th>GRAFT</th>
<th>OS at 3 yrs</th>
<th>DFS at 3 yrs</th>
<th>TRM at 3 yrs</th>
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<tr>
<td>Ciurea28</td>
<td>28</td>
<td>70% BM</td>
<td>19%</td>
<td>19%</td>
<td>40%</td>
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<tr>
<td>Mehta77</td>
<td>201</td>
<td>BM</td>
<td>19% at 5 yrs</td>
<td>18% at 5 yrs</td>
<td>51% at 5 yrs</td>
</tr>
<tr>
<td>Laughlin13</td>
<td>83</td>
<td>BM</td>
<td>20% at 3 yrs</td>
<td>19% at 3 yrs</td>
<td>65% at 3 yrs</td>
</tr>
<tr>
<td>Lee45</td>
<td>985</td>
<td>&gt;93% BM</td>
<td>29% at 5 yrs</td>
<td>38% at 1 yr</td>
<td>45% at 1 yr</td>
</tr>
<tr>
<td>Fernandez-Vina91</td>
<td>1854</td>
<td>60% BM</td>
<td>30% at 5 yrs</td>
<td>30% at 5 yrs</td>
<td>30% at 5 yrs</td>
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<tr>
<td>Hasegawa30</td>
<td>60</td>
<td>BM or PB</td>
<td>35% at 5 yrs</td>
<td>30% at 5 yrs</td>
<td>42% at 5 yrs</td>
</tr>
<tr>
<td>Greinix54</td>
<td>144</td>
<td>BM</td>
<td>38% at 3 yrs</td>
<td>40% at 3 yrs</td>
<td>NR</td>
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<tr>
<td>Weisdorf47</td>
<td>24</td>
<td>PB</td>
<td>40% at 2 yrs</td>
<td>40% at 2 yrs</td>
<td>35% at 1 yr</td>
</tr>
<tr>
<td>Arora53</td>
<td>215</td>
<td>BM or PB</td>
<td>40% at 5 yrs</td>
<td>38% at 5 yrs</td>
<td>50% at 5 yrs</td>
</tr>
<tr>
<td>Hauzenberger31</td>
<td>49</td>
<td>40% BM</td>
<td>45% at 5 yrs</td>
<td>24% at 2 yrs</td>
<td>27% at 5 yrs</td>
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<td>MMURD</td>
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<td>Drobyski11</td>
<td>48</td>
<td>BM</td>
<td>21% at 2 yrs</td>
<td>NR</td>
<td>42% at 2 yrs</td>
</tr>
<tr>
<td>Aversa54</td>
<td>104</td>
<td>PB</td>
<td>40% at 22 mos</td>
<td>25% at 6 mos</td>
<td>36.5% at 1 yr</td>
</tr>
<tr>
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<td>80</td>
<td>BM</td>
<td>45% at 3 yrs</td>
<td>38% at 3 yrs</td>
<td>36% at 3 yrs</td>
</tr>
<tr>
<td>Grosso39</td>
<td>27</td>
<td>BM</td>
<td>48% at 3 yrs</td>
<td>NR</td>
<td>11% at 3 yrs</td>
</tr>
<tr>
<td>Raiola36</td>
<td>50</td>
<td>BM</td>
<td>62% at 1.5 yrs</td>
<td>51% at 1.5 yrs</td>
<td>16% at 100 days</td>
</tr>
<tr>
<td>Wang49</td>
<td>756</td>
<td>BM + PB</td>
<td>67% at 3 yrs</td>
<td>63% at 3 yrs</td>
<td>18% at 3 yrs</td>
</tr>
<tr>
<td>Solomon81</td>
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<td>PBSC</td>
<td>69% at 20 mos</td>
<td>40% at 20 mos</td>
<td>10% at 100 days</td>
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<tr>
<td>Huang41</td>
<td>132</td>
<td>BM + PB</td>
<td>77.5% at 4 yrs</td>
<td>73.1% at 4 yrs</td>
<td>NR</td>
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<td>PB</td>
<td>40% at 22 mos</td>
<td>25% at 6 mos</td>
<td>36.5% at 1 yr</td>
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<tr>
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<td>80</td>
<td>BM</td>
<td>45% at 3 yrs</td>
<td>38% at 3 yrs</td>
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<td>BM</td>
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<tr>
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<td>BM</td>
<td>62% at 1.5 yrs</td>
<td>51% at 1.5 yrs</td>
<td>16% at 100 days</td>
</tr>
<tr>
<td>Wang49</td>
<td>756</td>
<td>BM + PB</td>
<td>67% at 3 yrs</td>
<td>63% at 3 yrs</td>
<td>18% at 3 yrs</td>
</tr>
<tr>
<td>Solomon81</td>
<td>20</td>
<td>PBSC</td>
<td>69% at 20 mos</td>
<td>40% at 20 mos</td>
<td>10% at 100 days</td>
</tr>
<tr>
<td>Huang41</td>
<td>132</td>
<td>BM + PB</td>
<td>77.5% at 4 yrs</td>
<td>73.1% at 4 yrs</td>
<td>NR</td>
</tr>
<tr>
<td>UMBILICAL CORD BLOOD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laughlin13</td>
<td>150</td>
<td>Single</td>
<td>26% at 3 yrs</td>
<td>23% at 3 yrs</td>
<td>63% at 3 yrs</td>
</tr>
<tr>
<td>Rocha16</td>
<td>98</td>
<td>Single</td>
<td>36% at 2 yrs</td>
<td>33% at 2 yrs</td>
<td>44% at 2 yrs</td>
</tr>
<tr>
<td>Cohen73</td>
<td>514</td>
<td>Single</td>
<td>37% at 1 yr</td>
<td>51% at 1 yr</td>
<td>34% at 1 yr</td>
</tr>
<tr>
<td>van Heeckeren18</td>
<td>31</td>
<td>Single</td>
<td>37% at 3 yrs</td>
<td>37% at 3 yrs</td>
<td>NR</td>
</tr>
<tr>
<td>Eapen66</td>
<td>165</td>
<td>Single</td>
<td>NR</td>
<td>53% at 2.5 yrs</td>
<td>19% at 2.5 yrs</td>
</tr>
<tr>
<td>Sanz17</td>
<td>49</td>
<td>Single</td>
<td>NR</td>
<td>42% at 2 yrs</td>
<td>39% at 2 yrs</td>
</tr>
<tr>
<td>Ooi14</td>
<td>77</td>
<td>Single</td>
<td>NR</td>
<td>63% at 5 yrs</td>
<td>9.7% at 5 yrs</td>
</tr>
<tr>
<td>Takahashi65</td>
<td>100</td>
<td>Single</td>
<td>NR</td>
<td>70% at 3 yrs</td>
<td>9% at 1 yr</td>
</tr>
<tr>
<td>Brunstein51</td>
<td>128</td>
<td>Double</td>
<td>NR</td>
<td>51% at 5 yrs</td>
<td>34% at 5 yrs</td>
</tr>
</tbody>
</table>

MMURD= mismatched unrelated donor, OS=overall survival, DFS=disease-free survival, TRM=transplant-related mortality, BM=bone marrow, PB=peripheral blood stem cells, NR=not reported
Table 4. Survival outcomes with RIC conditioning

<table>
<thead>
<tr>
<th>REFERENCE</th>
<th>N</th>
<th>GRAFT</th>
<th>OS</th>
<th>DFS</th>
<th>TRM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MMURD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakamae82</td>
<td>59</td>
<td>PB</td>
<td>29% at 2 yrs</td>
<td>28% at 2 yrs</td>
<td>36% at 1 yr</td>
</tr>
<tr>
<td>Koreth83</td>
<td>45</td>
<td>PB</td>
<td>64% at 2 yrs</td>
<td>51% at 2 yrs</td>
<td>11% at 2 yrs</td>
</tr>
<tr>
<td><strong>HAPLOIDENTICAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Federmann86</td>
<td>61</td>
<td>PB</td>
<td>28% at 2 yrs</td>
<td>25% at 2 yrs</td>
<td>42% at 2 yrs</td>
</tr>
<tr>
<td>Rizzieri84</td>
<td>49</td>
<td>PB</td>
<td>31% at 1 yr</td>
<td>43% at 1 yr</td>
<td>10.2% at 100 days</td>
</tr>
<tr>
<td>Luznik85</td>
<td>68</td>
<td>BM</td>
<td>36% at 2 yrs</td>
<td>26% at 2 yrs</td>
<td>15% at 1 yr</td>
</tr>
<tr>
<td>Burroughs82</td>
<td>28</td>
<td>BM</td>
<td>58% at 2 yrs</td>
<td>51% at 2 yrs</td>
<td>8% at 2 yrs</td>
</tr>
<tr>
<td>Lee72</td>
<td>16</td>
<td>PB</td>
<td>60% at 2 yrs</td>
<td>60% at 2 yrs</td>
<td>18% at 2 yrs</td>
</tr>
<tr>
<td>Brunstein99</td>
<td>50</td>
<td>BM</td>
<td>62% at 1 yr</td>
<td>48% at 1 yr</td>
<td>7% at 1 yr</td>
</tr>
<tr>
<td>Bashey89</td>
<td>53</td>
<td>60% BM</td>
<td>64% at 2 yrs</td>
<td>60% at 2 yrs</td>
<td>7% at 2 yrs</td>
</tr>
<tr>
<td><strong>UMBILICAL CORD BLOOD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miyakoshi90</td>
<td>30</td>
<td>Single</td>
<td>33% at 1 yr</td>
<td>22% at 1 yr</td>
<td>27% at 100 days</td>
</tr>
<tr>
<td>Majhail90</td>
<td>43</td>
<td>Double</td>
<td>34% at 3 yrs</td>
<td>34% at 3 yrs</td>
<td>28% at 6 mos</td>
</tr>
<tr>
<td>Brunstein88</td>
<td>110</td>
<td>Double</td>
<td>45% at 3 yrs</td>
<td>38% at 3 yrs</td>
<td>26% at 3 yrs</td>
</tr>
<tr>
<td>Chen84</td>
<td>64</td>
<td>Double</td>
<td>46% at 3 yrs</td>
<td>30% at 3 yrs</td>
<td>27% at 3 yrs</td>
</tr>
<tr>
<td>Rodrigues99</td>
<td>104</td>
<td>75% Single</td>
<td>48% at 1 yr</td>
<td>40% at 1 yr</td>
<td>28% at 1 yr</td>
</tr>
<tr>
<td>Cutler19</td>
<td>32</td>
<td>Double</td>
<td>53% at 2 yrs</td>
<td>31.2% at 2 yrs</td>
<td>34% at 2 yrs</td>
</tr>
<tr>
<td>Brunstein99</td>
<td>50</td>
<td>Double</td>
<td>54% at 1 yr</td>
<td>46% at 1 yr</td>
<td>24% at 1 yr</td>
</tr>
<tr>
<td>Brunstein76</td>
<td>65</td>
<td>Double</td>
<td>55% at 3 yrs</td>
<td>34% at 3 yrs</td>
<td>15% at 3 yrs</td>
</tr>
<tr>
<td>Ballen19</td>
<td>21</td>
<td>Double</td>
<td>71% at 2 yrs</td>
<td>55% at 2 yrs</td>
<td>19% at 6 mos</td>
</tr>
</tbody>
</table>

MMURD = mismatched unrelated donor, OS = overall survival, DFS = disease-free survival, TRM = transplant-related mortality, BM = bone marrow, PB = peripheral blood stem cells, NR = not reported
Hematopoietic stem cell transplantation donor sources in the 21st century: choosing the ideal donor when a perfect match doesn't exist

Natasha Kekre and Joseph H. Antin

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