Related haploidentical donors are a better choice than matched unrelated donors: Counterpoint

Bronwen E. Shaw

Center for International Blood and Marrow Transplant Research, Froedtert & the Medical College of Wisconsin, Milwaukee, WI

This article has a companion Point by Fuchs.

In this article, I will argue that a transplant using a matched unrelated donor (UD) remains the first choice for patients lacking an HLA-identical sibling donor and should be prioritized above a related haploidentical (haplo) donor.

The first successful UD transplant was performed in the United States in 1973. Since then, >60,000 UD transplants have been performed, with long-term survivors of >25 years. As a community, we are very experienced in the practice of UD transplantation, and numerous studies have now shown that survival following a UD transplant is not different from that using an HLA-identical sibling.1,2

Several studies have recently compared the outcomes for patients receiving related haplo transplants (concentrating predominately on the posttransplant cyclophosphamide [PTCY] approach) with those receiving UD transplants (Table 1), and all 10 of these studies show no significant difference in overall survival between donor types. However, this should be interpreted with caution, as all of these studies are retrospective, nonrandomized comparisons. The numbers of patients studied are small, particularly in the haplo setting (a total of 813 patients are reported in 10 studies, but individual patients may be represented more than once), such that individual studies are almost certainly underpowered to detect significant differences in outcomes. Additionally, the haplo transplants are performed in more recent years and in some studies have a shorter median follow-up. Importantly, the patient characteristics in many of the studies differ significantly between groups, particularly regarding not only the choice of stem cell source (bone marrow [BM] vs peripheral blood stem cells [PBSCs]) but also in some cases disease risk, comorbidities, and time to transplant. Finally, in all cases, the graft-versus-host disease (GVHD) prophylaxis differs (consistently PTCY for all haplo recipients, but more traditional pharmacological agents in the UD recipients).

While survival in all studies is similar, other outcomes, including engraftment, relapse, and GVHD, do differ.

Engraftment

Numerous publications have shown that engraftment and/or immune reconstitution is delayed after haplo transplant compared with UD transplant,3,4 and 6 out of 8 (not reported in 2) comparative studies (Table 1) report slower neutrophil and/or platelet engraftment with haplo donors.5-10

Relapse

Early studies using the PTCY approach raised a concern regarding an increased relapse risk compared with contemporary approaches.11-13 This has not in general been borne out in more recent studies, and in the comparative studies shown in Table 1, only 1 study showed a higher incidence of relapse in the haplo setting (acute myeloid leukemia [AML] patients receiving reduced-intensity conditioning).7 Conversely the incidence of relapse in Hodgkin lymphoma was lower in the haplo setting than in UD setting.14

It has been suggested, however, that relapse after haplo may differ from that seen in other settings. Bashey et al15,16 reported that the postrelapse survival was significantly worse after PTCY haplo transplant than after transplantation using UDs (17% vs 63%, P < .001). Although none of these patients were treated with donor lymphocyte infusions (DLIs), the outcome in haplo transplants remained worse even when those receiving DLIs in the UD setting were excluded from the analysis.

An interesting phenomenon recently reported in relapsed patients has been termed “HLA loss relapse.” In this situation, leukemic cells can escape from the donor’s antileukemic T cells through loss of the mismatched HLA haplotype. This was first identified in patients relapsing after haplo transplantation.17,18 In a more recent study from a single center, Crucitti et al19 evaluated the incidence in 233 consecutive
<table>
<thead>
<tr>
<th>Reference</th>
<th>Donor</th>
<th>N</th>
<th>Disease</th>
<th>Conditioning for haplo</th>
<th>GVHD prophylaxis</th>
<th>Overall survival (%)</th>
<th>Disease-free survival (%)</th>
<th>Nonrelapse mortality (%)</th>
<th>Acute GVHD (%)</th>
<th>Chronic GVHD (%)</th>
<th>Relapse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burroughs et al 14 (multi-center)</td>
<td>MRD</td>
<td>38</td>
<td>Hodgkin</td>
<td>NMA (fludarabine, 2-Gy TBI, cyclophosphamide)</td>
<td>CNI/MMF</td>
<td>53</td>
<td>23</td>
<td>21</td>
<td>16</td>
<td>50</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>(m)MUD</td>
<td>24</td>
<td>Lymphoma</td>
<td>CNI/MMF</td>
<td>58</td>
<td>29</td>
<td>8</td>
<td>8</td>
<td>86</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Haplo</td>
<td>28</td>
<td></td>
<td>PTCY/FK/MMF</td>
<td>58 (2 y)</td>
<td>51 (2 y)</td>
<td>9 (2 y)</td>
<td>11 (B/W)</td>
<td>35 (extensive, 2 y)</td>
<td>40 (2 y)</td>
<td>34</td>
</tr>
<tr>
<td>Bashey et al 15 (single center)</td>
<td>MRD</td>
<td>117</td>
<td>Mixed malignancy</td>
<td>NMA (fludarabine, 2-Gy TBI, cyclophosphamide)</td>
<td>NR</td>
<td>76</td>
<td>53</td>
<td>13</td>
<td>8</td>
<td>54</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>(m)MUD</td>
<td>101</td>
<td></td>
<td>NR</td>
<td>67</td>
<td>52</td>
<td>16</td>
<td>11</td>
<td>54</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Haplo</td>
<td>53</td>
<td></td>
<td>PTCY/FK/MMF</td>
<td>64 (2 y)</td>
<td>60 (2 y)</td>
<td>7 (2 y)</td>
<td>11 (B/W, 6 mo)</td>
<td>38 (extensive)</td>
<td>33 (2 y)</td>
<td>34</td>
</tr>
<tr>
<td>Di Stasi et al 8 (single center)</td>
<td>MRD</td>
<td>87</td>
<td>AML/MDS</td>
<td>NMA (fludarabine, melphalan, thiotepa)</td>
<td>FK/MTX</td>
<td>NR</td>
<td>36</td>
<td>20</td>
<td>11</td>
<td>31</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>(m)MUD</td>
<td>108</td>
<td></td>
<td>NR</td>
<td>52</td>
<td>43</td>
<td>18</td>
<td>4</td>
<td>15</td>
<td>35</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Haplo</td>
<td>32</td>
<td></td>
<td>PTCY/FK/MMF</td>
<td>NR</td>
<td>30 (3 y)</td>
<td>24 (1 y)</td>
<td>0 (B/W)</td>
<td>11 (extensive, 3 y)</td>
<td>NR</td>
<td>34</td>
</tr>
<tr>
<td>Raim et al 9 (single center)</td>
<td>MUD</td>
<td>491</td>
<td>Lymphoma</td>
<td>NMA (fludarabine, 2-Gy TBI, cyclophosphamide)</td>
<td>CNI</td>
<td>45</td>
<td>32</td>
<td>24</td>
<td>7</td>
<td>29</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>MUD</td>
<td>21</td>
<td></td>
<td>CNI + ATG</td>
<td>43</td>
<td>36</td>
<td>33</td>
<td>3</td>
<td>22</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Haplo</td>
<td>92</td>
<td></td>
<td>PTCY/CNI/MMF</td>
<td>52</td>
<td>43</td>
<td>18</td>
<td>4</td>
<td>15</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>UCB</td>
<td>103</td>
<td></td>
<td>CNI/MMF + ATG</td>
<td>34 (4 y)</td>
<td>33 (4 y)</td>
<td>35 (1000 d)</td>
<td>1 (B/W)</td>
<td>11 (extensive)</td>
<td>23 (2 y)</td>
<td>30</td>
</tr>
<tr>
<td>Solomon et al 10 (single center)</td>
<td>MRD</td>
<td>176</td>
<td>Mixed malignancy</td>
<td>Multiple different regimens used MA in 77%</td>
<td>CsA/MTX</td>
<td>78</td>
<td>73</td>
<td>23</td>
<td>63</td>
<td>58</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>(m)MUD</td>
<td>30</td>
<td></td>
<td>PTCY/tacro/MMF</td>
<td>71 (2 y)</td>
<td>64 (2 y)</td>
<td>3 (2 y)</td>
<td>43 (all grade)</td>
<td>22 (moderate/severe)</td>
<td>24 (2 y)</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Haplo</td>
<td>98</td>
<td></td>
<td>PTCY/tacro/MMF</td>
<td>60 (3 y)</td>
<td>38 (3 y)</td>
<td>17 (3 y)</td>
<td>52 (all grade, 6 mo)</td>
<td>15 (all grade, 2 y)</td>
<td>36 (3 y)</td>
<td>36</td>
</tr>
<tr>
<td>Kanes et al 11 (registry study)</td>
<td>MUD</td>
<td>491</td>
<td>Lymphoma</td>
<td>NMA (fludarabine, 2-Gy TBI, cyclophosphamide)</td>
<td>CNI</td>
<td>62</td>
<td>49</td>
<td>22</td>
<td>60</td>
<td>62</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>MUD</td>
<td>21</td>
<td></td>
<td>CNI + ATG</td>
<td>50</td>
<td>47</td>
<td>26</td>
<td>56</td>
<td>37</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Haplo</td>
<td>185</td>
<td></td>
<td>PTCY/CNI/MMF</td>
<td>50 (3 y)</td>
<td>38 (3 y)</td>
<td>17 (3 y)</td>
<td>52 (all grade, 6 mo)</td>
<td>15 (all grade, 2 y)</td>
<td>36 (3 y)</td>
<td>36</td>
</tr>
<tr>
<td>Guria et al 12 (registry study)</td>
<td>MUD</td>
<td>1982</td>
<td>AML</td>
<td>Multiple different regimens used MA in 54%</td>
<td>CNI + MMF/TXC</td>
<td>44 (RIC500/MA)</td>
<td>NR</td>
<td>23 (RIC), 20 (MA) (3 y)</td>
<td>11 (RIC), 13 (MA)</td>
<td>52 (RIC), 30 (MA)</td>
<td>42 (RIC), 39 (MA)</td>
</tr>
<tr>
<td></td>
<td>Haplo</td>
<td>192</td>
<td></td>
<td>PTCY/CNI/MMF</td>
<td>44 (RIC)</td>
<td>45 (MA) (3 y)</td>
<td>34 (4 y)</td>
<td>34 (1000 d)</td>
<td>23 (extensive)</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Blase et al 13 (single center)</td>
<td>MRD</td>
<td>47</td>
<td>Mixed malignancy</td>
<td>Multiple different regimens used NMA in 68%</td>
<td>CsA + ATG</td>
<td>78</td>
<td>64</td>
<td>11</td>
<td>13</td>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>(m)MUD</td>
<td>63</td>
<td></td>
<td>CsA + ATG (1x-MMF)</td>
<td>51</td>
<td>38</td>
<td>34</td>
<td>25</td>
<td>14</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Haplo</td>
<td>31</td>
<td></td>
<td>PTCY/CNI/MMF</td>
<td>70 (2 y)</td>
<td>67 (2 y)</td>
<td>10 (2 y)</td>
<td>10 (B/W)</td>
<td>0 (severe, 2 y)</td>
<td>23 (2 y)</td>
<td>23</td>
</tr>
<tr>
<td>Bashe et al 14 (single center)</td>
<td>MRD</td>
<td>181</td>
<td>Mixed malignancy</td>
<td>Multiple different regimens used</td>
<td>Tacro/MTX + ATG</td>
<td>72</td>
<td>56</td>
<td>14</td>
<td>28</td>
<td>44</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>MUD</td>
<td>178</td>
<td></td>
<td>Tacro/MTX + alemtuzumab</td>
<td>59</td>
<td>50</td>
<td>16</td>
<td>48</td>
<td>47</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Haplo</td>
<td>116</td>
<td></td>
<td>PTCY</td>
<td>57 (2 y)</td>
<td>54 (2 y)</td>
<td>17 (2 y)</td>
<td>41 (2 y)</td>
<td>31 (moderate/severe)</td>
<td>29 (2 y)</td>
<td>29 (2 y)</td>
</tr>
<tr>
<td>Baker et al 15 (single center)</td>
<td>MRD</td>
<td>59</td>
<td>Mixed malignancy</td>
<td>NMA (fludarabine, 2-Gy TBI, cyclophosphamide)</td>
<td>Tacro/MTX or MMF</td>
<td>403</td>
<td>293</td>
<td>29</td>
<td>8</td>
<td>18</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>(m)MUD</td>
<td>54</td>
<td></td>
<td>PTCY/tacro/MMF</td>
<td>465 (median days)</td>
<td>245 (median days)</td>
<td>28 (2 y)</td>
<td>13 (III-IV, day 180)</td>
<td>24 (moderate/severe, 2 y)</td>
<td>44 (2 y)</td>
<td>44 (2 y)</td>
</tr>
</tbody>
</table>

Bold indicates significant differences between haplo and matched UD.

AML, acute myeloid leukemia; ATG, anti-thymocyte globulin; CNI, calcineurin inhibitor; CsA, cyclosporine; FK, FK506 (tacrolimus); GVHD, graft-versus-host disease; MA, myeloablative conditioning; MDS, myelodysplastic syndrome; MMF, mycophenolate mofetil; MTX, methotrexate; MRD, matched related donor; (m)MUD, (mis)matched unrelated donor; NR, not reported; NMA, nonmyeloablative conditioning; PTCY, pretransplant cyclophosphamide; RIC, reduced-intensity conditioning; tacro, tacrolimus; TBI, total body irradiation; UCB, umbilical cord blood.
transplants from partially HLA-mismatched related and UDs. Of 84 relapses, 23 were with HLA loss and, in the haplo setting, accounted for 33% of the relapses. Postrelapse survival was poor, regardless of whether patients had HLA loss or not. In this study, no case of HLA loss relapse was seen in the UD setting. Although case reports have been published in UD, to date, this mechanism of relapse in that setting appears to be rare or anecdotal.

GVHD
A fairly consistent finding and major stated benefit to the haplo platform is the reduction in GVHD, in particular chronic GVHD. This has been shown in numerous studies. Of the 10 comparative studies, 6 studies show that haplo patients are less likely to experience chronic GVHD (either overall or moderate and/or extensive; Table 1). Severe acute GVHD is more commonly shown to be similar between these groups, although 3 of the 10 studies (Table 1) reported a significant reduction in acute GVHD.

There are several reasons other than the donor source that might explain this difference in (predominantly chronic) GVHD between the groups. Firstly, in many of the comparative studies, mismatched UDs are included in the UD comparator group. Secondly, BM is more commonly used in the haplo setting. Thirdly, the GVHD prophylaxis is PTCY in all haplo cases and the more traditional calcineurin (CNI)/methotrexate or mycophenolate (MMF) combination in the UD setting, with or without additional TCD depending on the study. This raises the question of whether it is the donor source or the “transplant package” that has the greater association with the reduction in GVHD.

This question has been addressed in a few studies. When restricting the population to those who received BM only in the Center for International Blood and Marrow Transplantation Research (CIBMTR) AM study, there were no differences in the rates of chronic GVHD at 3 years between haplo or UD transplantation using either myeloablative (30% [95% confidence interval (CI), 21-39]; n = 85 vs 36% [95% CI, 30-43]; n = 231) or reduced-intensity conditioning (34% [95% CI, 24-44]; n = 77 vs 30% [95% CI, 20-41]; n = 80),

Finally, in a retrospective comparative study of haplo and UD transplant recipients, all of whom were treated with PTCY, CNI, and MMF, Rashidi et al reported no significant difference in the incidence of acute or chronic GVHD (there were no significant differences found in any outcome, with the exception of neutrophil engraftment, which was faster after UD transplantation).

Donor factors
By studying thousands of patient-donor pairs, we have gained a better understanding of how to improve outcomes post–UD transplant through the judicious selection of secondary donor characteristics in those with multiple equally HLA-matched donors. It is well understood in this setting that selection of a younger donor improves survival, that avoiding disadvantageous HLA-DPB1 and killer-cell immunoglobulin-like receptor (KIR) types improves survival, and that selection by cytomegalovirus status, ABO type, and sex can mitigate transplant complications. Algorithms to prioritize these factors are being developed. In addition, it is known that the selection of BM over PBSCs reduces chronic GVHD. The use of a haplo donor in general offers fewer choices of secondary characteristics, and few studies have addressed donor selection algorithms. Another important factor is donor-specific antibodies, which present a barrier to transplant in the haplo setting.

In conclusion, through the study of thousands of patients receiving UD transplants over 4 decades, the transplant community has gained an excellent understanding of the expected short- and long-term toxicities and outcomes. We know how to select a UD to maximize good outcomes, and we have a solid backbone on which to investigate newer factors to further this improvement (HLA-DPB1 and KIR). Importantly, we have an extensive registry of volunteer UDs, with multiple protections in place to ensure their participation is clinically, ethically and morally appropriate. Physicians performing haplo transplants should ensure that the health and well-being of their patient’s related donors are being given equal consideration.

In contrast, haplo transplants are more recent, and while these clearly show the benefit of extending the possibility of transplant to certain patients, particularly those from ethnic minority groups, or when the cost of UD provision is high, certain long-term outcomes (including cost) are uncertain. Finally, while comparative studies show survival to be similar to UD transplants, these studies are nonrandomized and underpowered, and none to date have shown survival with a haplo donor to be superior. Since an appropriately powered randomized trial to show noninferiority in disease-free survival in haplos would require >3000 patients, this is unlikely to be feasible. For all these reasons, it is currently too early to know whether transplantation with a haplo donor will ultimately be as good or better than transplantation using a matched UD.

Acknowledgments
The CIBMTR is supported by grant 5U24-CA076518 from the National Institutes of Health, National Cancer Institute, National Heart, Lung, and Blood Institute, and National Institute of Allergy and Infectious Diseases; and by grant 5U10HL069294 from the National Institutes of Health, National Heart, Lung, and Blood Institute and National Cancer Institute.

Authorship
Contribution: The article was written in its entirety by B.E.S.

Conflict-of-interest disclosure: The author declares no competing financial interests.

Correspondence: Bronwen E. Shaw, CIBMTR/Froedtert & the Medical College of Wisconsin, 9200 W Wisconsin Ave, Suite C5500, Milwaukee, WI 53226; e-mail: beshaw@mcw.edu.
References


24. McCurdy SR, Fuchs EJ. Comparable outcomes for hematologic malignancies after HLA-haploidentical transplantation with...


49. Ciurea SO, Champlin RE. Donor selection in T cell-replete haploididentical hematopoietic stem cell transplantation:


DOI 10.1182/bloodadvances.2016002188 © 2017 by The American Society of Hematology