Umbilical cord blood transplantation in adults: An update and future prospects

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Introduction

The first umbilical cord blood (UCB) transplantation (UCBT) was done in 1988 for a 5-year-old boy suffering from Fanconi anemia¹. Already more than 2 decades have passed since then, and a tremendous effort and contribution by patients and physicians in transplant hematology have been made during the period, allowing UCB to be used as a graft source to treat a variety of hematological disorders, including in adults. One unique fact related to UCBT is that Asia performs the highest number of UCBT procedures, contrasting with the results for unrelated peripheral blood progenitor cells (u-PBPC) transplantation (u-PBPCT) or bone marrow (u-BM) transplantation (u-BMT), according to a survey done in 2006². So far, UCB has been considered as an alternative hematopoietic stem cell (HSC) source, mainly due to higher incidences of engraftment failure and non-relapse mortality compared to related PBPC or BM. However, the mechanisms behind the above issues have now become clearer.

Global activities of UCBT

50,417 transplants were performed worldwide in 2006, and the numbers are reported to be increasing year by year³. European countries as a whole performed the highest number (24,216) of transplants, North America was next (17,875), and Asian countries as a whole were third (7,096). When the numbers of UCBT were compared among these regions, the highest numbers were performed in Asian countries ranging from 700 to 900 per year, which outweighed those of North America (500–700 per year) or European countries (400–600 per year) from 2006 to 2008. The average body weight in Asian countries was lower than in Europe or in North America, which makes the likelihood of finding a suitable UCB graft higher. In Europe or North America, UCBT using double units has become more popular. According to Eurocord reports, the number of adult patients receiving double units has become more popular. According to Eurocord reports, the number of adult patients receiving double units surpassed the number of adults transplanted with single units in 2005⁴. Thus, it should be noted that there are regional differences in terms of prioritizing graft selection and ways to use grafts.
## Table 1. Comparative studies between unrelated UCB vs. unrelated PBPC/BM or mismatched related PBPC/BM.

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Study group</th>
<th>Donor source</th>
<th>HLA typing method</th>
<th>No. of HLA mismatches</th>
<th>Conditioning regimen</th>
<th>No. of patients</th>
<th>Diagnosis</th>
<th>OS</th>
<th>LFS</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laughlin (5)</td>
<td>IBMTR &amp; NCBP</td>
<td>CB</td>
<td>A, B: low resolution DRB1: high resolution</td>
<td>1 to 2 MAC</td>
<td>AML, ALL, CML, MDS</td>
<td>150</td>
<td>26% (3yr)</td>
<td>23% (3yr)</td>
<td>2004</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BM</td>
<td>A, B: low resolution DRB1: high resolution</td>
<td>0 MAC</td>
<td>AML, ALL, CML, MDS</td>
<td>367</td>
<td>35% (3yr)</td>
<td>33% (3yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 MAC</td>
<td>AML, ALL, CML, MDS</td>
<td>83</td>
<td>20% (3yr)</td>
<td>19% (3yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rocha (6)</td>
<td>Eurocord &amp; EBMT</td>
<td>CB</td>
<td>A, B: low resolution DRB1: high resolution</td>
<td>0 to 3 MAC</td>
<td>AML, ALL</td>
<td>98</td>
<td>36% (2yr)</td>
<td>33% (2yr)</td>
<td>2004</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BM</td>
<td>A, B: low resolution DRB1: high resolution</td>
<td>0 MAC</td>
<td>AML, ALL</td>
<td>584</td>
<td>42% (2yr)</td>
<td>38% (2yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atsuta (8)</td>
<td>JCBBN &amp; JMDP</td>
<td>CB</td>
<td>A, B: low resolution DRB1: high resolution</td>
<td>0 to 2 MAC</td>
<td>AML</td>
<td>173</td>
<td>43% (2yr)</td>
<td>36% (2yr)</td>
<td>2009</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BM</td>
<td>A, B, C, DRB1: high resolution</td>
<td>0 MAC</td>
<td>AML</td>
<td>311</td>
<td>60% (2yr)</td>
<td>54% (2yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CB</td>
<td>A, B: low resolution DRB1: high resolution</td>
<td>0 to 2 MAC</td>
<td>ALL</td>
<td>114</td>
<td>49% (2yr)</td>
<td>45% (2yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BM</td>
<td>A, B, C, DRB1: high resolution</td>
<td>0 MAC</td>
<td>ALL</td>
<td>222</td>
<td>57% (2yr)</td>
<td>51% (2yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eapen (7)</td>
<td>CIBMTR &amp; NCBP &amp; EBMT</td>
<td>CB</td>
<td>A, B: intermediate resolution DRB1: high resolution</td>
<td>0 to 2 MAC</td>
<td>AML, ALL</td>
<td>165</td>
<td>NR</td>
<td>44% (2yr, in remission)</td>
<td>15% (2yr, not in remission)</td>
<td>2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BM</td>
<td>A, B, C, DRB1: high resolution</td>
<td>0 MAC</td>
<td>AML, ALL</td>
<td>322</td>
<td>NR</td>
<td>52% (2yr, in remission)</td>
<td>17% (2yr, not in remission)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>PBPC</td>
<td>A, B, C, DRB1: high resolution</td>
<td>0 MAC</td>
<td>AML, ALL</td>
<td>632</td>
<td>NR</td>
<td>50% (2yr, in remission)</td>
<td>17% (2yr, not in remission)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BM</td>
<td>A, B, C, DRB1: high resolution</td>
<td>1 MAC</td>
<td>AML, ALL</td>
<td>140</td>
<td>NR</td>
<td>41% (2yr, in remission)</td>
<td>14% (2yr, not in remission)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PBPC</td>
<td>A, B, C, DRB1: high resolution</td>
<td>1 MAC</td>
<td>AML, ALL</td>
<td>256</td>
<td>NR</td>
<td>39% (2yr, in remission)</td>
<td>17% (2yr, not in remission)</td>
<td></td>
</tr>
<tr>
<td>Kanda (9)</td>
<td>JCBBN &amp; JSHCT</td>
<td>CB</td>
<td>A, B, DRB1: low resolution</td>
<td>0 to 2 MAC</td>
<td>AML, ALL, CML, MDS</td>
<td>1390</td>
<td>38% (3yr)</td>
<td>NR</td>
<td>2012</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>related PBPC/ BM</td>
<td>A, B, DRB1: low resolution</td>
<td>1 MAC</td>
<td>AML, ALL, CML, MDS</td>
<td>894</td>
<td>39% (3yr)</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atsuta (8)</td>
<td>JCBBN &amp; JMDP</td>
<td>CB</td>
<td>A, B: intermediate resolution DRB1: high resolution</td>
<td>0 to 2 MAC</td>
<td>AML, ALL, MDS</td>
<td>351</td>
<td>47% (3yr)</td>
<td>42% (3yr)</td>
<td>2012</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BM</td>
<td>A, B, C, DRB1: high resolution</td>
<td>1 (class I) MAC</td>
<td>AML, ALL, MDS</td>
<td>424</td>
<td>47% (3yr)</td>
<td>44% (3yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (class II) MAC</td>
<td>AML, ALL, MDS</td>
<td>248</td>
<td>41% (3yr)</td>
<td>36% (3yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 MAC</td>
<td>AML, ALL, MDS</td>
<td>356</td>
<td>38% (3yr)</td>
<td>36% (3yr)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CB, cord blood; BM, bone marrow; PB, peripheral blood progenitor cell; IBMTR, International Bone Marrow Transplant Registry; NCBP, National Cord Blood Program; EBMT, European Blood and Marrow Transplant Group; JCBBN, Japan Cord Blood Bank Network; JMDP, Japan Marrow Donor Program; CIBMTR, Center for International Blood and Marrow Transplant Research; JSHCT, The Japan Society of Hematopoietic Cell Transplantation; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; NR, not reported.
Clinical outcomes of UCBT in comparison with u-PBPCT/u-BMT

The major results of research comparing UCBT vs. u-PBPCT/u-BMT are shown in Table 1. Laughlin et al. compared outcomes of UCBT and u-BMT by analyzing data reported to the International Bone Marrow Transplant Registry and the National Cord Blood Program (NCBP) of the New York Blood Center (150 UCB and 450 u-BM recipients). In UCBT, hematopoietic recovery was slower (median times to neutrophil recovery were 27, 18, and 20 days for UCB, HLA-matched, and mismatched u-BM recipients, respectively), while grade II–IV acute graft-versus-host disease (GVHD) was similar to HLA-matched u-BM and less likely than HLA-mismatched u-BM. The overall mortality of UCB recipients was inferior to matched u-BM, but similar to mismatched u-BM. Eurocord and the European Blood and Marrow Transplant Group (EBMT) performed similar analysis with different patient cohorts (98 UCB and 584 u-BM recipients), and showed delayed neutrophil recovery and lower risk of grade II–IV acute GVHD in UCBT. The incidence of chronic GVHD, transplantation-related mortality (TRM), relapse rate, and leukemia-free survival were not significantly different between UCBT and u-BMT. These 2 papers suggest UCBT can be an alternative to u-BMT when there is no suitable unrelated donor available. Since these 2 papers assessed HLA compatibility defined by serology or low-resolution DNA typing for class I, Eapen et al. analyzed more recent data by using high resolution HLA typing for both class I and II, and added u-PBPC recipients to the analysis. Data on 1,525 acute leukemia patients (165 UCB, 888 u-PBPC, and 472 u-BM recipients) who were transplanted between 2002 and 2006 are available from the Center for International Blood and Marrow Transplant Research (CIBMTR), NCBP, the Acute Leukemia Working Party of the EBMT, and the Eurocord-Netcord registry. Again, neutrophil recovery was slower in UCB recipients than in u-PBPC or u-BM recipients (median times to neutrophil recovery were 24, 14, and 19 days for UCB, u-PBPC, and u-BM recipients, respectively). In UCBT, the incidence of grade II–IV acute GVHD was comparable to or lower, while that of chronic GVHD was lower than, u-PBPCT or u-BMT. TRM was significantly higher after UCBT than matched u-PBPCT or u-BMT, while leukemia relapse was similar regardless of HSC source. Leukemia-free survival after UCBT was comparable with u-PBPCT or u-BMT. In Japan, Atsuta et al. analyzed data from the Japanese registry (the Japan Cord Blood bank Network and the Japan Marrow Donor Program) comparing UCBT and u-BMT, and the outcomes for acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) patients were assessed separately. In AML patients, UCB recipients showed a higher TRM rate and a similar relapse rate, resulting in inferior overall and leukemia-free survival compared to u-BM recipients. In ALL patients, all the above parameters assessed were comparable between UCB and u-BM recipients. These results came from registry data confirmed UCB as an acceptable alternative to 8/8 and 7/8 HLA-matched u-PBPC and u-BM when there is no suitable unrelated donor available, or when a transplant is needed urgently.

Kanda et al. compared UCBT outcomes with related donors with an HLA 1-antigen mismatch in the GVH direction (RD/1AG-MM-GVH) by using the Japan national registry data set. Both can serve as alternatives to HLA-identical siblings or matched unrelated donors (MUD), particularly for those who need immediate transplantation. The survival rate in the UCBT group was comparable to that in the RD/1AG-MM-GVH group, and even favorable compared to that in an RD/1AG-MM-GVH group with an HLA-B mismatch. Another paper from the Japanese registry reported that outcomes were comparable between UCBT and 1 locus mismatched u-BM.

To date, there are not many data demonstrating superiority of UCBT over matched u-BMT, as mentioned above. However, considering the fact that all these previous reports were retrospective, that these results produced in early 2000 are from patients whose diseases were in a clinically desperate situation when UCBs were the only possible graft source for allo-HSCT, and that most of the transplant hematologists were in the process of establishing technologies to successfully perform UCBT, there is every reason for UCBT to be considered inferior to u-PBPCT/u-BMT. According to CIBMTR and NCBP registry data analysis, pediatric patients with acute leukemia who received HLA-matched UCB (n = 35) showed better 5-year probability of leukemia-free survival (60%) than HLA-matched u-BM recipients (n = 116, 38%). In adult patients, a group from Tokyo University reported better survival for UCB recipients than u-BM patients treated with the same myeloablative pretransplant conditioning and supportive care done in a single institute. The 1-year TRM was only 9% in UCBT,
but 29% in u-BMT. These intriguing and encouraging results need to be confirmed by prospective multi-center trials, but suggests the possibility that UCBT could be prioritized over u-PBPC/u-BM in the future.

Higher incidence of engraftment failure and associated factors

One of the major obstacles to be overcome in UCBT is engraftment failure, which can often be a life-threatening complication. There have been many reports showing that higher doses of total nucleated cells (TNC) or CD34+ cells were associated with better engraftment\textsuperscript{13-16}. Rubinstein et al. reported that the time to myeloid engraftment correlated significantly with the TNCs per kg of recipient body weight. This is the principal reason for selecting a UCB unit that has higher cell doses per recipient body weight. Similarly, a higher number of CD34+ cells was shown to be associated with better engraftment\textsuperscript{15,16}. Therefore, transplantable UCB units have been considered to be \(2\times10^7\) TNC/kg body weight or higher. However, the “threshold” cell dose does not imply all the recipients of UCB units containing TNC doses less than \(2\times10^7\)/kg will develop engraftment failure. Takahashi et al. reported 7 recipients who received less than \(2\times10^7\)/kg TNC and 5 achieved donor cell engraftment, although the duration to neutrophil recovery took longer than the average (median 24 days, range, 23–41)\textsuperscript{12}.

The degree of HLA disparity has been significantly associated with engraftment\textsuperscript{15,17,18}. Kurtzberg et al. collected data from a multicenter prospective phase II study and analyzed them retrospectively in terms of HLA allele mismatches, and found better neutrophil engraftment was observed in those who received 5 or 6 of 6 matched units than those who received 3 or 4 of 6 (Hazard ratio 1.39, \(P = .04\) in multivariate analysis). Barker et al. analyzed 1,061 patients to investigate the combined impact of TNC and HLA matches on outcome\textsuperscript{19}. Patients received myeloablative conditioning in a single unit UCBT for treatment of leukemia or myelodysplasia. HLA-match (o-mismatch,O-MM) were associated with improved neutrophil engraftment (\(P < .001\)), while there was no difference between recipients of units with 1-or 2-MM. TNC dose and HLA-matches each affected survival independently via their effect on transplant-related mortality, so patients were subdivided into 4 groups in terms of TRM; (i) 0 -MM with any cell dose, (ii) 1-MM units with TNC \(\geq 2.5\times10^7$/kg and 2-MM units with TNC \(\geq 5.0\times10^7$/kg, (iii) 2-MM units with TNC 2.5–4.9\(10^7$/kg, and (iv) 1-or 2-MM units with TNC \(<2.5\times10^7$/kg. Group (i) showed the lowest TRM, and it increased along with increasing group number. TRM and survival were comparable between 1-MM recipients with a TNC dose of 2.5 to 4.9\(10^7$/kg and those receiving 2-MM units with a dose \(5.0\times10^7$/kg or greater, suggesting better HLA matching could compensate for a lower TNC dose. There are several reports on the differential impact of the vector of HLA mismatches on engraftment. Kögler et al. reported by analyzing 122 UCBT that 1 or 2 HLA-A locus disparities in the HVG direction, based on high resolution HLA typing, were associated with significantly reduced incidence of engraftment\textsuperscript{20}. Stevens et al. reported that patients with HLA mismatches only in the GVH direction showed faster engraftment than those with 1 bidirectional mismatch (HR = 1.6, \(P = .003\)), while those who received grafts with mismatches only in the HVG direction tended to have a lower rate of myeloid engraftment (\(P = .095\)), by analyzing data from 1,202 UCBT recipients\textsuperscript{21}. In contrast, Matsuno et al. reported a higher number of HLA mismatches in the GVH direction, but not in the HVG direction, negatively affects engraftment\textsuperscript{22}. The discrepancy between these results is likely due to the differences in patients’ backgrounds, such as pretransplant conditioning or GVHD prophylaxis (Table 2). When a similar analysis was done using a much larger cohort of patients, the differential effects were not seen in either direction, most likely due to the fact that there were so many variations in the registry data, resulted in a diluted impact of each factor that could affect engraftment\textsuperscript{23}.

The presence of donor-specific anti-HLA antibodies was also shown to be associated with poor engraftment. Takanashi et al. reported that among 89 patients who had anti-HLA antibodies, 20 cases whose antibody had specificity against the cord blood HLA showed only 32% neutrophil recovery, which was significantly worse than those who did not have antibodies (83%) or who had antibodies that had no specificity against UCB HLA (73%)\textsuperscript{23}. Moreover, insufficient suppression of host immune cells seems to have an impact on engraftment failure. Horwitz reported that of 10 adult patients who underwent UCBT with a myeloablative dose of intravenous busulfan along with fludarabine as pretransplant conditioning, donor-derived neutrophil recovery was observed only in 2 patients\textsuperscript{24}. Considering that the same regimen has been widely used for
Table 2. Reports on the effect of the HLA mismatch direction on engraftment

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Study group</th>
<th>No. of patients</th>
<th>Conditioning regimen</th>
<th>Diagnosis</th>
<th>HLA typing at selecting CB unit</th>
<th>GVHD prophylaxis</th>
<th>Cumulative incidence of neutrophil recovery</th>
<th>HLA mismatch direction and engraftment</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kögler (19)</td>
<td>Eurocord &amp; CB bank in Düsseldorf</td>
<td>122</td>
<td>Various</td>
<td>Various</td>
<td>A, B: low resolution DRB1: high resolution</td>
<td>CsA alone (14%)</td>
<td>78 +/- 4% (day 60) high resolution typing in HVG direction: 0 mismatch (n=70) 87% 1+2 mismatches (n=52) 65% (P = 0.01)</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Matsuno (15)</td>
<td>Toranomon Hospital</td>
<td>163</td>
<td>Various</td>
<td>Various</td>
<td>A, B, DR: intermediate resolution</td>
<td>CsA alone (45%) TAC alone (55%)</td>
<td>89% (day 60) among 152 evaluable pts 0+1 mismatch (n=53) 96% 2+3 mismatches (n=99) 85% (P &lt; 0.001)</td>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>Stevens (20)</td>
<td>NYBC</td>
<td>1202</td>
<td>MAC (92%)</td>
<td>Various</td>
<td>A, B: intermediate resolution DRB1: high resolution</td>
<td>CsA + PSL (62%) MTX containing (17%) TAC (11%) Others (1%)</td>
<td>76%</td>
<td>2011</td>
<td></td>
</tr>
<tr>
<td>Kanda (21)</td>
<td>JCBBN</td>
<td>2977</td>
<td>Various</td>
<td>Various</td>
<td>A, B, DR: intermediate resolution</td>
<td>CsA alone (8%) Tac alone (14%) CsA + MTX (33%) TAC + MTX (25%) CsA + MMF (3%) TAC + MMF (5%) CsA + corticosteroid (3%) TAC + corticosteroid (1%) Other (2%) Missing (1%)</td>
<td>70%</td>
<td>2012</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NYBC, New York Blood Center; JCBBN, Japan Cord Blood Bank Network; MAC, myeloablative conditioning; CsA, ciclosporine; PSL, prednisolone; MTX, methotrexate; ATG, antithymocyte globulin; TAC, tacrolimus.
allo-PBPC/BM transplants without increased incidence of engraftment failure, more intensive suppression of host immune cells is required so that UCB cells outcompete and can dominate hematopoiesis.

**Pre-engraftment immune reactions and hemophagocytic syndrome**

The vast majority of the T cells contained in UCB are shown to have a naïve phenotype, and the initial idea of using an HLA-mismatched UCB unit was based on the assumption that the immature T cells are less capable of causing severe allogeneic immune reactions. However, several groups including us have observed unique clinical symptoms characterized by high fever in the absence of infection, diffuse erythematous skin rash, or body weight gain due to fluid retention. Median day of onset was day 9 post-transplant, and we termed this a pre-engraftment immune reaction (PIR) or “day 9 fever”. The etiology of PIR has not been well clarified, although the presence of a cytokine storm has been postulated considering that the onset of PIR is considerably earlier than WBC recovery and clinical manifestations involved multiple organs resembling diseases associated with hypercytokinemia, such as severe systemic infections, autoimmune disorders, lymphoid malignancies, and phagocyte hematopoietic cells, resulting in decreased hematopoiesis. Our study, in which patients received less intensive GVHD prophylaxis with a calcineurin inhibitor alone, showed that 20 out of 119 patients were diagnosed as HPS, and all 14 who failed engraftment revealed features of HPS. As mentioned earlier, the degree of HLA mismatches in the GVH direction had more impact on engraftment kinetics in a similar patient cohort, suggesting immune cells in UCB were likely activated by mismatched HLA under relatively less intensive GVHD prophylaxis.

**Table 3. Reports on pre-engraftment immune reactions**

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Study group</th>
<th>Conditioning regimen (No.)</th>
<th>Diagnosis</th>
<th>GVHD prophylaxis</th>
<th>Incidence of PIR</th>
<th>Overall survival</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kishi (26)</td>
<td>Toranomon, Japan</td>
<td>RIC (57)</td>
<td>Various</td>
<td>CsA</td>
<td>78%</td>
<td>NR</td>
<td>2005</td>
</tr>
<tr>
<td>Narimatsu (27)</td>
<td>Nagoya, Japan</td>
<td>MAC (31), RIC (46)</td>
<td>Various</td>
<td>CsA/TAC alone (35) (MTX-), TAC/PDL (2)</td>
<td>49%</td>
<td>16% at day 180 (MTX-)</td>
<td>2007</td>
</tr>
<tr>
<td>Patel (29)</td>
<td>MSKCC, USA</td>
<td>MAC (36), RIC (16)</td>
<td>Various</td>
<td>CsA/MMF</td>
<td>31%</td>
<td>64% at 1 year, 61% at 1 year (PIR+), 62% at 1 year (PIR-)</td>
<td>2009</td>
</tr>
<tr>
<td>Frangoul (28)</td>
<td>COBLT, USA</td>
<td>MAC (326)</td>
<td>Various</td>
<td>CsA/PSL/ATG</td>
<td>20%</td>
<td>NR</td>
<td>2009</td>
</tr>
<tr>
<td>Wang (30)</td>
<td>Anhui, China</td>
<td>MAC (72), RIC (9)</td>
<td>Various</td>
<td>CsA/MMF</td>
<td>63%</td>
<td>56.6% at 1 year, 56.8% at 1 year (PIR+), 56.0% at 1 year (PIR-)</td>
<td>2011</td>
</tr>
<tr>
<td>Uchida (48)</td>
<td>Toranomon, Japan</td>
<td>RIC (58)</td>
<td>Various</td>
<td>TAC (29), TAC/MMF (29)</td>
<td>76% (severe 52%), 69% (severe 16%)</td>
<td>45% at 2 years, 33% at 2 years</td>
<td>2011</td>
</tr>
</tbody>
</table>

Abbreviations: MSKCC, Memorial Sloan Kettering Cancer Center; COBLT, Cord blood transplant study of National Institute of Health; RIC, reduced intensity-conditioning; MAC, myeloablative conditioning; CsA, ciclosporine; TAC, tacrolimus; MTX, methotrexate; MMF, mycophenolate mofetil; PIR, pre-engraftment immune reactions; NR, not reported.
Thus, immune cells in UCB have unique biological properties distinct from those in PBPC or BM. Although the incidence and severity of GVHD in UCBT were reported to be lower than, or comparable to, PBPC or BM transplantation even with HLA-mismatched units, it is surprising to see how active T cells in UCB proliferate and dominate from a very early time point post-UCBT.

**Strategies to overcome engraftment failure**

The total number of nucleated cells per kg recipient body weight has been the main factor associated with engraftment. In an attempt to increase the total cell numbers to be infused, co-transplantation of two UCB units has been tried by various institutes. Verneris et al. reported outcomes of 93 patients with acute leukemia who underwent UCBT with double units (dUCBT) and compared them with 84 single unit UCBT (sUCBT) recipients. The incidence of sustained engraftment (90% vs. 86%, P = .36), time to neutrophil recovery (22 days vs. 25 days, P = .11), the proportion of patients achieving platelet recovery > 5 x 10^10/L at 6 months (70% vs. 62%, P = .24) were similar for recipients of sUCB and dUCB. The overall survival was also similar for both groups, while interestingly recipients of dUCB showed a higher incidence of T-cell engraftment failure.
of grade II–IV acute GVHD (48% vs. 29%, P<.01) and a lower incidence of relapse (19% vs. 34%, P = .04) compared to sUCB. Based on these early results, the number of adult patients receiving dUCBT has surpassed the number of adults transplanted with sUCB reported to Eurocord since 20054. Although the results are promising, they are all from retrospective analysis. Only one of two units eventually engrafted and the role of adding another unit which was excluded remains unclear. The mechanisms of increased incidence of GVHD and reduction of relapse incidence are not clear. There are two phase III trials ongoing comparing single versus double UCBT in the US (NCT00412360) and in France (NCT01067300).

Another attempt to improve the engraftment rate is to inject UCB cells directly into the bone marrow space. An Italian group reported 32 patients who received UCBT by graft infusion in the superior-posterior iliac crest. There were no complications related to the procedure, and except 4 who had advanced-stage disease and died within 12 days, all remaining 28 patients achieved neutrophil recovery at a median of 23 days (range, 14–44) and platelet recovery ≥ 20 × 10^9/L at a median of 36 days (range, 16–64)42. There was a somewhat conflicting report from a group in Minnesota who tried intra-bone marrow injection of one of the 2 UCBs to enhance engraftment. Nine of 10 patients enrolled achieved neutrophil engraftment, but only 4 of them were with the unit injected intra-bone marrow, and the median time was 21 days, which was comparable to that of i. v. dUCBT43. Thus, the superiority of using intra-bone marrow injection over intravenous infusion needs further investigation, although faster platelet recovery or lower incidence of severe acute GVHD, suggested by the Italian group, are promising42.

Other strategies to enhance engraftment are hematopoietic stem cell expansion. There have been several reports on clinical trials using expanded units along with unmanipulated ones. The Fred Hutchinson Cancer Research Center group utilized a notch ligand (Delta1 fused to the Fc domain of human IgG) and found a reduction in time to engraftment to 16 days46. This result is promising, although the engraftment of an expanded unit was transient and the majority of long-term hematopoiesis was derived from unmanipulated units. A group in France is currently recruiting patients for a clinical trial using an expanded single unit UCB (NCT01034449). Positively selected CD34+ cells were cultured in liquid media with cytokines, and were infused on day 0 along with cells in a CD34⁺ fraction. So far, 6 out of 7 patients achieved engraftment, and the median time to engraftment was reduced to 7 days (range, 6–19)45. This phase II trial is estimated to be completed in 2014.

There are groups who co-infuse third-party hematopoietic stem cells from either donor haploidentical or with no shared haplotype to recipients with UCB. Fernandez et al. reported 55 patients who received UCBT and third-party CD34+ and/or CD133+ cells. There were 2 deaths before neutrophil recovery, and estimated cumulative incidence of neutrophil recovery was 96%. Median times to neutrophil recovery and platelet ≥ 20 × 10^10/L were 10 days (range, 9–36) and 32 days (range, 13–98), respectively. Sequential chimerism analysis showed initial predominance of third-party donor cells followed by progressive replacement by cells from UCB at a median 44 days (range, 11–186)46, 47. A group in Chicago reported 45 patients who received co-transplantation of CD34+ cells from haploidentical donors and UCB following reduced-intensity conditioning. Neutrophil engraftment occurred at day 11 post transplant, and the majority of the patients showed early engraftment of haplo-donor cells, followed by durable engraftment of UCB by 100 days post-transplant48.

HPS has been reported to be one of the significant causes of engraftment failure following UCBT79. For HPS, although several treatment strategies have been reported to be successful, such as low dose etoposide49 or dexamethasone palmitate50, the outcomes are generally poor once it develops due to eventual engraftment failure39. To prevent development of HPS, choosing UCB units that have fewer HLA mismatches in the GVH direction would be beneficial, considering the previous report16, although this is not always possible since the factor of cell dose comes first, before HLA mismatches. To reduce severe PIR, we conducted a matched pair analysis comparing 2 regimens for GVHD prophylaxis, tacrolimus (Tac) + mycophenolate mofetil (MMF) vs. Tac alone, to investigate the effect of MMF. Although the total incidence of any PIR was comparable between Tac + MMF and Tac alone, the incidences of severe forms of PIR was decreased significantly in the Tac + MMF group, resulting in lower TRM before engraftment and in higher engraftment (90% vs. 66% for Tac + MMF vs. Tac alone, P<0.05)50. No HPS was observed in the Tac + MMF group. The majority of institutes worldwide use GVHD prophylaxis consisting of a combination of a calcineurin inhibitor and a corticosteroid14, MMF51, sirolimus52, or methotrexate12, which is much more intensive than using a calcineurin inhibitor alone. To reduce
TRM, intensive GVHD prophylaxis is of benefit, particularly for those who are elderly or have comorbidities not eligible for conventional pretransplant conditioning.

Once engraftment failure develops, the treatment options are limited, and salvage transplantation is generally attempted. Waki et al. reported a nationwide retrospective study of secondary UCBT for 80 patients who developed graft failure. Forty-five out of 61 patients who survived for more than 28 days post-second transplant achieved neutrophil engraftment (74%) at a median of 21 days, and the 1-year overall survival was 33%. Patients who received pretransplant conditioning incorporating alkylating agents showed better engraftment. There is another report on secondary transplants using haploidentical donors and reduced-intensity conditioning (haplo-RIC) from a group in Hyogo. All 8 patients who underwent secondary transplants with haplo-RIC achieved neutrophil engraftment at a median of 10 days, faster than described in the previous report on UCBT, and the probability of overall and disease-free survival at 5 years were 75% and 56%, respectively. Prolonged neutropenia in those who had engraftment failure put them at high risk of fatal infections. In order to reduce the duration of neutropenia, a pretransplant regimen consisting of fludarabine (30 mg/m²), TBI (2 Gy), and cyclophosphamide (2g/m²) in 1 day, a so called ‘one-day regimen’, was reported to be useful. Closely monitoring patients who are at risk of engraftment failure by frequent bone marrow examination or chimerism analysis (particularly in T-cell fractions) is also necessary to determine the optimal timing of the secondary transplant without delay.

Conclusions

Recent advances in cord blood banking systems have made it possible to provide transplantable units for more than 90% of patients in need. The number of UCBT procedures, particularly for adult patients, is increasing in Japan. Although a higher rate of engraftment failure and associated higher early mortality compared to other stem cell sources are still big problems to be solved, the mechanisms behind them have gradually become clear by analyzing accumulated clinical data, and strategies for how to cope with them are now being developed based on scientific evidence. There are still many other barriers to be overcome, such as infections, GVHD, non-infectious lung complications, or disease relapse, to improve the overall outcome of UCBT, although not discussed here. Asian countries, particularly Japan, are leading the world in terms of the numbers of UCBT procedures, and are responsible for providing clinical results and data to improve UCBT outcomes. Once various problems have been solved, given the obvious advantages of UCB such as its rapid availability and zero risk for donors, a time when UCB becomes the primary graft source for allogeneic transplantation may not be far away.

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References

10. Atsuta Y, Morishima Y, Suzuki R, et al. Comparison of


