

## REVIEW

# Umbilical cord blood transplantation in adult myeloid leukemia

WW Tse, SL Zang, KD Bunting and MJ Laughlin

Division of Hematology/Oncology, Department of Medicine, Case Western Reserve University, Case Comprehensive Cancer Center, Abraham J. and Phyllis Katz Cord Blood Foundation, Center for Stem Cell and Regenerative Medicine, Cleveland, OH, USA

**Allogeneic hematopoietic stem cell (HSC) transplantation is a life-saving procedure for hematopoietic malignancies, marrow failure syndromes and hereditary immunodeficiency disorders. However, wide application of this procedure is limited by availability of suitable human leucocyte antigen (HLA)-matched adult donors. Umbilical cord blood (UCB) has been increasingly used as an alternative HSC source for patients lacking matched-HSC donors. The clinical experience of using UCB transplantation to treat pediatric acute leukemias has already shown that higher-level HLA-mismatched UCB can be equally as good as or even better than matched HSC. Recently, large registries and multiple single institutional studies conclusively demonstrated that UCB is an acceptable source of HSCs for adult acute leukemia patients who lack HLA-matched donors. These studies will impact the future clinical allogeneic stem cell transplantation for acute myeloid leukemia (AML), which is the most common acute leukemia in adults. UCB has unique advantages of easy procurement, absence of risk to donors, low risk of transmitting infections, immediate availability, greater tolerance of HLA disparity and lower-than-expected incidence of severe graft-versus-host disease. These features of UCB permit successful transplantation available to almost every patient who needs it. We anticipate that using UCB as a HSC source for allogeneic transplantation for adult AML will increase dramatically over the next 5 years, by expanding the available allogeneic donor pool. Clinical studies are needed with focus on disease-specific UCB transplantation outcomes, including AML, acute lymphoblastic leukemia, and lymphoma.**

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## Introduction

Allogeneic blood and bone marrow stem cell transplantation (SCT) has been used successfully to treat children and adults with high-risk or relapsed hematopoietic malignancies, marrow failure syndromes and hereditary immunodeficiency disorders. However, its clinical use is largely limited by the availability of suitable human leucocyte antigen (HLA)-matched hematopoietic stem cell (HSC) donors. In general, only 30% of patients have HLA-identical sibling donors and through the National Marrow Donors Program (NMDP) and other registries worldwide nearly 75% of Caucasians, but far fewer racial minorities can find suitable HLA-matched donors.

Use of umbilical cord blood (UCB) for hematopoietic reconstitution was first reported by Ende *et al.*<sup>1</sup> who infused multiple UCB units into a young man with acute lymphoblastic leukemia in 1972. Although the long-term hematopoietic reconstitution was not reached, Ende *et al.* found that the patient had transient red cell antigen alteration presumably from one of the UCB units. In the 1980s, Broxmeyer *et al.*<sup>2</sup> studied UCB as a potential source of HSC and found that UCB contained hematopoietic progenitors cells and it could be cryopreserved. This discovery opened the door that led to the concept of modern UCB banking and transplantation. These observations ultimately led to a US–French collaborative effort to conduct the first sibling UCB transplant conducted by Elaine Gluckman at the Hospital St Louis in Paris to treat a child with Fanconi anemia in October 1989.<sup>3</sup> Subsequently, more than 8000 transplant procedures have been performed worldwide using UCB from related and unrelated donors into pediatric<sup>4,5–10</sup> and adult patients.<sup>7,11–16</sup> UCB offers the advantages of easy procurement and cryopreservation, no risk to donors, the reduced risk of transmitting infections, immediate availability for emergent transplant and acceptable transplant outcomes despite infusion of partially HLA-mismatched grafts. Because of immunologic permissiveness of UCB, nearly all patients can find at least one potential four of six or better HLA-matched UCB unit through worldwide UCB banks.

To date, the major limitation to the wide use of UCB for allogeneic transplantation has been the low absolute number of HSCs. The advantages and disadvantages of UCB as a source of HSC for allogeneic transplantation are shown in Tables 1 and 2. *Ex vivo* expansion of UCB HSC

Correspondence: Dr MJ Laughlin, Department of Medicine, Case Western Reserve University, University Hospitals Ireland Comprehensive Cancer Center, 10900 Euclid Avenue, WRB2-125, Cleveland, OH 44106-7284, USA.

E-mail: mj113@case.edu

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and transplantation of double UCB is likely to effectively overcome the low cell dose barrier for clinical transplantation for adult recipients. The large registries and multiple single-institutional studies have conclusively demonstrated that UCB is a valuable alternative HSC source for adult acute leukemia patients who need allogeneic SCT. In this review article, we extrapolated the clinical outcomes for adult acute myeloid leukemia (AML) patients who received UCB transplantation. We anticipate exponential increases in the use of UCB transplantation for AML, which is the most common acute leukemia in adults.

## The biological and immunological characteristics of UCB

### UCB biology and hematopoietic reconstitution

Umbilical cord blood permits greater HLA mismatching for recipients compared with traditional marrow or blood HSCs and still has an acceptable incidence of severe graft-versus-host disease (GVHD). Conventional graft characteristics known to allow rapid donor engraftment in recipients include cell dose, CD34 content and HLA matching. Variables in UCB grafts, which have predictive value for time to donor myeloid engraftment, include cryopreserved and reinfused total nucleated graft cell content, CD34 content and infused colony-forming units.<sup>4,7,10,11</sup> In general, each UCB unit has an average of up to 10-fold fewer nucleated and CD34 cells compared with conventional HSC grafts.<sup>17</sup> Therefore, UCB hematopoietic reconstitution is slower and the kinetics of engraftment are delayed.<sup>13,14,18</sup>

In conventional HSC grafts, HLA class I mismatching including HLA-C, with natural killer epitope mismatching in the rejection direction is associated with higher rates of graft rejection and severe acute GVHD,<sup>19,20</sup> and minor

histocompatibility disparity may contribute to graft rejection and graft vs leukemia (GVL) effects.<sup>21</sup> In UCB grafts, specific HLA disparities that may impact its engraftment have not been fully studied. High-resolution HLA matching for UCB graft selection might improve successful engraftment, although most patients will not have allele-matched UCB donors available.

Although delayed or failed engraftment of UCB may be attributable to the lower nucleated cell dose, other characteristics of UCB progenitor cells, such as expression of adhesion molecules,<sup>22</sup> homing capacity<sup>23,24</sup> and differentiation stage may also affect homing and maturation in the recipient and confound engraftment. Improving UCB engraftment in non-obese diabetic/severe combined immunodeficiency mice has been achieved by direct intrafemoral injection of Lin<sup>-</sup>CD34<sup>+</sup> cord blood cells.<sup>25</sup> This work has further identified a sub-population of rapid SRCs within the Lin<sup>-</sup>CD34<sup>+</sup>CD38<sup>lo</sup>CD36<sup>-</sup> population that have a robust reconstitution potential. Because the graft lymphocytes are important for engraftment through inhibiting or eliminating the residual recipient immune cells,<sup>26</sup> future research focusing on these areas may potentially improve the quality and kinetics of the UCB reconstitution.

Unlike marrow and blood HSCs, CD34 quantification in UCB has not been consistently predictive of time to donor hematopoietic engraftment. Variable correlation between CD34 content in the infused UCB grafts and time to hematopoietic engraftment may be confounded by quantification of CD34 in UCB grafts pre-freezing vs post-thaw and by reduced surface epitope density of CD34 on UCB progenitor cells.<sup>27</sup> *In vitro* analyses of UCB CD34 progenitors point to a less mature phenotype compared to marrow and mobilized peripheral blood grafts.<sup>28</sup> The frequency of early HSC is similar in adult marrow, mobilized peripheral blood and UCB, but the proliferative potential of UCB is significantly higher.<sup>29</sup> Cobblestone area-forming cell (CAFC) assays show that UCB CD34<sup>+</sup> cells contain the highest frequency of Cobblestone area-forming cell (week 6) (3.6- to 10-fold higher than bone marrow (BM) CD34<sup>+</sup> cells and peripheral blood stem cell, respectively), and the engraftment capacity *in vivo* by non-obese diabetic/severe combined immunodeficiency repopulation assay is also significantly greater than BM CD34<sup>+</sup> cells.<sup>30</sup> These unique characteristics of UCB allow durable engraftment despite reduced graft cellular content. After UCB transplantation, late graft failure has been uncommon.<sup>8</sup>

**Table 1** Advantages of UCB as HSCs for allogeneic transplantation

1. UCB is considered as 'medical waste', which can be harvested and banked at no risk to the mother or infant.
2. Since collection occurs after birth of a full-term normal infant, UCB is not associated with current ethical concerns raised in use of embryonic stem cells.
3. Ethnic balance in a cord blood repository can be reached and maintained automatically in heterogeneous populations or can be controlled via collection from birthing centers representing targeted minority populations.
4. There is low viral contamination of UCB including cytomegalovirus and Epstein-Barr virus.
5. Banked UCB units are immediately available to patients who need emergency allogeneic stem cell transplantation.
6. Frozen UCB can be easily shipped and thawed for use when needed, compared to freshly donated BM which has a limited shelf-life, necessitating coordination between harvesting physicians, transportation personnel and transplantation teams.
7. There is an undistorted accumulation of HLA genotypes acquired in a UCB bank because stored UCB suffers no attrition except by clinical use, unlike volunteer unrelated adult donor registries in which donors are lost due to advancing age, new medical conditions or geographic relocation.

Abbreviations: HLA = human leucocyte antigen; UCB = umbilical cord blood.

**Table 2** Disadvantages of UCB as HSCs for allogeneic transplantation

1. The limited number of hematopoietic progenitor cells contained in collected UCB units may contribute to failed and delayed kinetics of donor hematologic engraftment and restrict its use in adult recipients.
2. Future development of potential abnormalities of the newborn donor's HSC into adult life and their effects on the recipient is unknown at the time of transplant.
3. It is not feasible to collect additional donor HSC for patients experiencing either graft failure, or donor lymphocytes for recipients who relapse after initial UCB allografting.

Abbreviation: UCB = umbilical cord blood.

### UCB immunology

Human leucocyte antigen disparity between the donor and recipient in allogeneic transplantation is one of the most important determining factors for the incidence and severity of acute and chronic GVHD. Nevertheless, a higher incidence of acute and chronic GVHD has been observed in patients transplanted with HLA-matched unrelated grafts when compared with matched sibling grafts, despite class II HLA matching at high-resolution molecular tissue typing. This may be attributable to reactivity of donor T cells with recipient minor histocompatibility antigens presented within the major histocompatibility complex (MHC). Minor histocompatibility antigen disparity is expectedly greater between unrelated individuals.

Recipients of HLA 4-5/6-matched UCB have acceptable incidence and severity of GVHD when compared with that observed in patients receiving fully HLA-matched marrow and mobilized peripheral blood grafts.<sup>2,4,10-12,28</sup> UCB T lymphocytes are typically CD45RA<sup>+</sup> and express low levels of activated markers, both of which are consistent with a naive Th0 phenotype.<sup>31</sup> Multiple factors that are associated with the reduction of GVHD in UCB recipients include lower lymphocyte numbers, altered recognition of recipient self-antigens by UCB donor T cells interacting with antigen-presenting cells (APCs), and/or reduction in the amplification response of these naive donor T cells activated by recipient alloantigen presented within the context of MHC; thereby limiting the cytokine and cellular cascade necessary to amplify donor alloreactivity to recipient antigens.<sup>32</sup> Alternatively, the low incidence of GVHD among UCB recipients might be also related to the added immunosuppression provided by anti-thymic globulin (ATG) or fludarabine included in myeloablative preparative regimens provided to ensure donor engraftment.

Several *in vitro* studies point to the inherent lack of full expression of immunomodulatory cytokines in the UCB's alloreactive T cells.<sup>31,33</sup> CD4<sup>+</sup>CD25<sup>+</sup> T regulatory cells have been shown to critically regulate self and allograft tolerance in mice in a number of studies. Recent reports also indicate that UCB contains a significant number of T regulatory precursor cells capable of potent suppressor function after culture activation.<sup>34-36</sup> In primary mixed lymphocyte culture, the UCB T cells demonstrate proliferative responses to allogeneic stimulation, but less cytotoxic effector function, proliferative unresponsiveness and activation-induced cell death. Further mechanisms potentially underlying UCB immune tolerance include altered toll-like receptors and adhesion molecule expression on donor graft APCs.<sup>37</sup> Early recovery of natural killer cells that are capable of activating the granzyme/perforin lytic pathway and Fas/Fas ligand activity may explain the low incidence and less severe aGVHD in UCB recipients.<sup>38</sup> Reduced expression of nuclear factor of activated T cells-1 may be one important molecular mechanism underlying reduced cytokine production by UCB graft T cells.<sup>33</sup>

The nature of lymphocyte and APCs in UCB is not only related to lower than expected incidence and severity of acute and chronic GVHD, but also to increased infection risk and/or delayed immune reconstitution. Recent reports suggest that UCB recipients have relatively higher infection

rates in the early post-transplantation period, but comparable infection rates later compared with unrelated adult HSC recipients.<sup>18</sup> One important factor contributing to higher early bacterial infection rates in UCB patients may be related to the prolonged neutropenia and lymphopenia. A second factor may be related to selection of UCB recipients who are more likely to be high-risk and heavily treated patients. UCB patients generally have a longer interval between diagnosis and transplantation, and a higher proportion of these patients are considered intermediate-high risk hematological malignancy.<sup>11</sup> Saavedra<sup>39</sup> reported a high incidence of bacteremia (55%) in 27 adults at early time points after UCB transplant. Ten patients (37%) died prior to day 100. Infection was a direct cause of death in four patients.

Tomonari<sup>40</sup> reported cytomegalovirus (CMV) infection following UCB in 28 adults compared with sibling-matched (related BMT (R-BMT)) and URD BM recipients. CMV antigenemia was observed in 19 (79%) of UCB patients at median 42 days. A higher proportion of UCB patients treated with pre-emptive ganciclovir therapy required a second course of treatment compared with R-BMT and URD BM patients, suggesting that CMV-specific immunity after UCB may be delayed. These higher infection rates, however, are not observed after pediatric UCB transplantation; and are comparable to those observed in children transplanted with marrow from adult unrelated donors.<sup>41</sup> Given the fact that engraftment kinetics and immune reconstitution are not significantly different between pediatric and adult recipients, one of the possible contributing factors may be due to adults being more likely to have had primary CMV infection than children.

Epstein-Barr virus (EBV)-associated post-transplantation lymphoproliferative disease (EBV-PTLD) after allogeneic HSC transplantation is almost exclusively of donor origin. Hence, the onset of EBV-PTLD was initially thought to be less likely or much lower in UCB recipients. However, there are two recent large retrospective studies suggesting that UCB recipients may have comparable or even higher incidence of EBV-PTLD, particularly in the reduced intensity setting. The first study was conducted by the investigators from the University of Minnesota and Duke University after review of 272 patients who received myeloablative unrelated UCB transplantation. They found five cases (three pediatric patients and two adult patients) of EBV-PTLD with a cumulative incidence of about 2% at 2-year post transplantation that was comparable with conventional unrelated marrow and blood HSC transplantation.<sup>42</sup> These five patients all received ATG as part of the total body irradiation (TBI)-based conditioning. The second study was also reported by the investigators at the University of Minnesota after they investigated 335 patients who underwent myeloablative and non-myeloablative unrelated UCB transplantation. The incidence of EBV-PTLD seemed higher in this series with 3.3% in patients who received myeloablative conditioning and 7% in patients who received non-myeloablative conditioning. The investigators found that EBV-related complications were significantly higher in a subset of patients whose non-myeloablative conditioning regimens contained ATG. This observation was consistent with the first study. In both

studies, the investigators treated EBV-PTLD with rituximab infusion and withdrawing immunosuppressants and about half of patients had significant clinical response.<sup>43</sup> Comprehensive laboratory analyses of the origin of the EBV-PTLD in UCB recipients suggest that the donor UCB is not the source of EBV infection since the UCB cells are believed to be exclusively EBV negative. Hence, the primary EBV infection must be transmitted to the engrafted donor cells by the reactivated EBV in the host cells or via frequent transfusions.<sup>44</sup>

Lower-than-expected incidence of severe acute/chronic GVHD in UCB transplant recipients was initially expected to be associated with higher rates of malignancy relapse, particularly since UCB has been tested as a new allogeneic stem cell source in high-risk patients. However, relapse rates after UCB transplant remain low and the mechanisms underlying the strong GVL effects mediated by UCB have not been clearly delineated. Clinical reports of allogeneic UCB recipients have not identified increased relapse rates, despite the majority of patients having more advanced disease at the time of transplant, and many pediatric UCB recipients having acute lymphocytic leukemia, which has lower sensitivity to allogeneic GVL. Mismatched UCB recipients have acceptable clinical outcomes compared with marrow and blood HSC recipients so that T-cell depletion is therefore not required. These UCB graft immunologic features may facilitate elimination of HLA disparate host hematopoietic cells and thereby facilitate engraftment despite low CD34 stem cell content. This may, in part, underlie the observed potent GVL accompanying UCB allografts.

### Transplant methods using UCB for adult AML patients

Both myeloablative and non-myeloablative UCB transplants can be effectively performed and engrafted in adult AML patients. Usually, patients are not eligible for myeloablative transplant due to advanced age (>55–60), prior extensive therapies (autologous/allogeneic HSC transplant), significant comorbidities, vital organs malfunction or life threatening infections, these patients are appropriate candidates for non-myeloablative UCB transplant.

#### Donor selection

Gluckman *et al.*<sup>16</sup> summarized the UCB unit-selective criteria on the basis of current available scientific and clinical data. In general, patients and UCB units must be at least 4/6 HLA matched in HLA-A, HLA-B and HLA-DRB1 with possible higher cell doses. Single unit UCB is suitable for performing transplant if it is 4–6/6 matched with total nucleated cell dose  $>2.5\text{--}3.0 \times 10^7$  cells/kg.<sup>45</sup> Regarding the degree of HLA disparity, priority will be given for selecting UCB grafts in the following order: 6/6 > 5/6 > 4/6. If multiple UCB units with the same level of HLA matched are available, the priority should be given to the UCB units with HLA-DRB1 matched and higher cell doses because recipients seemed to have a better overall

survival (OS) and disease-free survival (personal communication with Dr Cladd Stevens, New York Blood Center).

#### Myeloablative preparative regimens and GVHD prophylaxis

The cyclophosphamide/TBI (CY/TBI)  $\pm$  ATG-based preparative regimens are one of the most commonly used for adult UCB recipients (Table 3).<sup>13,14</sup> In our institution, TBI is fractionated at 150 cGy twice a day on days –8 to –5 with total of 1200 cGy. CY is given intravenously at 60 mg/kg/day on days –4 to –3. ATG 30 mg/kg/day is given intravenously on days –3 to –1 aimed to enhance the UCB engraftment. If patients cannot tolerate ATG, then methylprednisolone is given at 1 g/kg twice a day for 3 days. For patients who are not TBI candidates, busulfan (BU) is given at 1 mg/kg every 6 h with total of 16 doses on days –8 to –5 targeted at 800–900 ng/ml.

All UCB recipients receive combination GVHD prophylaxis with cyclosporine (CYA) and mycophenylate mofetil (Table 3). CYA is given at 1.5 mg/kg twice a day starting from days –2 to 270 and then gradually tapering. When tacrolimus substitutes CYA, it is given at 0.15 mg/kg twice a day and dosage should be adjusted on the basis of serum level. Mycophenylate mofetil is given from days +1 to +28 at dose of 15 mg/kg intravenously q 8 h.

#### Non-myeloablative preparative regimens and GVHD prophylaxis

To date, most of the reported UCB non-myeloablative regimens include low-dose TBI and fludarabine in combination with CY, BU or melphalan (Table 3).<sup>46–52</sup> For AML patients who are not appropriate candidates for the myeloablative preparative regimens because of advanced age, significant comorbidities or history of HSC transplants, the non-myeloablative preparative regimens can be safely delivered to these patients before UCB infusion. In our institution, the non-myeloablative regimen for UCB contains the combination of fludarabine, CY, ATG and low-dose TBI. Fludarabine is given intravenously at dose of 35 mg/m<sup>2</sup>/day from days –8 to –4, CY intravenously 1 g/m<sup>2</sup>/day from days –3 to –2, ATG 30 mg/kg/day from days –3 to –2 and TBI 200 cGy on day –1.

The combination of mycophenolate mofetil and CYA is widely accepted as GVHD prophylaxis for UCB non-myeloablative transplant (Table 3). Mycophenolate mofetil is given at dose of 15 mg/kg three times a day from days 1 to 30 and CYA 1.5 mg/kg twice a day from day –2 with targeted serum concentration of 400 ng/ml. If patients have absence of GVHD after day 60, dose of CYA should be gradually tapering off to day 100 to induce GVL effect.

#### Double UCB transplant

To overcome the cell dose barrier in UCB units, preclinical studies using double UCB transplantation have been reported by many groups around the world.<sup>53–55</sup> Dr Wagner's group in Minnesota was the first and has the largest single institution experience in double UCB transplant for pediatric and adult AML patients.<sup>56,57</sup> The UCB selection algorithm for double cord transplant is complex and has not yet been well-established. According

**Table 3** Common preparative and GVHD prophylactic regimens in myeloablative and non-myeloablative UCB transplantation

|                     | <i>Myeloablative</i>           | <i>Non-myeloablative</i>   |
|---------------------|--------------------------------|--|
| Preparative regimen | CY/TBI ± ATG<br>CY/targeted BU | Low-dose TBI/Flu/CY/ATG<br>Low-dose TBI/Flu/Bu/ATG<br>Low-dose TBI/Flu/Mel/ATG |
| GVHD prophylaxis    | CYA + MMF                      | CYA (targeted at 400 ng/ml) + MMF  |

Abbreviations: ATG = anti-thymic globulin; Flu = fludarabine; Mel = melphalan; MMF = mycophenolate mofetil; UCB = umbilical cord blood.

to the Minnesota experience, each UCB unit needs to be 4–6/6 HLA matched to recipients with total nucleated cell dose  $>1.5 \times 10^7$  cells/kg and with partial HLA matching between the two UCB units. HLA-mismatched loci do not necessarily have to be the same between UCB units and recipients.<sup>45</sup> The preparative regimens for myeloablative and non-myeloablative double UCB transplantation are usually as same as the preparative regimens for single UCB transplantation.

### Clinical outcomes of adult recipients with AML

#### *Myeloablative UCB transplantation for adult AML*

Using UCB transplantation for adults with malignant hematologic diseases has been increasing rapidly. Two large registry studies representing Europe<sup>14</sup> and North America<sup>13</sup> experiences described transplants of UCB or bone marrow from unrelated donors in adults with acute leukemia. The Acute Leukemia Working Party of European Blood and Marrow Transplant Group and Eurocord–Netcord Registry compared outcomes in 682 adults with acute leukemia who received HSC transplant from unrelated donors: 98 patients received UCB and 584 received bone marrow from 1998 to 2002. UCB recipients were younger (median, 24.5 vs 32 years;  $P < 0.001$ ), weighed less (median, 58 vs 68 kg;  $P < 0.001$ ) and had more advanced disease (52 vs 33%,  $P < 0.001$ ). The median number of UCB nucleated cells infused was  $0.23 \times 10^8$  and  $2.9 \times 10^8$ /kg for bone marrow ( $P < 0.001$ ). Multivariate analysis showed UCB to yield lower risks of grades II–IV acute GVHD (relative risk, 0.57; 95% confidence interval, 0.37–0.87;  $P = 0.01$ ), but neutrophil recovery was significantly delayed (relative risk, 0.49; 95% confidence interval, 0.41–0.58;  $P < 0.001$ ). The incidence of chronic GVHD, transplantation-related mortality, relapse and leukemia-free survival were not significantly different in the two groups. Among these 98 adult UCB recipients, 45 of them are AML patients with 72% of intermediate and poor cytogenetics. The unadjusted 2-year probability of leukemia-free survival is 32%, relapse 14% and OS 30% that are comparable to the results of matched marrow<sup>14</sup> (reviewed by Brunstein *et al.*<sup>58</sup>).

Investigators in the International Bone Marrow Transplant Registry (IBMTR) compared the outcomes of the transplantation of unrelated HSCs in adults with leukemia from UCB that was mismatched for one HLA antigen

(34 patients) or two antigens (116 patients), marrow that had one HLA mismatch (83 patients) and HLA-matched marrow (367 patients). Similar to the European patients, UCB recipients were younger, had advanced leukemia and received lower doses of nucleated cells. Hematopoietic recovery was slower with mismatched bone marrow or UCB than with matched marrow. Acute GVHD was more likely after marrow mismatch, and chronic GVHD was more likely after UCB transplantation. The rates of treatment-related mortality, treatment failure and overall mortality were lowest following matched marrow transplants. Patients who received mismatched bone marrow or mismatched UCB had similar rates of treatment-related mortality ( $P = 0.96$ ), treatment failure ( $P = 0.69$ ) and overall mortality ( $P = 0.62$ ). There were no differences in the rate of recurrence of leukemia. Among UCB recipients, outcomes were similar between grafts with 1 or 2 HLA mismatches. Among 150 UCB recipients, there were 58 AML, 10 myelodysplasia (MDS), 37 CML patients. The 3-year leukemia-free survival was 23%, OS was 26% (reviewed by Brunstein *et al.*<sup>58</sup>). However, the IBMTR found UCB to be equivalent to HLA-mismatched marrow, but inferior to HLA matched marrow. These investigators concluded that HLA-mismatched UCB should be considered an acceptable graft only for adults in the absence of an HLA-matched adult donor.<sup>13</sup>

Recent UCB clinical reports from single institutional experiences also supported observations from larger multi-center studies. In one example, Takahashi *et al.*<sup>59</sup> showed that UCB recipients with myeloid malignancies had a significantly better 1-year cumulative incidence of treatment-related mortality, 2-year probability of relapse and 2-year disease-free survival compared with matched marrow recipients (9 vs 29, 16 vs 25, 74 vs 44%, respectively). In a separate report from the same authors, they further confirmed their previous observations.<sup>60</sup> At the University of Minnesota, adult AML patients ( $n = 33$ ) receiving a myeloablative preparative regimen had 54% 3-year leukemia-free survival and 58% OS (reviewed by Brunstein *et al.*<sup>58</sup>). These data are impressively better than the large registry studies, which implicate patient selection and the transplant center's experience as factors impacting upon the overall UCB transplant outcomes.

#### *Non-myeloablative UCB transplantation for adult AML*

Elderly patients with significant comorbidities or patients that relapsed after extensive treatment may have unacceptable risk if treated by conventional allogeneic transplantation. To date, there are no large registry studies available for non-myeloablative UCB transplantation for adult AML patients. Brunstein *et al.*<sup>49</sup> reported the largest non-myeloablative UCB experience in myeloid malignancy patients (AML 29, MDS 16, CML 7). These patients tended to have more advanced diseases and significant comorbidities following conditioning with CY/fludarabine/low-dose TBI ± ATG. The relapse rate was 31% with 2-year OS 44%. Miyakoshi *et al.*<sup>51</sup> reported experience in patients who were mostly adult AML patients (AML 14, MDS 1, CML 1). Patients were conditioned with fludarabine/melphalan/low-dose TBI. The 1-year OS was 33%

with a relapse rate of 11%. Others reported an OS around mid 30%. In general, the non-myeloablative UCB data are less well defined compared to the myeloablative UCB transplant.

#### *Double UCB transplantation for adult AML patients*

Using double UCB units for adult AML patients can effectively overcome the low cell dose barrier observed in clinical practice. The most updated and largest data of double UCB transplantation were also from the Minnesota group that has performed nearly 200 double UCB transplantations in the myeloablative and non-myeloablative settings.<sup>58</sup> The data mostly included various hematologic malignancies in pediatric and adult patients. These studies indicate that double UCB transplantation is technically feasible and clinically safe. UCB transplant increases eligibility of adult patients for SCT. Brunstein *et al.*<sup>58</sup> analyzed their unpublished double UCB transplantation experience in 61 patients, mostly in adult with different hematologic malignancies who received myeloablative conditioning regimens. They showed an incidence of day 100 grades II–IV acute GVHD of 57%, transplant-related mortality at 6-month of 18%, 2-year disease-free survival of 55% and OS of 63%. These results were similar to adult patients who received single UCB transplantation. The same investigators also found that patients who received double UCB transplantation had 10-fold decreased risk of relapse compared with single UCB recipients when the transplant was performed in the first or second complete remission.

#### **Conclusion**

Banked unrelated UCB has rapidly emerged as an alternative allogeneic stem cell source, providing suitable HLA-matched donors for more adult patients requiring transplantation but lacking matched sibling donors. The UCB has unique biological and immunological characteristics that allow recipients to successfully accept HLA mismatched and lower cell dose of UCB. Emergent data suggest that UCB transplantation is a feasible, safe and effective transplantation strategy for adult AML patients resulting in durable, although delayed, hematopoietic reconstitution, with low incidence and severity of GVHD. Using non-myeloablative conditioning and double UCB transplantation techniques can effectively lower the treatment-related mortality and overcome the low cell dose barrier that makes UCB transplantation safer to adult AML patients. Future clinical trials need to focus on studying the UCB transplantation outcomes in disease-specific settings, such as AML, acute lymphoblastic leukemia and lymphoma.

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