**Concise Review: Umbilical Cord Blood Transplantation: Past, Present, and Future**

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**Key Words.** Umbilical cord blood transplantation • Lymphoma • Leukemia • Graft versus host disease • Hematopoietic stem cell transplantation • Transplant related mortality

**ABSTRACT**

Allogeneic hematopoietic stem cell transplantation is an important treatment option for fit patients with poor-risk hematological malignancies; nevertheless, the lack of available fully matched donors limits the extent of its use. Umbilical cord blood has emerged as an effective alternate source of hematopoietic stem cell support. Transplantation with cord blood allows for faster availability of frozen sample and avoids invasive procedures for donors. In addition, this procedure has demonstrated reduced relapse rates and similar overall survival when compared with unrelated allogeneic hematopoietic stem cell transplantation. The limited dose of CD34-positive stem cells available with single-unit cord transplantation has been addressed by the development of double-unit cord transplantation. In combination with improved conditioning regimens, double-unit cord transplantation has allowed for the treatment of larger children, as well as adult patients with hematological malignancies. Current excitement in the field revolves around the development of safer techniques to improve homing, engraftment, and immune reconstitution after cord blood transplantation. Here the authors review the past, present, and future of cord transplantation. Stem Cells Translational Medicine 2014;3:1435–1443

**INTRODUCTION**

Stem cell therapy has the potential to treat several life-threatening and debilitating conditions including cancer, Alzheimer’s disease, and neurological injury. Although investigation is ongoing in developing areas such as human embryonic stem cells and inducible pluripotent stem cells, hematopoietic stem cells have been clinically applied for decades now. Although these hematopoietic stem cells are perhaps more differentiated than embryonic stem cells, autologous and allogeneic sources of hematopoietic stem cells can restore the hematopoietic system in a patient with a hematologic malignancy after high-dose chemotherapy. Hematopoietic stem cells can be readily obtained from different adult tissues such as bone marrow and peripheral blood. More recently, umbilical cord blood has become recognized as yet another source of these valuable cells. Previously exposed to fetal development, hematopoiesis transitions from the fetal yolk sac to the liver and finally to the adult bone marrow. Fetal liver cells as a hematopoietic stem cell source were abandoned because of poor success rates. It was then hypothesized that cord blood might be a better provider of progenitor cells because of increased availability and long-term maintenance of a higher number of stem cells [3].

During fetal development, hematopoiesis transitions from the fetal yolk sac to the liver and finally to the adult bone marrow. Fetal liver cells as a hematopoietic stem cell source were abandoned because of poor success rates. It was then hypothesized that cord blood might be a better provider of progenitor cells because of increased availability and long-term maintenance of a higher number of stem cells [3].

The first cord blood transplant recipient was a patient with Fanconi’s anemia who received a cord blood unit from his human leukocyte antigen (HLA)-identical sibling in 1988 [4]. A combination of factors triggered the use of this new technology in Fanconi’s anemia, including the recently acquired
capability of prenatally diagnosing this condition via amniotic fluid sampling, improved HLA testing, and mastering the harvesting/cryopreservation/thawing of cord blood cells. The patient engrafted completely with donor cells and has remained in complete hematological remission for more than 20 years, without graft-versus-host disease (GVHD). It was hypothesized that fewer or less-developed T cells in the cord blood unit compared with bone marrow or peripheral blood would yield less GVHD. Less acute/chronic GVHD [5] and similar survival from HLA-identical sibling cord blood transplantation, albeit with delayed granulocyte/platelet engraftment, were observed in subsequent studies.

After encouraging outcomes in the matched related sibling arena [3], the first unrelated mismatched cord blood transplants followed in children and adults [5–7]. Subsequently, an international cooperative cord blood bank network, the Netcord group, was established in 1998 [8]. The availability and ease of cord blood collection and banking made cord blood searching and acquisition faster [7] than the search for bone marrow stem cells. Furthermore, the appeal of cord blood increased as it became apparent that less stringent HLA matching (in comparison with bone marrow or peripheral blood progenitor cells) was required [9], perhaps because fewer activated lymphocytes are present in cord blood [10]. All those advantages brought cord blood to its present role as a prime candidate for use in hematopoietic stem cell transplantation.

**CURRENT APPLICATIONS OF CORD BLOOD TRANSPLANTATION: THE PRESENT**

Much progress has occurred since the pioneering of the first cord blood transplant, with more than 35,000 transplants performed to date. The indication for transplantation has now transitioned from nonmalignant to malignant diseases, and the majority of recipients are now adults lacking an HLA-matched donor.

**Pediatric Patients With Malignancies**

The initial positive results of cord blood transplantation in pediatric patients [11, 12] prompted the Cord Blood Transplantation study: a pivotal prospective multicenter trial of cord blood transplantation (CBT) in 191 pediatric patients with hematologic malignancies [13]. In this study, the median time to neutrophil engraftment was 27 days; the rate of acute grade 3/4 GVHD by day 100 was 19.5%, and chronic GVHD at 2 years was 20.8%. The probability of 2-year survival was 49.5% [13], that faired favorably compared with previous reports. A larger study from the Center for International Blood and Marrow Transplant Research was conducted with 503 children with acute leukemia transplanted with cord blood versus 282 children transplanted with HLA-matched unrelated donors [14]. The 5-year leukemia-free survival was similar for allele-matched bone marrow transplants and cord blood units mismatched at either one or two antigens. These data suggested that the progression-free survival was similar to allogeneic bone marrow transplantation. The decreased risk of GVHD made CBT more attractive because it allowed greater donor-recipient HLA disparity. Despite the fact that GVHD was lower, a graft-versus-leukemia effect was observed.

**Pediatric Patients With Nonmalignant Diseases**

Nonmalignant conditions that have been treated by cord blood transplantation include severe combined immune deficiency [15], hemoglobinopathies [16], Krabbe’s disease [17], chronic
granulomatous disease [18], and Hurler’s syndrome [19]. Boe- lens et al. [20] evaluated the outcomes of transplantation using various hematopoietic cell sources in 258 children with Hurler’s syndrome after myeloablative conditioning. Event-free survival after HLA-matched sibling donor and 6 of 6 matched unrelated cord blood donor was similar at 81% but lower at 68% after 5 of 6 matched cord blood donor and at 57% after 4 of 6 matched unrelated cord blood donor. Interestingly, full-donor chimerism was higher after cord blood transplantation (92% versus 69%, p = .039). A low progenitor cell dose is one of the major disad- vantages of single-unit cord blood transplantation, resulting in slower engraftment and higher rates of graft failure. As such, CBT for other bone marrow syndromes, such as severe aplastic anemia and Fanconi’s anemia, remains uncertain because of higher graft failure in this population when compared with other indications [21].

Adult Patients

Encouraging pediatric results led to the first large study of cord blood transplantation in adults in 2003. This study enrolled 68 patients with hematologic malignancies who received myeloablative conditioning. At 40 months after single-cord blood transplan- tation, 26% of patients remained disease-free [22]. Compared with unrelated stem cell transplantation with myeloablative condition- ing, cord blood transplantation displayed similar leukemia-free sur- vival (LFS), chronic GVHD rates, transplant-related mortality, and relapse rate in patients with acute leukemia [23]. In a subsequent study of matched unrelated, mismatched related and one- or two-HLA-antigen-mismatched cord blood transplants, there were similar rates of treatment-related mortality, treatment failure, and overall mortality [24]. Similarly, a retrospective analysis com- paring unrelated bone marrow (472 patients) or peripheral blood progenitor cells (888 patients) with cord blood (165 patients) transplantation in adults with acute leukemia found that LFS after CBT was comparable with outcomes seen with 8 or 8 or 7 of 8 allele-matched peripheral blood progenitor cells or bone marrow trans- plantation [25]. The incidence of chronic, but not acute, GVHD was lower after CBT compared with 8 of 8 allele-matched bone marrow transplantation (p = .01). However, transplant-related mortality was higher after CBT when compared with 8 of 8 allele-matched peripheral blood progenitor cell recipients (p = .003) or bone mar- row transplantation (p = .003) [25]. Therefore, this study encour- aged the use of cord blood transplantation if no HLA-matched unrelated adult donors are available.

Double Cord Blood Transplantation

In an effort to overcome the relatively low number of progenitor cells present in a single cord blood unit, double cord blood trans- plantation (DCBT) was developed. In a study of 23 adults with high-risk hematological malignancies undergoing DCBT, the me- dian time to engraftment was 23 days [26]. Engraftment was de- rived from a single donor, in 76% of patients at day 21, with one predominate unit in all patients at day 100. Single-unit domi- nance after double-unit cord blood transplantation has been con- firmed in subsequent studies [27, 28] and CD3+ cell dose is an independent factor associated with unit predominance [27]. Of note, despite higher incidence of grade 2 acute GVHD in recipients of two partially HLA-matched cord blood units, there were no det- rimental effects on transplantation-related mortality at 1 year (24 versus 39%, p = .02) [29]. Incidence of relapse or progression was found to be 31% at 1 year with a significantly lower risk (p = .03) in recipients of double-unit cord blood in patients with non-Hodgkin’s lymphoma (n = 61), Hodgkin’s lymphoma (n = 29), and chronic lymphocytic leukemia (n = 14) [30]. Furthermore, a prospective study comparing single versus double cord blood transplantation con- firmed a lower relapse risk after infusion of two units (30.4% versus 59.3%, p = .045) [31]. A study that compared double cord blood transplant- ation (n = 128) to matched-related (n = 204) and matched-unrelated donor transplantation (n = 152) for adult leukemia patients found a significantly lower risk of relapse in recipients of double cord blood (15%) compared with matched-related donor (43%) and matched-unrelated donor (37%). However, nonrelapse mortality was higher for double cord blood (34%) compared with matched-related donor (24%) and matched-unrelated donor (14%) [32].

To improve these outcomes, cord blood transplantation has been explored after reduced intensity conditioning (RIC) regimens including the fludarabine, cyclophosphamide, and low-dose total body irradiation regimen [33] and the fludarabine, melphalan, and rabbit anti-thymocyte globulin [34] regimen. Adults with acute leukemia undergoing DCBT with the RIC regimen (n = 120), DCBT with alternative RIC regimens (including an alkylation agent plus fludarabine plus or minus total body irradiation) (n = 40), and 8 of 8 (n = 313) or 7 or 8 HLA-matched (n = 111) peripheral blood progenitor cells RIC transplants demonstrated a probability of survival of 38%, 19%, 44%, and 37%, respectively. All groups showed similar outcomes with the exception of recipients of double cord-treated patients with alternative RIC regimens, who dis- played higher transplant-related mortality and higher overall mortality [35]. Similarly, the Blood and Marrow Transplant Clinical Trials Network conducted two parallel multicenter phase II trials for patients without a suitable related donor [36]. The outcomes of RIC with fludarabine, cyclophosphamide, and total body irradiation with subsequent unrelated double cord versus HLA-haploidentical related donor marrow were compared in both trials. The 1-year cumu- lative incidence of nonrelapse mortality was higher after cord blood (24% versus 7%), although the relapse rate was higher after haplomarrow transplantation (31% versus 45%) [36]. These phase II trials endorsed the value of double cord transplantation as an alternative donor source and set the stage for a multicenter, phase III, randomized trial of RIC and transplantation of double unrelated cord blood versus HLA-haploidentical related bone marrow for patients with hematologic malignancies (BMT CTN #1101, NCT01597778).

Additional preliminary data have recently been presented to further highlight cord blood as a viable transplant option.
Collins et al. [38] documented long-term durability of cord blood grafts in children with acute leukemia with an 8-year probability of overall survival of 78% compared with 81% with HLA-matched and 68% with HLA-mismatched bone transplantation. Of note, there were differences in transplant characteristics because the patients that received cord blood transplants were more likely to have received a non-irradiation-containing conditioning regimen [38]. Bachanova et al. [40] explored alternative donor sources for stem cell transplantation.

Table 2. Milestones in hematopoietic cell transplantation and blood cord transplantation [68, 69]

<table>
<thead>
<tr>
<th>Year</th>
<th>Milestones in HCT and blood cord transplantation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1868</td>
<td>The bone marrow is first described as blood-forming tissue.</td>
<td>[70]</td>
</tr>
<tr>
<td>1939</td>
<td>The first clinical marrow transplant is attempted, although unsuccessful.</td>
<td>[71]</td>
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<tr>
<td>1957</td>
<td>Infusions of normal marrow prevented death from marrow failure in animals after lethal doses of radiation.</td>
<td>[72]</td>
</tr>
<tr>
<td>1957–1959</td>
<td>Marrow transplantation in man after lethal whole-body irradiation.</td>
<td>[73–76]</td>
</tr>
<tr>
<td>1968–1969</td>
<td>The first successful allogeneic HCT procedures are performed in patients with severe combined immunodeficiency diseases.</td>
<td>[77]</td>
</tr>
<tr>
<td>1975</td>
<td>The first successful allogeneic HCT for leukemia is performed.</td>
<td>[78, 79]</td>
</tr>
<tr>
<td>1978</td>
<td>Successful autologous HCT for lymphoma.</td>
<td>[80]</td>
</tr>
<tr>
<td>1988</td>
<td>The first HLA identical-sibling human cord blood was performed in a patient with Fanconi’s anemia.</td>
<td>[4]</td>
</tr>
<tr>
<td>1990</td>
<td>E. Donnell Thomas is awarded the Nobel Prize in Medicine/Physiology for the development of HCT as a cure for hematologic disorders.</td>
<td>[81]</td>
</tr>
<tr>
<td>1996</td>
<td>First unrelated cord blood transplant in adult.</td>
<td>[82]</td>
</tr>
<tr>
<td>1997</td>
<td>The Eurocord-Netcord network was formed.</td>
<td>[83]</td>
</tr>
<tr>
<td>2000</td>
<td>Cord blood transplants in HLA identical siblings resulted in similar survival when compared with bone marrow transplants in children.</td>
<td>[84]</td>
</tr>
<tr>
<td>1996–2001</td>
<td>Demonstration that long-term leukemia-free survival is similar for cord blood and matched unrelated bone marrow transplants.</td>
<td>[5, 11, 21, 22, 85, 86]</td>
</tr>
<tr>
<td>2002</td>
<td>Transplantation of ex vivo expanded cord blood.</td>
<td>[87]</td>
</tr>
<tr>
<td>2004</td>
<td>Nonhematopoietic stem cells from cord blood as a first step for regenerative medicine.</td>
<td>[88]</td>
</tr>
<tr>
<td>2005–2010</td>
<td>Improving results with double cord blood transplants and nonmyeloablative conditioning regimens.</td>
<td>[26, 89, 90]</td>
</tr>
<tr>
<td>2008</td>
<td>Transplantation of ex vivo expanded cord blood cells using the copper chelator tetraethylpentamidine.</td>
<td>[82]</td>
</tr>
<tr>
<td>2010</td>
<td>Notch-mediated ex vivo expansion system of cord blood progenitors.</td>
<td>[53]</td>
</tr>
<tr>
<td>2011</td>
<td>In a “first-in-human” clinical trial, infusion of ex vivo expanded T regulatory cells reduced GVHD in adults transplanted with cord blood.</td>
<td>[64]</td>
</tr>
<tr>
<td>2012</td>
<td>Cord blood engraftment with ex vivo mesenchymal cell coculture.</td>
<td>[56]</td>
</tr>
<tr>
<td>2013</td>
<td>In a phase I trial, prostaglandin-modulated cord blood transplantation showed accelerated neutrophil recovery (17.5 vs. 21 days).</td>
<td>[63]</td>
</tr>
<tr>
<td>2014</td>
<td>Fucosylation with fucosyltransferase VI or fucosyltransferase VII improves cord blood engraftment.</td>
<td>[91]</td>
</tr>
</tbody>
</table>

Abbreviations: GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen.

Figure 2. Schematic of ex vivo expansion techniques for cord blood transplantation (based on [55]). Abbreviations: CB, cord blood; HDAC, histone deacetylase.
<table>
<thead>
<tr>
<th>Authors, journal, and year</th>
<th>Title or description</th>
<th>Cytokines or agents used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durand et al. (Leuk Lymphoma, 1993)</td>
<td>Long-term generation of colony-forming cells from CD34+ human umbilical cord blood</td>
<td>SCF, IL-3, EPO, G-CSF</td>
<td>[92]</td>
</tr>
<tr>
<td>Kurata et al. (Hematol Pathol, 1995)</td>
<td>Ex vivo expansion of hematopoietic progenitor cells in human cord blood: An effect enhanced by cord blood serum</td>
<td>SCF, IL-3, CBS, FCS</td>
<td>[93]</td>
</tr>
<tr>
<td>Bertolini et al. (Br J Haematol 1995)</td>
<td>The effect of interleukin-12 in ex vivo expansion of human hematopoietic progenitors</td>
<td>SCF, IL-3, IL-11, IL-12</td>
<td>[94]</td>
</tr>
<tr>
<td>DiGiusto et al. (Blood, 1996)</td>
<td>Hematopoietic potential of cryopreserved and ex vivo manipulated umbilical cord blood progenitor cells evaluated in vitro and in vivo</td>
<td>SCF, IL-3, IL-6</td>
<td>[96]</td>
</tr>
<tr>
<td>Scaradavou et al. (Blood, 1997)</td>
<td>A murine model for human cord blood transplantation</td>
<td>SCF, IL-3, IL-6</td>
<td>[97]</td>
</tr>
<tr>
<td>Ohmizono et al. (Leukemia, 1997)</td>
<td>Thrombopoietin augments ex vivo expansion of human cord blood-derived hematopoietic progenitors in combination with stem cell factor and flt3 ligand</td>
<td>SCF, IL-3, IL-6, IL-11, TPO, FL</td>
<td>[98]</td>
</tr>
<tr>
<td>De Bruyn et al. (J Hematother, 1997)</td>
<td>Ex vivo expansion of CD34 + CD38− cord blood cells</td>
<td>SCF, IL-3, IL-6, GM-CSF, anti-TGF-β</td>
<td>[99]</td>
</tr>
<tr>
<td>Piacibello et al. (Blood, 1997)</td>
<td>Extensive amplification and self-renewal of human primitive hematopoietic stem cells from cord blood</td>
<td>SCF, IL-3, IL-6, GM-CSF, G-CSF, EPO, TPO</td>
<td>[100]</td>
</tr>
<tr>
<td>Kögler et al. (Bone Marrow Transplant, 1998)</td>
<td>The effect of different thawing methods, growth factor combinations and media on the ex vivo expansion of umbilical cord blood</td>
<td>SCF, Flt3-L, IL-3, EPO, GM-CSF</td>
<td>[101]</td>
</tr>
<tr>
<td>Kögler et al. (Bone Marrow Transplant, 1998)</td>
<td>An eightfold ex vivo expansion of long-term culture-initiating cells from umbilical cord blood in stirred suspension cultures</td>
<td>SCF, Flt3-L, IL-3</td>
<td>[102]</td>
</tr>
<tr>
<td>Köhler et al. (Stem Cells, 1999)</td>
<td>Optimum results for ex vivo expansion of cord blood cells were reached by a combination of SCF, Flt3-L at 300 ng/ml and IL-3 at 50 ng/ml</td>
<td>SCF, Flt3-L, IL-3</td>
<td>[103]</td>
</tr>
<tr>
<td>Nakamura et al. (Blood, 1999)</td>
<td>The first in vitro demonstration of the precursor of CD34(+) cells in the human CD34(−) cell population</td>
<td>SCF, FCS, G-CSF, IL-3, IL-6</td>
<td>[104]</td>
</tr>
<tr>
<td>McNiece et al. (Exp Hematol, 2000)</td>
<td>Increased expansion and differentiation of cord blood products using a two-step expansion culture</td>
<td>SCF, G-CSF, MGDF</td>
<td>[105]</td>
</tr>
<tr>
<td>Lewis et al. (Blood, 2001)</td>
<td>The first demonstration that ex vivo culture in stroma-noncontact and stroma-free cultures maintains long-term engrafting cells</td>
<td>SCF, IL-7, FL, TPO</td>
<td>[106]</td>
</tr>
<tr>
<td>Pecora et al. (Bone Marrow Transplant, 2000)</td>
<td>Durable engraftment in two older adult patients using ex vivo expanded and unmanipulated unrelated umbilical cord blood</td>
<td>PIXI321, FL, EPO</td>
<td>[107]</td>
</tr>
<tr>
<td>Broxmeyer et al. (Proc Natl Acad Sci USA, 2003)</td>
<td>Stem cells from human cord blood cryopreserved for 15 years</td>
<td>SCF, EPO, IL-3, GM-CSF</td>
<td>[108]</td>
</tr>
<tr>
<td>Jarosckak et al. (Blood, 2003)</td>
<td>Aastrom Biosciences developed an automated continuous perfusion culture device (AastromReplicell System) for expansion of hematopoietic stem cells</td>
<td>FBS, HS, PIXI321, Flt3-L, EPO</td>
<td>[109]</td>
</tr>
<tr>
<td>Peled et al. (Blood, 2003)</td>
<td>Cord blood-derived progenitor cell graft expanded ex vivo with cytokines and the polyamine copper chelator tetraethylenepentamine</td>
<td>SCF, TPO, IL-6 and Flt3-L</td>
<td>[110]</td>
</tr>
<tr>
<td>Serrano et al. (Blood, 2006)</td>
<td>Differentiation of naive cord-blood T cells into CD19-specific cytolytic effectors for posttransplantation adoptive immunotherapy</td>
<td>FCS, other</td>
<td>[111]</td>
</tr>
<tr>
<td>Robinson et al. (Exp Hematol, 2012)</td>
<td>Ex vivo fucosylation improves human cord blood engraftment in NOD-SCID IL-2R(−/−) mice</td>
<td>SCF, Flt3-L, TPO, G-CSF</td>
<td>[61]</td>
</tr>
<tr>
<td>Shah et al. (PLoS One, 2013)</td>
<td>Antigen presenting cell-mediated expansion of human umbilical cord blood yields log-scale expansion of natural killer cells</td>
<td>IL-2</td>
<td>[65]</td>
</tr>
<tr>
<td>Chaurasia et al. (J Clin Invest, 2014)</td>
<td>Epigenetic reprogramming with the HDAC inhibitor valproic acid induces the expansion of cord blood stem cells</td>
<td>SCF, FBS, Flt3-L, TPO, IL-3</td>
<td>[112]</td>
</tr>
</tbody>
</table>

Abbreviations: anti-TGF-β, anti-transforming growth factor-β antibody; CBS, cord blood serum; EPO, erythropoietin; FBS, fetal bovine serum; FCS, fetal calf serum; FL, flt3 ligand; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HDAC, histone deacetylase; HS, horse serum; IL, interleukin; MGDF, megakaryocyte growth and development factor; SCF, stem cell factor; TNF, tumor necrosis factor; TPO, thrombopoietin.
transplantation for 1,593 adults with non-Hodgkin and Hodgkin lymphoma and compared cord blood versus 8 of 8 HLA-matched unrelated donor versus 7 of 8 unrelated donor. They found similar results in a multivariate analysis among the 3 groups in 3-year relapse/progression, progression-free survival, and overall survival [40]. Although clinical outcomes continue to be optimized, the development of CBT has expanded the use of allogeneic transplantation to patients who were previously unable to find a suitable donor. Dahi et al. [39] recently reported on the decline in the percentage of non-Europeans with no available graft, in part because of the availability of cord blood as a source. Increasing experience with cord blood transplant has thus changed the landscape in hematopoietic cell sources for patients undergoing allogeneic hematopoietic stem cell transplantation (Fig. 1).

**Single Versus Double CBT in Pediatric Patients**

In the pediatric population, the use of two partially HLA-matched cord blood units has not been shown to be superior to a single unit, if the unit contains a sufficient number of hematopoietic stem cells. In a randomised study of 224 pediatric patients with hematologic malignancies by Wagner et al. [37], there was no difference between single-unit versus double-unit cord blood transplant in the overall rate of engraftment (89% versus 86%), chronic GVHD (28% versus 31%), risk of relapse at 1 year (12% versus 14%), or disease-free survival (68% versus 64%) [51]. Economically, the use of two units would be justifiable in the pediatric setting only when one unit does not contain enough number of progenitor cells. There are no randomized data of single versus double CBT in adult patients.

**Table 4.** Selected single and double-unit cord blood transplantation studies at ClinicalTrials.gov (search included only open studies and excluded studies with unknown status; accessed December 30, 2013)

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Title</th>
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<tbody>
<tr>
<td>NCT01163201</td>
<td>T-regulatory cell and CD3 depleted double umbilical cord blood transplantation in hematologic malignancies</td>
</tr>
<tr>
<td>NCT00881933</td>
<td>Study of fludarabine + cyclophosphamide + TBI conditioning regimen for double units CBT in SAA</td>
</tr>
<tr>
<td>NCT01051742</td>
<td>Unrelated double umbilical cord blood units transplantation</td>
</tr>
<tr>
<td>NCT01464359</td>
<td>T-cell-depleted double UCB for refractory AML</td>
</tr>
<tr>
<td>NCT01408563</td>
<td>Reduced intensity double umbilical cord blood transplantation</td>
</tr>
<tr>
<td>NCT01745913</td>
<td>Randomized HaploCord blood transplantation vs. double umbilical cord blood transplantation for hematologic malignancies</td>
</tr>
<tr>
<td>NCT01597778</td>
<td>Double cord versus haploidentical (Blood and Marrow Transplant Clinical Trials Network #1101)</td>
</tr>
<tr>
<td>NCT01471067</td>
<td>Cord blood fucosylation</td>
</tr>
<tr>
<td>NCT00862719</td>
<td>Sitagliptin umbilical cord blood transplant study</td>
</tr>
<tr>
<td>NCT00890500</td>
<td>Safety and efficacy of ProHema modulated umbilical cord blood units in subjects with hematologic malignancies</td>
</tr>
<tr>
<td>NCT01690520</td>
<td>Donor umbilical cord blood transplant with or without ex vivo expanded cord blood progenitor cells in treating patients with AML, ALL, CML, or MDS</td>
</tr>
<tr>
<td>NCT00412360</td>
<td>Single versus double umbilical cord blood transplantation in children with high risk leukemia and myelodysplasia (BMT CTN 0501)</td>
</tr>
<tr>
<td>NCT00880789</td>
<td>Safety, toxicity and MTD of one intravenous IV injection of donor CTLs specific for CMV and adenovirus (ACT-CAT)</td>
</tr>
<tr>
<td>NCT01923766</td>
<td>Cytotoxic T cells to prevent virus infections</td>
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Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMT CTN, Blood and Marrow Transplant Clinical Trials Network; CBT, cord blood transplantation; CML, chronic myelogenous leukemia; CMV, cytomegalovirus; CTL, donor-derived cytotoxic T lymphocyte; MDS, myelodysplastic syndrome; MTD, maximum tolerated dose; SAA, severe aplastic anemia; TBI, total body irradiation; UCB, umbilical cord blood.

Novel strategies to improve cord blood transplantation outcomes include improving cord blood engraftment by the transplantation of ex vivo expanded cord blood cells. A potential advantage of expansion is the ability to use smaller cord blood units, which could in turn increase the number of available allografts. Expansion techniques currently reported include using the copper chelator tetraethylpentamine [52], notch ligand-based cultures [53], and coculture of cord blood cells with bone marrow-derived mesenchymal stem cells [54] (Fig. 2). Expansion with notch ligand and the mesenchymal stem cell-based cocultures have resulted in rapid engraftment of neutrophils in a median of 15 days [53, 56]. Other strategies to improve engraftment include the direct intrabone injection of unrelated cord blood cells [57], supportive confuision from an HLA-haploidentical third party donor [58, 59], and the use of agents to enhance the homing of cord blood to the marrow via fucosylation [60, 61] or by prostaglandin E2 modulation [62, 63].

Ongoing clinical trials are also evaluating cord blood-derived immune cells to improve the rate of GVHD and antitumor efficacy. Expanding cord blood regulatory T cells, a subset of CD4+ T cells, may potentially represent a novel cell-based approach for reducing the risk of GVHD [64]. Antigen presenting cell-mediated expansion of human cord blood natural killer cells as an antitumor cellular therapy is being explored as well [65].

Delayed immune reconstitution after cord blood transplantation remains one of the most daunting obstacles to the widespread use of cord blood transplantation. As such, the expansion of cytotoxic T-cell lymphocytes from cord blood has been instituted to target the most common viral infections in this setting: cytomegalovirus, Epstein-Barr virus, and adenovirus [66]. It has also been suggested that combining haploidentical donors with cord blood transplantation can lead to faster immune reconstitution with rapid B-cell and delayed T-cell recovery [67].

Despite the numerous milestones achieved in hematopoietic cell transplantation (Table 2) and ex vivo cord blood stem cell expansion (Table 3), many questions remain unanswered in the field of cord blood transplantation. Fortunately, answers may be forthcoming from numerous ongoing clinical trials (Table 4): ex vivo
CONCLUSION: UMBILICAL CORD TRANSPLANTATION COMING OF AGE

The future for stem cell transplantation forecasts a combination of supportive care optimization and advances in conditioning chemotherapy and immunotherapy to increase survival and decrease morbidity. Cord blood transplantation as a source of stem cells has the potential to fill the gap of a growing population of patients who do not have a fully matched donor but need allogeneic hematopoietic stem cell transplantation. Our experience in this field has evolved from initial single-unit cord blood transplantation for a few diseases in children to double-unit cord blood transplantation for multiple hematologic malignancies in adults. In addition, cord blood provides countless hematopoietic and nonhematopoietic stem cells whose full potential in stem cell biology and regenerative medicine has yet to be fully uncovered.

ACKNOWLEDGMENT

C.M.B. and E.J.S. have been funded by NIH Program Project Grant P01CA148600.

AUTHOR CONTRIBUTIONS


DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

N.S. is a compensated consultant with Sanofi and has compensated research funding from Celgene.

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