Umbilical cord blood transplantation for acute myeloid leukemia

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Purpose of review

To discuss the recent advances in the field of umbilical cord blood (UCB) transplant (UCBT) for the treatment of adult acute myeloid leukemia. This topic is particularly relevant given the increasing use of UCBT and the plethora of clinical and biological studies being done to further optimize UCBT.

Recent findings

We will focus on clinical outcomes, results of nonmyeloablative UCBT, graft-versus-leukemia effect and graft-versus-host disease, the effects of UCBT on the immune system, and the role of multiple UCBTs and ex-vivo expansion.

Summary

Ultimately, these findings and research will allow us to expand UCB to a larger number of patients. In addition, a better understanding of the biology of UCB and subsequent manipulation of UCB and the immune system will allow us to improve the graft-versus-leukemia effect, improve engraftment, and decrease infectious complications after transplant.

Keywords

acute myeloid leukemia, prognosis, umbilical cord blood transplant

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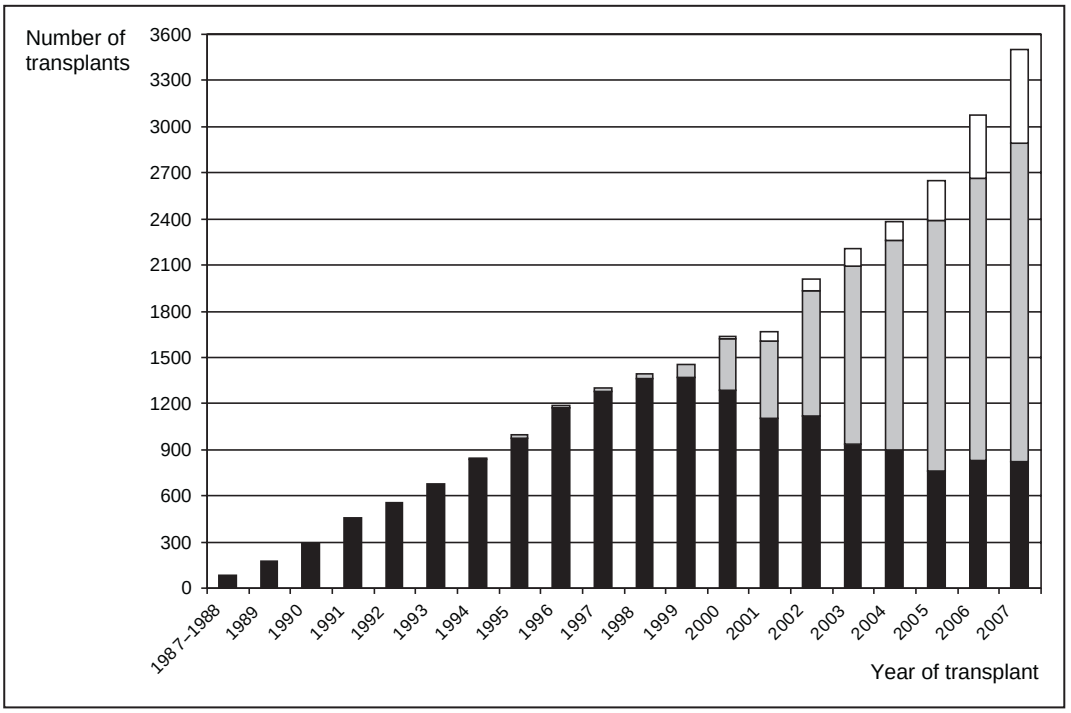
Introduction

Current barriers to effective therapy for acute myeloid leukemia (AML) remain disease recurrence and chemoresistance. For patients with recurrent or refractory disease, the only curative treatment option is an allogeneic bone marrow transplant (BMT). However, many patients are unable to proceed to an allogeneic transplant because of the lack of a suitable related or unrelated bone marrow donor. The advent of umbilical cord blood (UCB) transplant (UCBT) has significantly improved allogeneic transplantation as a treatment option by expanding the available donor pool. However, UCBT remains fairly new, particularly in the treatment of adults, and unique features of UCB as an allogeneic graft source pose new challenges for transplant teams not familiar with its use. To date, most experience with UCBT has been in the arena of pediatric acute lymphocytic leukemia. This review will focus on the recent evolution of the field from both a biologic and clinical standpoint over the last few years, and what new strategies are being evaluated to improve the outcome of patients receiving UCBT.

Umbilical cord blood transplant for acute myeloid leukemia

AML is a disease of the elderly. As patients age, the probability of an available healthy sibling, who is a suitable match and donor, decreases. An unrelated donor (URD) search can require 3–4 months [1], thereby limiting its usefulness in patients with a rapidly evolving clinical course. Ultimately, only 30–40% of patients are able to find a suitable unrelated adult donor, and one-third of donors are not available at the time they are needed [2,3]. For patients of particular racial/ethnic minorities, the chances of finding a suitable donor are even lower. This is a major obstacle in a disease such as AML, in which the disease recurs in a short time if a second remission is achieved. Therefore, UCB represents a potential solution to provide rapid availability for an ethnically diverse American population. In addition, the degree of match is less stringent for UCBT. Unlike in unrelated adult donor transplants, in which high-resolution typing is critical, retrospective studies demonstrate no advantage to high-resolution typing for UCBT [4•]. The decreased incidence of graft-versus-host disease (GVHD) with UCBT despite human leukocyte antigen (HLA) mismatch may be attributable in part to the immaturity and lower number of immunocompetent donor T cells [4•]. Further advantages of UCB as an unrelated allogeneic graft source include: disease status and HLA typing are immediately available, cells are transported easily, and there is a low risk of viral transmission [1]. Figure 1 delineates the growing proportion of UCB as a graft source in allogeneic transplantation. UCB, to date, comprises 28% of all unrelated procedures performed.

Figure 1 Umbilical cord blood is increasingly being used as a graft source for allogeneic transplantation



UCB, this year to date, comprises 28% of all unrelated procedures performed. PBSCs, peripheral blood stem cells; UCB, umbilical cord blood. □, UCB; ▒, PBSCs; ■, bone marrow.

Are the outcomes with umbilical cord blood transplant suitable?

Previous studies have demonstrated conflicting results regarding transplant-related mortality (TRM) in UCBT. Although the US study [5] demonstrated a poor outcome for TRM in UCBT recipients compared with HLA-matched recipients, the European study [6] demonstrated similar TRM in both groups. The major reason for the divergent results is likely patient selection. Most recipients of UCBT do not have an HLA-matched URD, and present with more advanced disease. Takahashi *et al.* [7••] recently examined outcomes from their institution, comparing UCBT from URDs ($n = 100$) with bone marrow or peripheral blood stem cell (PBSC) transplants from related donors ($n = 71$) in adults with hematologic malignancies after a myeloablative-conditioning regimen. The median patient age was 38 years, and a significant proportion of patients in this study had recurrent or high-risk AML. Although this study was retrospective, this study has several advantages: it was a single-institution study and all patients received the same supportive care; when a patient was eligible for allogeneic transplantation but did not have a related donor, UCBT was performed at the same time as for patients who had a related donor; all patients received a total body irradiation-containing myeloablative pretransplantation-conditioning regimen. Although neutrophil count recovery was slower for those patients receiving an UCBT, there was no significant difference in TRM (9% UCBT versus 13% related BMT) or disease-free survival (70% UCBT versus 60% related BMT) at 3 years [7••]. The incidence of grade 3–4 acute and extensive type chronic GVHD was also decreased among patients receiving UCBT [7••]. Potential problems in interpreting this study are: patients receiving UCBT received them in a later calendar year, and also received slightly different conditioning regimens, both of which may have biased the results; Japanese are smaller in size so sufficient cell number was not a problem with UCBT (see below) and may have led to more favorable results; the immunogenetics of the Japanese may be more favorable in the setting of unrelated HLA-mismatched transplantation. Regardless, the above results are encouraging, have been confirmed by other groups [1,8], and support the use of UCBT as a well tolerated and effective alternative to unrelated allogeneic BMT, in which an URD is not available.

How about the safety of nonmyeloablative umbilical cord blood transplant?

Because AML is a disease of the elderly, many patients are not suitable for myeloablative regimens, and need to be considered for nonmyeloablative (NMA) regimens. However, few studies with NMA UCBT have been

published. Majhail *et al.* [9••] prospectively evaluated 90 patients 55–60 years of age receiving NMA BMT between January 2000 and December 2005. Forty-seven patients had a matched-related donor (MRD), 43 patients received a NMA UCBT [9••]. Almost half of the patients receiving UCBT had a diagnosis of AML, whereas only 21% of patients receiving a MRD transplant had a diagnosis of AML. Pretransplantation comorbidities were scored retrospectively using the hematopoietic cell transplantation (HCT)-specific comorbidity index described by Sorror *et al.* [10]. Patients with AML in first remission were considered to have standard-risk disease, whereas all other AML patients were considered high-risk. The median patient age was 58 years. The median follow-up for survivors was 27 months and the 3-year progression-free survival was 30 versus 34% (P = not significant) (MRD versus UCBT) and overall survival 43 versus 34% (P = not significant) (MRD versus UCBT). There was a significant decreased risk of chronic GVHD at 1 year in patients receiving UCBT (40 versus 17%, $P = 0.02$) [9••]. Of note, most of the UCBT recipients in this study (88%) received two units, which has been shown to improve rates and kinetics of donor engraftment [11]. The major drawbacks to this study are the small numbers and the imbalance in the HCT-specific scores between the two arms (16% of MRD had a score of zero versus 36% of patients with UCBT). However, this is a prospective study conducted at a single institution and remains one of the largest experiences with NMA UCBT reported to date. In addition, a significant proportion of the patients receiving UCBT had high-risk disease (including AML in relapse or subsequent remission) or high HCT score index; further validating the safety and efficacy of this approach for patients who do not have a suitable MRD.

What about graft-versus-leukemia effect and graft-versus-host disease in umbilical cord blood transplant?

Because of the decreased incidence of GVHD in patients undergoing UCBT and the delayed T-cell recovery, one concern has been the potential for a decreased graft-versus-leukemia (GVL) effect. However, studies thus far [7••] have not demonstrated an increased risk of relapse after UCBT. This suggests that the mechanism of GVL in UCBT may be different. Lu *et al.* [12•] recently demonstrated a marked increased in $CD16^+CD56^-$ natural killer (NK) cells in the peripheral blood after an UCBT in a patient with refractory AML, who subsequently achieved a molecular remission. They found a similar NK phenotype in seven out of 11 (64%) UCBT recipients, but in none of 13 bone marrow/PBSC transplant recipients [12•]. Further in-vitro studies suggested that mature NK cells derived from this NK cell subset may contribute to the killing of leukemic cells expressing NKG2D ligands [12•]. Although this study was elegantly performed, further studies on a larger number of UCBT recipients are needed to determine whether $CD16^+CD56^-$ NK cells actually play a role in the GVL effect.

In addition to GVHD being lower in incidence after UCBT, a recent study [13•] also suggests that GVHD in these patients may be more responsive to therapy. Arora *et al.* [13•] evaluated 170 patients with chronic GVHD and demonstrated a statistically significant higher incidence of response to treatment in UCBT patients with GVHD at 2 months, 6 months, and 1 year, as compared with patients receiving an unrelated-donor transplant. Although this study was retrospective, patients receiving an UCBT were older and had inferior HLA matching; therefore, clinical responses in this patient cohort would have been expected to be lower. The decreased risk of GVHD and improved response to treatment for GVHD in patients undergoing UCBT is encouraging, and may help improve clinical outcomes and allow us to extend this approach to elderly patients, in whom the incidence and mortality of GVHD is typically increased.

What about the immune system after umbilical cord blood transplant?

Infection is a leading cause of mortality after UCBT. A better understanding of the effects of UCBT on the immune system may help us to improve the outcome of patients after UCBT. Komanduri *et al.* [14••] prospectively evaluated T-cell immune recovery after UCBT in adults. They demonstrated prolonged T lymphopenia and impaired functional T-cell recovery. Most impressive was the observed thymopoietic failure, which is not seen in other types of transplant [14••]. Thymopoietic failure, in turn, was associated with late memory T-cell skewing. This suggests that strategies that improve the engraftment of lymphoid precursors, protect the thymus during pretransplant conditioning, improve thymic homing, augment the recovery of thymopoiesis, or all may help us to improve outcomes after transplant by decreasing the risk of infectious complications. One adoptive immunotherapy technique currently being evaluated has been the expansion of UCB T cells using anti-CD3/anti-CD28-coated beads with subsequent reinfusion after transplant [15,16]. Park *et al.* [17] also recently demonstrated the ability to in-vitro prime and expand cytomegalovirus (CMV)-specific T helper 1 (Th1) and T cytotoxic type 1 (Tc1) T cells from naïve cord blood. Further refinement of these latter strategies, and incorporation into the clinical setting, are ongoing.

How to address the issue of cell dose and umbilical cord blood transplant in adults?

The issue of a fixed cell dose in UCBT has been a major obstacle to the development of UCBT in adults.

Only 6000 UCBTs have been performed worldwide, as compared with 25 000 URD transplants through the National Marrow Donor Program [1]. In a study of 550 single-cord transplants in both adults and children, the median CD34 cell dose was only 1.37×10^5/kg [18,19]. Cell dose is clearly important in the outcome of patients undergoing UCBT. Terakura *et al.* [20••] demonstrated a significant association between a higher incidence of successful engraftment and a dose of $CD34^+$ and $CD8^+$ cells above a median level of 1.4×10^5 and 15.7×10^5 cells/kg, respectively. Engraftment occurred 4 days earlier in patients who received UCB with more than the median dose of $CD34^+$ cells than those receiving UCB at or below the median level [20••]. There was a significant influence of $CD8^+$ cell dose only if a patient received a decreased CD34 dose [20••]. Therefore, incorporating these numbers in a clinical decision about whether a single cord is sufficient is important.

Brunstein *et al.* [3] and Barker *et al.* [11,21] were among the first to report on the use of double UCB grafts to overcome the issue of cell dose limitation. They demonstrated improved kinetics of neutrophil engraftment with double UCB grafts, and have performed approximately 200 transplants in the myelobalative and NMA setting, demonstrating the safety of this approach with no obvious deleterious effect on GVHD or GVL [3]. Preliminary data suggest that the relapse rate may be lower in patients receiving a double UCBT because of the increased HLA antigen mismatch [22]. Therefore, there are plans for a prospective clinical trial comparing single versus double UCBT. An advantage of the dual-cord approach over ex-vivo expansion (see below) is that the cord's properties with respect to engrafting, homing, or apoptosis are not changed [23]. Further studies are evaluating multiple-unit UCBT [24]. Studies thus far reveal that one-cord UCBT typically dominates [24]. Determining which cord predominates when more than one cord is infused is still the topic of significant investigation. In addition, it is possible that we may be able to 'select' which cord predominates by manipulation such as coculture with complement and upregulation of chemokine (C-X-C motif) receptor 4 (CXCR4). This latter strategy will be evaluated in an upcoming clinical trial.

Another approach to increase cord blood unit cell dose has been ex-vivo expansion utilizing techniques such as epigenetic modification, copper chelation, retinoids, and WNT activation [15]. One concern with this approach has been the introduction of immune dysregulation. However, studies thus far have only demonstrated a decrease in dendritic cell function [25]. Several clinical trials evaluating ex-vivo expansion have been completed or are planned [15]. A phase 1 trial by ViaCell, examining ex-vivo expansion by removing committed cells, has recently completed accrual, and results are expected shortly [15]. Shpall *et al.* [26] are conducting a randomized clinical trial, in which patients either receive two unmanipulated cords or one unmanipulated and one from which all cells are expanded. Cells are expanded by isolating the $CD133^+$ fraction, using the CliniMACS system (Miltenyi Biotec, Bergisch Gladbach, Germany), and culturing this fraction with stem cell factor, granulocyte colony stimulating factor, and thrombopoietin. Gamida Cell (Jerusalem, Israel) has initiated a phase 2 clinical trial using copper chelation for ex-vivo expansion in the myeloablative setting [15]. Further refinement of the ex-vivo expansion techniques to increase cell yield are underway. Robinson *et al.* [27] recently demonstrated superior ex-vivo cord blood expansion following coculture with bone marrow-derived mesenchymal stem cells over their previous method of $CD133^+$ selection. Coculture required less cell manipulation and resulted in less initial hematopoietic progenitor cell loss and markedly improved total nuclear cell dose and hematopoietic progenitor cell output [27].

Conclusion

There has been significant advancement in the field of UCBT over the last decade. UCBT plays an important role in the treatment of relapsed/recurrent AML in which a suitable related or URD is not available. The increasing use of NMA UCBT will expand the population of patients able to receive a transplant. Further optimization of cord selection, ex-vivo expansion, and biologic manipulation of UCB and the immune system should help to improve TRM and decrease the risk of recurrent leukemia.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 151).

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