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UMBILICAL CORD BLOOD FOR HEMATOPOETIC STEM CELL TRANSPLANTATION

Stem cell comparison: what can we learn clinically from unrelated cord blood transplantation as an alternative stem cell source?

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Abstract

Allogeneic hematopoietic cell transplantation (HCT) is an important therapeutic option for a variety of malignant and non-malignant disorders (NMD). The use of umbilical cord blood transplantation (UCBT) has made HCT available to many more patients. The increased level of human leukocyte antigen disparity that can be tolerated makes UCBT a very attractive alternative source of hematopoietic stem cells; however, the increased risk of early death observed after UCBT remains an obstacle. Novel strategies such as *ex vivo* stem cell expansion are now becoming part of the standard clinical approach, and preliminary results are extremely encouraging with suggestion of reduction of early transplant–related mortality. Although there are no randomized studies that compare the risks and benefits of UCBT relative to those observed with related and unrelated donors both for malignant and NMD, several retrospective studies have compared outcomes between UCBT and other stem cell sources. In this review, we aim to describe and summarize the findings of the principal studies in this field. We hope that what we can learn from these studies and how we can use this information will improve the outcomes of HCT for patients with malignant and NMD.

Key Words: *benign hematological disorders, cord blood transplantation, hematological malignancies, unrelated donor transplants*

Introduction

Allogeneic hematopoietic cell transplantation (HCT) has become the "standard-of-care" treatment for a variety of malignant and non-malignant disorders (NMD) such as immunodeficiencies, bone marrow failure syndromes, inborn errors of metabolism (IEM) and hemoglobinopathies [1–6]. Despite the fact that over the past decades HCT has become much safer and more effective, resulting in higher disease-free survival (DFS), relapse-related (in malignancies) and transplantation-related mortality remain major limitations.

In recent years, umbilical donor cord blood transplantation (UCBT) has emerged as a feasible alternative source of hematopoietic progenitors for pediatric and adult patients with hematological malignancies and NMD lacking a related and an unrelated donor [7,8]. The increased level of human leukocyte antigen (HLA) disparity that can be tolerated makes UCBT a very attractive alternative source of hematopoietic stem cells. Furthermore, recent advances in UCBT have provided patients with increased choices for a second alternative donor/stem cell source [9,10]. Novel strategies, including *ex vivo* stem cell expansion [9–12], are now becoming part of standard clinical approach, and preliminary results are extremely encouraging with suggestion of reduction of early transplant-related mortality and low risk of relapse.

Despite the increased use of UCBT, to date, there are no randomized studies that compare the risks and benefits of UCBT relative to those observed with related and unrelated donors both for malignant disease and NMD. However, several retrospective

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studies have compared outcomes between UCBT and other stem cell sources. In this Review, we aim to describe and summarize the findings of the principal studies in this field. What can we learn from these studies, and how can we use this information in the development of individualized conditioning regimens and future cell therapies to improve the outcomes of HCT in malignant and NMD?

Hematological malignancies

The first two larger registry studies comparing outcomes for adults with leukemia undergoing UCBT or unrelated bone marrow (BM) transplantation after myelo-ablative conditioning were both published in 2004 by Rocha *et al.* [12] and Laughlin *et al.* [11]. In both studies, single UCBT was compared with either 5-6/6 [11] or 6/6 [12] HLA-matched unrelated donors (MUD). Recipients of UCBT showed delayed neutrophil recovery and lower incidence of acute graft-versus-host disease (GVHD). Overall treatment-related mortality (TRM) was reported to be similar [12] or higher [11] compared with HLA-matched BM. Soon after, similar TRM and better DFS were reported in UCBT recipients in a single-institution study by Takahashi *et al.* [13] comparing single UCBT with 5-6/6 HLA MUD grafts in adults with hematological malignancies. The 2-year probabilities of DFS were 74% after UCBT and 25% in patients receiving unrelated BM transplants. Takahashi *et al.* [14] also compared recipients of single myelo-ablative UCBT with 5-6/6 or 6/6 HLA-matched related donors (MRD). They observed no differences in DFS, TRM and relapse between the two different stem cell sources [14].

The rising interest in UCBT brought Eapen *et al.* [15] to retrospectively compare, in a large registry study, the outcomes of pediatric patients who received either single-unit HLA-matched ($n = 35$), mismatched for one antigen ($n = 201$) and mismatched for two antigens ($n = 267$) UCBT or matched ($n = 116$) and mismatched ($n = 166$) BM transplants. In comparison to patients receiving BM, DFS at 5 years was somewhat better in patients receiving 6/6 matched cord blood (CB) grafts, whereas similar results were observed when patients received 4-6/6 or 5/6 HLA-mismatched CB grafts. Interestingly, TRM rates among UCBT recipients were affected by cell dose ($\leq 3 \times 10^7$/kg was identified as low cell dose) and HLA matching. TRM was higher both in patients receiving one-antigen–mismatched UCBT with low cell dose and in UCBT recipients receiving mismatched UCBT at two antigens at any cell dose.

Similarly to the previous analysis, Eapen *et al.* [16] also compared results in adult patients who received single-unit myelo-ablative UCBT ($n = 165$) with patients who received peripheral blood (PB) ($n = 888$) or BM ($n = 472$) MUD or mismatched unrelated transplants (MMUD). Once again, DFS was comparable among the three groups, although TRM was higher for patients who received UCBT. Anti-thymocyte globulin (ATG) was used more often in UCBT recipients (72%) compared with BM (28%) and PB (18%), probably contributing to the higher TRM observed [17,18]. This study differed from the one in children in that the authors could not assess the role of HLA matching (only few patients received 6/6 UCBT) and failed to identify a specific cell dose associated with survival advantage.

After these reports, single UCBT was compared with MUD and MMUD BM in a disease-specific analysis including adult patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) [19]. Atsuta *et al.* [19] showed similar outcomes for patients with ALL, whereas patients with AML who received UCBT had a worse leukemia-free survival (LFS) as the result of significantly higher TRM. Better overall survival was instead observed in patients with ALL in a small single-institution study comparing single myelo-ablative UCBT with MUD, MMUD and MRD [20].

Although several studies have compared outcomes after single UCBT, more limited are the data of comparison between double UCBT and other stem cell sources. The double UCBT platform, initially developed at the University of Minnesota, was designed to overcome the cell dose limitation that prevented most adults from receiving a UCBT graft [21]. The Fred Hutchinson Cancer Research Center and the University of Minnesota compared outcomes in 128 patients who received myelo-ablative double UCBT with those of patients who received MRD ($n = 204$), MUD ($n = 152$) and MMUD ($n = 52$) [22]. DFS at 5 years was similar between the different donor types, whereas, interestingly, the risk of relapse was lower in recipients of double UCBT. Similar findings were observed in two subsequent smaller studies [23,24]. In the first study, Gutman *et al.* [23] showed equivalent LFS as result of lower risk of relapse and higher TRM in patients who received double UCBT compared with MUD or MMUD recipients. In the second study, Ponce *et al.* [24] observed similar DFS with an higher risk of TRM in the first 180 days compensated by a low risk of TRM after day 180 among UCBT recipients. More recently, Milano *et al.* [25] compared outcomes between UCBT and MUD and MMUD in the largest single-institution study thus far conducted. They retrospectively compared outcomes in 556 patients who received a first HCT for hematologic malignancies with either UCBT ($n = 112$) or MUD ($n = 334$) or MMUD ($n = 110$). DFS was similar among the three groups with suggestively