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Umbilical cord blood cells from unrelated donor as an alternative source of hematopoietic stem cells for transplantation in children and adults

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ABSTRACT

Umbilical cord blood (CB) is an alternative source of hematopoietic stem cells (HSC) for patients requiring allogeneic HSC transplantation but lacking a suitable human leukocyte antigen (HLA)-matched donor. Using CB has many advantages, including lower HLA-matching requirements, increased donor availability, and low rates of graft-versus-host disease. Furthermore, with over 630,000 cryopreserved volunteer CB units currently stored in international CB banks worldwide, CB is rapidly available for those patients requiring urgent transplantation. However, concern remains over the low HSC doses available in CB grafts, resulting in delayed engraftment and poor immune reconstitution. This article reviews the current use and future developments of unrelated allogeneic CB transplantation (CBT). An overview of the encouraging results of CBT and the comparisons with other HSC sources and transplant strategies both in children and adults with malignant and non-malignant diseases are shown. We will discuss important factors that need to be considered when selecting CB units for transplantation to further improve the results of CBT.

1. Introduction

Allogeneic hematopoietic stem cell (HSC) transplantation (HSCT) is the transfer of HSC from a healthy donor into an immunosuppressed host, allowing the formation of new donor hematopoiesis and re-establishing functional immunity. Over the last 50 years, allogeneic HSC transplantation has become an established curative therapy for the treatment of many malignant and non-malignant disorders, particularly acute leukemia and lymphoproliferative conditions. In Europe there are around 40,000 HSCTs, including more than 15,000 allogeneic HSCTs, performed each year [1].

Over the last 25 years, there have been many improvements in clinical HSC transplantation. One of the most significant advancements has been the extended use of "alternative donors" [2]. For many years, a human leukocyte antigen (HLA)-matched sibling was the only donor routinely used. However, only 25%–30% of patients who need an allogeneic HSCT will have a suitable HLA-identical sibling, with only a one in four chance of any individual sibling being HLA-matched. For the remainder, the preferred strategy is to search for an unrelated HLA-matched volunteer donor through international donor registries. However, to extend the possibility of HSC transplantation to even more patients, single HLA-mismatched unrelated donors, cord blood (CB) donors, and full haplotype-mismatched family members have increasingly been used. Nowadays, an alternative HSC donor can be found for virtually all patients and many retrospective studies have shown that both CB donors and haploidentical family donors are suitable alternatives to HLA-matched or -mismatched unrelated donors with acceptable overall outcomes [3–6]. The decision on whether to employ an HLA-mismatched unrelated volunteer, an unrelated CB unit or an haploidentical relative depends on patient-, disease-, and transplant-related factors. The advantages and limitations of each of these strategies (HLA-mismatched donor, CB, and haploidentical relative) have been discussed extensively [2–6].

Umbilical CB transplantation has extended the possibility of performing allogeneic HSCT to patients that otherwise lack a suitable HLA-matched donor. Due to the relative immaturity of

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placental cells, CB lymphocytes have lower alloreactivity compared to conventional bone marrow (BM) or peripheral blood (PB) lymphocytes [7]. As such, HLA mismatches between CB and recipient are better tolerated, with a lower incidence of graft-versus-host disease (GVHD) and less stringent HLA-matching requirements compared to BM and peripheral blood stem cells (PBSC) transplants [8–10]. Traditionally, only HLA matching at HLA-A and HLA-B (low resolution; antigen) and HLA-DRB1 (high resolution; allele) have been used, with mismatches at one or two HLA loci usually being tolerated if sufficient cell doses are transplanted [11–13]. Suitable CB units for transplantation can, therefore, be found for the vast majority of patients, including those with infrequent haplotypes and/or from ethnic minority groups that are underrepresented in international volunteer donor registries. Cryopreserved CB units also have many logistical advantages including being immediately available, avoiding long delays to transplantation; lack of donor attrition with the ability to process and store the donor cells long-term; and without associated risks to the donor [5].

Today, clinical cord blood transplantation includes:

1) Use of CB from an HLA-identical sibling donor (related CB transplantation); administered as a single CB unit or in combination with bone marrow cells from the same donor (*will not be discussed in this chapter*).
2) Use of cryopreserved ("banked") CB units from unrelated donors; administered as single (one donor) or double CB units (two different donors).
3) Investigational use of unrelated CB injected directly into bone, expanded in vitro, or in combination with third party donor cells (haploidentical or mesenchymal cells).
4) Use of autologous CB cells; remains controversial with little scientific data to support its routine use in clinical practice (*will not be discussed in this chapter*).

2. Clinical use of unrelated cord blood cells for allogeneic transplantation

Following the promising results with related CB transplantation and the lower incidence of GVHD [14–17], many centers proposed the use of unrelated CB and the formation of volunteer unrelated CB banks. In 1991, the first public cord blood bank was established at the New York Blood Center. Shortly afterwards in 1993, the first unrelated CB transplant was performed in a 4-year-old boy with acute lymphoblastic leukemia and results of a feasibility trial using unrelated CB were reported [18,19]. To date, more than 130 public CB banks across the world have now collected over 630,000 volunteer, altruistic CB units. Basic HLA-typing and clinical data for each unit are stored on searchable international registry databases, such as the as Bone Marrow Donor World Wide (BMDW) and Netcord Foundation, allowing transplant centers to identify and locate potentially suitable CB units for transplantation. As a direct result of these initiatives, more than 30,000 unrelated CB transplants have now been performed worldwide.

Initial progress in unrelated CB transplantation was made with the improved understanding of minimum cell dose and HLA-matching requirements for successful outcomes. CB units, on average, contain only 10% of the number of $CD34^+$ HSC/progenitor cells compared to BM grafts and only 5% compared to PBSC grafts. From the seminal publications on unrelated CB transplantation in the late 1990s, it was recognized that low CB cell doses (total nucleated cells and/or $CD34^+$ cells) were associated with in an increased risk of graft failure, significant delays in engraftment and increased risk of early non-relapse mortality (NRM), mainly due to infection [11,19]. Inferior transplant outcomes were also associated with higher number of HLA mismatches between CB unit and recipient. This new understanding, therefore, directly led to improvements in collection and use of CB units with higher cell doses and less HLA disparity. Combined with improvements in supportive care, several studies showed outcomes of unrelated CB transplantation comparable to that of HSCT using conventional donors [8,9,12,20,21]. Furthermore, with increased use of CB transplantation in adults and the need to increase the infused CB cell dose in larger patients, the use of double CB transplants was pioneered [22]. The use of two CB units, each from a different unrelated donor (double CB transplantion), produced a reduction in the risk of graft failure and opened up the possibility of HSCT with CB donors for all patients.

2.1. Unrelated cord blood transplantation in children

Many published studies have demonstrated that unrelated CB transplantation in children is associated with sustained myeloid engraftment, a low incidence of GVHD, and comparable overall outcomes to using conventional HSCT donors [8,12,17,18]. Results from a prospective phase II multicenter trial of unrelated CB transplantation (COBLT) for children (<18 years) with hematological malignancies were published in 2008 [22]. Unrelated CB transplants were performed in 191 children with a median age of 7.7 years. Most patients were transplanted for acute leukemia (n = 161; 84%).Two-year overall survival (OS) was 50%. In multivariate analysis, cytomegalovirus (CMV) serostatus ($P < .01$), ABO matching ($P = .02$), recipient gender ($P < .01$), and total nucleated cell (TNC) dose ($P = .04$) were independent predictors for OS. This prospective trial, therefore, reinforced the use of CB donors in children with malignant diseases. Many retrospective series of children receiving unrelated CB transplantation for specific diseases have also been published, including acute lymphoblastic leukemia (ALL) [8,23], acute myeloid leukemia (AML) [24], myelodysplastic syndrome (MDS) [25], juvenile myelomonocytic leukemia (JMML) [26], hemoglobinopathies [27,28], Hurler syndrome [29], Fanconi anemia [30], and primary immunodeficiency [31].

2.2. Outcomes of cord blood transplantation compared to other graft sources in children with leukemia and non-malignant disorders

As the number of registered volunteer donors and/or number of cryopreserved CB units continues to rise, for many children, the search process may identify multiple donor options. Therefore, to aid the clinician in selecting the most appropriate donor, several retrospective studies [8,32], including a meta-analysis [33], have attempted to directly compare the outcomes of CB transplantation with unrelated BM transplantation (BMT) in children with malignant disorders, mostly acute leukemia. Overall, recipients of CB transplantation were generally transplanted sooner compared to children given an unrelated BMT. In CB transplantation, neutrophil and platelet recovery were delayed and acute GVHD was decreased, but OS was not significantly different compared to BMTs. Of note, all of these earlier studies analyzed HLA-matched BMT using low-resolution typing for HLA-A and -B, and high-resolution typing for HLA-DRB1.However, current selection of unrelated BMT donors is now based on high-resolution typing (allelic) at HLA class I (HLA-A, -B, and -C) and class II (DRB1 $\pm$ DQB1). Therefore, on behalf of the CIBMTR and the New York Cord Blood (NYCB) program, Eapen and colleagues (2007) reviewed the outcomes in 885 children with acute leukemia transplanted using unrelated CB (n = 503) or unrelated BM (n = 282) [12]. Compared to BMT (HLA-matched and -mismatched), the cumulative incidence of neutrophil recovery at day 42 was significantly lower after a mismatched CB transplant ($P < .0001$). Matched CB transplants also showed a non-significant trend towards lower neutrophil recovery ($P = \cdot 06$). NRM was