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Clinical Use of Umbilical Cord Blood Hematopoietic Stem Cells

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ABSTRACT

Umbilical cord blood hematopoietic stem cells coming from related or unrelated donors are an alternative source of hematopoietic stem cells for patients undergoing transplantation for a wide variety of diseases. In the unrelated donor transplant setting, shorter time to transplant, which is particularly relevant to patients requiring urgent transplantation, and tolerance of 1–2 human leukocyte antigen mismatch, which increases the chance of finding a suitable donor, are evident advantages over bone marrow transplantation. The speed of engraftment is slower after cord blood transplantation but it is counterbalanced by a lower incidence of severe graft-versus-host disease. Cell dose and human leukocyte antigen are major factors influencing outcome after umbilical cord blood transplantation. Retrospective comparisons of clinical outcomes between unrelated cord blood and unrelated bone transplantation in children and adults have shown similar results, showing the value of this source of hematopoietic stem cell for transplantation. This review describes the recent clinical results and discusses developing research strategies aimed at optimizing the results of cord blood transplantation.

KEY WORDS

Umbilical cord blood transplantation • Related donor • Unrelated donor

INTRODUCTION

Umbilical cord blood transplantation (UCBT) has extended the availability of allogeneic hematopoietic stem cell transplantation (HSCT) to patients who would otherwise not be eligible for this curative approach. Since the first successful UCBT from an HLA-identical sibling in a child with severe Fanconi anemia reported by Gluckman et al. [1] in 1989, the number of UCBTs from siblings and unrelated donors has increased dramatically, and we estimate that more than 5000 patients have undergone UCBT from unrelated donors thus far. A recent survey of the International Bone Marrow Transplant Registry (IBMTR) estimates that after 1998, 20% of stem cell transplantations performed in young patients (<20 years old) have been cord blood transplantations. In Japan, nowadays approximately 50% of HSCTs from unrelated donors are being performed with cord blood cells (T. Takahashi, Medical Director, Tokyo Cord Blood Bank, personal communication, 2005). The inventory of Netcord, the cooperative network of large experienced umbilical cord blood (UCB) banks, currently has more than 100 000 cryopreserved UCB units ready for clinical use, and a reasonably accurate worldwide estimate would be 250 000 cord blood units. In comparison with other sources of allogeneic HSCT, UCB offers substantial logistic and clinical advantages, such as (1) significantly faster availability of banked cryopreserved UCB units, with patients receiving UCBTs a median of 25 to 36 days earlier than those receiving bone marrow (BM) [2,3]; (2) expansion of the donor pool, because sufficiently large UCB units mismatched for 1 or 2 HLA-A, -B, and -DR antigens seem tolerated for survival; (3) a lower incidence and severity of acute graft-versus-host disease (GVHD); (4) a lower risk of transmitting infections by latent viruses, such as cytomegalovirus and Epstein-Barr virus; (5) reduced donor attrition, because cords can likely be stored longer than an average living donor remains available in a registry; and (6) easier targeting of ethnic minorities and an increased pool of rare haplotypes [4]. The disadvantages of UCBT are (1) the low number of hematopoietic progenitor

cells and hematopoietic stem cells in UCB compared with BM or mobilized peripheral blood (this translates into an increased risk of graft failure and delayed hematopoietic engraftment); (2) increased resource utilization in hospitalization days and blood and platelet transfusions; and (3) the impossibility of using donor lymphocyte transfusion for immunotherapy.

CLINICAL EXPERIENCE WITH UCBT

UCBT from Related Donors

Related UCBT has been performed almost exclusively in children [5]. In an update of the Eurocord experience with a median follow-up of 41 months after related UCBT for children, the survival estimate at 3 years was 47% ± 5% in patients with malignancies (n = 96), 82% ± 7% in patients with BM failure (n = 33), 100% in patients with hemoglobinopathies (n = 52), of which 90% had a donor graft, and 70% ± 15% (n = 10) in patients with inborn errors of metabolism or primary immunodeficiencies (Eurocord, unpublished data). For children with malignancies, the 3-year overall survival was 71% ± 12% for those in the early phase of the disease (first complete remission of leukemia), 45% ± 7% for those in the intermediate phase of the disease (second complete remission), and 24% ± 7% for those with an advanced phase of the disease. A joint study by Eurocord and the IBMTR [6] compared the outcome of 113 children who received UCB from HLA-identical siblings with that of 2052 children who underwent HLA-identical sibling BM transplantation (BMT). UCBT recipients had slower recovery of neutrophils and platelets and a lower risk of acute and chronic GVHD. It is interesting to note that relapse-related deaths, the mortality rate at 100 days after transplantation, and overall survival were not significantly different between the 2 groups [6]. Although longer follow-up is required, these findings suggest that in the HLA-identical sibling setting, UCBT is as useful as BMT in children. On the basis of these results, we recommend collecting and freezing cord blood units in families in which a sibling child is affected with genetic or hematologic diseases.

UCBT from Unrelated Donors in Children

Multicenter [4-8], single-institution [3,9,10], and consortium [11,12] studies have shown that unrelated donor UCBT in children was able to reconstitute hematopoiesis and achieve sustained engraftment in most cases, was associated with a low incidence of GVHD, and did not result in a higher relapse risk. Almost all pediatric series on UCBT from unrelated donors have demonstrated the profound effect of cell dose—measured as total nucleated cells, colony-forming cells, and $CD34^+$ cells—on engraftment, adverse transplant-related events, and survival [5,7-9,13]. Although the prognostic importance of HLA disparity

Table 1. *Patient Disease and Transplant Characteristics and Outcomes of 323 Children with ALL Receiving an Unrelated UCBT According to Disease Status at Transplantation*

Characteristic	CR1 (n = 76)	CR2 (n = 136)	Advanced Phase (n = 111)
Median age (y)	4	6	8
Immunophenotype (pre-B/B/T/null or biphenoptypic)	18%/47%/17%/15%	17%/57%/17%/8%	10%/67%/12%/5%
Previous autologous transplantation, (n)	1 (1%)	5 (4%)	20 (18%)
Caryotype, (n)			
Not available	5 (7%)	35 (26%)	31 (28%)
Normal	14 (18%)	53 (39%)	37 (33%)
Abnormal	57 (75%)	48 (35%)	43 (39%)
Good and intermediate	6 (11%)	32 (57%)	25 (58%)
Poor risk	51 (89%)	16 (33%)	18 (42%)
Median time from diagnosis to UCBT (mo)	6	28	33
HLA disparities (6/6), (n)			
0	10 (14%)	14 (11%)	10 (10%)
1	29 (42%)	61 (48%)	47 (47%)
2	27 (39%)	47 (37%)	40 (39%)
3-4	3 (4%)	4 (3%)	4 (4%)
Nucleated cell dose infused, median ($\times 10^7$/kg)	5.3	3.7	3.4
TBI-based regimen	39 (51%)	107 (79%)	68 (61%)
Median follow-up, mo (range)	17 (3-60)	29 (3-93)	23 (3-96)
Outcomes			
Neutrophil recovery at day 60	75 ± 5%	85 ± 3%	65 ± 5%
Acute GVHD (II-IV) at day 100	46 ± 6%	43 ± 4%	36 ± 5%
Chronic GVHD at 2 y	15 ± 4%	16 ± 3%	12 ± 3%
TRM at day 100	22 ± 5%	25 ± 4%	34 ± 5%
Relapse at 2 y	34 ± 8%	37 ± 5%	48 ± 7%
LFS at 2 y	42 ± 6%	41 ± 4%	24 ± 4%

CR indicates complete remission; TBI, total body irradiation.