Blood Reviews xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

Review

Umbilical cord blood transplantation: Pros, cons and beyond

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ARTICLE INFO

Keywords:
Cord blood
Double
Expansion
Transplantation
Leukemia

SUMMARY

Large body of clinical and scientific data has been generated since the first cord blood transplantation (CBT) was performed in 1989. Superior immune plasticity of CB grafts, that allows for less stringent HLA matching, is especially valuable in the face of a persistently growing need for unrelated donor (UD) transplants. Limited cell dose remains the main setback of CBT, particularly in adult population. New strategies, such as transplantation with two cord blood units or using non-myeloablative conditioning, have remarkably expanded the availability of CB transplants in adults with hematological malignancies. Clinical trials with in vitro expanded CB-derived stem cells are under way. Currently cord blood is considered a second best choice after matched bone marrow. However, results of recent international studies indicate that in particular clinical settings, such as in children with leukemia, CB may become a frontline hematopoietic stem cell (HSC) source for transplantation. Recent advances in understanding the unique biology of cord blood will further expand indications for its use in different settings, including those beyond hematopoietic stem cells transplantation (HSCT).

Introduction

In 1989, the first umbilical cord blood transplantation (CBT) was reported by Gluckman et al. in a child with Fanconi's anemia, using cord blood (CB) from his HLA matched sister.[1]

It took another 7 years until the first CBT was performed in an adult recipient.[2] To date nearly 14,000 of umbilical cord blood transplants have been performed worldwide in pediatric and adult patients.[3]

Compared to peripheral blood and bone marrow, CB has several advantages, making it an attractive alternative source of hematopoietic stem cells (Table 1).

The concept of CBT is mainly regulated by two unique counter weighing properties of umbilical cord blood. First, CB transplants are being performed with 10 times less HSC than bone marrow (BM) transplants. This is clinically translated in a greater incidence of engraftment failure and prolonged time to engraftment. On the other hand, these risks are offset by significantly lower rates of acute and chronic graft versus host disease (GVHD) despite broader HLA disparity. The lower GVHD incidence may be explained by the lower number and mostly naïve repertoire of CB-derived T cells.[4–7] Importantly, the graft versus leukemia (GVL) effect is preserved, most probably due to higher number and unique properties of NK cells in CB grafts.[8] Different strategies are being developed in order to overcome stem cell dose limitation of cord blood. Transplantation using two cord blood units or applying non-myeloablative conditioning have already significantly increased the eligibility of adult patients to CBT. Surprisingly, since 2005 more cord blood transplants have been done in adults than in children.[9] Due to superior immune plasticity of CB, more than 95% of patients who are in need for transplantation are able to find 4–6/6 matched unit in CB registries, such as NetCord or National Marrow Donor Program (NMDP). Refined donor's and CB graft's selection may extend the availability of hematopoietic stem cell transplantation for patients who otherwise would not be eligible for this curative modality. Current and future approaches for improving CBT outcomes, based on results of recent clinical studies and new insights in cord blood biology, will be discussed in this review.

Banking on cord blood

Public cord blood banks

The first public banking on unrelated umbilical cord blood was started in New York in 1993. Today there are about 225,000 CB units frozen in 38 public cord banks in 25 countries.[3] Although there are few organizations (FDA, NMDP, FAHCT/NetCord, AABB) trying to ensure the quality of the CB units registered for transplantation, there are still few challenges to face. Processing, testing and freezing of successfully collected CB, taking place in a cord blood

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doi:10.1016/j.blre.2009.02.001

Table1
Advantages of CB as a source of HPSC.

Simple collection that poses no risk for a mother or a newborn
No donor attrition
Low risk of viral transmitting
Immediate availability when emergent HPST is needed
Easy delivery process compared to freshly harvested BM
Grater proportion of rare haplotypes present in UCB banks then in BMT registries

bank, usually results in a loss of 10–20% of the initially harvested blood volume and cell dose. Present insufficient standardization of each of these steps between different banks, as well as inadequate storage policy, may lead to an even greater cell loss. Given that some of the CB transplants are performed with cell dose near the engraftment threshold, modest loss of potency of a product may have a major impact on clinical outcome.

Additionally, few of the non-regulated cord blood banks have still a track record of slow response time; absence of infectious disease serology; lack of attached segments for quality control testing (proof of unit identity and HLA type); high cost or payment requirement prior to unit confirmation. A lot of effort and resources are still required to improve the functioning of public cord blood banks. Commercial CB banking is a rather controversial issue.

Private cord blood banks

Private banks offer expectant parents the opportunity to store their newborn child's cord blood for future need of autologous or related allogeneic transplantation. Today this issue raises growing scientific and ethical criticism. Since private banking began 15 years ago, the results of contemporary chemotherapy and the proven effect of GVL from allogeneic HSCT have restricted the role of autologous HSCT to very limited number of clinical settings. Furthermore, in these cases when autologous HSCT is indicated, autologous CB has no known clinical advantage over standard bone marrow-harvested stem cells. As for related allogeneic HSCT, the chance of particular family to ever use the stored CB unit in this setup is far remote. Again, a fully matched sibling can donate bone marrow at any time in the future should it become necessary, with no need in expensive long term storage. Interestingly, so far there are no published statistical data as for use of CB units stored in commercial banks. Based on the last Eurocord report out of 3,372 umbilical cord transplants in 1988–2007, done in 43 countries at 373 transplant centers, 2965 were unrelated donors, 359 were related but only three were autologous.[9] Despite that, the pace of CB collection in private banks exceeds that of public ones. This raises serious concerns and may indicate both the failure to inform prospective parents about the lack of future benefit from autologous UCB banking, and the insufficient support of public banks – the only way to make such a precious product as umbilical cord blood available for everyone.

CBT, two decades of clinical experience

The clinical experience of CBT could be divided into three important periods.

The first large series of CBT started to appear in the beginning of the third millennium and provided initial important observations as to the unique characteristics of CB transplants.[10–16] The success of neutrophil engraftment, approaching 70–100% within a median time of 23–33 days, has been directly associated with the cell dose. Given the high level of HLA disparity of CB grafts, low rate of severe acute (11–39%) and chronic GVHD (9–31%) was particularly surprising finding.

However, transplant related mortality (TRM) was as high as 50%, at least partially related to primarily advanced and high risk patients studied. All together, these reports demonstrated that CB is a legitimate source for HSCT, with problematic engraftment kinetics, but less restriction of HLA matching, comparing to BM.

The next step was to address by direct comparative analysis whether unrelated mismatched CBT may represent a real alternative to the "gold standard" – matched BMT (Table 2). Several of the largest retrospective studies published for adult and pediatric patients with hematological malignancies,[17–22] were recently summarized by Gluckman et al.[23] In conclusion, mismatched CBT compared to matched BMT results in delayed engraftment, decreased or the same incidence of acute and chronic GVHD and same relapse rate. Overall, in terms of the crucial end point – event free survival – no significant difference was found between matched BMT, related and unrelated, and unrelated mismatched CBT. For the first time, TRM was shown to be comparable in both groups which may be explained by the better unit and recipient selection applied after 1998.[24] As a result of these comparative studies, unrelated cord blood transplantation became a valid alternative for adult and not just pediatric patients with no matched BM donor available.

Studies conducted in the last several years performed detailed analyses of the role of cell dose and HLA disparity on the main outcomes of CB transplantation.

Cell dose was found to be the most important factor impacting engraftment and hence survival.[20,25–27] While in general more is better, the recommended threshold was defined as $>3 \times 10^7$ NC/kg on collection and $>2 \times 10^7$ NC/kg on infusion (EuroCord group, 23). Since counting nucleated cells (NC) involves most probably subsets that are not contributing to engraftment potential, Wagner et al. demonstrated a correlation between $CD34^+$ dose of 1.7×10^5 cell/kg and faster neutrophil recovery.[11] Unfortunately, this measurement can still not be used for comparative studies because of the absence of standardization of the counting method between different centers.

HLA disparity was shown to be an additional factor affecting the outcome of CB transplants.[28] Historically cord blood unit's match is defined by low resolution-A and HLA-B typing and high resolution-DR typing. Increasing number of HLA mismatches was associated

Table 2
Comparative studies of unrelated cord blood and 6/6 matched bone marrow transplants in adults with hematological malignancies.

Study	Patients (*n*)	Engraftment			GVHD		TRM (%)	DFS (%)
	(CBT/BMT)	ANC (d)	PLT (d)	Primary failure (%)	Acute II–IV	Chronic		
Laughlin et al.[17]	150/367	27/18	60/29	30/1	41/48	51/35	63/46	23/33[b]
Rosha et al.[18]	98/584	26/19	N/S	20/7	26/39	30/46	69/63	33/38[c]
Takahashi et al.[22]	68/39[a]	22/18	40/25	8/0	50/66	78/74	9/29	74/44[c]

Abbreviations: ANC, absolute neutrophil count > 500; PLT, platelets > 20,000; GVHD, graft versus host disease; N/S, not stated; TRM, treatment related mortality; DFS, disease-free survival.

[a] Outcomes include additional 5/6 mismatched BM recipients.
[b] Survival data are reported at 3 years after transplantation.
[c] Survival data are reported at 2 years after transplantation.

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Table 3
Outcomes of 8/8 allele matched UD–BMT and 4–6 A, B antigen, DRB1 allele matched CBT in children with acute leukemia.[31]

HSC source	TRM (%)	Relapse (%)	DFS (%)	OS[a] (%)
8/8 matched BM (n = 116)	19	41	38	45
UCB (n = 503)				
6/6	6	34	60	63
5/6 (>3.0 × 10^7 NC/kg)	29	31	41	45
5/6 (<3.0 × 10^7 NC/kg)	43	21	37	36
4/6 (any cell dose)	49	20	33	33

Abbreviations: TRM, treatment related mortality; DFS, disease-free survival; OS, overall survival.
[a] Survival data are reported at 5 years after transplantation.

with delayed engraftment, higher TRM and chronic GVHD, and decreased risk of relapse. No clear importance was shown for a type of HLA mismatch, but Gluckman et al. suggested that matching for type II HLA may give better results.[29]

Importantly, increasing the cell dose overcomes, at least partially, the HLA disparity impact. Furthermore, when an adequate cell dose was administered in children with leukemia, high resolution HLA-A, -B and -DR matching was not shown to improve survival, even in case of 10/10 matching.[30]

Clinical updates

In recently completed analysis, Eapen et al.[31] compared outcomes of children with acute leukemia, who received matched and mismatched UD–CB (n = 503) or 8/8 allele matched UD–BM (n = 116). Five-year leukemia free survival (LFS) was similar for recipients of matched UD–BM and UD–CB mismatched at 1 or 2 loci, when matched CB showed even superior results (Table 3). This new intriguing finding may indicate that matched or high-dose mismatched CBT can potentially become a front line therapy for pediatric patients with acute leukemia, even if matched bone marrow donor is available.

As for adult population, in 2007 Takahashi et al.[32] published a pilot report on CBT as a first option for unrelated donor graft in 100 patients with hematological malignancies and no matched related donor available. Upon comparison with results of matched related BM or PBSC transplantations, outcomes have been similar in all groups.

These results may refine the acceptable approach for unrelated donor search. Already today many believe that a search for a BM donor and a CB unit should generally be started simultaneously and cord blood (matched or mismatched in up to 2 HLA antigens) should be preferred if matched BM donor cannot be found within a reasonable period of time.

CBT for non-malignant diseases

HSCT can offer the only true chance for cure in many non-malignant diseases, and cord blood has some unique advantages in these settings. Many of these patients are children such that the nucleated cells dose is satisfactory in most cases. Since there is no presumed benefit from GVL, lower rates of GVHD tempt to prefer CB, especially in an unrelated donor setup.

Hemoglobinopathies

Although the role of HSCT for Thalassemia in the era of novel iron chelating agents is yet to be determined, this strategy is still being widely evaluated as an therapeutic option. Locatelli et al. had reported on related CBT in 44 children with Thalassemia and Sickle Cell Disease, and showed high engraftment rates (89% at day 60) and EFS (79% for Thalassemia and 90% for Sickle Cell Disease).[33] A recent report from the French group on RD–HSCT in Sickle Cell Anemia emphasizes that after a 6 year follow up the group of patients that received CB graft did not develop the main contributing factor for morbidity – GVHD.[34]

Bone marrow failure syndromes

Bone marrow failure syndromes are traditionally associated with high rates of graft rejection. Possible reasons include previous multiple transfusions, infections at the time of transplants, and the fact that most of these patients did not get chemotherapy before conditioning. Adding the negative impact of CB's tendency for delayed engraftment, cord blood transplantation seems to be a problematic solution for such patients. Indeed, the overall survival in patients with bone marrow failure syndromes, transplanted with UD–CB in 1994–2005 was 35% (EUROCORD data) with engraftment rate of 36%.[23] In their recent report on unrelated CBT in 72 Fanconi patients, the European group reported a more superior engraftment rate, 60% by day 60. Fludarabine based conditioning, higher cell dose and recipient's CMV negativity, was associated with better outcome.[35] However, OS still remains low.

Some limited experience was gained by us with a few bone marrow failure syndromes, namely Fanconi anemia. We observed high rates of event free survival (EFS), especially in children who received a matched family donor transplant.[36] In one case we used a novel strategy of pre-implantation genetic diagnosis. This, based on CBT use, could pave the way for many malignant, and non-malignant, diseases.[37]

Encouraging results have been obtained with CBT in the cure of *primary immune deficiencies*[38] and *inborn errors of metabolism*.[39,40]

Engraftment hastening

Since delayed engraftment due to low cell dose represents the main restriction of cord blood transplants, several strategies have been developed in order to overcome this obstacle.

Transplantations with double cord blood units

Transplantation with two CB units, pioneered by the Minnesota group, has become a major breakthrough in the field of CBT during the last 2 years. By increasing the finally transplanted cell dose, this approach is aimed to improve engraftment, and as a result increase the availability of CBT for adult population. For reasons yet not elucidated, following a month just one of two transplanted units will be responsible for sustained hematopoesis, while the second one disappears. However, this transient contribution of the second unit may explain faster neutrophil recovery and higher engraftment rate. Neither cell dose, nor viability of the cells, CD3 cell number, HLA matching, ABO typing, gender or order of units' administration can help to predict which unit will finally dominate. Recently Verneris et al.[41] have updated their largest single institution experience as for double CBT in 200 adults with hematological malignancies after myeloablative and non-myeloablative conditioning. The incidence of GVHD and overall survival were comparable with those reported for single unit transplants. Ninety two percent of the patients achieved neutrophil recovery at a median time of 12 days. Interestingly, in the acute leukemia group, recipients of two CB units had 10 fold less relapses rate than those transplanted with a single unit. It could be explained by more prominent GVL effect due to greater HLA disparity in double CB recipients. It might also be a consequence of non-HLA disparity, such as killer inhibitory receptors (KIR) mismatch, between the CB units and the recipient, or between themselves.

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A randomized clinical trial has been designed in Minnesota in order to confirm these promising data.

Reduced intensity conditioning

HSCT with reduced intensity conditioning (RIC) has emerged for patients unable to tolerate usual conditioning regiments because of older age, serious co morbidities or those who have got intensive chemotherapy before. The main principle of RIC is that in certain cases the immunological impact of the graft is more important than the ablative power of the conditioning regimen. Patients who benefit mostly from RIC are those with diseases of more indolent nature.

A few studies of RIC–CBT in adult and pediatric patients showed that RIC is feasible in this setting.[42–45] Promising findings included GVHD rates comparable to UD–BMT, and relatively low TRM at 100 days post transplantation. In a recently completed report on 110 adults with hematological malignancies, Brunstein et al.[46] showed TRM 26% at 3 years. However, 95% of patients in this study got second CB unit in order to achieve a target cell dose of 3×10^7 NC/kg. Though survival rates reported so far are low, it must be emphasized that most studies included mainly high risk, heavily pretreated, patients. Because of the small number of patients and diversity of methods, conclusions regarding the optimal RIC conditioning regimen, or GVHD prophylaxis, cannot be made at this point.

Co-transplantation with haploidentical donor

In 2006, Magro et al.[47] reported on co-transplantation of cord blood together with limited number of HSC from haploidentical sibling. The rationale somewhat resembles that for double cord transplants. Transient hematopoesis from haploidentical cells results in faster neutrophil recovery, while these cells completely disappear later on. Impressively, 69% of these high risk patients survived for 4 years.

Intra-osseous transplantation

In BMT in adults, intra bone graft injection could speed an engraftment due to better stem cells homing. Frassoni et al. recently reported results of the phase I/II study in 32 patients with acute leukemia.[48] The median time of neutrophil and platelet recovery was 23 and 36 days, respectively. These preliminary data need to be confirmed in a large number of patients.

Ex vivo expansion of UCB-derived stem cells

In vitro studies have shown that CB-derived stem cells proliferate even better then hematopoietic SC of BM upon cytokines addition.[49] Shpall et al. showed that co-transplantation of ex vivo expanded grafts is feasible, yet no improvement in engraftment kinetics was achieved.[50] When several approaches for CB cells expansion are currently investigated, the most encouraging results were obtained with copper chelator, tetraethylenepentamine (TEPA) in phase I trial.[51] A phase II multi center study has just started and the first eight adults with hematological malignancies were already recruited. Possible reactivation of genes important for HSC self renewal underlies using histone deacetylase inhibitors, such as Valproic acid.[52] Successful in vitro experiments facilitated a clinical study which recruited the first patients (Arcese William, personal communication).

Currently, there is no mechanism to use umbilical cord blood for adoptive cancer cellular immunotherapy after CBT. Avello et al. suggested that NK cells, ex vivo engineered from cryopreserved cord blood, could be a potential solution for this problem.[53]

Table 4
Major CBT challenges and strategies for their overcoming.

Delayed engraftment	• Co-transplantation of more than one CB unit[41] • Expansion of $CD34^+$ progenitor cells[51] • Non-myeloablative conditioning[46] • Simultaneous infusion of CB and highly purified haploidentical stem cells[47] • Co-transplantation of CB and mesenchymal cells[58] • Intra-osseous CBT[48]
Infections	• Aggressive early and preemptive therapy • Potential use of the pathogen-specific T cells[68]
Relapse	• Transplantation with two cord blood units in patients with acute leukemia[41] • Adoptive immunotherapy - The use of CB-derived T cells expressing chimeric antigen receptor to target B-cell malignancies[66] - The use of CB-derived NK cells following ex vivo expansion[53,65] - NK cell immunotherapy as a part of a novel triple CBT[67] - Potential DLI from a haploidentical donor, in the setting of CBT supported by haploidentical stem cells[47]

Table 4 summarizes current and potential strategies for overcoming the major remaining challenges of CBT – delayed engraftment, infections and relapse.

Conclusions: CB unit selection in different clinical setting

The experience of last 20 years indicates that CBT is a valid alternative for BM and PBSC transplants. A low rate of GVHD in the presence of higher HLA disparity represents the main advantage of umbilical cord blood grafts, while delayed engraftment due to limited cell dose is still the major drawback. Optimal unit selection may help to find a balance between these two variables and further improve CBT outcomes. Recently Gluckman et al.[23] and Wall and Chan[54] have published criteria for CB unit selection based on a currently available data. In general, patient and CB unit should be at least 4/6 HLA matching at -A, -B and -DRB1 loci, with a minimal cell dose infused being $>2 \times 10^7$ NC/kg. If several units with the same degree of HLA match are available, the one matched in DRB1 and higher cell dose should be chosen. According to the most recent reports, transplantation with two CB units seems to augment GVL in patients with malignant diseases. It opens the question whether double CBT should be preferred in this setup even if a single unit with sufficient cell dose is available. Interestingly, in case of double CBT, not just unit–recipient matching, but also intraunit matching seems to be important.[55]

In contrast to patients with hematological malignancies, in the setting of non-malignant disease, HLA disparity is crucial for engraftment, GVH and survival and just partially abrogated by increasing cell dose. For this reason, units with a higher cell number, being at least 3.5×10^7 NC/kg on infusion, and minimum HLA mismatches should be chosen. For the same rationale, transplantation with two units currently seems to be too risky in this group.[23]

The greatest limitation for using umbilical cord blood transplantation in every clinical setting and age group is the relative absence of randomized prospective trials comparing CB and BM transplants. Hopefully, promising findings of the current ongoing international studies and new perspectives coming from scientific bench will make it happen in near future.

Cord blood beyond transplantation

Differentiation potential and proliferative response of CB-derived *mesenchymal stem cells* (*MSC*) is different from those in BM or adipose tissue[56] and interest in them is growing continuously.

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MSCs have been shown to modulate immune response, probably owing to their suppressive effect on T cells.[57] Le Blanc et al. had showed that MSCs transfused in parallel with HSC grafts contribute to faster engraftment.[58] Preliminary studies are on their way for using MSCs as an anti-GVHD prophylaxis.[59] Besides that, their future use in tissue repair represents another novel field for investigation. But MSC are not the only cord blood derived cells in which a role in regenerative medicine is intensively studied. It was demonstrated that cells with pluripotent differentiation abilities could be found in CB.[60] First results have been obtained with CB in regeneration of myocardial and neural tissues.[61–64] While the potential use of CB in regenerative medicine evokes great interest and controversy, it is too early to define whether CB HSC' plasticity will have real clinical implication.

Conflict of interest statement

No conflict of interest.

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