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REVIEW

Umbilical cord blood transplantation: Pros, cons and beyond

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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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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.