

REVIEW

Adult umbilical cord blood transplantation: a comprehensive review

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Recent registry studies have established umbilical cord blood (UCB) transplantation as a safe and feasible alternative to bone marrow transplantation in adults when no sibling donor is available. There is, however, no gold standard to guide optimal treatment choices. We review here factors leading to the choice of the ‘best available donor’ and ‘best available unit’ in the case of UCB. For instance, it is clear that higher cell dose may partially overcome the negative impact of certain histocompatibility leukocyte antigen (HLA) disparities in UCB transplantation, leading us to choose the more closely HLA-matched unit with a cell dose $>2.5 \times 10^7/\text{kg}$. New approaches in adult UCB transplantation are systematically covered, with a quantitative appreciation of the evidence available to date. Reduced intensity conditioning, for example, broadens the range of potential recipients by reducing transplant-related mortality, but suffers from unproven risks and benefits long term. Potential advantages of multiple units over single unit transplants are discussed, with a particular emphasis on confounding factors that impact interpretation. The limited clinical results of *ex vivo* UCB expansion, the possible benefits of co-infusion of haploidentical cells and controversial issues (e.g. killer immunoglobulin-like receptor matching and alternative graft sources) are also addressed with a debate on the future of UCB transplantation.

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Evidence supporting the efficacy of umbilical cord blood (UCB) transplantation in adults has significantly increased over the past years, as it now becomes a standard alternative to bone marrow transplantation (BMT) in some hematopoietic stem cell transplantation (HSCT) centers. As

of August 2005, there were 3724 UCB transplantations recorded in the NETCORD inventory, almost half of which performed in adults ($n=1405$). This article summarizes the evidence available to date supporting the efficacy of umbilical cord blood transplant (UCBT) in adults based on published UCB transplant clinical trials and puts into perspective the various approaches currently under investigation to improve these results.

We have reviewed the current literature on UCB transplantation in adults, from January 2001 until December 2005. Clinical cohorts containing less than 10 patients, reviews lacking original results or abstracts with incomplete or non-concordant information have been excluded. Contact with authors has been made to limit the risk of duplication between reports from individual institutions or multi-institutional studies.

Comparing UCBT to BMT

The three most distinctive features distinguishing unrelated donor UCB transplantation from peripheral blood stem cells (PBSC) or BMT (Table 1) are: (1) the number of stem cells available for transplantation, (2) the speed of their availability and (3) the histocompatibility leukocyte antigen (HLA) matching requirements.

Cell dose

It is clear that transplantation outcome after UCB transplantation is correlated with the cell dose infused: a threshold must be reached to get consistent engraftment and lower incidence of transplant-related events.^{1–3} Cell dose also directly correlates with rate of neutrophil and platelet recovery^{1–3} such that recipients of higher cell doses have significantly more rapid recovery as compared to those with lower cell doses. The current empirically accepted threshold limits are 1.7×10^5 infused CD34⁺ cells/kg³ or 2.5×10^7 cryopreserved nucleated cells/kg.⁴ UCB transplantation requires consequently about one log less cells than BMT, possibly because of the high proliferation index of the infused UCB stem cells. Unfortunately, UCB stem and progenitor cells are intrinsically limited by the amount that can be collected from a placenta, thereby restricting the choice of the recipient as body weight becomes a limiting factor. Additional cell

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Table 1 Comparison of the main features of UCBT and BMT (adapted from Grewal *et al.*⁵⁷)

	<i>UCB transplant</i>	<i>PBSC* – BMT**</i>
Number of available donors (worldwide), as of 10/2005 (www.bmdw.org) ⁵⁸	208 000 units 208 000 (100%) ABDR typed, 189 000 (91%) DNA class II typed and 113 000 (54%) DNA class I typed.	9 840 000 donors 6 650 000 (68%) ABDR typed, 5 770 000 (59%) DNA class II typed and 3 880 000 (39%) DNA class I typed
Major limiting factor	Fixed unit cell content	HLA match and donor attrition
Minimum number of total nucleated cells (TNC) needed for transplantation	~2.5 × 10 ⁷ /kg	~2.0 × 10 ⁸ /kg
Second graft or DLI	Impossible	Possible
Median Speed of donor availability	~1 day	~3–4 months
Donor morbidity	None	(50–68%)* – (80–85%)** fatigue, local pain and/or lower-back pain ^{59–61} Median time to return to normal activity: 7 days ⁵⁹
EBV/CMV transmission to recipient	Negligible	Possible
Risk for transmission of congenital disease	Theoretically possible	None
Standard HLA match requirements	Minimum 4/6	Mostly 8/8

infusions from the same donor are also rendered impossible, since the whole UCB unit needs to be used for the primary transplantation.

Graft availability

UCB units are almost immediately available for transplant as they are fully HLA-typed before storage without risk of donor morbidity or attrition. According to Barker *et al.*,⁵ the median time to donor identification is 13.5 days (range: 2–387 days) for a UCB unit in contrast to 49 days (range: 32–393 days) for bone marrow. With the expansion of the UCB banks, the search of a unit now takes now about 1 day for University of Minnesota searches, whereas an unrelated PBSC/BMT donor search will take an average of 3–4 months.

Such rapid availability can be particularly useful for patients with high-risk malignancy or rapidly progressive non-malignant diseases. Unfortunately, the clinical significance of this potential advantage is as yet unknown since most studies published to date first ruled out the possibility of an unrelated BMT before UCB transplantation was considered (Hamza *et al.*⁶ showed that the time from diagnosis to transplant was 21.7 months for cord blood, and 8.2 months for bone marrow), except if the practitioner considered the recipient was too sick to wait any longer. This reflects the fact that UCB has historically been a second choice and that only high-risk patients were offered this stem cell source.

HLA matching

UCB is less restricted with regards to HLA matching requirements relative to bone marrow stem cells from adult donors.^{7–9} In fact, Kögler *et al.* have recently reported that HLA matching was only predictive for survival after UCB transplantation if performed at the serological level for HLA-A and HLA-B, and high resolution allelic typing for HLA-DRB1. Any other attempts to better define compatibility through high resolution typing failed to correlate with survival, in sharp contrast to unrelated BMT where

any single serological mismatch or multiple high resolution mismatch are considered as risk factors.¹⁰

This permissive HLA mismatching consequently increases the number of potential units available per patient, thereby improving the odds of finding a suitable unit for patients with uncommon tissue types,⁹ without increased risk of engraftment failure or graft-versus-host reactions. It was recently shown that patients had a 99% chance of finding a 4/6 HLA matched UCB unit, and a 70% chance of finding a well-matched UCB unit (defined as 5/6 or 6/6 HLA match, without mismatch in the graft-versus-host disease (GVHD) direction) within the New York Blood Center (NYBC) inventory, with further limitations being rather linked to the cell content of the unit.¹¹

This apparent immune-tolerance may be attributed to the immaturity of the cord blood lymphocytes, as suggested by the observation that: (1) activated UCB mononuclear cells (MNC) have a different mRNA and protein expression proper for several growth factors and interleukins important in immune cells as compared to normal adult peripheral blood MNC, (2) UCB cells generate decreased T-helper-1(Th1)-type cytotoxic cellular responses to mitogenic stimulation, (3) the phenotype of UCB B-cells is more immature than in normal adults, (4) there is a lower number of CD4+/CD45+ T-cells in UCB, (5) the activity of the UCB CD4+/CD45+ T-cells and natural killer-cells (NK-cells) is relatively low and (6) most UCB dendritic cells tend to have a lymphoid and immature phenotype, with a decreased capacity to produce IL-12 (thus further impairing Th1 response).¹²

Beyond HLA-matching, killer immunoglobulin-like receptor (KIR)-ligand mismatch is an area of intense investigation, based on the search for 'perfect mismatch' between donor NK-cells possessing an inhibitory KIR receptor and recipient cells lacking the corresponding HLA, theoretically leading to selective killing of residual host leukemia cells and antigen presenting cells. Consequently, better survival through increased GVL and decreased GVHD might be expected. Clinical results with PBSC or BMT, however, show relatively inconsistent results, potentially modulated by a variability of the

transcriptional KIR repertoire and the impact of viral reactivations and infections.¹³ Interestingly, Brunstein *et al.*¹⁴ recently showed that KIR-ligand mismatch in UCB transplant recipients seemed to have no effect on overall survival, relapse graft failure or GVHD, but were predictive of increased transplant-related mortality (TRM).

Choosing the 'best' unit

Choosing 'the best unit' for transplantation remains a challenge, as no study has formally demonstrated to date which parameter has higher priority (cell dose or HLA match). While higher cell dose may partially overcome the negative impact of HLA disparity,³ the best matched unit with a cell dose $>2.5 \times 10^7$ cryo-preserved nucleated cells per kilogram should be used.⁴ Further studies, however, are needed to more precisely define this algorithm. This also calls for rationalization of the methods of determining both compatibility (serological versus high resolution allelic typing) and cell dose (total nucleated cells versus CD34⁺ fraction).

Studies comparing UCB transplantation and unrelated BMT

Prospective comparative studies exploring the differences in outcomes of UCB transplant versus unrelated BMT have yet to be performed. The most recent reports concerning adult patients are from the International Bone Marrow Transplant Registry (IBMTR)/NYBC,¹⁵ the European Bone Marrow transplant (EBMT) consortium¹⁶ and a single center retrospective Japanese study¹⁷ (Table 2). Although retrospective, they demonstrate the feasibility of UCB transplantation in adults and highlight major differences between the two stem cell sources. Several other US,^{18,19} European^{20–22} and Japanese^{23–28} authors have published earlier smaller scale reports concerning myeloablative, single unit UCB transplantation in adults, but these are not described here to avoid overlap with the larger reports.

As detailed in Table 2, the most frequent indications for transplantation were acute and chronic leukemia. The UCB grafts contained a median of $2.2–2.5 \times 10^7$ total nucleated cells (TNC) per kilogram, zero to three HLA mismatches and were administered after a myeloablative conditioning. Engraftment was slower in the UCB cohort, with a time to neutrophil recovery ranging from 22 to 27 days, and poorer engraftment as reported by the EBMT (75% at day 60). In spite of the high level of HLA disparity in the UCB group, similar rates of acute GVHD (aGVHD) were observed as compared to the HLA-matched unrelated BMT in the US study. Rocha *et al.* demonstrated less aGVHD and Takahashi *et al.* demonstrated less high-grade aGVHD in recipients of HLA-mismatched unrelated UCB transplantation as compared to HLA-matched unrelated BMT; chronic GVHD (cGVHD), however, was found to be similar. In the US study, a higher risk of cGVHD in the UCB cohort was observed, but with a smaller fraction of extensive disease.

Although follow-up remains limited (25–40 months), we note similar relapse rates in all groups (range: 16–23% for

UCB transplantation versus 23–25% for unrelated BMT at 2 years), and similar overall survival (range: 26–74% versus 35–44% at minimum 2 years for UCB transplantation and unrelated BMT, respectively). Notably, Takahashi *et al.* showed a survival of 74% at 2 years in the UCB transplant cohort, which is markedly higher than that observed in recipients of unrelated BMT.

In summary, Laughlin *et al.* concluded that UCBT was safe, considering its results were comparable to those observed in recipients of one-HLA-mismatch unrelated BMT, but inferior to a fully HLA-matched unrelated BMT. The EBMT report considered both transplantation modalities (HLA-mismatched UCB transplantation versus HLA-matched unrelated BMT) to be equivalent and Takahashi *et al.* concluded that UCB transplantation was superior to unrelated BMT in the light of their survival results.

Discrepancies in results between those three reports have been commented on at length after their publication. The difference in results between the IBMTR/NYBC and EBMT reports could be explained by several factors: lower mean weight of the European population, difference in observation periods (which included the pioneering period of UCB transplantation in the US study) and differences in HLA disparity (greater HLA mismatch in the IBMTR/NYBC cohort).²⁹ Furthermore, the impressive results of the Japanese study might be accounted for by specific characteristics such as: an extensive experience with UCB in more than 555 adults to date (Takahashi 2004, personal communication), lower median weight of Japanese patients, more homologous HLA genotype on the island,²⁴ prolonged hospitalization of patients after transplant, the high proportion of limited cGVHD and possibly differences in conditioning therapy.²⁵

In addition to these comparative studies, the Cord Blood Transplantation (COBLT) Study reported the first prospective multi-center UCB transplantation study in 32 adults.³⁰ This study is remarkable by its unexpectedly poor engraftment (median 31 days for neutrophil recovery, with 75% engraftment at day 42) and very poor 1-year survival estimate (17% at 1 year) all attributed to the high-risk profile of the transplant population.

Improving transplantation outcome by reducing TRM

Even if the greatest body of evidence available to date undeniably concerns myeloablative single unit UCBT, several approaches have been proposed to circumvent the slow engraftment kinetics and high TRM of conventional myeloablative UCB transplantation (Table 3). The use of reduced intensity conditioning, co-infusion of multiple UCB units, expansion of the UCB progenitor cells and co-infusion of PBSC have been tested with varying degrees of popularity. Many other tactics are also currently being explored but remain at the preclinical or case-report level, for instance: improvement of bone marrow homing via inhibition of the truncation of stromal cell-derived factor-1 (SDF-1)/CXCL12,³¹ UCB-derived somatic stem cells³² or *in vivo* injection of SCF and filgrastim in adult recipients of unrelated UCBT.³³

Table 2 Studies comparing single unit Unrelated UCB Transplantation and Matched Unrelated BMT in Adults (2001–2005)

	<i>Laughlin et al.¹⁵</i> <i>Multicentric registry based (IBMTR+ NYBC)</i> <i>1996–2001</i>		<i>Rocha et al.¹⁶</i> <i>Multicentric registry based (Eurocord and EBMT)</i> <i>1998–2002</i>		<i>Takahashi et al.¹⁷</i> <i>Single center (retrospective)</i> <i>1996–2003</i>	
	<i>UCB Transplantation</i>	<i>Unrelated BMT</i>	<i>UCB Transplantation</i>	<i>Unrelated BMT</i>	<i>UCB Transplantation</i>	<i>Unrelated BMT</i>
Number of patients	150	367	98	584	68	45
Age (years)	31 (16–58)	37 (16–60)	24 (15–55)	32 (15–59)	36 (16–53)	26 (16–50)
Weight (kg)	68 (44–133)	76 (40–156)	58 (38–92)	68 (40–108)	55 (36–76)	60 (37–85)
<i>Diagnosis</i>						
AML	68 (45%)	140	45 (46%)	317 (54%)	39 (57%)	15 (33%)
ALL	45 (30%)	82	53 (54%)	267 (46%)	15 (22%)	8 (18%)
CML	37 (25%)	145	0	0	5 (7%)	18 (40%)
Other	0	0	0	0	10 (14%)	4 (9%)
<i>Donor Recipient match</i>						
0 Mismatch	0	367 (100%)	6 (6%)	584 (100%)	0	39 (87%)
1 Mismatch	34 (23%)	0	48 (51%)	0	14 (21%)	6 (13%)
2 Mismatch	116 (77%)	0	37 (39%)	0	37 (54%)	0
≥3 Mismatch	0	0	4 (4%)	0	17 (25%)	0
<i>Cell dose median</i>						
TNC ($\times 10^7$ /kg weight)	2.2 (1.0–6.5) [§]	24 (0.2–170)	2.3 (0.9–6.0) [§]	29 (10–90)	2.5 (1.1–5.3) [§]	33 (6.6–50)
<i>Hematopoietic recovery</i>						
Time to ANC engraftment (days)	27 (25–29) [§]	18 (18–19)	26 (14–80) [§]	19 (5–72)	22 (16–41) [§]	18 (12–33)
Cum. Incid. of neutrophil recovery	Not Av.	Not Av.	75% (66–84)* at d60 [§]	89% (87–91)* at d60	92% (85–99)* at d42	100% at d42
Graft failure/secondary graft rejection	Not Av.	Not Av.	20 (20%) [§]	43 (7%)	5 (8%) [§]	0
<i>GVHD</i>						
Acute GVHD II–IV (% Cum. Incid.)	61/150 pt	176/367 pt	26% (14–38)* at d100 [§]	39% (31–47)* at d100	30/60 pt	30/45 pt
Chronic GVHD (% Cum. Incid.)	35/69 pt [§]	86/243 pt	30% (20–40)* at 2 years	46% (44–48)* at 2 years	42/54 pt	26/35 pt
<i>Statistical analysis</i>						
Median follow-up (months)	40 (12–85)	48 (12–78)	27 (3–66)	24 (1–76)	26 (4–68)	14 (1–100)
TRM (% Cum. Incid.)	95/150 [§] pt	169/367 pt	44% at 2 years	38% at 2 years	9% (2–16)* at 1–2 years [§]	29% (15–42)* at 1–2 years
Median overall survival %	26% (19–32)* at 3 years [§]	35% (30–39)* at 3 years	36% at 2 years	42% at 2 years	74% (63–85)* at 2 years [§]	44% (30–59)* at 2 years
Relapse (% Cum. Incid.)	Not Av.	Not Av.	23% at 2 years	23% at 2 years	16% (7–25)* at 2 years	25% (12–37)* at 2 years

All values are given as median (% or range), unless otherwise specified.

Abbreviations: AML = acute myeloid leukemia; ALL = acute lymphocytic leukemia; ANC = absolute neutrophil count; CML = chronic myeloid leukemia; Cum. Incid. = cumulative incidence; GVHD = graft-versus-host disease; Not Av. = not available; Pt = patients; TNC = total nucleated cells; TRM = transplant-related mortality.

A superscript '§' indicates a significant difference between UCB transplantation and unrelated BMT cohorts.

*95% confidence interval.

Table 3 Selection of major studies relative to UCB transplantation in adults published between 2001 and 2005

	Total	Myeloablative	Nonmyeloablative
Standard single UCB unit	573 Patients ^a	350 Patients: 150 patients, ¹⁵ 98 patients, ¹⁶ 68 patients, ¹⁷ 34 patients ³⁰	223 Patients: 18 patients, ³⁷ 21 patients, ³⁹ 13 patients, ³⁶ 129 patients, ³⁸ 13 patients, ³⁵ 17/95 patients received single units ^{a,34} 12/21 patients received single units ^{a,41}
Multiple UCB units	142 Patients ^a	34 Patients: 23 patients, ⁴⁴ 11 patients ⁴⁵	108 Patients: 21 patients, ⁴⁰ 78/95 patients received double units ^{a,34} 9/21 patients received double units ^{a,41}
Expansion of UCB units	64 Patients (27 adults)	64 patients (27 adults): 37 patients (25 adults), ⁴⁹ 27 patients (2 adults) ⁵⁰	None
Co-infusion of peripheral blood CD34 ⁺ cells	28 Patients	28 patients: 28 patients ⁵³	None
		Total: 439 adult patients	Total: 331 adult patients

^aThere is some overlap between reports, since some studies report both single and double unit cord blood transplants and some reports include registry data.

Reduced intensity conditioning in the setting of UCBT

From 2001 to 2005, the early results of about 330 reduced intensity conditioning (RIC) UCBT have been published (Table 4 shows the largest studies published by each group^{34–41}), with a follow-up of 7.5–23 months. As expected, patients were 10–20 years older than those included in myeloablative studies and transplant indications crossed a wide range of hematological diseases. The number of days to neutrophil recovery were highly variable (range: 12–26), with relatively high rates of graft failure or secondary graft rejection (range: 14–67%). Interpretation of this data is difficult as some of these studies were carried out with multiple UCB units and conditioning regimens varied between centers. Recent analysis also suggested a positive correlation between engraftment and the timing of chemotherapy received until transplantation,^{42,43} a parameter which is not frequently mentioned in studies, and thus hardly comparable retrospectively. GVHD was roughly similar to that observed after myeloablation (aGVHD: 20–61 and 26% for RIC and myeloablative conditioning, respectively; cGVHD: 21–26 versus 30%, respectively), with one notable exception: in a direct comparison of myeloablative versus RIC in a single center study, significantly more grade III–IV aGVHD was observed in the RIC group.³⁵ Finally, in these high-risk, heavily pre-treated patients with significant comorbidities at the time of UCBT, survival was comparable to that observed in younger, fitter patients transplanted after a myeloablative therapy (31–80% Kaplan Meier survival at 1 year), probably relating to higher TRM and/or relapse rates. Unfortunately, this comparison suffers lack of adjustment for disease stage at time of UCB transplant, as it is not systematically reported. Reassuring disease-free survival results (64–79% at 1 year), also seem to indicate that GVL effect is preserved despite the low T-cell dose,⁴⁰ although this needs confirmed once longer follow-up is achieved.

Multiple unit UCB transplantation

Results of double unit UCB transplantation in 142 patients have been reported (Table 5), the majority having taken

place at the University of Minnesota.^{34,40,41,44,45} These studies are recent and offer follow-up periods ranging from 7 to 23 months. We note a wide range of neutrophil engraftment, partially explained by the different conditionings used (12–26 days), but impressively low frequencies of graft failure (0–22%). Interestingly, only one of the two units infused predominated over time (by day 100, most patients have chimerism derived from one of the two units), with no factor predicting which unit would prevail (Wagner, personal communication 2005). Incidence of grade II–IV aGVHD appeared to be slightly higher and cGVHD seemed to lie in the same range as that previously described (44–65% for aGVHD and 21–25% for cGVHD). TRM rates remained low (14–48%) and 1-year overall survival ranged from 31 to 79%. UCB transplantation with 2 units appears therefore safe and feasible both in the myeloablative and non-myeloablative setting; extending the application of this treatment to almost all adults for whom a single cord blood unit would have been insufficient.

Some recent studies compare single unit to double unit UCB transplantation. The retrospective comparative analysis of the University of Minnesota data set demonstrated high engraftment and less relapse, but increased grade II–IV aGVHD, with possibly improved survival with double unit UCB transplantation.⁴⁶ Although this might suggest an improved GVL effect, several other factors differed between the two groups. As double UCB unit transplants were initiated, the standard conditioning regimen also shifted from ATG to fludarabine and GVHD prophylaxis was changed from methylprednisone/cyclosporine to mycophenolate mofetyl/cyclosporine. Analysis of the NYBC data set suggested shorter time to engraftment and better overall survival in patients treated with fludarabine-containing regimen and double UCB transplantation.⁴⁷ Creer *et al.*⁴⁸ also showed better time to engraftment in the double unit UCB transplant group (17 versus 20 days) and better survival (14 versus 80%), essentially because of the absence of deaths due to opportunistic infections in the double UCB transplant cohort. These results highlight the success of using double UCB units but the underlying mechanisms are still unclear. Prospective trials are now

Table 4 Studies using reduced intensity conditioning in adult UCB transplantation (2001–2005)

	<i>Chao et al.³⁶</i>	<i>Miyakoshi et al.³⁸</i>	<i>Tashiro et al.³⁵</i>	<i>Hamaki et al.³⁹</i>	<i>Rio et al.³⁷</i>	<i>Brunstein et al.³⁴</i>	<i>Barker et al.⁴¹</i>	<i>Ballen et al.⁴⁰</i>
	<i>Flu-Cy-(200 cGy TBI) single unit 2000–2003</i>	<i>Flu-melphalan-400 cGy TBI single unit 2002–2004</i>	<i>Flu-melphalan/Flu-TBI (+/-Bu or Cy) single unit 1999–2005</i>	<i>Cy or Bu-Flu-TBI single unit Not Av.</i>	<i>Flu-Cy-200 cGy TBI single unit 2003–2005</i>	<i>Flu-Cy-200 cGy TBI single and double unit 2001–2004</i>	<i>Bu-Flu-TBI single and double unit 2000–2001</i>	<i>Flu-melphalan-rabbit ATG double unit 2004–2005</i>
Number of patients	13	129	22	21	24	95	21	21
Age (years)	49 (19–62)	55 (17–79)	55	54 (30–76)	48 (20–69)	50 (18–64)	49 (22–65)	49 (24–63)
Weight (kg)	66 (42–99)	54 (38–75)	Not Av.	Not Av.	66 (45–90)	78 (50–134)	75 (55–109)	78
<i>Diagnosis</i>								
AML	2 (15%)	52 (40%)	6 (27%)	Not Av.	2 (8%)	Not Av.	10 (48%)	8 (38%)
ALL	3 (24%)	32 (25%)	1 (5%)	Not Av.	14 (58%)	Not Av.	0	1(5%)
CML	1 (8%)	3 (2%)	0	Not Av.	1 (4%)	Not Av.	2 (9%)	0
Other	7 (53%)	42 (32%)	15 (68%)	Not Av.	7 (29%)	Not Av.	9 (42%)	12 (57%)
<i>Donor recipient match</i>								
0 Mismatch	0	2 (2%)	Not Av.	Not Av.	1 (4%)	Not applicable	Not applicable	Not applicable
1 Mismatch	3 (23%)	19 (15%)	Not Av.	Not Av.	7 (29%)	Not applicable	Not applicable	Not applicable
2 Mismatch	10 (76%)	107 (83%)	Not Av.	Not Av.	16 (67%)	Not applicable	Not applicable	Not applicable
≥3 Mismatch	0	1 (1%)	Not Av.	Not Av.	0	Not applicable	Not applicable	Not applicable
<i>Cell dose median</i>								
TNC ($\times 10^7$ /kg weight)	2.1 (1.1–5.5)	2.8 (1.7–5.2)	Not Av.	Not Av.	3.4 (2.6–5.0)	3.6 (1.1–6.8)	3.3 (2.3–5.1)	4.0 (3.0–5.3)
<i>Hematopoietic recovery</i>								
Time to ANC engraftment (days)	12 (6–34)	20 (10–53)	21	22 (11–33)	14 (1–28)	12 (0–32)	26 (12–30)	20 (15–34)
Cum. Incid. of neutrophil recovery	Not Av.	80% at d60	Not Av.	Not Av.	88±7% at d30	87%	Not Av.	Not Av.
Graft failure/secondary graft rejection	8/12 pt (67%)	Not Av.	32%	6/16 pt	2 pt	Not Av.	4 pt (22%)	3 pt (14%)
<i>GVHD</i>								
Acute GVHD II–IV (% Cum. Incid.)	2/5 pt	37% (27.5–46.7)*	Not Av.	9 pt	20±8%	61% (49–73)*	44% (28–62)*	4 pt (21%)
Chronic GVHD (% Cum. Incid.)	1pt	26%	Not Av.	Not Av.	7/17 pt	25 % (15–35)*	21% (8–34)*	3/12 pt (25%)
<i>Statistical analysis</i>								
Median follow-up (months)	20	14 (3–32)	Not Av.	17.5 (8.4–29)	7.5 (0.5–16)	14 (3.3–42.7)	23 (14–28)	7 (2–16)
TRM (% Cum. Incid.)	Not Av.	48% (38.9–56.9)* at d100	Not Av.	Not Av.	1 pt	18% (10–26)* at d180	48% (26–70)* at d100	14% at d100
1-Year Overall survival (Kaplan Meier)	43%	32% (22.4–42.4)*	Not Av.	Not Av.	Not Av.	44% at 2 years	31% (15–47)*	79% (64% DFS)
Relapse/Progression (% Cum. Incid.)	Not Av.	Not Av.	Not Av.	Not Av.	3 pt	32% (31–55)*	Not Av. (DFS at 1 year: 24%)	1 pt

All values are given as median (% or range), unless otherwise specified.

Abbreviations: AML = acute myeloid leukemia; ALL = acute lymphocytic leukemia; ANC = absolute neutrophil count; ATG = antithymoglobulin; Bu = busulphan; cGy = centiGray; CML = chronic myeloid leukemia; Cum. Incid. = cumulative incidence; Cy = cyclophosphamide; DFS = disease-free survival; Flu = fludarabine; GVHD = graft-versus-host disease; Not Av. = not available; Pt = patients; TBI = total body irradiation; TNC = total nucleated cells; TRM = transplant-related mortality.

*95% confidence interval.

Table 5 Multiple Cords in Adult UCB transplantation (2001–2005)

	<i>Barker et al.⁴⁴</i>	<i>Kai et al.⁴⁵</i>	<i>Ballen et al.⁴⁰</i>	<i>Brunstein et al.³⁴</i>	<i>Barker et al.⁴¹</i>
	<i>Cy-TBI (myeloablative) double unit only 2000–2003</i>	<i>Cy-TBI (+/-AraC) (myeloablative) double unit only Not Av.</i>	<i>Flu-Melphalan-Rabbit ATG (RIC) double unit only 2004–2005</i>	<i>Flu-Cy-200cGy TBI (RIC) single (25%) and double (75%) unit 2001–2004</i>	<i>Bu-Flu-TBI (RIC) single and double unit 2000–2001</i>
Number of patients	23	11	21	95	21
Age (years)	24 (13–53)	33 (19–52)	49 (24–63)	50 (18–64)	49 (22–65)
Weight (kg)	73 (48–120)	68 (48–84)	Not Av.	78 (50–134)	75 (55–109)
<i>Diagnosis</i>					
AML	13 (56%)	7 (63%)	8 (38%)	Not Av.	10 (48%)
ALL	8 (35%)	1 (10%)	1(5%)	Not Av.	0
CML	2 (9%)	0	0	Not Av.	2 (9%)
Other	0	3 (27%)	12 (57%)	Not Av.	9 (42%)
Donor recipient match	#	Not Av.	#	#	#
<i>Cell dose median</i>					
TNC ($\times 10^7$ /kg weight)	4.8 (1.6–7.0)	3.9 (2.83–4.79)	4.0 (3.0–5.3)	3.6 (1.1–6.8)	3.3 (2.3–5.1)
<i>Hematopoietic recovery</i>					
Time to ANC engraftment (days)	23 (15–41)	21 (16–26)	20 (15–34)	12 (0–32)	26 (12–30)
Cum. Incid. of neutrophil recovery	100% at d42	9/11 pt	Not Av.	87%	Not Av.
Graft failure/secondary Graft rejection	0%	2/11 pt	3 pt (14%)	Not Av.	4 pt (22%)
<i>GVHD</i>					
Acute GVHD II–IV (% Cum. Incid.)	65% (42–88)*	4/9 pt	4 pt (21%)	61% (49–73)*	44% (28–62)*
Chronic GVHD (% Cum. Incid.)	23% (6–40)*	4/6 pt	3/12 pt (25%)	25 % (15–35)*	21% (8–34)*
<i>Statistical analysis</i>					
Median follow-up (months)	10 (3.5–30)	(3–16)	7 (2–16)	14 (3.3–42.7)	23 (14–28)
TRM (% Cum. Incid.)	22% (5–39)* at d180	2/11 pt	14% at d100	18% (10–26)* at d180	48% (26–70)* at d100
1-Year overall survival (Kaplan Meier)	57% (35–79)* (DFS)	9/11 pt	79% (64% DFS)	44% at 2 years	31% (15–47)*
Relapse/progression (% Cum. Incid.)	Not Av.	1/11 pt	1 pt	32% (31–55)*	Not Av. (DFS at 1 year: 24%)

All values are given as median (% or range), unless otherwise specified.

Abbreviations: AML = acute myeloid leukemia; ALL = acute lymphocytic leukemia; ANC = absolute neutrophil count; ATG = antithymoglobulin; Bu = busulphan; cGy = centiGray; CML = Chronic myeloid leukemia; Cum. Incid. = cumulative incidence; Cy = cyclophosphamide; DFS = disease-free survival; Flu = fludarabine; GVHD = graft-versus-host disease. Not Av. = not available; Pt = patients; TBI = total body irradiation; TNC = total nucleated cells; TRM = transplant-related mortality.

*95% confidence interval.

= units matched at least 4/6 (HLA-A, -B and -DR β 1) to each other and to the patient.

being developed in children and adults and should clarify this in the near future.

Ex vivo expansion

The clinical use of expanded UCB stem and progenitor cells has been explored in two major phase I studies (Table 6),^{49,50} including both adult and pediatric patients. In both studies, the UCB unit was split and a fraction of it was infused, while the rest was expanded and infused after expansion. Shpall *et al.*, divided their patients in two strata which either received the unmanipulated fraction on day 0 and the expanded fraction 10 days later or both fractions on day 0. Jaroscak *et al.* infused the unmanipulated

fraction on day 0 and the remaining expanded cells on day 12. The cell numbers infused are difficult to interpret because of the great variation in weights of the individuals included in the study, the variable amounts of cells kept for expansion and the unpredictable yield after the expansion procedure.

Furthermore, since the expansion systems used in these clinical studies had never proved to expand true, long-term re-populating colony (LTRC)-forming cells, the strategy was to expand the mature progenitors to shorten the time to engraftment by bridging the pancytopenic period without necessarily trying to increase the number of stem cells infused.

Although confirming the feasibility and safety of the procedure in terms of infusional toxicity, these studies

Table 6 Studies presenting other approaches in Adult UCB transplantation (2001–2005)

	<i>Fernandez et al.⁵³ Single UCB transplantation with PBSC from a third party haploidentical-related donor Period not mentioned</i>	<i>Schpall et al.⁴⁹ Transplantation of ex vivo expanded cord blood 1997–2000</i>	<i>Jaroscak et al.⁵⁰ Transplantation of ex vivo expanded cord blood 1997–1998</i>
Number of patients	28	37 (25 adults)	27 (2 adults)
Age (years)	30 (16–60)	38 (1–60)	4.5 (1–36)
Weight (kg)	67 (43–87)	61 (9–116)	17 (6–77)
<i>Diagnosis</i>			
AML	Not Av.	10 (27%)	1 (4%)
ALL	Not Av.	10 (27%)	4 (14%)
CML	Not Av.	3 (8%)	1 (4%)
Other	Not Av.	14 (38%)	22 (79%)
<i>Donor recipient match</i>			
0 Mismatch	Not Av.	9 (24%)	0
1 Mismatch	Not Av.	22 (59%)	7 (25%)
2 Mismatch	Not Av.	6 (16%)	19 (68%)
≥3 Mismatch	Not Av.	0	2 (7%)
<i>Cell dose median</i>			
TNC ($\times 10^7$ /kg weight)	2.4 (1.31–3.7)	0.95 unmanipulated + 0.79 post expansion (for adult patients)	2.05 (1.1–1.5) unmanipulated + 2.05 (0.06–10.2) post expansion
<i>Hematopoietic recovery</i>			
Time to ANC engraftment (days)	10 (9–36)	35 (for adult patients)	22 (13–40)
Cum. Incid. of neutrophil recovery	93% at day 54	Not Av.	95% at d42
Graft failure/Secondary Graft rejection	Not Av.	7/37 pt died before engraftment	3/21 pt
<i>GVHD</i>			
Acute GVHD II–IV	Not Av.	16/20 pt (for adult patients)	8/22 pt
Chronic GVHD	Not Av.	9/10 pt (for adult patients)	Not Av.
<i>Statistical analysis</i>			
Median follow-up (months)	10 (1–75)	30	Not Av.
TRM	Not Av.	14/37 pt	Not Av.
Median overall survival (Kaplan Meier)	67% at 4 years (65–82)*	5/25 pt (for adult patients)	65% (47–84)* at d100
Relapse/progression	Not Av.	11/37 pt	Not Av.

All values are given as median (% or range), unless otherwise specified.

Abbreviations: AML = acute myeloid leukemia; ALL = acute lymphocytic leukemia; ANC = absolute neutrophil count; ATG = antithymoglobulin; CML = chronic myeloid leukemia; Cum. Incid. = cumulative incidence; GVHD = graft-versus-host disease; Not Av. = not available; Pt = patients; TNC = total nucleated cells; TRM = transplant-related mortality.

*95% confidence interval.

failed to show better recovery kinetics than historical controls possibly because of: (1) the late infusion of the expanded hematopoietic stem and progenitor cell pool, and (2) the impoverishment of the graft quality through expansion techniques (the expansion cocktail may have actually depleted the stem cell pool, thereby decreasing the graft's proliferative potential).⁵¹ Interestingly, Schpall *et al.* reported a median four-fold increase in the CD34⁺ cells, and explored both immediate and delayed infusion of the expanded cells. However, they failed to demonstrate a significant difference in terms of engraftment. Although not the primary objective of this study (all trials were designed to address the primary endpoint of safety), incidence of both acute and cGVHD was high, and survival was

relatively poor owing to high TRM and relapse rates in the high-risk populations enrolled.⁵¹

Hence, too little clinical information is currently available to fully understand the safety and efficacy of *ex vivo* expansion culture of UCB. Of note, however, pre-clinical data suggest superior engraftment capacity of UCB progenitor cells compared to BM and peripheral blood stem cells, thus perhaps signifying that these cells still represent optimal targets for *ex vivo* expansion. At this stage, ideal methods for evaluating the stem cell re-populating potential after expansion culture, means of detecting early as well as late engraftment in murine models, validation of good animal models, and identification of homing defects still need to be studied in order to

make substantial improvements in clinical outcomes possible.⁵¹

Co-infusion of PBSC in the context of UCB transplantation

Fernandez *et al.*⁵² published their first results in 2003 (results reported in Table 6 are updated), where they attempted to improve the results with UCB transplantation after a myeloablative preparative regimen by the co-infusion of highly purified, T-cell depleted PBSC from a haploidentical-related donor. The rationale of the strategy was to make use of the typically rapid neutrophil recovery observed with PBSC as a 'cover' while waiting for UCB recovery.⁵³ Interestingly, neutrophil recovery was indeed faster (median 10 days) and was initially derived from the PBSC donor, provided the cells came from another relative than the patient's mother. UCB stem cells, however, proved to have a competitive advantage for long term engraftment, with at least partial UCB chimerism achieved in all engrafting patients at day 42 and regression analysis failed to show any influence of the number of third party donor cells on time to UCB engraftment. The impressive overall survival statistics (67% at four years, or 20/28 patients) of this small patient cohort warrant further study of this novel approach.

Future of UCB transplantation

Over the last few years, the expansion of cord blood banks has tremendously increased unit availability, making the use of multiple UCB units a true option. This also opens the way to safer clinical trials involving *ex vivo* expansion of UCB, where simultaneous infusions of manipulated and unmanipulated units can attempt to bridge the pancytopenic period or improve engraftment, while remaining 'traceable' thanks to their chimeric signature. Reduced intensity conditioning also offers an attractive way to reduce TRM, thereby broadening the range of potential recipients, but the impact of this on graft failure and long-term relapse rates still needs to be determined.

Obviously, many questions still remain unanswered at this stage. Unfortunately, it is impossible to determine which diseases should be preferentially treated with UCB as graft source, since the great majority of the studies reported to date include a wide variety of diseases, at various stages of evolution. Furthermore, most published series remain too small to allow for meaningful sub-group analysis. Interestingly, two small pilot studies have attempted to answer this question. Majhail *et al.*⁵⁴ have reported comparable outcomes for adult advanced Hodgkin lymphoma treated with reduced intensity conditioning, regardless of stem cell source (UCB or a sibling donor). Kumar *et al.*⁵⁵ have performed a small retrospective study on the impact of donor source on clinical outcome in ALL, where UCB transplants had the lowest TRM and a survival advantage on other related and unrelated stem cell sources. One would intuitively think that rapidly progressing disease should benefit most from the fast availability of UCB units, but this has not formally been demonstrated to date.

Choosing UCB as opposed to a haploidentical donor is also an area of controversy. A retrospective registry study from Rocha *et al.*⁵⁶ on high-risk adults with AML or ALL suggested similar results in terms of TRM, relapse and disease-free survival (DFS) for adults with AML if treated by UCB or haploidentical transplantation; for patients with ALL by contrast, DFS seemed to be superior in the UCB transplant group because of a decreased incidence of relapse. It must be noted, however, that ALL patients receiving UCB grafts were also younger and had received less TBI. So, the true advantage of the donor source obviously remains to be established by prospective studies.

Many unique features place UCB transplantation in a critical position between bench-work and clinical trials. This makes it an ideal platform for applying translational research to immediate patient care in order to improve transplantation results. Therefore, we are confident that the near future will show rapid evolution of this new transplant modality, offering new ways to overcome the shortage of donors for patients needing an HSCT.

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