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REVIEW

Cord blood transplantation for adults

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Allogeneic haematopoietic stem cell transplant has become an import tool for the treatment of high risk and advanced haematological diseases. However, allogeneic transplantation has been limited by the availability of suitable related and unrelated donors. The positive results with umbilical cord blood as an alternative source of haematopoietic stem cells for transplantation in the paediatric setting encouraged studies in adult patients. In adults, however, the progress of cord blood transplantation has been slower, in part limited by the limitation of cell dose. We review here the current state of the art on cord blood transplantation for adults, and discuss some of the newer strategies being pursued in order to improve its safety and efficacy.

Key words: myeloablative transplantation, non-myeloablative transplantation, umbilical cord blood.

Introduction

Allogeneic haematopoietic stem cell (HSC) transplant has become the standard of care for a number of high-risk and advanced haematological diseases. However, only about one-third of all patients who would potentially benefit from HSC transplant will have a suitable human leucocyte antigen (HLA)-matched related donor, and another third may be able to find an appropriately HLA-matched unrelated donor out of approximately five and a half million adult volunteers registered with the National Marrow Donor Program (NMDP) in the USA [1,2] and approximately 10 million donors registered worldwide. Unfortunately, individuals who are part of a racial or ethnic minority, or mixed ethnic background, have a reduced probability of identifying an unrelated donor in the marrow donor registries [1,3]. Moreover, the donor search process requires a significant amount of time (median 4 months) [4], and a substantial proportion of donors (35%) are not available at the time of the request (Roberta King, NMDP, United States, personal communication). Despite high-resolution HLA typing and improved HLA matching, unrelated donor transplantation is still complicated by acute and chronic graft-versus-host disease (GvHD) and opportunistic infections with concomitant risk of transplantation morbidity and mortality.

In 1989, Gluckman *et al*. reported the first successful haematopoietic reconstitution after umbilical cord blood (UCB) transplantation from an HLA-matched sibling donor in a child with Fanconi anaemia [5]. A few years later, Kurtzberg & Wagner performed the first transplants with unrelated donor UCB [6,7]. Since then, the number of UCB transplants for patients with malignant and non-malignant disorders has rapidly grown and, among children, grew from fewer than 10 in 1993 to approximately 300 in 2003, approaching that of unrelated bone marrow and peripheral blood [Center for International Bone Marrow Transplant Research (CIBMTR), personal communication). Important lessons learned from the early UCB transplantation experience are that utilization of HLA-mismatched UCB is acceptable (at least when matched at four of six HLA-A, -B and -DRB1 antigens), the incidence of GvHD is less than that expected based on the degree of HLA mismatch, time to haematopoietic recovery is consistently longer than that of other HSC sources, and both nucleated cell (NC) and $CD34^+$ cell doses influence success after UCB transplantation [8–12]. The promising results obtained after UCB transplantation among children encouraged its investigation in the treatment of adults with lymphohaematopoietic disorders who would potentially benefit from an allogeneic HSC transplant.

It is clear that UCB has several advantages over donations from unrelated adults [13–15]. First, UCB units are immediately

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available for transplantation as they are frozen and banked with defined HLA typing. Once a unit is identified for a patient, it can be rapidly shipped to the transplant centre anywhere in the world with relative ease. Second, as the collection of UCB takes place after the delivery of the newborn and the placenta, there is no risk to the donor. Third, there is low risk of viral transmission of cytomegalovirus (CMV), hepatitis and human immunodeficiency virus (HIV). Last, possibly owing to the immunological naivety of UCB, a higher degree of mismatch appears to be acceptable with a comparatively lower risk of acute and chronic GvHD [16]. This last aspect is particularly important for patients who have a mixed or under-represented ethnic background for whom it would be difficult to find a suitable unrelated donor in marrow donor registries worldwide.

However, it is important to recognize several critical limitations of UCB. First, the number of haematopoietic progenitor cells in a single UCB unit is limited. As cell dose has been shown to be a major determinant of engraftment and survival after UCB transplantation, this represents the most significant barrier to its success [9,11,17]. The minimum total NC dose recommended to determine if a patient can proceed to UCB transplant has increased from $\geq 1 \times 10^7$ NC/kg to ≥ 2 or 3×10^7 NC/kg [18]. Despite this, the total NC dose per kilogram for recipients of UCB transplant still is a log less than what recipients of transplants from adult stem cell sources receive [16,19]. Second, in the event of relapse after UCB transplantation, there is no access to donor lymphocytes. This may be particularly important for diseases like chronic myelogenous leukaemia, where donor lymphocyte infusion (DLI) has been shown to be particularly effective. Last, there is significantly less experience with UCB than with unrelated donors as an alternative source of HSC for transplantation, particularly in adults.

Early experience

In the initial reports of UCB transplantation in adults, the results were poor, largely owing to the frequent use of an inadequate cell dose, with 1×10^7 NC/kg often described as the lower limit. In those reports, the median UCB NC dose per kg for adult patients was approximately half of the cell doses for paediatric patients [18,20–22]. However, prolonged time to neutrophil recovery was consistent with what would have been predicted based on similar cell doses in paediatric reports, ranging from 22 to 32 days to achieve 500 neutrophils/μl [18,20–22], and 130 days for platelets ≥ 50 000/μl [20]. Graft failure was common, being observed in 20–40% of patients [20,21,23]. The incidence of acute GvHD tended to be higher than that reported in the paediatric population, with grade II–IV acute GvHD occurring in 30–70% of patients [18,20–22]. The higher incidence of acute GvHD was somewhat unexpected [8,9,11], but can, at least in part, be explained by thymus involution with age. Importantly, transplant-related mortality (TRM) at day 100 was reported to be as high as 50% [18,20–22], contrasting with 20–35% in the paediatric population [7–9,11]. In these early series, the observed survival rate was 20% to 30% at 1 year [18,20–22].

There are several important points to take into consideration when analysing these early results. First, in the late 1990s, adults referred for UCB transplantation were more often very high risk, based on disease status (e.g. heavily pretreated or with advanced malignancy). For example, in the COBLT study [23] (1999–2000), 15% of patients were in relapse at the time of transplantation and 12% died during the preparative therapy before the infusion of UCB. Furthermore, many patients had waited for an unrelated adult donor for prolonged intervals before eventual referral to UCB transplantation as the 'last chance'. Second, as described above, both nucleated and CD34 cell doses were substantially lower than what would be considered as acceptable today. While a cell dose of 1×10^7 NC/kg was considered to be the lower acceptable limit in 1996 [18,20], currently $2{\cdot}5 \times 10^7$ NC/kg is considered to be the lower limit [11,17]. Last, owing to the very limited inventory of UCB units with suitable cell doses, most adults have access only to two antigen HLA-mismatched grafts. An increasing body of evidence suggests that better HLA-matched UCB grafts positively influence outcomes [17,24,25]. In summary, the combination of advanced disease, older age, low cell dose and high degree of HLA mismatch led to slow engraftment, high TRM and poor survival.

Comparisons of umbilical cord blood and other HSC sources

Related donor HSC vs. unrelated UCB transplantation

There are currently at least two studies, both reported in abstract form, that have compared transplantation with unrelated UCB to HLA-matched and mismatched related donors in the adult population, and their results are summarized in Table 1 [26,27].

One study [27], is a single-centre analysis comparing unrelated UCB to HLA- and partially HLA-matched related donors after a myeloablative preparative regimen [27]. Except for the degree of HLA matching, pretransplant characteristics were similar between the two groups. All UCB grafts were HLA mismatched, while 74% of related donors were fully HLA matched at HLA-A, -B and -DRB1 alleles. As previously reported, time to neutrophil and platelet recovery were longer in the UCB cohort, but overall donor-derived engraftment was comparable in the two groups by day 42 (UCB 94% vs. 98% related donor, not significant). The rate of acute GvHD grades II–IV was the same between the two groups. In contrast, grade III–IV GvHD was significantly more frequent among

Table 1 Overview of studies comparing umbilical cord blood (UCB) transplant with other haematopoietic stem cell sources in adult patients

Author	HSC source	*n*	Median age (range)	Infused NCD × 10^7/kg (range)	Median time to ANC > 500/μl (days)	Median time to platelet count > 20 × 10^9/l (days)	Graft failure (%)	aGvHD II–IV (%)	Extensive cGvHD (%)	Relapse rate (%)	TRM (%)	Survival or DFS (%)
UCB vs. URD transplant												
Laughlin *et al.* [15]	UCB	150	(16–60)[a]	2·2 (1·0–6·5)*	27	60 (20)	NS	41	33	17	63	26
	URD marrow	367	(16–60)[a]	24 (0·2–170)	20	29 (20)	NS	48	52	23	46	35
	URD MM marrow	83	(16–60)[a]	22 (0·1–58)	18	29 (20)		51	71	14	65	20
P-value					< 0·001	< 0·001	0·29	[c]	0·03	[d]	[e]	[f]
Rocha *et al.* [27]	UCB	98	25 (15–55)	2·3 (0·9–6·0)	26		20	26	30	23	44	36
	URD marrow	584	32 (15–59)	29 (< 10–90)	19		7	39	46	23	38	42
P-value					0·001		NA	0·008	0·07	0·71	0·13	0·08
Takahashi *et al.* [26]	UCB	68	36 (16–53)	2·5[b] (1·1–5·3)	22	40 (20)	8	30	13	16	9	DFS 74
	URD marrow	45	26 (16–50)	33 (6·6–50)	18	25 (20)	Zero	30	14	25	29	DFS 44
P-value					0·01	0·01	NA	[g]	[g]	[g]	0·02	< 0·01
UCB vs. related donor transplant												
Takahashi *et al.* [25]	UCB	92		2·4[b]	22	39 (20)		52	23	18 at 3 years	9	DFS 71
	REL marrow	55			17	22 (20)		52	44	23 at 3 years	13	DFS 60
	PB	16										
UCB vs. haploidentical donor transplant												
Rocha *et al.* [24]	AML											
	UCB	66						23		24	46	DFS 30
	Haplo	154						5		18	58	DFS 24
			31		23			< 0·001		0·44	0·23	0·39
	ALL		38		13							
	UCB	73						26		23	41	DFS 36
	Haplo	75						8		38	49	DFS 13
P-value								0·004		0·07	0·55	0·01

[a]Age reported in intervals of 16–20, 21–30, 31–40, 41–50 and 51–60 years. No median available.

[b]Cryopreserved nucleated cell dose.

[c]Multivariate analysis for acute graft-versus-host disease (GvHD) showed a hazard ratio (HR) of 0·81 ($P = 0·17$) for UCB vs. matched unrelated marrow, and an HR of 0·66 ($P < 0·04$) for UCB vs. mismatched unrelated marrow.

[d]Multivariate analysis for relapse showed an HR of 0·85 ($P < 0·61$) for mismatched unrelated marrow vs. matched unrelated marrow, an HR 0·73 ($P < 0·16$) for UCB vs. matched unrelated marrow, and an HR of 0·85 ($P = 0·65$) for UCB vs. mismatched unrelated marrow.

[e]Multivariate analysis for transplant-related mortality (TRM) showed an HR of 1·91 ($P < 0·001$) for mismatched unrelated marrow, an HR of 1·89 ($P < 0·001$) for UCB vs. matched unrelated marrow and an HR of 0·99 ($P = 0·96$) for mismatched unrelated marrow vs. UCB.

[f]Adjusted probability of 3-year survival showed no difference between mismatched unrelated marrow and UCB ($P = 0·62$), but superior 3-year survival for recipient-matched unrelated marrow ($P < 0·001$).

[g]Multivariate analysis of UCB vs. unrelated marrow for acute GvHD grades II–IV showed an HR of 0·61 ($P = 0·05$), for extensive chronic GvHD and an HR of 0·60 ($P = 0·18$) for chronic graft-versus-host disease. For relapse, the HR was 0·76 ($P = 0·73$).

aGvHD, acute graft-versus-host disease; ALL, acute lymphoblastic leukaemia; AML, acute myelogenous leukaemia; ANC, absolute neutrophil count; cGvHD, chronic graft-versus-host disease; DFS, disease-free survival; HSC, haematopoietic stem cell; Haplo, haploidentical donor; MM, mismatched; NA, not available; NCD, nucleated cell dose; NS, not significant; PB, peripheral blood; REL, related donor; TRM, treatment-related mortality; UCB, umbilical cord blood; URD, unrelated donor.

recipients of a related donor graft (8% vs. 19%, $P = 0{\cdot}04$). The incidences of chronic GvHD and TRM, and the 3-year relapse rate, as well as the probability of and 3-year survival, were comparable between the two groups.

A second study [26] compared outcomes in patient transplanted with unrelated UCB and haploidentical T-cell-depleted (TCD) marrow grafts for the treatment of acute myelogenous leukaemia (AML) and acute lymphoblastic leukaemia (ALL) [26]. In this study, about half of the patients in each group were allografted in advanced-stage disease. Once again, median time to neutrophil recovery was longer in the UCB cohort (23 vs. 13 days, $P < 0{\cdot}001$) (V. Rocha, personal communication). In this initial analysis, the incidence of grades II–IV acute GvHD was higher for the UCB group (23% vs. 5%, $P < 0{\cdot}001$) (V. Rocha, personal communication). As shown in Table 1, other than GvHD, patients with AML had similar outcomes, regardless of graft source. However, patients with ALL had a higher probability of 2-year leukaemia-free survival (LFS) if they received a UCB graft (i.e. UCB vs. TCD bone marrow). This finding suggests that UCB may offer a survival benefit, possibly as a result of the enhanced graft-vs.-leukaemia (GVL) effect, compared with TCD haploidentical bone marrow in ALL.

Despite limitations of this retrospective analysis, these two studies suggest that UCB transplantation compares favourably with HLA-matched and HLA-mismatched related donor transplantation.

Unrelated donor HSC vs. unrelated UCB transplantation

At least three retrospective studies have been reported, to date, comparing UCB with unrelated donor transplantation in adults after a myeloablative preparative regimen [16,19,28]. The results are summarized in Table 1. Although the age ranges were similar in the three studies, the median age tended to be lower among recipients of UCB [19,28]. Importantly, in UCB grafts the number of cryopreserved [28] or infused NC [16,19] doses were one log lower. Again, time to neutrophil and platelet recovery was significantly delayed (Table 1), and graft failure was higher after UCB transplantation. Despite a higher degree of HLA mismatch for recipients of UCB grafts, the incidence of grades II–IV acute GvHD after UCB transplantation was similar or lower [16,19,28]. Importantly, despite initial concerns of impaired GVL secondary to reduced alloreactivity, the relapse rates were similar between UCB and unrelated donor grafts in all studies. The impact of graft source on TRM and survival, however, has been more controversial. The study by Laughlin *et al*., comparing HLA-mismatched UCB to HLA-matched and mismatched unrelated marrow, observed a 63% incidence of TRM after UCB transplantation. Although this rate was similar to HLA-mismatched unrelated marrow (65%), it was significantly higher than the 46% observed after HLA-matched unrelated marrow ($P = 0{\cdot}001$). Rocha *et al.* [19], however, observed similar TRM rates for UCB and unrelated marrow grafts, while Takahashi *et al.* [28] observed lower TRM for the UCB group compared with unrelated marrow (Table 1). Laughlin *et al.* [16] reported survival to be comparable after UCB transplantation relative to HLA-mismatched unrelated marrow, but inferior to HLA-matched unrelated marrow. Rocha *et al.* [19] observed no significant difference between the groups, and Takahashi *et al.* [28] reported significantly superior disease-free survival for recipients of UCB grafts.

Methodological differences have to be taken into account when interpreting the results above. First, all three studies were retrospective, and two were registry based with heterogeneous patient populations. Differences in the centre experience with UCB and unrelated donor transplantation may influence the results. In particular, the two larger registry reports contain results of patients transplanted in the mid-1990s when the standards of cell dose were different. It is important to note that the latter two studies only evaluate patients transplanted after 1998. Data from the European Group for Blood and Marrow Transplantation (EBMT) suggests that outcomes overall have improved over time (V. Rocha, personal communication). The results reported by Takahashi *et al.* [28] may represent differences in patient selection, single-centre expertise and different care model. Overall, these studies, however, suggest that UCB transplantation is an acceptable alternative for all patients who do not have a suitable related (5–6/6 allele level HLA match at A, B and DRB1) and unrelated (8/8 allele level HLA match at A, B, C and DRB1) donor. The question, at present, is the relative place of UCB – first-line or second-line therapy.

Multiple UCB units

It is unequivocally clear that cell dose and HLA match are central factors in predicting the risk of TRM. Furthermore, it is clear that low cell dose amplifies the deleterious effect of HLA mismatch [18,20,23]. Therefore, cell dose is a critical determinant that can be addressed. Potential strategies are: *ex vivo* expansion; homing; reduction of host resistance; and combining two partially matched UCB units. As previously stated, cell dose is an important factor that prevents adults and larger adolescents from undergoing UCB transplantation and is, at least in part, responsible for the anticipated results in terms of engraftment and survival. Our group has reported on the successful use of 'double' UCB transplantation as a strategy to overcome the cell dose limitation [29]. Our rationale was that if a single unit does not provide an adequate cell dose for an adult patient, perhaps the combined cell dose of two partially HLA-matched units could improve the outcome. We and others have embarked on studies utilizing multiple UCB units in the myeloablative [30–35] and non-myeloablative [36–38] settings.

Table 2 Adult umbilical cord blood (UCB) transplant with double-unit grafts

Author	*n*	Median Age (range)	Cryopreserved NCD × 10^7/kg (range)	Median time to ANC > 500/μl (days)	Median time to platelet recovery (> 50 × 10^9)	Graft failure (%)	aGvHD II–IV (%)	Extensive cGvHD (%)	Relapse rate (%)	TRM (%)	Survival (%)
Barker *et al.* [29]	23	24 (13–53)	4·8 (1·6–7·0)	23	71% at 6 months	Zero	65	23	13	22	DFS 57% at 1 year
Kai *et al.* [30]	11	33 (19–52)	3·9 (2·8–4·8)	21	53	18	44	0			

aGvHD, acute graft-versus-host disease; ANC, absolute neutrophil count; Bu/Flu/TBI, busulfan, fludarabine, and total body irradiation; cGvHD, chronic graft-versus-host disease; Cy/Flu/TBI, cyclophosphamide, fludarabine and total body irradiation; DFS, disease-free survival; NCD, nucleated cell dose; REL, related; TRM, treatment-related mortality; UCB, umbilical cord blood; URD, unrelated.

Myeloablative UCB transplantation

The Minnesota experience in adult and larger adolescent patients receiving a 'double' UCB graft after a myeloablative preparative regimen has been recently reported and is summarized in Table 2 [30]. The combination of two units allowed this group of patients to receive grafts similar to what is routinely anticipated in children. Median time to neutrophil recovery was consequently lower than expected for adult patients after a single UCB transplantation [16,18–23,39]. TRM, relapse rate and disease-free survival were encouraging after double UCB transplantation (Table 2). Kai *et al.* [31] reported similar results. While it might be conjectured that more is better, reports of the utilization of three or more UCB unit grafts, however, has not clearly been of benefit [33,35].

We recently compared the outcomes of acute leukaemia patients who received a single or double UCB unit graft [40]. In this series, 39% received a double, and 61% received a single, UCB unit graft. Single UCB unit grafts were given only if the cell dose exceeded $3{\cdot}5 \times 10^7$ NC/kg or $2{\cdot}5 \times 10^7$ NC/kg if or a second suitable UCB unit was not available. Sustained neutrophil engraftment and TRM were virtually the same between groups, reflecting the fact that patients can receive single UCB unit grafts if the cell dose is high. However, there was a threefold higher incidence of grade II–IV GvHD among recipients of double cords, but no difference in the incidence grades in patients with grade III–IV acute and chronic GvHD. While other outcomes were similar, an unexpected finding was a lower leukaemia relapse rate among recipients of a double UCB graft when transplanted in first and second complete remission. The results of the multivariate analysis indicated that transplantation with two units is associated with a 10-fold lower risk of relapse. This may be explained by the fact that recipients of a double UCB graft most often receive a 4/6 HLA-matched graft, which may lead to more GVL effect.

Future studies are currently being designed that will prospectively compare single vs. double UCB unit grafts in the setting of a common preparative therapy, GvHD prophylaxis and single set of outcome definitions. This randomized study is the only way to definitely determine the true advantage of double UCB transplantation, other than the fact that double UCB transplantation allows the patient to go to transplantation at all.

Non-myeloablative UCB transplantation

The median age of presentation of most haematological malignancies is in the 5th and 6th decades of life [41], making most adult patients who could potentially benefit from transplantation ineligible as a result of risk associated with a conventional dose [42,43]. Moreover, younger patients who have end-organ dysfunction, infection or who have frequently received extensive therapy, such as autologous transplantation, are also at high risk of TRM with conventional conditioning regimens [44–46]. Therefore, non-myeloablative (NMA) regimens have been developed based on the understanding that the GVH and GVL effects of allogeneic HSC sources are, at least in part, responsible for engraftment and long-term disease control. Current NMA preparative regimens were based on reports by Storb *et al.* [47] and Quesenberry *et al.* [48]. This type of approach has allowed patients who are older, and heavily pretreated, and with significant comorbidities (e.g. organ dysfunction, recent fungal infection), to undergo allogeneic transplantation [49–53]. The initial question to be evaluated was whether UCB was a sufficient source of HSC and immune cells to effect engraftment reliably after a NMA therapy. Therefore, our group and others evaluated the efficacy of UCB transplantation in the setting of a NMA preparative regimen [36–38,54–59]. A summary of selected adult NMA UCB transplantation studies are shown in Table 3.

Importantly, most groups have used fludarabine combined with an alkylating agent preparative regimen, with or without low-dose total body irradiation (TBI) (2–4 Gy) regimen [36–38,57–59]. In two studies, patients who received double UCB unit grafts, with a higher median infused NCD and CD34 cell dose [36–38], were more likely to have sustained donor engraftment, at a median of approximately 2 weeks

Table 3 Overview of adult non-myeloablative umbilical cord blood (UCB) transplant

Author [ref]	*n*	Preparative regimen	Median age (range)	Infused NCD × 10^7/kg (range)	Infused CD34 cell dose × 10^5/kg (range)	Median time to ANC > 500/μl (days)	Graft failure (%)	Median time to platelet count recovery (days) (> 20 × 10^9)	aGvHD II–IV (%)	Extensive cGvHD (%)	Relapse rate (%)	TRM (%)	Survival (%)
Barker *et al.*[a,b] [40]	21	Bu/Flu/TBI	49 (22–65)	2·6 (1·6–3·8)	3·7 (1·1–8·1)	26	24	24% (20) at 6 months	44	21		48 at 100 days	39 at 1 year
	22	Cy/Flu/TBI	49 (24–58)	3·2 (1·1–5·1)	4·3 (1·1–10)	9·5	6	80% (20) at 6 months				28 at 100 days	
Brunstein *et al.*[a,b] [35]	95	Cy/Flu/TBI	50 (18–69)	3·6 (1·1–6·8)	4·5 (0·7–18·8)	12	13		61	25	31	18 at 180 days	44 at 2 years
Rio *et al.* [59]	18	Cy/Flu/TBI	46 (19–64)	2·3 (1·7–3·7)	0·7 (0·4–1·2)	14		28	11	38		Zero	EFS 80%[c]
Morii *et al.* [58]	14	Cy/Flu/TBI Bu/Flu/TBI	57 (31–72)	2·6 (2·1–3·8)		21	14	43	21	50		19	37% at 1 year
Ballen *et al.*[b] [36]	21	Flu/Mel/TBI	49 (24–63)	4·0 (3·0–5·3)	2·0 (0·6–10·0)	20		41	21	25		14	DFS 64% at 1 year
Miyakoshi *et al.* [57]	30	Flu/Mel/TBI	59 (20–70)	3·1 (2·0–4·3)	0·7 (0·2–2·5)	17·5	7	39	27	23	11	27	33 at 1 year

[a]The 22 patients who receive the combination of cyclophosphamide, fludarabine and total body irradiation (Cy/Flu/TBI) in the series by Barker *et al.* are included in the series by Brunstein *et al.*

[b]Study included patients receiving multiple unit UCB grafts.

[c]Median follow-up of 4·5 months.

ANC, absolute neutrophil count; aGvHD, acute graft-versus-host disease; Bu/Flu/TBI, busulfan, fludarabine, and total body irradiation; cGvHD, chronic graft-versus-host disease; DFS, disease-free survival; EFS, event-free survival; Flu/Mel/TBI, fludarabine, melphalan, and total body irradiation; NCD, nucleated cell dose; TRM, treatment-related mortality.

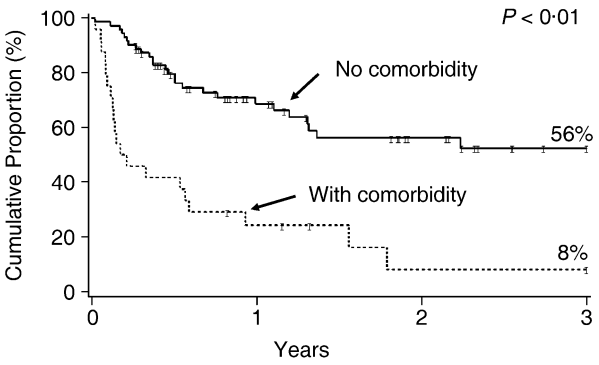

Fig. 1 Impact of the presence of comorbidities on survival after non-myeloablative unbilical cord blood (UCB) transplant (n = 95). Comorbidity was defined as serious concurrent medical conditions, invasive fungal infection within 60 days, Karnofsky score of 50–60, intensive care unit admission for life-threatening infection or major surgery in the last 90 days, or serious organ dysfunction.

[36–38,57–59]. In this older group of patients, the incidence of acute and chronic GvHD ranged widely and was reported to be as high as 60% [36]. TRM, however, was consistently lower than 30% (Table 3). In our series [36], which represents the largest single-centre experience to date, progression-free survival (PFS) of 38% and overall survival of 44% was found. Others, however, have reported overall survival of 33–37% [57,58]. Preliminary analysis of results in patients who received NMA UCB for Hodgkin's and non-Hodgkin's lymphoma at our centre, showed promising outcomes in these subgroups [60,61]. Despite encouraging results overall, we observed that patients who receive an NMA preparative regimen because of poor organ function, recent fungal infection, or low performance status, still have a significantly higher risk of TRM and poor survival (Fig. 1).

We observed that patients who were not exposed to multi-agent chemotherapy in the 3 months before NMA UCB were at high risk of graft failure. We hypothesized that these patients were rejecting their UCB grafts because of a more intact immune system. The engraftment rate was significantly improved by adding antithymocyte globulin (ATG) as part of the preparative regimen [36]. Unexpectedly, we found that patients who receive ATG as part of the preparative regimen for an NMA UCB transplantation have an increased risk of Epstein–Barr virus (EBV) viraemia and post-transplant lymphoproliferative disorder [62]. These patients require close monitoring for evidence of viral reactivation, and possibly pre-emptive therapy, to prevent the development of full-blown lymphoma.

In summary, the data above clearly support the utilization of UCB as an HSC source for NMA transplantation. Future studies will focus on disease-specific outcomes and the comparison of UCB with other HSC in the NMA setting.

Future directions in adult umbilical cord blood transplantation

Although initially slower than in paediatrics, the development of adult UCB transplantation is rapidly increasing. Larger numbers of adult patients at multiple sites need to be evaluated to provide a better definition of the role of UCB and reproducibility of results in specific diseases and subgroups. Expansion of the current UCB inventory, with the greater representation of racial and ethnic minorities, will allow UCB transplantation to be performed with better HLA match and larger units potentially improving outcomes. Further research and new techniques to improve engraftment, reduce the incidence of GvHD and promote immune reconstitution could have a major impact on TRM and survival (Fig. 2).

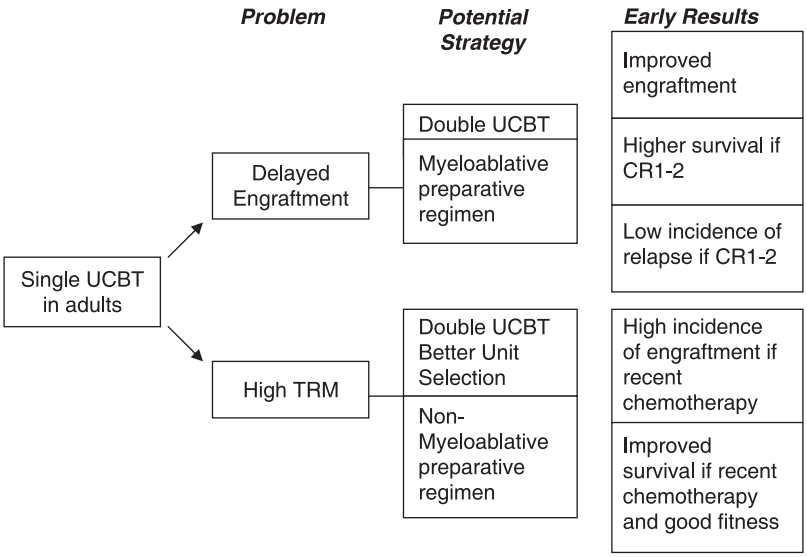

Fig. 2 Overview of umbilical cord blood transplantation for adults.

Table 4 Strategies to improve outcomes after umbilical cord blood transplant

	Rationale	Potential benefit	Current status
Ex vivo expansion	Increase cell dose	1) ↓ time to neutrophil recovery 2) ↑ engraftment	Clinical trials
Intra-bone marrow injection	Improve homing	1) ↓ time to neutrophil recovery 2) ↑ engraftment	Clinical trials
Co-infusion mobilized PBSC	Increase commited progenitors	1) ↓ time to neutrophil recovery	Clinical trials
Co-infusion T-regulatory cells	Cell mediated immune regulation Cell–cell signalling Cytokines	1) ↓ time to neutrophil recovery 2) ↑ engraftment 3) ↓ GvHD	Preclinical trials
Co-infusion MSC	Microenvironment cell–cell signalling Cytokines	1) ↑ engraftment	Clinical trials

GvHD, graft-versus-host disease; MSC, mesenchymal stem cells; PBSC, peripheral blood stem cells.

Novel strategies to improve engraftment, reduce GvHD, reduce TRM and enhance GVL are currently under investigation (Table 4). There are numerous approaches that might be considered for reducing the negative impact of low cell dose on engraftment. These include the following.

(1) Use of drugs or cell populations to reduce host resistance.

(2) *Ex vivo* expansion culture to augment the HSC and progenitor cell numbers.

(3) Use of novel therapies that limit the use of myelotoxic drugs in the peritransplant period.

(4) Ways to minimize the non-specific loss of circulating HSCs and potentially improve homing to the marrow microenvironment.

Other strategies are being employed to decrease the risk of TRM. Strategies to increase the speed of haematopoietic recovery, reduce the risk of acute and chronic GvHD, improve the pace of immune reconstitution, reduce the intensity of the preparative regimens and promote tissue repair will be evaluated over the next few years. Moreover, any means to enhance the antimalignancy effect of allogeneic haematopoietic cell transplantation will probably provide a positive impact on survival. Preliminary data suggest that the co-infusion of two partially HLA-matched UCB units may be a step in that direction because there appears to be a reduction in risk of relapse in patients transplanted in complete remission [40]. Other potential strategies include infusion of allogeneic natural killer cells, use of genetically modified T cells and graft selection based on predicted alloreactivity.

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