Cord Blood Biology and Transplantation

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Abstract

In recent years, umbilical cord blood has emerged as an alternative source of hematopoietic progenitors (CD34+) for allogeneic stem cell transplantation, mainly in patients who lack an human leukocyte antigen-matched marrow donor. Since 1998, about 2,500 patients have received UCB transplants for a variety of malignant and non-malignant diseases. The vast majority of recipients were children with an average weight of 20 kg, however more than 500 UCB transplantations have already been performed in adults. The "naive" nature of UCB lymphocytes may explain the lower incidence and severity of graft versus host disease encountered in UCBT compared to the allogeneic transplant setting. Furthermore, UCB is rich in primitive $CD16^{-}CD56^{++}$ natural killer cells, which possess significant proliferative and cytotoxic capacities and can be expanded using interleukin-12 or 15, so as to mount a substantial graft versus leukemia effect. The major disadvantage of UCB is the low yield of stem cells, resulting in higher graft failure rates and slower time to engraftment compared to bone marrow transplantation. A rational approach thus involves *ex vivo* expansion of UCB-derived hematopoietic precursors.

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The first successful umbilical cord blood transplantation was reported in 1989 in a boy with aplastic anemia, from his human leukocyte antigen-matched sister [1]. Seven years later, UCBT was also reported in an adult recipient. There are two major differences between UCBT and bone marrow transplantation. First, the number of nucleated cells existing within each UCB unit approaches only a tenth of that of a typical bone marrow allograft, resulting in lower engraftment success and higher time to engraftment. Second, UCB grafts are more immune tolerant than BM grafts, permitting the use of HLA-disparate grafts. These subjects are discussed in the following sections.

Related donor UCBT

UCBT from a related donor was studied mainly in non-malignant disorders. The EUROCORD group reported the results of RD-UCBT in 44 children (median age 5 years) with hemoglobinopathies (thalassemia in 33 and sickle cell disease in 11) who mostly received full matched UCB grafts, with only 3 children receiving 1-locus mismatched grafts [2]. The preparative regimens consisted of busulfan, cyclophosphamide, thiothepa and fludarabine in various combinations, as well as antithymocyte globulin or antilymphocyte globulin in some of the patients. The median NC dose infused was $4.0x10^7$/kg (range 1.2–$10x10^7$/kg). For GvHD prophylaxis, cyclosporin A alone or combined with methotrexate was administered. This resulted in donor-type reconstitution of hematopoiesis in 86.4% of transplants, with median times to neutrophil and platelet engraftments of 23 and 39 days, respectively. Following two graft rejections, overall graft failure approached 18.2%. However, no grade III-IV acute GvHD occurred in any patient and only 2 of 36 patients at risk developed chronic GvHD, which was limited. With a median follow-up time of 27 months, all patients are alive and 36 (81.8%) remain disease-free (thalassemia 79%, sickle cell disease 90%).

Unrelated donor-UCBT

Pediatric patients

Six series of patients with a total number of 1,398 transplants (with some overlapping among EUROCORD groups) were reported until now. Similar characteristics among groups included a high proportion of patients with hematologic malignancies within each group, frequent use of HLA-mismatched grafts, and a relatively narrow median range of NCs infused. Other variables such as median recipient age (3.1–7.4 years), proportion of patients with any degree of HLA disparity, as well as the conditioning regimens and GvHD prophylaxis used were more heterogeneous.

The University of Minnesota series [3] comprised 102 recipients (median age 7.4 years), 64% with hematologic malignancies and 36% without malignant disorders. A Japanese study group of 49 transplants included 37 patients (75%) with hematologic malignancies (median age 3.1 years) and 12 non-malignant disorders (median age 4.1 years) [4]. The EUROCORD series included 291 children overall (median age 5 years), 69% of them with hematologic malignancies, 21% inborn errors and 10% bone marrow failure syndrome [5]. A more detailed analysis of the acute leukemia EUROCORD subgroup was reported later by Locatelli [6] and for 95 acute myeloid leukemia patients by Michel et al. [7]. Finally, the New York Blood Center series included 861 transplants, of whom two-thirds had leukemia or lymphoma, 25% inherited disorders and 7% acquired diseases [8]. Results of these studies are discussed following a brief presentation of patient and graft characteristics [Table 1].

UCB = umbilical cord blood
UCBT = UCB transplantations
BM = bone marrow
HLA = human leukocyte antigen
RD = related donor
NC = nucleated cells
GvHD = graft versus host disease

Table 1. Unrelated donor UCBT: characteristics of patients and grafts

References (No. of patients)	Age in years, media (range)	Malignant diseases (%) ALL AML MDS	CL	Other	High risk	Other diseases (%)	Cell dose, median (range) (x10^7/kg)	HLA disparate loci
Wagner [3] (n=102)	7.4 (0.2–57)	53	6	5	68	36	3.1 (0.7–57.9)	0=14%, I=43%
Ohnuma [4] (n=49)								
Malignancy	3.1 (0.5–28)	95	2	2.5	NA	0	4.2 (1.4–10.6)	0=0, I=62%
Other dis.	4.1 (0.3–16)	0	5	0		100	6.2 (2.1–13.1)	0=0, I=58%
Gluckman [5] (n=291)	5.0	62	5	2	NA	31	5.6 (0.8–60)	0=17%, ⩾I=83%
Locatelli [6] (n=102)	(0.2–15)							
Related (n=42)	5.5 (1.7–14)	100			43		4.0 (1.0–12.2)	0=71%, I=2%
Unrelated (n=60)	5.5 (>1–15)	100			30		5.0 (1.5–46.5)	0=10% I=45%
Michel [7] (n=95)	6.0 (0.3–16)	100			29	0	4.4 (infused) (0.4-36)	0=8%, I=46%
Rubinstein [8] (n=861)	>2=20%	53	9	5	37	33	⩾10=15%	0=6%, I=39%
	2–5=22%						5–9.9=22%	
	6–11=23%		7				2.5–4.9=34%	
	12–17						<2.5=29%	
	+14%							
	⩾18=21%							
Gluckman [5] (n=108)	26 (15–53)	62	3	4	56	0	2.2 (1.2–7.3)	0=6%, I=35%
			4					
Sanz [13] (n=22)	(18–46)	29	45	55	0	0	2.5	0=5%, I=59%
						73	(1.5–6.9)	
Iseki [14] (n=30)	38	90	3	7	50	0	2.4	NA
	(NA)						(infused)	
							(NA)	
Laughlin [15] (n=68)	31	54	2	6	74	18	2.1	0=3%, I=26%,
	(18–58)		2				(1–6.3)	⩾II=71%
Cornetta [16] (n=34)	34.5	85	9	3	NA	3	1.7	0=3%, I=26%,
	(18–55)						(infused)	II=68%
							(1.1–3.7)	
Barker [17] (n=32)	48.5	NA	NA	NA	NA	0	3.4	0=6%,
Bu/Flu/TBI (n=21)	(22–64)						(2.3–5.1)	I–II=94%
Cy/Flu/TBI (n=11)								

NA = not available, AML = acute myeloid leukemia, ALL = acute lymphoblastic leukemia, MDS = myelodysplasia; CML = chronic myelogenous leukemia, Bu = busulfan, Flu = fludarabine, TBI = total body irradiation.

- *NC dose:* Median numbers of cryopreserved NCs per recipient's body weight ranged from 3.1 to 6.2x10^7/kg in the various groups.
- *HLA disparity:* The proportion of fully matched HLA recipients ranged between 0 (Japanese) and 14% (University of Minnesota) among different groups.
- *Malignancy risk group:* Within each study group 35–39% of the malignancy cases were classified as being at high risk just before transplantation, defined for the University of Minnesota transplants as having no remission or relapse after less than 3 years for acute lymphoblastic leukemia and 1 year for AML or accelerated-phase chronic myelogenous leukemia; and for the EUROCORD transplants as status beyond first or second remission.
- *Conditioning regimens:* Total body irradiation was utilized in 85% of the Minnesota University transplants (including all patients with malignancy), 57% of the EUROCORD leukemia subgroup (Locatelli et al.) and 46% of all the AML cases (Michel et al.). Data regarding conditioning regimen were not provided in the Japanese report, whereas the New York Blood Center used its own regimens for conditioning and GvHD prophylaxis.
- *GvHD prophylaxis:* Cs-A/steroids were administered in 98% of the University of Minnesota transplants, 68% of the EUROCORD leukemia subset undergoing unrelated donor UCBT, and 60% of the EUROCORD AML subset, whereas Cs-A alone or Cs-A combined with MTX, ATG or ALG was used less frequently. Data on the GvHD prophylaxis method are not available for the Japanese and New York Blood Center groups.

Results [Table 2]

AML = acute myeloid leukemia

Cs-A = cyclosporin A
MTX = methotrexate
ATG = antithymocyte globulin
ALG = antilymphocyte globulin

Table 2. Unrelated donor cord blood transplantation: engraftment, GvHD and outcome

References	Neutrophil recovery# (median days)	GvHD acute III-IV/chronic (%)	TRM at day 100, or later* (%)	Relapse rate (%)	Survival/ EFS (%)
Wagner [3]	88% (23)	11/9	30*	37**	47/NA**
Ohnuma [4]	82.3% (28)	13/17	43*	28***	51.9/51.4***
	66.7% (22)	0/0	33*	-	64.2/37.5***
Gluckman [5]	82% (29)	39/NA	NA	NA	NA/aplastic anemia 21**, genetic 51, malignancy 36
Locatelli [6]		19/10	44*	41**	34/30**
Related	84% (27)	16/8	35	42	NA/39
Unrelated	79% (33)	23/12	52	40	NA/30
Michael [7]	78% (NA)	NA/15**	20**	29**	45/42**
Rubinstein [8]	92.7% (matched 23, mismatched 28)	24/31	56.8*	30*	Genetic*** 48, malignant 27, acquired 29
Gluckman [5]	81%(32)	38/26	54	NA	27/21*
Sanz [13]	100% (22)	32/90	43	NA	NA/53*
Iseki [24]	NA(22)	NA/NA	NA	NA	NA/76***
Laughlin [15]	90% (27)	20/36	51	5.9*	28/26 at 40 mo.
Cornetta [16]	100% (28.5)	18[1]/NA	53	NA	30 at 6 mo.
Barker [17]	71% (24)		NA	NA	33*/NA
Bu/Flu/TBI Cy/Flu/TBI	91% (7)		36	NA	NA

# For patients surviving > 42 days: 1 year*, 2 years**, 3 years***.
TRE = transplant-related episodes; grade II-IV, NA = not available, TRM = transplant-related mortality, EFS = event-free survival, Bu = busulfan, Flu = fludarabine, TBI = total body irradiation.

- *Engraftment:* The success of donor type neutrophil recovery approached 78–92.7%, and median times ranged between 23 (University of Minnesota) and 33 days (Locatelli et al.). Analyzing the results, it was evident that the single most dramatic influence on engraftment was exerted by the NC dose [3,6,8], more specifically the CD34 cell dose [3]. Some other variables influenced the engraftment less consistently. While HLA disparity strongly correlated to neutrophil recovery in the New York Blood Center study (illustrated by median time to engraft of 23 vs. 28 days in respective HLA-matched and mismatched recipients), such correlation was not evident in the Minnesota University, UROCORD and Japanese studies. The preparative regimen used had no influence on engraftment in any of the above series.
- *GvHD:* Despite the frequent use of HLA-mismatched grafts, the incidence of grade III-IV acute GvHD was comparable to that reported recently for unrelated donor blood marrow transplantation [34] (18%), approaching 11% (University of Minnesota) to 39% (EUROCORD) of patients within the various groups. The influence of HLA disparity on the incidence and severity of acute GvHD was controversial. In both the Japanese and New York Blood Center studies, a higher degree of HLA disparity was associated with increased incidence of severe GvHD (8.3 vs. 24% in the NY Blood Center fully matched and mismatched recipients, respectively). In contrast, no correlation between GvHD and HLA disparity was apparent in the Minnesota University, EUROCORD, Michel et al. and other studies [11,16]. This controversy may result from minor HLA mismatches, differences in GvHD prophylaxis methods, or other yet unrecognized variables. The incidence of chronic GvHD ranged between 9% (University of Minnesota) to 31% (New York Blood Center), as compared to 42% at 2 years following UD-BMT [24]. Chronic GvHD was associated with the development of severe acute GvHD but not with any degree of HLA disparity [8].
- *Relapse of hematologic malignancies:* At follow-up periods of 2–3 years, 30–40% of transplants with malignancy relapsed. This proportion should raise concern about the efficacy of the GvL phenomenon following UCBT. As expected, the predominant predictor of relapse appeared to be the malignancy risk group at transplant [3,6–8]. Thus, for Minnesota University transplants with ALL, the probability of relapse at 2 years was 0.43 for high risk vs. 0.10 for the standard risk group, and for AML 0.47 vs. 0.25, respectively. Similarly, for poor risk EUROCORD transplants, the probability of relapse approached 77% vs. 31% for good risk transplants. Finally, in the NY Blood Center group, 59% of CR1 transplants, 50% of CR2 and 16% of patients with advanced leukemia relapsed. Relapse also related to the age of the recipients [3–6] and reflected more aggressive leukemia at age above 6 years [6]. In some groups the incidence of relapse was lower in patients who developed severe acute GvHD (9%) compared to those who had only mild or no GvHD (29%), whereas relapse was also less likely in the presence of chronic GvHD, whether limited or extensive [8]. However, such inverse relationships between relapse risk and severity of GvHD is inconsistent with the results of the University of Minnesota, in which the only associations of relapse were with recipient's age and the underlying malignancy risk group, without any influence of GvHD. The probability of relapse was lower in CML (17%) than ALL (28%) and particularly AML (45%) [8]. Some other variables such as NC dose [3] and degree of HLA disparity [6] were not statistically correlated to relapse. Interestingly, various risk factors recorded at diagnosis – such as white blood cell count, blood blast percentage, morphology, immunophenotype, karyotype, organs involved, as well as the interval between

UD-BM = unrelated donor bone marrow
GvL = graft versus leukemia
CML = chronic myelogenous leukemia

diagnosis and transplantation – which play an important role in newly diagnosed patients, had no apparent influence either on post-transplant relapse risk or on transplant-related mortality or event-free survival [6].

- *Transplant-related mortality:* The second major drawback that accompanies UCBT is a high TRM, approaching 30–44% at 1 year. The NY group reported the transplant-related episodes, which included autologous reconstitution, re-transplantation and death, approaching 57% at 1 year. The transplant-related episodes correlated strongly to the degree of HLA disparity (39.4% in HLA-matched vs. 67.4% in more than three mismatched transplants). TRM was also influenced by degree of HLA disparity in the EURORORD leukemia subset [6], as compared to the Minnesota group. Both the transplanted-related mortality and the transplant-related episodes were also influenced by the age of recipients, NC dose [3,6–8], CD34 cell dose [3], disease status at transplant [6], development of severe acute GvHD [3,6], cytomegalovirus serostatus and a history of autologous transplantation [3], while TRM did not correlate to the type of malignancy, risk group or myeloablative regimen used [3]. Early death usually resulted from relapse, infection or GvHD [3,6].
- *Overall survival:* Survival was consistently inferior in malignancy as compared to non-malignant diseases, with a median 2 year survival of 0.38 for malignant vs. 0.60 for non-malignant Minnesota cases; median 2 year event-free survival of 36%, 21% and 51% for respective UROCORD cases with malignancy, inborn errors and aplastic anemia; as well as median 3 year EFS of 27%, 29% and 48% for respective NY Blood Center patients with hematologic malignancies, acquired diseases and genetic diseases. The Japanese group was exceptional in this regard with a median 3 year EFS rate of 51.4% in malignancy versus 37.5% in non-malignant diseases, however recent results of the Japanese Cord Blood Bank Network for 216 transplants with hematologic malignancies [9] reveal an EFS rate of 25.5% at 3.5 years, which resembles the results of the other groups. Over the past 2 years there is a trend for improved overall post-transplant survival, reflected by 2 year survival of 45% in the EUROCORD AML subset [7] and 46% in the entire group of already 690 transplants of whom almost 80% had malignancy [10]. This improvement is probably the result of better graft and patient selection that has been applied since 1998.

  Cell dose, particularly CD34+, has recently been recognized as a major determinant of post-UCBT survival, illustrated by 1 year survival of 0.70 in patients receiving >$1.7x10^5$ CD34+ cells/kg compared to 0.58 in the entire group.

  The malignancy risk group at transplant also proved to be a strong survival predictor through its relation to the risk of relapse [3,6–8]. Thus, for the Minnesota University standard and high risk ALL groups, the 1 year survival rate was 0.55 vs. 0.32, respectively, and 0.50 and 0.33 for respective AML patients. Similarly, for standard vs. poor risk EUROCORD cases the probability of EFS at 2 years was 48% and 8%, respectively. Finally, AML cases transplanted at CR1 had 2 year EFS of 59%, compared to 50% for CR2 transplants, and 16% for those transplanted at more advanced stages [7]. Recipient age had only a modest influence on survival [8], whereas risk factors at the initial diagnosis of leukemia, including karyotype [6,7], had no influence on EFS.

  The number of HLA mismatches did not influence the outcome in both the Minnesota group and the group of Gluckman et al., as compared to the EUROCORD and New York Blood Center leukemia subset in which HLA disparity appeared to be an independent risk factor. In addition, EFS was not different between ALL and AML, while cytomegalovirus serostatus had a controversial effect on survival [36].

TRM = transplant-related mortality
EFS = event-free survival

Adult recipients

Since the first report in 1996 of UCB transplantation in an adult recipient [11], more than 500 adults have undergone the procedure worldwide [12]: the record of many of these patients is included in the six series reported. In four of the series all patients had hematologic malignancies while the Laughlin et al. and the Cord Blood Transplantation groups included some patients with non-malignant disorders (18% and 3%, respectively) [Table 1]. The UROCORD series [5] included 108 recipients (median age 26 years), the Spanish (Sanz et al.) 22 recipients (median age 29 years) [13], the Japanese 30 (median age 38 years) [14], the Laughlin et al. 68 (median age 31.4 years) [15], the Cord Blood Transplantation 34 (median age 34.5 years) [16], and the Barker et al. group 32 recipients (median age 48.5 years) [17]. The malignancy risk group at transplant was high (beyond first or second remission; accelerated-phase CML) in >45% of cases (EUROCORD 57%, Spanish 73%, Japanese 50%, Laughlin et al. 73%, Cord Blood Transplantation 45%, Barker et al. 100%). Prior autologous transplantation was recorded in 10–19% of cases. The vast majority of transplants (94–97%) received HLA-mismatched grafts, and all but the Barker group received myeloablative conditioning regimens. The median NC doses infused were of the same range (1.6–$1.7x10^7$/kg), excluding the Japanese group ($2.39x10^7$ cells/kg), with no such data available for the Barker group. GvHD prophylaxis consisted of Cs-A/steroids in all but the Japanese (Cs-A or Cs-A/MTX) and the Barker groups (Cs-A/mycophenolate mofetil). Other variables were more heterogeneous, including median recipient age (26–38 years), proportion of any malignancy, prior treatments, and relating to the preparative regimens used.

Results [Table 2]

- *Engraftment:* The median rate of neutrophil recovery for patients surviving >30 days post-transplant ranged from 71 to 100% among groups, and time to engraftment from 22 to 32 days following myeloablative conditioning. There was no association between graft failure and any degree of HLA disparity [15].
- *GvHD:* Despite the frequent use of HLA-disparate grafts, the probability of grade III-IV GvHD was comparable to that reported for HLA-matched UD-BMT [24], ranging between 20 and 38%. In fact, no association was seen between the incidence of acute

GvHD and the degree of HLA disparity [5,15]. Chronic GvHD developed in about 30% of patients at risk in the two larger studies.

- *TRM:* Mortality before day +100 was the most important problem in adult series, ranging between 43–54% following myeloablative conditioning and 36% following non-myeloablative UCB transplantation [17].
- *Relapse*: Data regarding this endpoint, which is responsible for considerable mortality in pediatric patients surviving >100 days post-UCBT, were not available in most adult series of UCBT due to small sample sizes and short follow-up. In the larger Laughlin et al. study, the 1 year relapse rate was only 5.9%, however the real value appears to be underestimated due to >50% early death (TRM). Noteworthy in this regard is the remarkable relapse-related mortality of 22% following the non-myeloablative conditioning regimen [17], which may indicate that the combination of low nucleated cell dose together with the naive nature of UCB lymphocytes is far from being optimal for non-myeloablative conditioning regimens, especially in the context of high risk malignancy.
- *Survival:* During follow-up periods of $\geqslant$ 6 months, disease-free survival approached only 20–30% in four of the six adult series, in contrast to > 50% in the Spanish and Japanese series at 1 and 3 years, respectively. These differences probably reflect the heterogeneity among the various patient cohorts.

  Similar to pediatric series, the malignancy risk group at transplant (e.g., early vs. late remission/active disease) proved to be a strong predictor of disease-free survival. In addition, chronic-phase CML was associated with 1 year survival of 39% compared with 27% for acute leukemia [5]. Variables relating to the graft *per se* also had a major influence on outcome, with cell dose representing the predominant factor, being favorable when NC dose was greater than $2x10^7$/kg [5] and/or CD34+ cells $>1.2x10^5$kg [5,15]. In contrast, the degree of HLA disparity had no apparent influence on EFS [15,17].

In summary, despite cell dose limitations and frequent HLA disparity, adult recipients of a UCB transplant have an acceptable probability of engraftment and a low incidence of severe acute GvHD (4.4% in the Laughlin study, 18% in the EUROCORD series). On the other hand, TRM still remains a major obstacle to successful UCBT, approaching nearly 50% in this age group. The main causes of death following UCBT included regimen-related toxicity, infections and relapse. Better selection of patients and grafts will hopefully improve the success of UCBT, as already seen in EUROCORD cases transplanted since 1998 [10].

Comparison between UCB and BM transplantation

The EUROCORD [18] compared the results of UCBT from an HLA-identical sibling (n=113, median age 5 years) to those of BMT from an HLA-identical sibling (n=2,052, median age 8 years) [Table 3]. Despite a lower rate of neutrophil recovery at 1 month following UCB transplant, approaching 89% versus 98% following BM transplant, there were no differences in TRM (14 vs. 12%, respectively) or 3 year survival rates (64 vs. 66%, respectively), whereas the incidence of grade III-IV acute GvHD and probability of chronic GvHD (3 years) was lower following UCBT.

Table 3. Characteristics of the recipients of UCB and BM transplants from HLA-identical siblings, engraftement, GvHD and outcome

	UCBT	BMT
Age, median (yrs, range)	5 (<1–15)	8 (<1–15)
Malignancy	54%	62%
Acute leukemia	36%	48%
CML	5%	4%
Lymphoma	2%	2%
MDS	11%	6%
AA	7%	14%
Congenital	35%	22%
Others	4%	3%
Cell dose infused ($x10^7$/kg)	4.7	35
Range	>1–3.6	>10–41
Neutrophil recovery at day 60 (%)	89%	98%
Median days	26	18
Acute GvHD (III-IV) at day 100	2%	10%
Chronic GvHD at 3 years	6%	15%
Early TRM at day 100	14%	12%
Survival at 3 years	64%	66%
With malignancy	46%	55%
Without malignancy	86%	84%

UCBT = umbilical cord blood transplantation, BMT = bone marrow transplantation, CML = chronic myelogenous leukemia, MDS = myelodysplasia, AA = aplastic anemia, TRM = transplant-related mortality.

In five other studies the comparison between UCB and BM transplantation was in matched groups that received unrelated donor grafts. Despite differences in methodology, patient populations and regimens used, in principle these studies yielded similar outcomes, which is discussed after a brief summary of the results. The study by Barker et al. [19] was carried out by matched-pair analysis, comparing between UD-BMT from an HLA-identical graft and UD-UCBT from 0–3 mismatched HLA loci in groups equally matched for age (median 5 years), diagnoses (malignancy, storage diseases, BM failure and immunodeficiency), and clinical stages [Table 4]. GvHD prophylaxis in UCBT consisted of Cs-A/steroids versus Cs-A/MTX (26 pairs) or Cs-A/steroids/T cell depletion (31 pairs) in BM transplantation. Despite the lower rate of neutrophil recovery by day +45 following UCB as compared to BM transplantation, there were no significant differences with respect to platelet recovery, incidence of acute and chronic GvHD, and probability of 2 year survival (53% in UCBT vs. 41% in BMT-MTX; 52% in UCBT vs. 56% in BM-TCD). Two of the studies were limited to patients with hematologic malignancies. The New York Blood Center/International Bone Marrow Transplantation Registry enrolled patients with acute and chronic leukemias, juvenile CML and myelodysplasia [20]. HLA-identical grafts were used in 62% of UD-BMT versus 6% of UD-UCBT cases. As expected, neutrophil recovery was slower and the incidence of acute GvHD was lower following UCBT, whereas probabilities of chronic GvHD, relapse and survival at 3 years were

BM-TCD = bone marrow T cell deletion

Table 4. Characteristics of the recipients of 0-3 HLA-mismatched cord blood or bone marrow transplants from HLA-identical siblings. Comparison of engraftment, GvHD and outcome

Patient characteristics and outcome	UCB	BM-MTX	UCB	BM-TCD
Age, median (yrs), (range)	4.5 (0.2–17.9)	4.7 (0.6–17.7)	5.8 (0.2–17.9)	6.8 (0.5–17.7)
Diagnosis				
Acute leukemia	57%	57%	36%	36%
CML	4%	4%	0	0
Storage disease	12%	12%	52%	52%
Bone marrow failure/ immunodeficiency	24%	24%	10%	10%
Cell dose infused ($x10^7$/kg) range	3 (1–28)	20 (19–40)	3 (1–28)	5 (2–20)
HLA disparity	5 (19%)	26	4 (13%)	31
0	12 (46%)	(100%)	22 (71%)	(100%)
1	9 (35%)	0	5 (16%)	0
⩾2		0		
Neutrophil recovery at day 45 (%)	88%	96%	85%	90%
Acute GvHD (II-IV) at day 100	42%	35%	36%	35%
Chronic GvHD at 3 years	5%	20%	7%	13%
Early TRM at day 100	27%	15%	23%	16%
Death from relapse at 2 years	45%	27%	23%	7%
Survival at 2 years	53%	41%	52%	56%

UCB = umbilical cord blood, BM-MTX = bone marrow-methotrexate,
BM-TCD = BM-T cell depletion, MDS = myelodysplasia,
CML = chronic myelogenous leukemia, TRM = transplant related mortality.

similar between groups, except for >1 antigen-mismatched UCBT subset that had higher TRM as well as reduced disease-free and overall survival rates.

The EUROCORD group [21] compared the records of 541 children with acute leukemia undergoing either UD-UCBT (n = 99), UD-BMT (n = 262) or TCD-BMT (n = 180). Grafts were HLA-mismatched with recipients in 92%, 18% and 43% of cases respectively within the three groups. The probability of EFS at 2 years was 31%, 43% and 37%, respectively. With adjustment of results according to patient, disease and transplant variables, UD-UCBT was associated with delayed hematopoietic recovery (HR = 2.13), increased TRM at 100 days (HR = 2.13) and decreased acute GvHD relative to UD-BMT. In addition, the relapse risk of the three groups was comparable, whereas late mortality (>100 days post-transplant) was higher in TCD-UBMT as compared to UBMT and UCBT.

In conclusion, the above comparative studies indicate that UD-UCBT is indeed a feasible alternative to UD-BMT in pediatric patients lacking suitable donors. The similarities in survival endpoints between the two transplant modes seem to relate to the balance between the higher TRM [19,21] following UCBT versus higher GvHD-related mortality following BMT [19,21], whereas differences in relapse rates remain inconsistent [20,21].

Finally, two comparative studies were reported recently for adult recipients. The Japanese study [22] compared two groups of eight patients each who received uniform conditioning (total body irradiation/Cy, with Ara-C added to patients with leukemia) and GvHD prophylaxis regimens (Cs-A/MTX). In both groups, recovery of neutrophils approached 100%, while median time to engraftment was 20 days for UD-UCBT versus 15 days for UD-BMT. No grade III-IV acute GvHD developed following UCBT as compared with one case following BMT, whereas chronic GvHD appeared in five of eight UD-UCBT patients and two of seven BMT patients at risk. The probability of disease-free survival at 2 years was 85.7 following UCBT versus 75% following BMT.

The EUROCORD group performed matched-pair analysis of acute leukemia patients who had undergone UD-UCBT (n = 81) versus UD-BMT (n = 162). The groups were matched for age (median 24 years), diagnoses, status of diseases at transplant (CR1 25%, CR2 21%, advanced disease 54%) and use of total body irradiation [23]. All UD-BMT cases versus 10% of UCBT cases received HLA-matched grafts. GvHD prophylaxis in UD-UCBT consisted mainly of Cs-A/steroids, and in UD-BMT of Cs-A/MTX. Compared with UD-BMT, the UD-UCBT group had delayed neutrophil recovery time (28 versus 19 days), similar probability of chronic GvHD at 2 years, and somewhat higher TRM (35% versus 30% at 100 days, respectively) and overall 2 year mortality rates (54% and 47%, respectively). Nevertheless, the probabilities of 2 year survival and disease-free survival following UD-UCBT were 32% and 34%, respectively, being comparable to the respective probabilities of 32% and 24% following UD-BMT. Thus, UCBT seems to be a feasible alternative to UD-BMT also in adult recipients, despite difficulties derived from delayed engraftment.

Summary

In recent years umbilical cord blood transplantation has become an acceptable alternative transplant method for patients lacking a suitable donor, although NC dose limitations account for increased early post-transplant complications. The critical role of CD34+ cell dose [3,8,25] was recently demonstrated by a 1 year TRM rate of 68% in transplants receiving < 1.7 CD34+ cells/kg as compared to 15% in those receiving > $2.7x10^5$ CD34+ cells/kg [3]. Thus, it was speculated that by matching for each degree of HLA disparity a critical infused cell dose (below which survival is significantly impaired), the negative influence of HLA disparity on survival can be minimized [3].

The major advantage of UCBT over BMT is the higher immune tolerance of the former, permitting more liberal use of HLA-mismatched grafts with rapid availability when compared with conventional matched unrelated donor transplants. On the other hand, considering the strong association between GvL and GvHD [20,31], the milder GvHD accompanying UCBT might also express a reduced GvL potential, which might explain the high incidence of relapse following UCBT. Nevertheless, the immune reconstitution after UCBT [26–31] appears to parallel that following BMT.

TCD = T cell depletion
HR = hematopoietic recovery

Furthermore, the existence of effective GvL following UCBT is now well established [32], and explains the achievement of sustained remissions using non-myeloablative conditioning regimens [17,33] as well as the response of relapsed leukemia to reduction of immunosuppression or donor lymphocyte infusion [32]. In fact, the excess in mortality due to slower engraftment and/or graft failure following UCBT seems to be balanced by reduced death from GvHD relative to BMT, leading to comparable disease-free survival rates following each transplant procedure [6,12,20]. Also noteworthy is the success of UCBT both in pediatric transplants with very high risk ALL (mostly with 11q23 translocations) who achieved a 58% disease-free survival at 56 months [34] and in engrafted Ph+ALL transplants who achieved a 37% disease-free survival at 4 years follow-up [35].

Age *per se* does not seem to be a contraindication to UCBT, nor did it play a role in engraftment success, although older age was associated with inferior survival in the New York Blood Center transplants (as it also is after BMT) [36]. Finally, remembering the important influence of disease status and the state of the patient at the time of transplant on post-transplant survival [3,8,34], UCBT should be considered as soon as possible for eligible candidates.

Future directions

Various strategies have been evaluated for their ability to overcome cell dose limitations and reduce the time to engraftment, including simultaneous transfusion of two UCB units from different donors [37–39], *ex vivo* expansion of cord blood stem cells [40], and *in vivo* stimulation of UCB stem cells using growth factors or agents that up-regulate the expression of intercellular adhesion molecules and vascular cell adhesion molecule-1. These methods are still under investigation.

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