Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study

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Summary

Background **Although umbilical cord blood is an accepted alternative to bone marrow for transplantation, allele-matched bone marrow is generally regarded as the preferred graft source. Our aim was to assess leukaemia-free survival after transplantations of these alternatives compared with present HLA-matching practices, and to assess the relative effect of cell dose and HLA match, and their potential interaction on leukaemia-free survival after cord-blood transplantation.**

Methods **Outcomes of 503 children (<16 years) with acute leukaemia and transplanted with umbilical cord blood were compared with outcomes of 282 bone-marrow recipients. All transplantation took place in the USA. Recipients of umbilical cord blood were transplanted with grafts that were HLA-matched (n=35) or HLA-mismatched for one (n=201) or two antigens (n=267) (typing at antigen level for HLA-A and HLA-B, and allele level for HLA-DRB1). Bone-marrow recipients were transplanted with grafts that were matched at the allele level for HLA-A, HLA-B, HLA-C, and HLA-DRB (n=116), or mismatched (n=166). The primary endpoint was 5-year leukaemia-free survival.**

Findings **In comparison with allele-matched bone-marrow transplants, 5-year leukaemia-free survival was similar to that after transplants of umbilical cord blood mismatched for either one or two antigens and possibly higher after transplants of HLA-matched umbilical cord blood. Transplant-related mortality rates were higher after transplants of two-antigen HLA-mismatched umbilical cord blood (relative risk 2·31, p=0·0003) and possibly after one-antigen HLA-mismatched low-cell-dose umbilical-cord-blood transplants (1·88, p=0·0455). Relapse rates were lower after two-antigen HLA-mismatched umbilical-cord-blood transplants (0·54, p=0·0045).**

Interpretation **These data support the use of HLA-matched and one- or two-antigen HLA-mismatched umbilical cord blood in children with acute leukaemia who need transplantation. Because better HLA matching and higher cell doses significantly decrease the risk of transplant-related mortality after umbilical-cord-blood transplantation, greater investment in large-scale banking is needed to increase HLA diversity.**

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Introduction

When available, an HLA-matched sibling is always the donor of choice for children who need transplantation of allogeneic haemopoietic stem cells. However, only about 30% of candidates eligible for allogeneic haematopoietic stem cell transplantation will have such a donor. In the absence of such a donor, transplantation of haemopoietic stem cells from an unrelated volunteer adult donor or unrelated umbilical cord blood is a possibility. Transplantation of bone marrow from an unrelated adult volunteer donor, however, is limited by HLA-matching requirements, high risk of graft-versus-host disease (GVHD), opportunistic infection, and donor availability. In recent years, use of umbilical cord blood as an alternative source of transplantable haemopoietic stem cells has increased substantially, extending the availability of this treatment, especially for children.[1–12] Although rates of haemopoietic recovery are slower, most reports show a lower risk of severe GVHD after transplantation of unrelated-donor umbilical cord blood than of unrelated-donor bone marrow, despite the frequent use of HLA-mismatched grafts for transplantation of umbilical cord blood.

A prospective randomised clinical trial is the accepted standard to compare different treatments such as different graft types for unrelated-donor transplantation. However, to date, there have been no prospective studies that compared transplantation of umbilical cord blood with transplantation of bone marrow matched at the allele level of HLA-A, HLA-B, HLA-C, and HLA-DRB1 from unrelated donors (which are at present generally regarded as the gold standard). Therefore, we assessed the results of transplantations in children with acute leukaemia by use of data from the Center for International Blood and Marrow Transplant Research (CIBMTR) and the National Cord Blood Program (NCBP) of the New York Blood Center, New York, USA. Our aim was to compare leukaemia-free survival after transplantation of umbilical cord blood or bone marrow by present HLA-matching practices, and to assess the relative effect of cell dose, HLA matching, and their potential interaction on the outcome of cord-blood transplantation.

Methods

Patients and procedures

The study included patients younger than 16 years at transplantation with acute lymphoblastic or acute myeloid leukaemia who received either a single-unit cord-blood or a bone-marrow graft from an HLA-matched or HLA-mismatched unrelated donor in the USA, irrespective of disease status at transplantation. To be eligible, bone-marrow recipients had to have been typed at allele level at HLA-A, HLA-B, HLA-C, and HLA-DRB1 as present standard for this graft source. All patients underwent transplantation between 1995 and 2003. Patients were excluded if they were recipients of T-cell-depleted bone marrow, of more than two-antigen mismatched cord-blood transplantations, received two or more cord-blood units, or if they had received a previous autologous or allogeneic transplant.

Allele-level typing for HLA-A, HLA-B, HLA-C, and HLA-DRB1 was available for 282 bone-marrow recipients; 116 were HLA-matched at the allele level for HLA-A, HLA-B, HLA-C, and HLA-DRB1, and 166 were HLA-mismatched at allele level (44 with one allele mismatch and 122 with two mismatches). We did not consider matching at HLA-DQ and HLA-DP because these alleles do not greatly affect transplant outcome.[13] All cord-blood units were HLA-typed at antigen (serological) level for HLA-A and HLA-B, and at allele level for HLA-DRB1 with DNA techniques. For recipients of cord-blood grafts, an HLA-antigen mismatch was defined as the presence of a mismatch between donor and recipient at antigen level for HLA-A and HLA-B, and at allele level for HLA-DRB1; 35 cord-blood recipients were HLA-matched and 468 were HLA-mismatched at one (n=201) or two (n=267) antigens.

The CIBMTR is a group of more than 500 transplant centres worldwide that provide data for recipients of consecutive allogeneic transplants to the Statistical Center at the Medical College of Wisconsin, USA. Participating centres register and provide basic information about all consecutive transplants. Detailed demographic, disease, and transplant characteristics, and outcome data are obtained for a sample of registered patients and include about 90% of unrelated-donor transplants in the USA. All patients are followed up longitudinally. Computerised error checks, review of data by physicians, and on-site audits of participating centres ensure data quality. Centres that obtain cord-blood grafts from the NCBP are required, under the Investigational New Drug rules of the Food and Drug Administration, to report data for the outcome of transplantation procedures. In the USA, 53 transplant centres provided data for 282 bone-marrow transplantations and 66 provided data for 503 cord-blood transplantations.

The primary endpoint was leukaemia-free survival, which was defined as survival in continuous complete remission after transplantation. Neutrophil recovery was defined as the achievement of an absolute neutrophil count of $0{\cdot}5\times10^9$/L for 3 consecutive days; platelet recovery was defined as the achievement of an absolute platelet count of 20×10^9/L without the support of transfusions for 7 continuous days. All patients were assessed for acute and chronic GVHD by standard criteria.[14,15] Transplant-related mortality was defined as death during continuous post-transplant remission, and relapse was defined as haematological recurrence.

Statistical analysis

Variables that are related to patient, disease, and transplant characteristics were compared by use of the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. The probability of leukaemia-free survival was calculated by the Kaplan-Meier method.[16] For analysis of leukaemia-free survival, relapse or death (ie, treatment failure) was regarded as an event; data for patients alive and in continuous remission were censored at last follow-up. Probabilities of neutrophil and platelet recovery, acute and chronic GVHD, transplant-related mortality, and relapse were calculated by the cumulative-incidence function method.[16] For neutrophil and platelet recovery and GVHD, death without the event was the competing event. For transplant-related mortality, relapse was the competing event; for relapse, transplant-related death was the competing event. Data for patients without a competing event were censored at last follow-up. CIs were calculated with the use of log transformation. Cox's proportional-hazard regression models were constructed for acute and chronic GVHD, transplant-related mortality, relapse and leukaemia-free survival, with a $p\leq0{\cdot}008$ (Bonferroni's correction) to show statistical significance.[16,17]

Before comparing outcomes by graft type, we examined the effect of cell dose in cord-blood recipients and established a cell-dose threshold for units mismatched at one HLA antigen. We divided cell dose into two categories ($\leq0{\cdot}3\times10^8$/kg and $>0{\cdot}3\times10^8$/kg) by finding the cut point that had the highest partial likelihood in the Cox's model.[18] A cell-dose threshold could not be measured for units mismatched for two HLA antigens. Thus, the main effects in all models were: allele-matched bone marrow (baseline group), allele-mismatched bone marrow, matched cord blood, one-antigen mismatched cord blood with a high cell dose ($>0{\cdot}3\times10^8$/kg), one-antigen mismatched cord blood with a low cell dose ($\leq0{\cdot}3\times10^8$/kg), and two-antigen mismatched cord blood (any cell dose). All models were adjusted for the variables that are known to be associated with outcome: age at transplant, sex, race, leukaemia type, disease status at transplant, conditioning regimen, GVHD prophylaxis, and year of transplant (table 1). Results are expressed as relative risks—that is, the occurrence of the event with allele-matched bone marrow compared with the occurrence of the event with

	Matched bone marrow (n=116)	Mismatched bone marrow (n=166)	Matched umbilical cord blood (n=35)	One-antigen mismatched umbilical cord blood (low cell dose) (n=44)	One-antigen mismatched umbilical cord blood (high cell dose) (n=157)	Two-antigen mismatched umbilical cord blood (any cell dose) (n=267)
Male/female	73 (63%)/ 43 (37%)	98 (59%)/68 (41%)	22 (63%)/13 (37%)	26 (59%)/18 (41%)	76 (48%)/ 81 (52%)	160 (60%)/ 107 (40%)
Age at transplant (years)						
≤1	3 (3%)	5 (3%)	3 (9%)	2 (5%)	22 (14%)	11 (4%)
>1–5	28 (24%)	44 (27%)	14 (40%)	5 (11%)	66 (42%)	73 (27%)
>5–10	46 (40%)	56 (34%)	12 (34%)	19 (43%)	53 (34%)	89 (33%)
>10–<16	39 (34%)	61 (37%)	6 (17%)	18 (41%)	16 (10%)	94 (35%)
Race						
White	102 (88%)	116 (70%)	30 (86%)	27 (61%)	111 (71%)	139 (52%)
Non-white	14 (12%)	50 (30%)	5 (14%)	17 (39%)	46 (29%)	128 (48%)
Disease						
AML	36 (31%)	60 (36%)	16 (46%)	8 (18%)	69 (44%)	101 (38%)
ALL	80 (69%)	106 (64%)	19 (54%)	36 (82%)	88 (56%)	166 (62%)
Disease status						
First CR	20 (17%)	34 (20%)	6 (17%)	7 (16%)	44 (28%)	49 (18%)
≥ Second CR	78 (67%)	103 (62%)	20 (57%)	25 (57%)	71 (45%)	135 (51%)
Relapse	18 (16%)	29 (17%)	9 (26%)	12 (27%)	42 (27%)	83 (31%)
Median time from diagnosis to transplant* (range)†	23 (3–119)	20 (3–151)	13 (3–109)	16 (3–74)	10 (2–139)	15 (2–146)
Year of transplant						
1995–98	66 (57%)	97 (58%)	17 (49%)	11 (25%)	93 (59%)	158 (59%)
1999–2003	50 (43%)	69 (42%)	18 (51%)	33 (75%)	64 (41%)	109 (41%)
Conditioning regimen						
TBI	98 (84%)	153 (92%)	24 (69%)	36 (82%)	106 (68%)	208 (78%)
Non-TBI	18 (16%)	13 (8%)	11 (31%)	6 (14%)	48 (30%)	54 (20%)
Unknown	..	..	..	2 (4%)	3 (2%)	5 (2%)
GVHD prophylaxis						
Cyclosporine	89 (77%)	137 (83%)	33 (94%)	39 (89%)	136 (87%)	231 (87%)
Tacrolimus	25 (22%)	28 (17%)	2 (6%)	3 (7%)	15 (10%)	22 (8%)
Other agents	2 (2%)	1 (1%)	..	..	2 (1%)	9 (3%)
Unknown	..	..	..	2 (4%)	4 (3%)	5 (2%)
Donor–recipient sex match						
M–M	53 (46%)	60 (36%)	15 (43%)	12 (27%)	39 (25%)	71 (27%)
M–F	23 (20%)	39 (23%)	6 (17%)	6 (14%)	35 (22%)	54 (20%)
F–M	20 (17%)	38 (23%)	6 (17%)	13 (30%)	36 (23%)	85 (32%)
F–F	20 (17%)	29 (17%)	7 (20%)	12 (27%)	46 (29%)	50 (19%)
Unknown			1 (3%)	1 (2%)	1 (1%)	7 (3%)
Total nucleated cell dose						
Median (range)‡	4·2 (<1·0–8·0)	3·5(<1·0–9·0)	0·45 (0·10–2·0)	0·22 (0·10–0·30)	0·69 (0·30–3·5)	0·48(0·01–3·2)
Follow-up of survivors						
Median time* (range)	60 (8–123)	59 (11–121)	45 (3–124)	56 (12–120)	40 (3–121)	44 (3–119)

Data are number (%) unless specified otherwise. 91 transplant teams provided patients for this study, 45 of which contributed with one to five patients, 28 with six to ten patients, and 18 teams with more than ten patients. 28 teams reported bone-marrow and cord-blood grafts and contributed about 50% of the patients, 25 reported only bone-marrow grafts and 38 only cord-blood grafts. CR=continuous complete remission. TBI=total body irradiation. M=male. F=female. *Data are expressed in months. †70–80% of transplants took place within 3 years from diagnosis. ‡×10⁸/kg.

Table 1: **Characteristics of study patients**

matched or mismatched cord blood and allele-mismatched bone marrow. There were no significant centre effects by the random effect model[19] or by centre volume categorised in accordance to the number of transplants that have been undertaken per team (one to five *vs* six to ten *vs* more than ten). All p values are two-sided. Analyses were done with SAS software (version 9.1, Cary, NC).

	Number*	Neutrophil recovery at day 42 (95% CI)	Number*	Platelet recovery at 6 months (95% CI)
Allele-matched bone marrow	113/116	97 (92–99)	99/116	85 (77–91)
One- or two-allele mismatched bone marrow	161/166	97 (93–99)	125/166	74 (66–80)
Matched umbilical cord blood	32/35	85 (67–94)	28/35	79 (60–89)
One-antigen mismatched umbilical cord blood (high cell dose)	133/154	80 (72–86)	101/154	64 (56–72)
One-antigen mismatched umbilical cord blood (low cell dose)	29/44	59 (43–72)	19/44	43 (28–57)
Two-antigen mismatched umbilical cord blood (any cell dose)	217/267	76 (70–81)	124/263	47 (41–53)

*Number of patients who achieved recovery/number of evaluable patients. Data on neutrophil recovery are missing for three patients (<1%). Data on platelet recovery are missing for eight patients (1%).

Table 2: **Cumulative probabilities of neutrophil and platelet recovery**

Role of funding source

The funding sources had no role in the study design, data analysis, data interpretation, or writing of this report. The views expressed in this article are those of the authors and do not indicate the views of the National Institutes of Health, the Office of Naval Research, or the National Marrow Donor Program. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Table 1 shows characteristics of patients, their disease, and transplant regimens. Recipients of umbilical cord blood were younger than bone-marrow recipients, more likely to be non-white, to undergo transplantation in relapse, to receive an HLA-mismatched graft, and to receive cells from a female donor. The total nucleated cell dose of the graft was substantially lower, on average, for cord-blood than for bone-marrow grafts. In cord-blood grafts, the total nucleated cell dose did not vary significantly by HLA disparity; the cell dose was low ($\leq 0 \cdot 3 \times 10^8$/kg) in 44 of 201 one-antigen mismatched, and 55 of 267 two-antigen mismatched grafts. 81% of low-cell-dose cord-blood transplants were done before 2000. Cord-blood recipients were less likely to receive irradiation as part of their preparative regimen and bone-marrow recipients were more likely to receive tacrolimus for GVHD prophylaxis. The median period of follow-up for survivors was 59 months and 45 months after transplantation of bone marrow and umbilical cord blood, respectively.

The median times to neutrophil and platelet recovery were 19 (range 9–33) and 27 (12–285) days after bone-marrow transplantation, and 25 (9–90) and 59 (12–237) days after cord-blood transplantation, respectively. Neutrophil and platelet recovery varied with graft type, donor–recipient HLA disparity, and cell dose. The cumulative probabilities of neutrophil and platelet recovery

	Number *	Relative risk (95% CI)	p
Grade 2–4 acute GVHD			
Allele-matched bone marrow	53/116	1·00	
One- or two-allele mismatched bone marrow *vs* allele-matched bone marrow	100/166 *vs* 53/116	1·51 (1·08–2·13)	0·0163
Matched umbilical cord blood *vs* allele-matched bone marrow	8/34 *vs* 53/116	0·45 (0·22–0·96)	0·0387
One-antigen mismatched umbilical cord blood (high cell dose) *vs* allele-matched bone marrow	62/149 *vs* 53/116	0·92 (0·63–1·34)	0·6491
One-antigen mismatched umbilical cord blood (low cell dose) *vs* allele-matched bone marrow	16/44 *vs* 53/116	0·76 (0·43–1·34)	0·3399
Two-antigen mismatched umbilical cord blood(any cell dose) *vs* allele-matched bone marrow	107/259 *vs* 53/116	0·92 (0·66–1·30)	0·6521
Grade 3–4 acute GVHD			
Allele-matched bone marrow	21/116	1·00	Reference
One- or two-allele mismatched bone marrow *vs* allele-matched bone marrow	54/166 *vs* 21/116	1·90 (1·14–3·17)	0·0139
Matched umbilical cord blood *vs* allele-matched bone marrow	3/34 *vs* 21/116	0·50 (0·15–01·67)	0·2556
One-antigen mismatched umbilical cord blood (high cell dose) *vs* allele-matched bone marrow	29/149 *vs* 21/116	1·10 (0·62–1·97)	0·7366
One-antigen mismatched umbilical cord blood (low cell dose) *vs* allele-matched bone marrow	9/44 *vs* 21/116	0·98 (0·45–2·18)	0·9682
Two-antigen mismatched umbilical cord blood (any cell dose) *vs* allele-matched bone marrow	69/259 *vs* 21/116	1·44 (0·87–2·39)	0·1613
Chronic GVHD			
Allele-matched bone marrow	37/116	1·00	Reference
One- or two-allele mismatched bone marrow *vs* allele-matched bone marrow	66/166 *vs* 37/116	1·62 (1·08–2·45)	0·0201
Matched umbilical cord blood *vs* allele-matched bone marrow	10/33 *vs* 37/116	0·76 (0·35–1·64)	0·4774
One-antigen mismatched umbilical cord blood (high cell dose) *vs* allele-matched bone marrow	27/147 *vs* 37/116	0·60 (0·35–1·02)	0·0586
One-antigen mismatched umbilical cord blood (low cell dose) *vs* allele-matched bone marrow	7/39 *vs* 37/116	0·98 (0·43–2·22)	0·9523
Two-antigen mismatched umbilical cord blood (any cell dose) *vs* allele-matched bone marrow	38/247 *vs* 37/116	0·72 (0·45–1·14)	0·1615

Rates of grade 2–4 and 3–4 acute GVHD, and chronic GVHD were similar after transplantation of matched umbilical cord blood, one- and two-antigen mismatched umbilical cord blood (Wald test with 3 degrees of freedom; p=0·1708, p=0·0607, and p=0·6317, respectively). Because of the multiple comparisons, a p value≤0·008 (Bonferroni's correction) is regarded as significant. *Numbers of events/number of evaluable patients. Data on acute GVHD are missing for 18 patients (2%). Data on chronic GVHD are missing for 37 patients (5%).

Table 3: **Multivariable analysis of acute and chronic GVHD**

	Number*	Relative risk (95% CI)	p
Transplant-related mortality			
Allele-matched bone marrow	24/116	1·00	Reference
One- or two-allele mismatched bone marrow *vs* allele-matched bone marrow	51/166 *vs* 24/116	1·42 (0·87–2·32)	0·1574
Matched umbilical cord blood *vs* allele-matched bone marrow	2/35 *vs* 24/116	0·26 (0·06–1·09)	0·0659
One-antigen mismatched umbilical cord blood (high cell dose) *vs* allele-matched bone marrow	45/157 *vs* 24/116	1·48 (0·89–2·46)	0·1332
One-antigen mismatched umbilical cord blood (low cell dose) *vs* allele-matched bone marrow	19/44 *vs* 24/116	1·88 (1·01–3·47)	0·0455
Two-antigen mismatched umbilical cord blood (any cell dose) *vs* allele-matched bone marrow	124/267 *vs* 24/116	2·31 (1·47–3·62)	0·0003
Relapse			
Allele-matched bone marrow	45/116	1·00	Reference
One- or two-allele mismatched bone marrow *vs* allele-matched bone marrow	51/166 *vs* 45/116	0·77 (0·51–1·16)	0·2171
Matched umbilical cord blood *vs* allele-matched bone marrow	11/35 *vs* 45/116	0·68 (0·35–1·32)	0·2524
One-antigen mismatched umbilical cord blood (high cell dose) *vs* allele-matched bone marrow	46/157 *vs* 45/116	0·67 (0·43–1·02)	0·0593
One-antigen mismatched umbilical cord blood (low cell dose) *vs* allele-matched bone marrow	9/44 *vs* 45/116	0·72 (0·35–1·51)	0·3894
Two-antigen mismatched umbilical cord blood (any cell dose) *vs* allele-matched bone marrow	52/267 *vs* 45/116	0·54 (0·36–0·83)	0·0045
Treatment failure			
Allele-matched bone marrow	69/116	1·00	Reference
One- or two-allele mismatched bone marrow *vs* allele-matched bone marrow	102/166 *vs* 69/116	0·99 (0·73–1·36)	0·9729
Matched umbilical cord blood *vs* allele-matched bone marrow	13/35 *vs* 69/116	0·54 (0·30–0·97)	0·0406
One-antigen mismatched umbilical cord blood (high cell dose) *vs* allele-matched bone marrow	91/157 *vs* 69/116	0·94 (0·68–1·31)	0·7300
One-antigen mismatched umbilical cord blood (low cell dose) *vs* allele-matched bone marrow	28/44 *vs* 69/116	1·12 (0·71–1·75)	0·6338
Two-antigen mismatched umbilical cord blood (any cell dose) *vs* allele-matched bone marrow	176/267 *vs* 69/116	1·17 (0·87–1·57)	0·2970

Rates of transplant-related mortality differed after transplantation of matched umbilical cord blood, and one- and two-antigen mismatched umbilical cord blood (Wald test with 3 degrees of freedom; p=0·0026). Rates of relapse and treatment failure were similar (Wald test with 3 degrees of freedom; p=0·7306 and p=0·0377, respectively). Because of the multiple comparisons, a p value≤0·008 (Bonferroni's correction) is regarded as significant. *Number of events/number of evaluable patients. Data are complete.

Table 4: **Multivariable analysis of transplant-related mortality, relapse, and treatment failure**

are shown in table 2. The probabilities of neutrophil recovery at day 42 were lower after transplantation of mismatched cord blood at both high and low cell doses (p<0·0001), but not after matched cord-blood transplantation (p=0·0626), than after allele-matched and allele-mismatched bone-marrow transplantations. The probability of platelet recovery at 6 months was lower after mismatched cord-blood transplantation at both high and low cell dose (p<0·0001), but not after matched cord-blood transplantation (p=0·4006) or allele-mismatched bone-

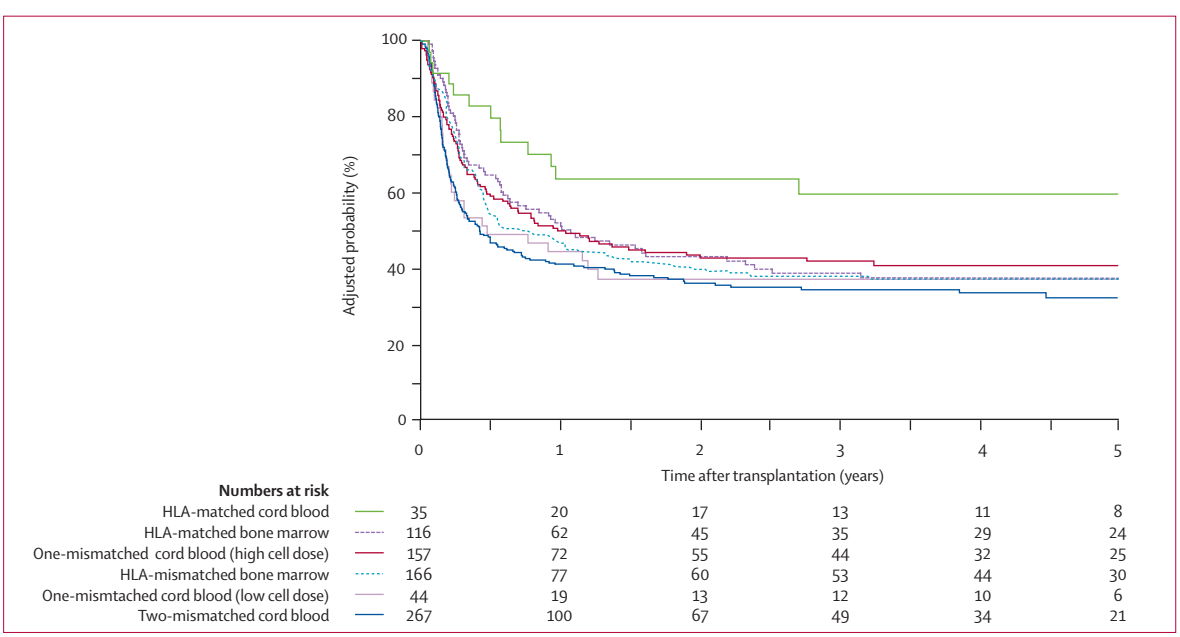

Figure: **Probability of leukaemia-free survival after bone-marrow and cord-blood transplantation adjusted for disease status at transplantation**

	Death before 100 days			Death after 100 days		
	Bone marrow (n=52)	Matched umbilical cord blood (n=4)	Mismatched umbilical cord blood (n=161)	Bone marrow (n=103)	Matched umbilical cord blood (n=8)	Mismatched umbilical cord blood (n=122)
Primary disease	9 (17%)	3	22 (14%)	72 (70%)	7	73 (60%)
GVHD	5 (10%)		20 (12%)	5 (5%)		13 (11%)
Interstitial pneumonitis	11 (21%)		45 (28%)	3 (3%)		11 (9%)
Infection	8 (15%)	1	39 (24%)	11 (10%)	1	11 (9%)
Organ failure	11 (21%)		15 (9%)	5 (5%)		6 (5%)
Other	8 (15%)		20 (12%)	7 (6%)		8 (6%)

The number in parentheses is the percentage of deaths in the group (column percentage). When the total number of patients in a group is <10, we have not provided a percentage.

Table 5: **Causes of death and type of transplant**

marrow transplantation (p=0·0147), than after allele-matched bone-marrow transplantation. In recipients of one-antigen mismatched cord-blood transplantation, the probability of platelet recovery was higher with high-cell-dose than with low-cell-dose grafts (p=0·0048). The probability of neutrophil recovery was not significantly lower with one-antigen mismatched low-cell-dose grafts than with high-cell-dose grafts (p=0·0106). In recipients of two-antigen mismatched cord-blood transplants, probabilities of neutrophil (p=0·2159) and platelet (p=0·5195) recovery did not differ by cell dose.

Rates of acute GVHD of grades 2–4 and 3–4 were similar after transplants of matched or mismatched cord blood, allele-mismatched bone marrow, and allele-matched bone marrow (table 3). Rates of chronic GVHD were similar after all types of transplantation (table 3).

Transplant-related mortality rates were similar after transplantations of HLA-matched cord blood, one-antigen mismatched high-cell-dose umbilical cord blood, allele-mismatched bone marrow, and allele-matched bone marrow (table 4). Transplant-related mortality rates were higher after cord blood mismatched at two antigens at any cell dose, and possibly after cord blood mismatched at one antigen at a low cell dose, than they were after allele-matched bone marrow. Notably, about 80% of events took place within 3 months after transplantation.

Relapse rates were similar in all groups with the exception of two-antigen mismatched cord-blood transplants for which relapse rates were lower than after allele-matched bone-marrow transplants (table 4). We examined this apparently lower relapse rate by comparison of transplant-related mortality and relapse rates of patients who were alive at 6 months and beyond 12 months. The aim was to ensure that the lower relapse rates after two-antigen mismatched transplants were not the result of higher transplant-related mortality and, thus, of fewer patients being at risk of relapse. Transplant-related mortality rates were similar at 6 months and beyond 12 months after two-antigen mismatched cord-blood transplants and allele-matched bone-marrow transplants, and relapse rates were lower after two-antigen mismatched cord-blood transplants than after allele-matched bone-marrow transplants (relative risk 0·50, p=0·0045 and 0·41, p=0·0001 at 6 months and beyond 12 months, respectively). The lower relapse rate with two-antigen mismatched cord-blood transplants is consistent with a more potent graft-versus-leukaemia effect, lending support to similar transplant-related mortality rates at 6 and 12 months after allele-matched bone marrow and two-antigen mismatched cord blood.

Treatment failure rates (inverse of leukaemia-free survival) after transplantation of matched cord blood, one- or two-antigen mismatched cord blood and allele-mismatched bone marrow were similar to those of allele-matched bone marrow (table 4).

The 5-year probabilities of leukaemia-free survival were 38% after HLA-matched bone-marrow transplants, 37% after mismatched bone-marrow transplants, 60% after HLA-matched cord-blood transplants, 36% after one-mismatched cord-blood transplant with low cell dose, 45% after one-mismatched cord-blood transplant with high cell dose, and 33% after two-mismatched cord-blood transplant (figure).

Interstitial pneumonitis and infections were frequent causes of early mortality after mismatched cord-blood transplants, but death from organ failure was more common after bone-marrow transplants than after cord-blood transplants (table 5). The proportions of early deaths due to recurrent leukaemia and GVHD were similar in both groups. Although recurrent leukaemia was the most frequent cause of late death in all groups, the proportion of patients with recurrent leukaemia as the cause of death was lowest after mismatched cord-blood transplantation.

Discussion

Our main objective was to compare leukaemia-free survival after transplantation of unrelated-donor cord blood and allele-matched bone marrow, and to provide guidelines for selection of an appropriate donor and graft source in children with acute leukaemia. This report differs from previous ones[1–7] because we compared the transplant outcomes after cord-blood transplantation with those after transplants of bone marrow matched at allele level for HLA-A, HLA-B, HLA-C, and HLA-DRB1, which are presently regarded as the standard of care. Furthermore, we assessed the relative influence of cell dose and HLA match of cord-blood grafts on these outcomes. In our analysis, there are four major findings that are either novel or disagree with previous reports:[1–12] leukaemia-free survival is similar in all subsets of patients; in comparison with allele-matched bone-marrow transplantation, early transplant-related mortality is higher after transplantation of cord blood mismatched for one antigen with low cell dose or mismatched for two antigens, but similar after transplantation of matched cord blood or one-antigen mismatched cord blood with high cell dose; risks of acute and chronic GVHD,

including grades 3–4 acute GVHD, are similar after matched or mismatched cord-blood and allele-matched bone-marrow transplantation; and relapse risk is lower in recipients of two-antigen-mismatched cord blood, indicating a greater graft-versus-leukaemia effect.

A major limitation to the use of cord blood is the availability of sufficient numbers of haemopoietic precursor cells, because HLA match and cell dose have effects on haemopoietic recovery and risk of transplant-related mortality. As reported in other series,[1–4] transplantation of cord blood was associated with slower neutrophil and platelet recovery than transplantation of bone marrow, irrespective of HLA match. However, both cell dose and HLA match influence the speed of haemopoietic recovery and might interact, mainly in the setting of HLA-mismatched cord-blood transplants.[4–9,20] In this report, cell dose and HLA match affected the risk of transplant-related mortality; recipients of two-antigen and one-antigen mismatched umbilical cord blood with low cell dose had worse outcomes. This effect might be particularly important for patients with non-malignant diseases who do not derive the benefit of the increased graft-versus-leukaemia effect that is present with two-antigen mismatched cord-blood transplants.

New strategies are needed to improve haemopoietic recovery and reduce early transplant-related mortality after cord-blood transplantation. Work is in progress, and future studies include the use of multi-unit transplants, co-infusion of mesenchymal stem cells, co-infusion of T-cell-depleted haploidentical peripheral blood stem cells, injection of cord blood into the bone-marrow, expansion culture of cord-blood haemopoietic stem and progenitor cells ex vivo, use of growth factors for in-vivo haemopoietic stem-cell expansion and improved homing, and development of safer preparative therapies.[21–27] Because cord-blood cell dose is a crucial determinant of engraftment and transplant-related mortality, particularly in adolescent and adult recipients of HLA-mismatched cord blood, these studies could increase the effectiveness of cord blood as a source of haemopoietic stem cells. There are trials of strategies to lower the risk of transplant-related mortality after bone-marrow and peripheral-blood transplantation, such as better methods of gene definition and donor–recipient HLA matching, lower-intensity conditioning regimens, and the use of cytokine antagonists, suicide genes, or the infusion of regulatory T cells to reduce the severity of GVHD.[28]

Although we found no clear advantage or disadvantage for allele-matched bone-marrow, matched cord-blood or one- and two-antigen mismatched cord-blood grafts for children with acute leukaemia, this study has limitations that are common to all observational studies in that the choice of intervention is established by the treating physician. Choice of intervention, in this case graft source, might be governed by complex criteria for selection of patients. Although we adjusted for all major known risk factors (age, race, disease status at transplantation, leukaemia type, and year of transplant), only a randomised trial that compared transplants of cord blood and allele-matched bone marrow could exclude a potentially confounding effect of selection bias. However, although several groups have seriously considered such a study, the logistics of doing a randomised trial in this specialty have proved formidable because very different processes are needed to identify and procure an adult donor and a cord-blood graft, and because few patients have both donor types available to them. Ethical considerations, such as the rationale for subjecting a child with an allele-matched bone-marrow donor to a mismatched cord-blood transplant, might be another impediment, although the results of our study might allay this concern.

Cord-blood banks and governments worldwide have invested substantially in the development of public cord-blood banks and unrelated-volunteer registries. For example, the US government, under legislation from Congress, plans to build an inventory of 150 000 cord-blood units, with the prediction that this larger inventory will provide about 80% of patients with a graft mismatched for one antigen of adequate cell dose. However, expected government funding might account for only a small portion of the funds that cord-blood banks in the USA require to create and maintain their inventories. Although banks can recover some of their costs from the distribution of umbilical cord blood units to transplant centres, most cord-blood banks in the USA presently operate at a loss and have difficulties in sustaining their programmes.

Our findings support the need for even greater investment in cord blood because of the importance of HLA matching and cell dose on survival. These data also support the practice of simultaneously searching accredited cord-blood banks and bone-marrow donor registries for all children with acute leukaemia who are eligible for transplantation of haemopoietic stem cells from unrelated donors. In the absence of a randomised trial, we cannot definitively state the relative efficacy of bone-marrow and cord-blood grafts, but the data support the use of cord-blood grafts in children with acute leukaemia.

Contributors

All co-authors contributed equally to the study design, interpretation of data, and approval of final report. ME, M-JZ and JPK did the statistical analysis. ME and JEW had primary responsibility for drafting the report.

Conflict of interest statement

We declare that we have no conflict of interest.

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