Unrelated umbilical cord blood transplant for adult acute lymphoblastic leukemia in first and second complete remission: a comparison with allografts from adult unrelated donors

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ABSTRACT

Allogeneic hematopoietic cell transplantation has an established role in the treatment of adults with acute lymphoblastic leukemia whose survival when recipients of grafts from adult unrelated donors approaches that of recipients of grafts from sibling donors. Our aim was to determine the role of mismatched unrelated cord blood grafts in transplantation for 802 adults with acute lymphoblastic leukemia in first or second complete remission. Using Cox regression we compared outcomes after 116 mismatched single or double cord blood transplants, 546 peripheral blood progenitor cell transplants and 140 bone marrow transplants. The characteristics of the recipients and their diseases were similar except cord blood recipients were younger, more likely to be non-Caucasians and more likely to have a low white blood cell count at diagnosis. There were differences in donor-recipient human leukocyte antigen-match depending on the source of the graft. Most adult donor transplants were matched at the allele-level considering human leukocyte antigens-A, -B, -C and –DRB1. In contrast, most cord blood transplants were mismatched and considered antigen-level matching; 57% were mismatched at two loci and 29% at one locus whereas only 29% of adult donor transplants were mismatched at one locus and none at two loci. There were no differences in the 3-year probabilities of survival between recipients of cord blood (44%), matched adult donor (44%) and mismatched adult donor (43%) transplants. Cord blood transplants engrafted slower and were associated with less grade 2-4 acute but similar chronic graft-*versus*-host disease, relapse, and transplant-related mortality. The survival of cord blood graft recipients was similar to that of recipients of matched or mismatched unrelated adult donor grafts and so cord blood should be considered a valid alternative source of stem cells for adults with acute lymphoblastic leukemia in the absence of a matched unrelated adult donor.

Introduction

Allogeneic hematopoietic cell transplantation is the most effective anti-leukemic therapy for adults with high-risk acute lymphoblastic leukemia (ALL) in first complete remission (CR1) but results are compromised by high transplant-related mortality especially in patients over the age of 35 years.[1,2] Allogeneic hematopoietic cell transplantation is also offered to adults with ALL in second complete remission (CR2). Recent large prospective donor-*versus*-no donor analyses have shown that matched sibling allografting produces superior outcomes to chemotherapy and such transplants remain the standard of care in the highest risk, Philadelphia chromosome-positive cohort.[1] Investigators from the Center of International Blood and Marrow Transplant Research have explored the use of myeloablative allografting with unrelated donors (URD) for patients with Philadelphia chromosome-negative ALL in CR1 at high risk of relapse.[2] This study of 169 patients demonstrated a 5-year survival rate of 40% in a high-risk cohort but also a high transplant-related mortality of 42%.

For adults with ALL in CR2 allogeneic transplantation is the treatment of choice and with sibling allografts disease-free survival rates of 25-40% are achieved. The outcome of unrelated donor transplants for ALL in CR2 is less successful, with the UKALLXII study reporting a 16% survival rate[3] although some recent German data are more encouraging.[4] Most conditioning regimens have involved the use of total body irradiation. In younger sibling donor transplants (median age 18 years) for ALL, doses of total body irradiation exceeding 13 Gy resulted in superior survival.[5] More recently there have been two small

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registry-based reports of the results of reduced intensity conditioning regimens; these studies involved small numbers of patients and did not include recipients of cord blood.[6,7]

The role of unrelated donor transplantation in adults with ALL in CR1 is being further evaluated in current prospective trials such as the current United Kingdom ALL XIV trial but about 15-30% of eligible patients do not have a suitably matched unrelated donor and this percentage may be higher in certain non-Caucasian ethnic groups. Three large registry-based studies have suggested that the overall survival of adults receiving unrelated donor cord blood (CB) transplants for acute leukemia is similar to that of patients receiving HLA-matched or mismatched unrelated donor bone marrow (BM) or peripheral blood progenitor cells (PBPC).[8-10] However, the post-allografting natural history of ALL in adults may differ from that of acute myeloid leukemia, making it necessary to do a focused up-to-date study in this group of patients.

CB cells and adult unrelated donor stem cells result in different profiles of major transplant outcomes. We wanted to examine if differences such as slower engraftment and potentially different rates of acute and chronic graft-*versus*-host disease (GVHD) might affect survival in adults being transplanted for ALL. In this study we compared outcomes after myeloablative transplant conditioning regimens for unrelated donor CB, BM and PBPC transplants in adults with ALL in CR1 and CR2 and attempt to delineate prognostic factors associated with those outcomes.

Methods

Eligibility criteria

Patients included were first allograft recipients, 16 years and older with ALL in CR1 or CR2 who had a single or double unit unrelated donor CB, BM or PBPC transplant and received myeloablative conditioning.[11] All transplants occurred in the United States between 2002 and 2010 and were reported to the Center for International Blood and Marrow Transplant Research. All patients provided consent to participation in research; the Institutional Review Boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

We excluded 20 patients older than 60 years of age because this cohort was insufficient for analysis and those with ALL–L3 (n=3). Recipients of CB received units that were HLA-matched or mismatched at one or two HLA-loci. Donor-recipient matching considered lower resolution HLA matching (antigen-level) at HLA-A and –B and allele-level at HLA-DRB1. When two CB units were infused, the transplant was assigned the lowest unit-recipient HLA-match. Recipients of BM or PBPC received grafts matched at the allele-level at HLA-A, -B, -C, -DRB1 or mismatched at a single HLA-locus.

Endpoints

Neutrophil recovery was defined as achieving absolute neutrophil counts of at least $0.5x10^9$/L at three consecutive measurements. Graft failure was defined as the absence of neutrophil recovery or sustained loss after initial recovery. Incidences of grade 2-4 acute and chronic GVHD were based on reports from each transplant center using standard criteria.[12,13] Transplant-related mortality was defined as death not related to disease recurrence and relapse, with disease recurrence based on morphological evaluation. Treatment failure was defined as death from any cause or relapse (inverse of leukemia-free survival – alive and in continuous clinical remission). Overall mortality was defined as death from any cause.

Statistical analysis

The probability of overall survival was calculated using the Kaplan-Meier estimator.[14] The probabilities of neutrophil and platelet recovery, acute and chronic GVHD, transplant-related mortality and relapse were calculated using the cumulative incidence estimator to accommodate competing risks.[15] Cox proportional hazard regression models were constructed for acute and chronic GVHD, transplant-related mortality, relapse, leukemia-free survival and overall mortality.[16] Results are expressed as hazard ratio (HR) with 95% confidence interval (CI). Having established that there were no significant differences between 8/8 HLA-matched PBPC *versus* 8/8 BM grafts and 7/8 PBPC *versus* 7/8 BM grafts (*data not shown*), categories were collapsed to create the following two categories: 8/8 PBPC or BM and 7/8 PBPC or BM. The main effect term, donor source (8/8 PBPC or BM *versus* 7/8 PBPC or BM *versus* CB) was held in all steps of model building, regardless of level of significance. Other variables tested included patient age, recipient CMV serostatus, ALL lineage, white blood cell count, cytogenetic risk, time to achieve CR1, disease status, conditioning regimen, GVHD prophylaxis and transplant period (2002 – 2005 *versus* 2006 – 2010). There were no first order interactions between the main effect term and other variables in the final models. All analyses were performed using SAS, version 9.3 (Cary, NC, USA).

Further details are provided in the *Online Supplementary Methods*.

Results

Patients: demographics, pre-transplant clinical, conditioning and graft characteristics

The characteristics of the patients, their diseases and transplants are shown in Table 1. Of 802 patients analyzed, 546 received 8/8 HLA-matched BM or PBPC (BM, n=185; PBPC, n=361), 140 received 7/8 HLA-matched BM or PBPC (BM, n=56; PBPC, n=84) and 116 received CB (44 received a single unit, 72 received two units). Most CB transplants were mismatched with 29% mismatched at one HLA-locus and 57%, mismatched at two HLA-loci. The median total nucleated cell count for single CB transplants was $3.2x10^7$/kg while that for transplants with two CB units was $4.6x10^7$/kg (sum of unit 1 and unit 2). Transplants involving an adequately dosed single CB unit and infusion of two CB units were considered as a single group because an earlier report from our group did not show differences in transplant outcomes.[17] Furthermore, in the current analysis, the unadjusted 1-year overall survival rate after transplantation of one and two CB units was 54% and 51%, respectively (P=0.74). Patient, disease and transplant characteristics were similar between the treatment groups except for patient age and race, white blood count at diagnosis, transplant-conditioning and GVHD prophylaxis regimens. Compared to recipients of 8/8 and 7/8 HLA-matched adult donor grafts, CB recipients were younger (median age: 32, 33 and 25 years, respectively), more likely to be non-Caucasian and present with a low white blood cell count at diagnosis. There were no significant differences in median time to transplantation from diagnosis; 8 months (range, 3 – 213) for recipients of 8/8 HLA-matched transplants compared to 8 months (range, 3 – 168) for recipients of 7/8 HLA-matched and 11 months (range, 2 – 109) for CB transplants. The most

common transplant-conditioning regimen for 8/8 and 7/8 HLA-matched transplants was total body irradiation with cyclophosphamide (482/686; 70%), while that for CB transplants was total body irradiation with cyclophosphamide and fludarabine. Recipients of 8/8 and 7/8 HLA-matched transplants were more likely to have received tacrolimus with methotrexate for GVHD prophylaxis while CB recipients were more likely to have received cyclosporine with mycophenolate mofetil. *In vivo* T-cell depletion with anti-thymocyte globulin or alemtuzumab was more common with CB transplants than with 8/8 and 7/8 HLA-matched BM or PBPC transplants [36/116 (31%) *versus* 144/686 (21%); *P*=0.010). One hundred and twenty-two transplant centers contributed patients; 37 centers performed BM, PBPC and CB transplants, 78 centers performed only BM or PBPC transplants and 7 centers performed only CB transplants. CB transplants were more frequently performed after 2005. Consequently, the median follow-up of CB recipients was, at 3 years, shorter than the 5 years for BM or PBPC recipients.

Neutrophil and platelet recovery

As expected the median time to myeloid engraftment was longest after CB transplants (25 days), shortest after PBPC transplants (14 days) and intermediate after BM transplants (19 days) (*P*<0.001). At 28 days, the cumulative incidence of neutrophil recovery was significantly lower after CB transplants (57%; 95% CI 48–66) than after either 8/8 HLA-matched PBPC/BM (95%; 95% CI 93–97) or 7/8 HLA-matched PBPC/BM (96%; 95% CI 92–98) transplants (*P*<0.001). By day 60, the incidence of neutrophil recovery after CB transplants (91%; 95% CI 85–95) was not significantly different from that after 8/8 HLA-matched PBPC/BM (97%; 95% CI 95–98) or 7/8 HLA-matched PBPC/BM (97%; 95% CI 94–99) transplants (*P*=0.08). Similarly, the cumulative incidence of platelet recovery at day 100 was significantly lower after CB transplants (56%; 95% CI 47–65) than after either 8/8 HLA-matched PBPC/BM (86%; 95% CI 83–89) or 7/8 HLA-matched PBPC/BM (82%; 95% CI 75–88) transplants (*P*<0.001).

Overall, there were 30 graft failures: 17/546 (3%) after 8/8 HLA-matched PBPC/BM, 3/139 (2%) after 7/8 HLA-matched PBPC/BM and 10/116 (8%) after CB transplants (*P*=0.01). Twenty-three of 30 patients died within 1 month and two patients died approximately 2 months after their first transplant; none of these patients received treatment specific for graft failure. Six patients received a second allogeneic transplant; two of these patients had had an 8/8 HLA-matched BM transplant and the remaining four had had a CB transplant. Both recipients of 8/8 HLA-matched BM transplants received PBPC from their same donors for their second transplants. One CB transplant recipient was given the second transplant from an HLA-mismatched relative, one was administered the back-up autologous unit and the other two patients were given a second CB transplant. However, all but one of the patients who received a second transplant are dead. The sole surviving patient is 6 years out from the second PBPC transplant (from the same donor as for the first transplant).

Graft-versus-host disease

In multivariate analysis the risk of grade 2-4 acute GVHD was higher after 8/8 HLA-matched and 7/8 HLA-matched PBPC and BM transplants than after CB transplants (Table 2). Compared to CB transplants, the risk of grade 3-4 acute

Table1. Characteristics of the patients, their diseases and trasplants.

	8/8 HLA-matched	7/8 HLA-matched	Cord blood	P
Number of patients	546	140	116	
Age at transplant, years				<0.001
16-19	75 (14%)	16 (11%)	32 (27%)	
20-29	153 (28%)	40 (29%)	41 (36%)	
30-39	134 (25%)	35 (25%)	18 (15%)	
40-49	101 (19%)	35 (25%)	17 (15%)	
50-59	83 (15%)	14 (10%)	8 (7%)	
Gender				
Male	321 (59%)	82 (59%)	64 (55%)	0.77
Female	225 (41%)	58 (41%)	52 (45%)	
Performance score				
90-100	347 (64%)	97 (69%)	85 (73%)	0.19
< 90	162 (30%)	32 (23%)	26 (22%)	
Missing	37 (7%)	11 (8%)	5 (4%)	
Race				
Caucasian	452 (83%)	96 (69)	60 (52)	<0.001
Non-Caucasian	49 (17%)	44 (31)	56 (48)	
Recipient cytomegalovirus serostatus				
Positive	234 (43%)	64 (46%)	43 (37%)	0.16
Negative	304 (56%)	76 (54%)	69 (60%)	
Unknown	8 (1%)	___	4 (3%)	
Disease status				
First complete remission	323 (59%)	83 (59)	57 (49)	0.13
Second complete remission	223 (41%)	57 (41)	59 (51)	
Disease sites at diagnosis				
Bone marrow + central nervous system	34 (6%)	5 (4%)	12 (10%)	0.43
Bone marrow + other extramedullary sites	50 (9%)	11 (8%)	12 (10%)	
Bone marrow alone	459 (84%)	123 (88%)	91 (78%)	
Unknown	3 (<1%)	1 (<1%)	1 (<1%)	
WBC at diagnosis				
Low count (B-cell≤30,000, T-cell≤100,000)	344 (63%)	89 (64%)	91 (78)	0.01
High count (B-cell>30,000, T-cell>100,000)	141 (26%)	31 (22%)	14 (12)	
Unknown	61 (11%)	20 (14%)	11 (9)	
Cytogenetic risk at diagnosis				
High risk[1]	206 (38%)	54 (39%)	48 (41%)	0.91
Standard risk[2]	115 (21%)	32 (23%)	25 (21%)	
Unknown	225 (41%)	54 (39%)	43 (38%)	
Time to achieve first complete remission				
< 8 weeks	298 (55)	80 (57)	71 (61)	0.25
≥ 8 weeks	214 (39)	47 (34)	41 (36)	
Unknown	34 (6)	13 (9)	4 (3)	
Duration of first complete remission (only for patients in second remission)				
< 12 months	70 (31)	19 (33)	26 (44)	0.23
12-23 months	48 (22)	14 (25)	13 (22)	
≥ 24 months	97 (43)	22 (39)	20 (34)	
Missing	8 (4)	2 (4)	___	
Conditioning regimens with/without *in vivo* depletion				
Total body irradiation + cyclophosphamide	387 (72)	111 (78)	25 (20)	<0.001
Total body irradiation + cyclophosphamide + fludarabine	3 (<1)	0 (0)	65 (56)	
Total body irradiation + other agents	94 (17)	15 (11)	21 (18)	
Busulfan – containing regimens[3]	62 (11)	14 (10)	5 (4)	

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Graft *vs.* host disease prophylaxis				
Tacrolimus + mycophenolate	64 (12)	18 (13)	27 (23)	<0.001
Tacrolimus + methotrexate	302 (55)	95 (68)	6 (5)	
Tacrolimus alone or with other agents	42 (8)	3 (2)	6 (5)	
Cyclosporine + mycophenolate	13 (2)	1 (<1)	67 (58)	
Cyclosporine + methotrexate	122 (22)	22 (16)	1 (<1)	
Cyclosporine alone or with other agents	3 (<1)	1 (<1)	9 (8)	
Transplant period				
2002-2005	258 (47)	74 (53)	15 (13)	<0.001
2006-2010	288 (53)	66 (47)	102 (87)	

8/8: allele-level HLA-matched at HLA-A, -B, -C, -DRB1 donor-recipient pairs; 7/8: single HLA-locus mismatched donor-recipient pairs. [1]High risk is defined as t(4;11), t(9;22), hypodiploidy or near triploidy; [2]Standard risk is all other abnormalities; [3]N = 41 received busulfan + cyclophosphamide; N = 30 received busulfan + fludarabine; N = 10 received busulfan + melphalan.

GVHD was higher after 7/8 HLA-matched PBPC or BM (HR 2.55, 95% CI 1.27–5.10; *P*=0.008) but not after 8/8 HLA-matched PBPC or BM transplants (HR 1.70, 95% CI 0.90–3.22; *P*=0.10). The day 100 cumulative incidences of grade 2-4 acute GVHD after CB, 8/8 and 7/8 HLA-matched transplants were 27% (95% CI 19–35), 47% (95% CI 39–55) and 41% (95% CI 37–45), respectively (*P*<0.001). The corresponding probabilities for grade 3-4 acute GVHD were 9% (95% CI 5–15), 16% (95% CI 13–20) and 24% (95% CI 18–32). Additionally, transplants prior to 2006 were associated with higher rates of acute grade 2-4 (HR 1.40, 95% CI 1.12–1.75; *P*=0.003) and grade 3-4 (HR 1.41, 95% CI 1.01–1.98; *P*=0.041) GVHD and this effect was independent of graft type. *In vivo* T-cell depletion lowered the risk of acute GVHD in all groups. In the absence of *in vivo* T-cell depletion, the probability of day 100 grade 2-4 acute GVHD was lowest after CB transplants (30%, 95% CI 21–40) compared to 44% (95% CI 39–48) and 53% (95% CI 44–62) after 8/8 and 7/8 HLA-matched PBPC or BM transplants, respectively (*P*=0.005).

The risks of chronic GVHD were not significantly different among the treatment groups (Table 2). The 3-year cumulative incidences of chronic GVHD after CB, 8/8 and 7/8 HLA-matched transplants were 39% (95% CI 30–49) 42% (95% CI 34–50) and 45% (95% CI 41–49), respectively (*P*=0.23). However, recipients of CB were less likely to report chronic GVHD severity as extensive (29/44; 66%) compared to recipients of 8/8 HLA-matched (197/247; 80%) or 7/8 HLA-matched (54/60; 90%) PBPC or BM transplants (*P*=0.01).

Relapse

In multivariate analysis, after adjusting for disease status and duration of CR1, there were no significant differences in relapse risk between the treatment groups (Table 2). The 3-year cumulative incidences of relapse after CB, 8/8 and 7/8 HLA-matched transplants were 22% (95% CI 15–31), 25% (95% CI 19–33) and 28% (95% CI 25–32), respectively (Figure 1). Compared to patients transplanted in CR1, relapse risks were higher in patients transplanted in CR2 with a CR1 lasting less than 12 months (HR 3.36, 95% CI 2.39–4.71; *P*<0.001) and when the duration of CR1 was 12 – 23 months (HR 2.11, 95% CI 1.36–3.27; *P*<0.001) but not when the CR1 lasted 24 months or longer (HR 1.33, 95% CI 0.92–1.92; *P*=0.13). We looked for differences in relapse risks among patients with and without acute or chronic GVHD. In patients with grade 2-4 acute GVHD, relapse risks were lower for those with acute GVHD than for those without acute GVHD although the difference did not reach statistical significance (HR 0.78, 95% CI 0.60–1.01; *P*=0.06). There were no differences in relapse risks between patients with and without chronic GVHD (HR 1.08, 95% CI 0.79–1.48; *P*=0.67).

Table 2. Results of multivariate analysis.

Variables	Hazard Ratio (95% Confidence Interval)	*P*
*Grade 2 – 4 acute GVHD**		
Umbilical cord blood	1.00	
8/8 HLA-matched PBPC/BM	1.57 (1.07-2.31)	0.021
7/8 HLA-matched PBPC/BM	1.89 (1.22-2.92)	0.004
Chronic GVHD		
Umbilical cord blood	1.00	
8/8 HLA-matched PBPC/BM	1.04 (0.75-1.43)	0.81
7/8 HLA-matched PBPC/BM	1.14 (0.77-1.68)	0.52
*Transplant-related mortality***		
Umbilical cord blood	1.00	
8/8 HLA-matched PBPC/BM	0.74 (0.53-1.03)	0.07
7/8 HLA-matched PBPC/BM	0.83 (0.56-1.23)	0.35
*Relapse****		
Umbilical cord blood	1.00	
8/8 HLA-matched PBPC/BM	1.35 (0.88-2.09)	0.17
7/8 HLA-matched PBPC/BM	1.37 (0.82-2.31)	0.24
*Treatment failure*****		
Umbilical cord blood	1.00	
8/8 HLA-matched PBPC/BM	0.97 (0.75-1.26)	0.82
7/8 HLA-matched PBPC/BM	1.03 (0.76-1.41)	0.85
*Overall mortality*****		
Umbilical cord blood	1.00	
8/8 HLA-matched PBPC/BM	0.89 (0.68-1.16)	0.38
7/8 HLA-matched PBPC/BM	0.96 (0.70-1.32)	0.81

*8/8: allele-level HLA-matched at HLA-A, -B, -C, -DRB1 donor-recipient pairs; 7/8: single HLA-locus mismatched donor-recipient pairs; PBPC: peripheral blood progenitor cells; BM: bone marrow. *Adjusted for transplant period; **Adjusted for patient age and race; ***Adjusted for disease status and duration of first complete remission, ****Adjusted for disease status and duration of first complete remission and patient race.*

Transplant-related mortality

There were no significant differences in transplant-related mortality risks after CB transplants compared to adult donor transplants (Table 2). The 3-year cumulative incidences of transplant-related mortality after CB, 8/8 and 7/8 HLA-matched transplants were 42% (95% CI 33–51), 31% (95% CI 27–35) and 39% (95% CI 31–47), respectively (Figure 2). Age at transplantation and race were associated with transplant-related mortality. Unsurprisingly there was a higher risk of transplant-related mortality in patients older than 35 years (HR 1.36, 95% CI 1.07–1.72; *P*=0.010). Compared to Caucasian recipients, transplant-related mortality was higher in non-Caucasian recipients (HR 1.54, 95% CI 1.18–1.99; *P*=0.001).

Overall and leukemia-free survival

Overall survival and leukemia-free survival were not significantly different between recipients of 8/8 or 7/8 adult donor grafts and CB (Table 2). The 3-year probabilities of overall survival adjusted for disease status, duration of CR1 and patient race were 44% (95% CI 34–54), 44% (95% CI 40–48) and 43% (95% CI 35–51) after CB, 8/8 and 7/8 HLA-matched transplants, respectively (Figure 3; *P*=0.98). Compared to patients transplanted in CR1, overall mortality

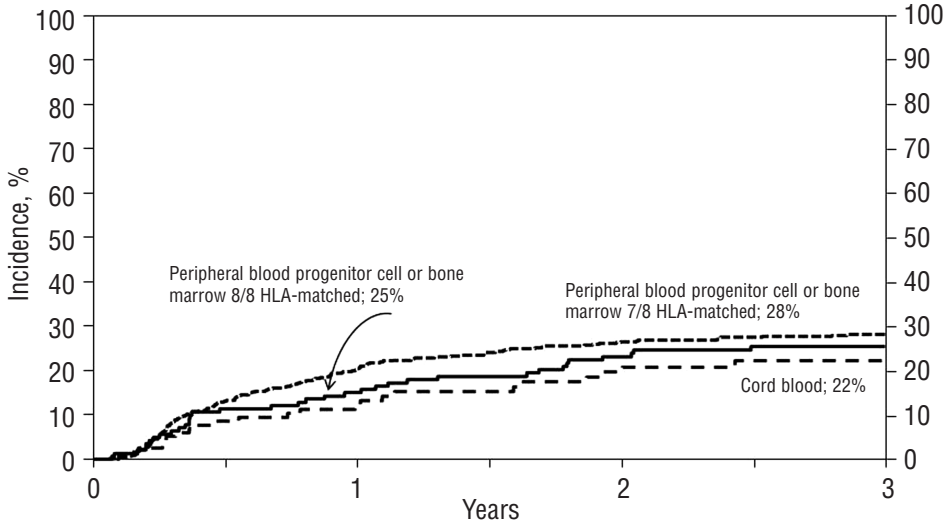

Figure 1. Cumulative incidence of relapse. The 3-year cumulative incidences of relapse after cord blood, 8/8 and 7/8 HLA-matched peripheral blood progenitor cell or bone marrow transplants were 22% (95% CI 15-31), 25% (95% CI 19-33) and 28% (95% CI 25-32), respectively.

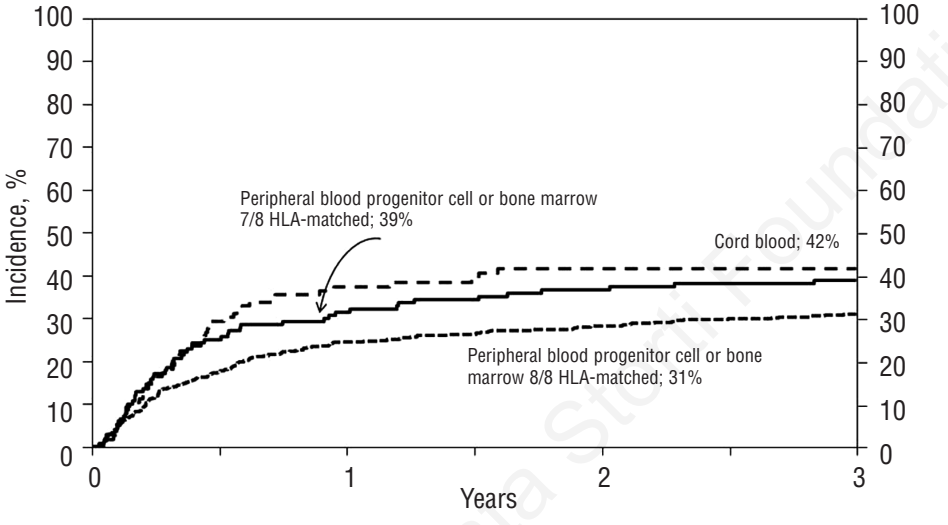

Figure 2. Cumulative incidence of transplant-related mortality. The 3-year cumulative incidences of transplant-related mortality after cord blood, 8/8 and 7/8 HLA-matched peripheral blood progenitor cell or bone marrow transplants were 42% (95% CI 33-51), 31% (95% CI 27-35) and 39% (95% CI 31-47), respectively.

risks were higher in patients transplanted in CR2 following a CR1 lasting less than 12 months (HR 1.68, 95% CI 1.31–2.14; $P<0.001$) or between 12 – 23 months (HR 1.41, 95% CI 1.05–1.91; $P=0.024$) but not when the CR1 lasted 24 months or longer (HR 0.88, 95% CI 0.68–1.14; $P=0.337$). Recurrent disease was the most common cause of death in the three treatment groups, with the rates ranging from 36-42% after 7/8 and 8/8 HLA-matched PBPC or BM transplants and being 47% after CB transplants. The mortality rate attributed to graft failure was higher after CB transplants, accounting for 15% of deaths. The GVHD and infection-related death rate was higher after 7/8 HLA-matched transplants (44%) than after 8/8 HLA-matched and CB transplants (29% and 23%, respectively). An effect of transplant center on overall survival was tested using the frailty model and there was none.[18]

Discussion

In this retrospective comparative study of alternative donor sources using transplant registry data, survival did not differ significantly after CB and 7-8/8 HLA-matched BM or PBPC transplants for more than 800 adults with ALL in CR1 and CR2. This study differed from previous comparisons by focusing only on adult ALL. The groups differed in prognostic characteristics with CB transplant recipients being younger and having a better performance status and lower white blood cell counts but also including significantly more non-Caucasians and more patients in CR2. Nevertheless we performed a carefully controlled analysis adjusting for relevant clinical characteristics that allowed us to compare transplant outcomes across the three treatment groups. Our findings extend and confirm reports from Japan.[19,20] There are differences between that study and the current analysis. The current analysis included adult donor transplants matched at the allele-level at HLA-A, -B, -C and DRB1 or mismatched at a single HLA-locus, the current accepted standard for selecting unrelated adult donors. In contrast the Japanese group selected unrelated donors matched at HLA-A, -B and –C at lower resolution (antigen-level) and at the allele-level at –DRB1. Using lower resolution HLA typing is better tolerated in the relatively homogenous Japanese island population than in the population in the USA with its greater genetic diversity.

Importantly, the rate of transplant-related mortality was high but similar in the three transplant groups (31-42% in absolute terms). As expected, CB recipients were slower to achieve myeloid engraftment, had twice the incidence of

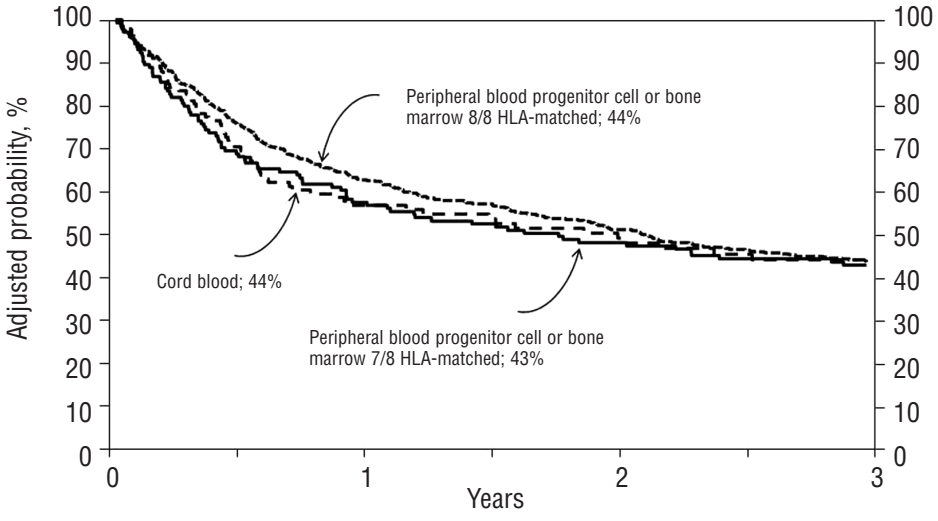

Figure 3. Probability of overall survival. The 3-year probabilities of overall survival adjusted for disease status, duration of first complete remission and patient race after cord blood, 8/8 and 7/8 HLA-matched peripheral blood progenitor cell or bone marrow transplants were 44% (95% CI 34-54), 44% (95% CI 40-48) and 43% (95% CI 35-51), respectively.

graft failure and platelet engraftment was very slow and often incomplete. The less favorable hematopoietic recovery kinetics of CB transplants did not, however, impact upon transplant-related mortality relative to that of adult donor transplants because adult donor transplant recipients were more likely to die from GVHD and/or infections. Nonetheless the finding of twice as much graft failure in the CB group is significant as nearly all patients with this complication died. Consistent with other reports, the transplant-related mortality rate was higher for non-Caucasians and independent of graft type.[21] A detailed exploration of the factors contributing to the high incidence of transplant-related mortality in non-Caucasians is beyond the scope of the current analyses. We hypothesize that the greater likelihood of transport-related mortality in non-Caucasians could be attributed to multiple factors such as genetic polymorphism, unmeasured comorbidities, socio-economic status and health behaviors, to mention a few.

Another significant finding was that relapse did not differ significantly between the three groups after adjusting for disease status and duration of CR1. The CB transplant group had more patients in CR2, more CR1 patients relapsed in the first 12 months and more received *in vivo* T-cell depletion. This is an interesting comparison because CB was associated with less acute GVHD than PBPC grafts but similar amounts of chronic GVHD although the chronic GVHD was less severe. Although we know the incidence and severity of chronic GVHD in our groups of patients we did not collect data on the duration of treatment or the patients' health-related quality of life. A large Center of International Blood and Marrow Transplant Research study conducted 15 years ago found a 40% reduction in relapse risks in ALL patients who got either acute and/or chronic GVHD.[22] In our study there was a suggestion that acute GVHD was associated with less relapse but there was no link with chronic GVHD. An important difference between the earlier study and the current one is sample size; it is plausible that within a larger cohort the observed lower relapse risk associated with acute GVHD in the current study may have been statistically significant. Furthermore, the earlier study[22] considered the combined effect of acute and chronic GVHD whereas the current analysis explored the effect of acute and chronic GVHD separately.

As is the case with all registry-based retrospective studies, this analysis has significant limitations. Nevertheless, this type of study may currently be the best way of comparing these stem cell sources as a randomized trial comparing 8/8 HLA-matched unrelated donor transplants and mismatched CB transplant in ALL patients would be difficult to perform as it is conceptually challenging to randomize between a fully matched and mismatched donor. Data for single unit CB transplants suggest matching units to recipients considering allele-level HLA-matches at HLA-A, -B, -C and –DRB1 lowers some of the excess transplant-related mortality associated with CB transplants.[23,24] We do not have allele-level HLA typing for CB units in the current analysis. However, it is worth noting that in this study over half of the CB transplants were mismatched at two HLA-loci and one third were mismatched at one HLA-locus. Only about 25% of transplants mismatched at one HLA-locus considering lower resolution HLA matching is a one-locus mismatch at the allele-level. This severely limits our ability to explore the effects of HLA-matching in the current analyses.

In interpreting the data, it is important to consider the factors that affected donor choice. Over the time period of the study most (but not all) centers would search for an 8/8 or 7/8 HLA-matched unrelated adult donor and then search for a CB graft if the search for an adult donor was unsuccessful. Even with changes in the unrelated donor registries that have hastened stem cell procurement from volunteer donors, obtaining CB units is substantially quicker. However, as the time to transplantation in patients in CR1 and CR2 was not faster in the CB group it seems likely they had an unrelated donor search first. Following the publication of several reports from both international transplant registries and single institutions, some centers with particular expertise in CB transplantation may have conducted CB transplants in patients without an 8/8 HLA-matched adult donor, especially if there was clinical urgency.[8-10,25,26] We do not have complete data about all the factors that may have contributed to the decision to perform an alternative donor allograft in CR1. For example we do not have complete data on adverse cytogenetics or problems with the delivery of induction and consolidation chemotherapy.

In summary, centers performing myeloablative alternative donor transplantation for adults with ALL in CR1 or

CR2 should consider CB as a source of stem cells from the outset because survival is broadly equivalent and transplant-related mortality and relapse are not increased. Of course, haploidentical donor transplants, particularly with post-transplant cyclophosphamide, are a potential alternative stem cell source but larger studies with sufficient follow-up are required before they can be recommended.[27,28] Finally it should be noted that the finding of the equivalence of the three graft sources only applies to myeloablative transplants. A separate study will be required for reduced intensity conditioning[6,7] transplants when numbers are sufficient for analysis.

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