REGULAR ARTICLE

blood advances

T-cell replete cord transplants give superior outcomes in high-risk and relapsed/refractory pediatric myeloid malignancy

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Key Points

- Compared with other cell sources, TRCB transplant results in improved disease-free survival and relapse risk in pediatric AML/MDS.
- Compared with other cell sources, cord-transplant cures with less chronic GvHD and particularly improves GvHD-free, relapse-free survival.

Stem cell transplant (SCT) outcomes in high-risk and relapsed/refractory (R/R) pediatric acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) have been historically poor. Cord blood (CB) allows T-cell replete CB transplant (TRCB), enabling enhanced graft-versus-leukemia. We consecutively collected data from 367 patients undergoing TRCB (112 patients) or other cell source (255 patients) SCT for pediatric AML/MDS in the United Kingdom and Ireland between January 2014 and December 2021. Data were collected about the patient's demographics, disease, and its treatment; including previous transplant, measurable residual disease (MRD) status at transplant, human leukocyte antigen–match, relapse, death, graft versus host disease (GvHD), and transplant-related mortality (TRM). Univariable and multivariable analyses were undertaken. There was a higher incidence of poor prognosis features in the TRCB cohort: 51.4% patients were MRD positive at transplant, 46.4% had refractory disease, and 21.4% had relapsed after a previous SCT, compared with 26.1%, 8.6%, and 5.1%, respectively, in the comparator group. Event free survival was 64.1% within the TRCB cohort, 50% in MRD-positive patients, and 79% in MRD-negative patients. To allow for the imbalance in baseline characteristics, a multivariable analysis was performed where the TRCB cohort had significantly improved event free survival, time to relapse, and reduced chronic GvHD, with some evidence of improved overall survival. The effect appeared similar regardless of the MRD status. CB transplant without serotherapy may be the optimal transplant option for children with myeloid malignancy.

Introduction

Allogeneic hematopoietic stem cell transplant (SCT) is the treatment of choice to cure high-risk, relapsed, and refractory acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).[1-3]

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Patients transplanted in remission do better than those with refractory disease.[4-6] This is also true for patients who relapse and are transplanted in second remission,[1,5,7,8] including those who relapse after transplant.[9]

Relapse is prevented by a graft-versus-leukemia (GVL) effect mediated by alloreactive donor T cells directed at residual recipient hematopoiesis and leukemia.[10] The increased risk of relapse in patients treated with T-cell depleted grafts, the efficacy of donor lymphocyte infusions posttransplant to achieve disease control and an inverse correlation between graft-versus-host disease (GvHD) and relapse,[11] indicate this critical role of donor-derived T-cells.

Milano et al[12] reported reduced relapse rates (RR) in cord blood (CB) SCT recipients compared with other donor cell sources in a single institution study of adult patients with all types of acute leukemia. This was particularly striking for patients who had positive measurable residual disease (MRD) before transplant, and in such patients, this reduced RR was associated with improved disease-free survival (DFS). In MRD negative patients the RR was still reduced compared with other cell sources, but this less clearly translated to an improved DFS because of the increased transplant-related mortality (TRM) in CB recipients. In a large, retrospective registry study of Japanese adult patients with non-remission AML, RR was reduced in CB SCT recipients compared with matched family donors, and their DFS was better.[13] The low incidence of chronic GvHD[14] combined with the GVL effect that CB affords has also resulted in superior chronic GvHD-free relapse-free survival (GFRFS) for CB compared with other donor sources in further studies.[15,16]

CB T cells might mediate an augmented GVL since such transplant is more often performed T-cell replete and is more often human leukocyte antigen (HLA)–mismatched, compared with other cell sources. There is therefore both more rapid T-cell reconstitution[17] and a greater difference between host and recipient. Indeed, more complete HLA-matching is associated with poorer DFS in adult patients with leukemia receiving a CB transplant.[18,19] The greater permissiveness for HLA disparity between donor and recipient with CB enhances the donor pool[20] and is associated with low rates of chronic GvHD.[15,16,21] These reasons, along with the rapid availability of CB units, make CB a particularly appealing donor source, especially for high-risk and relapsed or refractory malignancies where timely access to SCT is essential. In-vitro xenograft studies have also demonstrated an enhanced antileukemia effect for CB compared with similarly HLA-mismatched adult T cells, supporting the possibility that CB T cells have an ontogeny difference from adult T cells that may be beneficial in curing leukemia.[22]

We report the utility of T-cell replete CB transplant in high-risk pediatric myeloid malignancies in a large multicenter national analysis, compared with patients transplanted with similar disease and in the same period using other donor sources. We assessed DFS, RR, TRM, and GFRFS and compared outcomes in those with and without detectable MRD at the time of transplant.

Methods

Data were collected from consecutive patients undergoing T-cell replete (without serotherapy) CB transplant for pediatric AML or MDS in 10 United Kingdom and Republic of Ireland pediatric bone marrow transplant centers between January 2014 and December 2021. The comparator group consisted of consecutive pediatric patients undergoing either a T-cell depleted CB haematopoietic stem cell transplantation or a transplant using any other cell source at the same centers over the same period for the same indication. Information was gathered directly from the center using an agreed data proforma and checked for accuracy and completeness against the BSBMTCT/EBMT (British Society of Blood and Marrow Transplantation and Cellular Therapy/European Bone Marrow Transplant) Med A data submissions of each center. Patients were consented to provide data for outcomes analysis and the use of transplant data in research at the time of transplant, and information was gathered directly.

Data were collected about the patient's demographics, disease and its treatment; including previous transplant, MRD, disease status at transplant, donor and HLA-match, relapse, death, GvHD, and TRM.

Flow MRD was determined by multiparameter/multidimensional flow cytometry using aberrant expression of surface antigens on leukemic blasts and was considered positive if it was greater than 0.1%. The methodology used for measuring flow MRD was the same in both T-cell replete and comparator cohort, and all samples were assessed at centralized laboratories. The pretransplant MRD status was assessed after their most recent course of chemotherapy prior to starting transplant conditioning (within 4 weeks of transplant).

The patient's clinical disease status was clinician-determined, and patients were classified as having refractory disease if they had more than 5% blasts in bone marrow either morphologically or by cytogenetic or molecular methods, or proven extramedullary disease after ≥2 courses of induction or reinduction chemotherapy.

All cords were matched out of 8 loci at HLA-A, HLA-B, HLA-C, and HLA-DRB1 at allelic level. Related and unrelated donors were matched out of 10 HLA loci at allelic level which were HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1.

Acute GvHD was graded according to the Glucksberg criteria[23] and chronic GvHD according to the NIH consensus.[24]

Descriptive statistics were used to summarize the transplant characteristics for the whole cohort. Differences between treatment groups were assessed with chi-square test or Fisher exact tests (discrete variables) and Wilcoxon rank sum tests (continuous variables). Event-free survival (EFS) and overall survival (OS) were calculated using the Kaplan-Meier survival analyses and groups were compared using Cox regression and the log-rank test. Competing risks analysis by the method of Fine and Grey was used to calculate the hazard ratios (HR) for relapse, nonrelapse mortality, chronic, and acute GvHD with relapse, nonrelapse mortality, chronic, and acute GvHD considered as competing risks. All times were calculated from the date of transplant to the date of the events or competing risk. Patients without an event were censored at the date last seen.

Univariable Cox regression was used to examine the effect of treatment group and other transplant characteristics on each time to event outcome. Interactions between the treatment group and the other parameters were assessed. Univariable analyses were carried out for the whole cohort, within the group of patients

undergoing T-cell replete cord transplant and within the groups of patients with positive and negative MRD. Multivariable Cox regression analyses were performed for the whole cohort and forward selection was used when the number of events precluded full multivariable analyses (MVA). Analyses were performed by using Stata 17.0 (StataCorp, College Station, TX).

All patients consented to data collection, and all centers consented to the use of this data by BSBMT for data analysis.

Results

Data were collected from 112 consecutive patients undergoing TRCB transplantation and 255 consecutive patients in the comparator group (136 matched unrelated donors [MUDs], 63 matched sibling donors [MSDs], 36 mismatched unrelated donors [MMUDs], 9 T-cell deplete cord, and 11 haploidentical donors).

Table 1 shows transplant characteristics for the whole cohort. With the exception of disease type (AML/MDS), groups were unbalanced. Patients in the T-cell replete cord group were younger (median age, 6.5 [interquartile range (IQR), 2.5-11 years] vs 8.9 [IQR, 3.9-13.2]; $P < .005$) and less likely to have received an HLA-matched donor: 32 (28.6%) vs 208 (81.6%), $P < .001$. More patients in the cord group received reduced intensity conditioning: 20 (17.9%) vs 22 (8.6%), $P = .011$. Importantly, there was an excess of poor prognostic features in the TRCB group, including almost twice as many MRD-positive patients; 57 (51.4%) vs 60 (26.1%), $P < .001$, more refractory patients; 52 (46.4%) vs 22 (8.6%), $P < .001$, and 4 times higher proportion of second transplants in the TRCB group; 20 (21.4%) vs 13 (5.1%), $P < .001$.

Table 1. Patient and transplant characteristics

	T-replete cord (n = 112)	Comparator (n = 255)	*P* value*
Age, y	6.5 (2.5-11)	8.9 (3.9-13.2)	.005
Diagnosis			
AML	102 (91.1)	232 (91)	.978
MDS	10 (9)	23 (9)	
Conditioning			
MAC	92 (82.1)	233 (91.4)	
RIC	20 (17.9)	22 (8.6)	.011
HLA-match			
Fully matched (8/8 cord or 10/10 MUD or sib)	32 (28.6)	208 (81.6)	
Mismatched (≤7/8 or ≤9/10)	80 (71.4)	47 (18.4)	<.001
MRD			
Positive	57 (51.4)	60 (26.1)	
Negative	54 (48.7)	170 (73.9)	
No marker	0	25	<.001†
Clinical disease status			
Primary refractory	29 (25.9)	13 (5.1)	
Relapsed refractory	23 (20.5)	9 (3.5)	
CR2	22 (19.6)	84 (32.9)	
High risk CR1	38 (33.9)	118 (46.3)	
Other (untreated MDS)	0	31 (12.2)	<.001†
Previous BMT	24 (21.4)	13 (5.1)	<.001

Data are median (interquartile range) or number (percentage).

BMT, bone marrow transplant; CR, complete remission; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; sib, sibling.

*Wilcoxon rank-sum test (continuous), Pearson chi-square test or Fisher exact test (discrete variables).

†Category "Other" of clinical disease status and category "No marker" of MRD were not included in the calculation of *P* value.

In the TRCB group, 24 patients had received a previous transplant. The majority of these (18/24) were from matched unrelated donor transplants, with 3 out of 24 mismatched unrelated donor transplants, 1 haploidentical transplant, and 2 T-cell deplete cords.

Although data were collected over the same time period, TRCB transplants were more common in later years (63% of the patients in the comparator vs 36% in the TRCB group had undergone transplantation in 2014-2017) leading to a shorter median follow-up; 54.2 months (IQR, 47.8-58.3) in the comparator and 24.6 months (IQR, 16.3-34.4) in the T-cell replete group. Owing to this imbalance all survival rates and cumulative incidences have been calculated at 2 years.

The OS of the TRCB cohort was 64.7% and the EFS was 64.1%. The EFS was 79% in patients who were flow MRD negative before transplant, and 50% in those that were flow MRD positive at transplant ($P = .009$; HR, 2.58 [95% CI, 1.27-5.26]); Figure 1. EFS stratified by clinical disease status was 60.9% for those with primary refractory disease, 44.8% in those with relapsed refractory disease, 67.6% for those in high risk CR (complete remission)1, and 79.6% for those in CR2, Figure 2. For the 24 patients who had received a previous bone marrow transplant, EFS was 69%. Of all the TRCB recipients, 67% developed acute GvHD of which 30% was grade 3 to 4 and 37% grade 1 to 2, but the cumulative incidence of chronic GvHD was very low at 5% (95% CI, 0.02-0.11). HLA match did not influence EFS.

Univariable analyses showed that there was no significant difference in EFS by cell source groups (HR, 1.04 [95% CI, 0.72-1.52]; $P = .82$) with 2-year EFS rates of 64.1% (95% CI, 53.3-73) for TRCB vs 60.3% (95% CI, 53.8-66.21) for comparator group. Analyses of OS showed similar effects with no significant difference between the groups (HR, 1.32 [95% CI, 0.89-1.96]; $P = .17$). TRCB was associated with significantly higher nonrelapse mortality (HR, 2.05 [95% CI, 1.05-4.01]; $P = .04$) with 2-year cumulative incidence of 12.3% (95% CI, 7.3-20.4) for T-replete vs 7.2% (95% CI, 4.6-11.2) for comparator group, Figure 3. Despite this, the TRCB group were at significantly lower risk of developing chronic GvHD, (HR, 0.25 [95% CI, 0.10-0.62]; $P = .003$), Figure 4.

Associations between other prognostic factors and time to event outcomes were as expected; MRD positive patients had significantly worse EFS and OS and were at a higher risk of relapse and non-relapse mortality. Patients given reduced intensity conditioning had a significantly inferior EFS, whereas we observed that patients with fully-matched cords were at lower risk of non-relapse mortality. Older patients in the cohort were at a significantly higher risk of developing chronic GvHD.

Owing to the discrepancy in proportion of MRD positive patients between the TRCB and comparator groups, patients were stratified by flow MRD status for a further univariable analysis. In patients who were flow MRD positive going into transplant, TRCB recipients had significantly superior EFS compared with recipients of

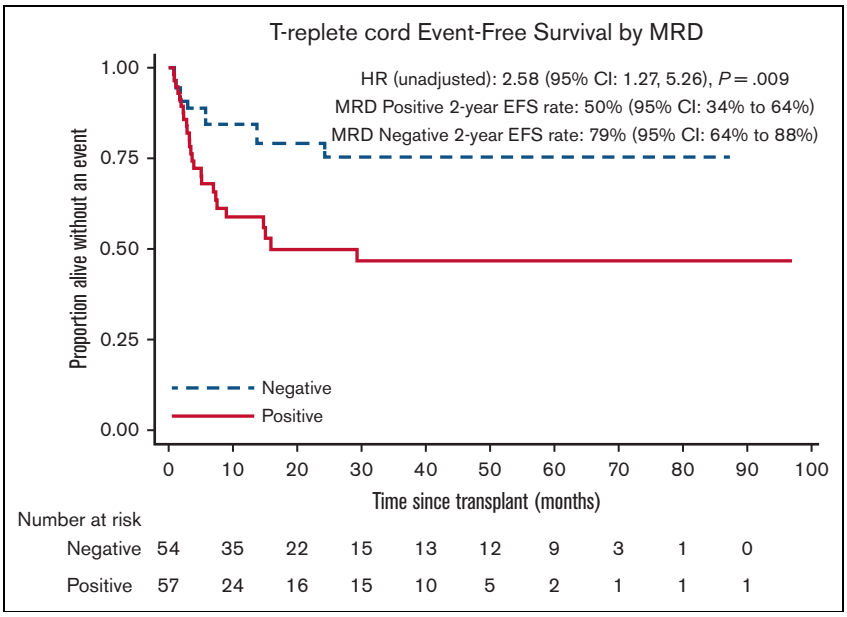

Figure 1. T-cell replete cord EFS stratified by MRD. Patients who were MRD negative at transplant have significantly improved EFS compared with MRD positive patients, 2-year EFS 79% (95% CI, 64-88) vs 50% (95% CI, 34-64), (HR, 2.58 [95% CI, 1.27-5.26]; $P = .009$).

other transplants, 50% (95% CI, 34-64) vs 21% (95% CI, 12-32) (HR, 0.55 [95% CI, 0.34-0.90]; $P = .017$), Figure 5A. EFS was similar between the 2 cohorts for patients who were MRD negative at transplant by univariable analysis, 79% (95% CI, 64-88) for the TRCB group, and 71% (95% CI, 64-78) for the comparators (HR, 0.86 [95% CI, 0.45-1.65]; $P = .649$), Figure 5B (P value for interaction = .29).

Chronic GFRFS was significantly improved for MRD positive recipients of a T-cell replete cord compared with other transplant type, 48% (95% CI, 32-62) vs 11% (95% CI, 5-21) ($P = .001$; HR, 0.44 [95% CI, 0.28-0.71]), Figure 6A. In MRD-negative patients, chronic GFRFS was 67% and 56% for TRCB and comparator transplant recipients respectively, ($P = .30$; HR, 0.75 [95% CI, 0.43-1.3]), Figure 6B (P value for interaction = .22).

The 2-year cumulative incidence of relapse was 23.2% (95% CI, 15.8-33.3) for the entire TRCB cohort vs 32.5% (95% CI, 27-38.9) for comparator group and again was not significantly different (HR, 0.71 [95% CI, 0.44-1.14]; $P = .16$). When this was stratified by flow MRD status, a striking reduction in relapse was observed for flow MRD positive patients in the TRCB setting, where the risk of relapse was 36.2% compared with 66.2% for other donors, ($P = .007$; HR, 0.46 [95% CI, 0.26-0.80]), Figure 7A. In MRD negative

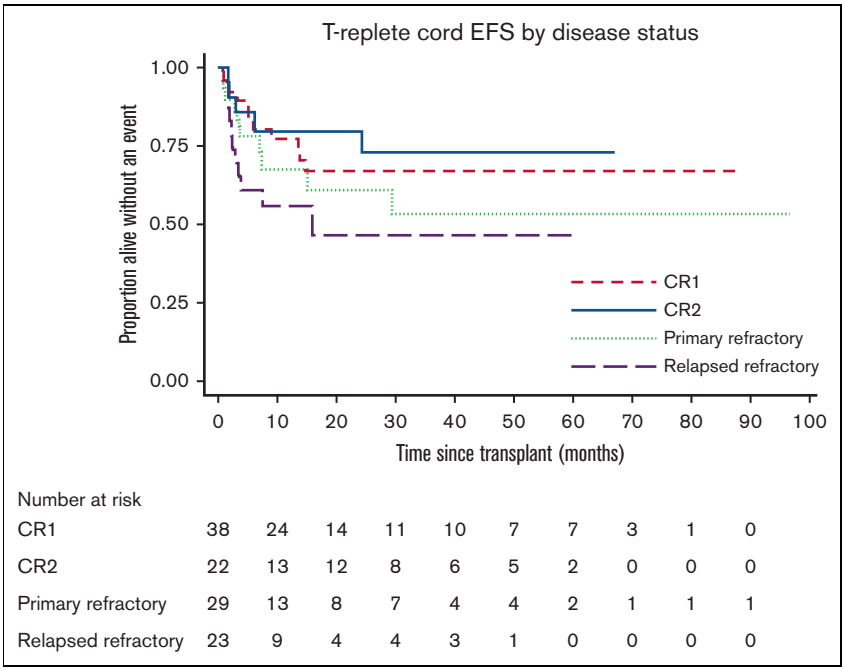

Figure 2. T-cell replete cord EFS stratified by clinical disease status. Two-year EFS was 79.6% for those in CR2, 67% for high risk CR1, 60.9% for those with primary refractory disease, and 46.5% for those with relapsed refractory disease. CR, complete remission.

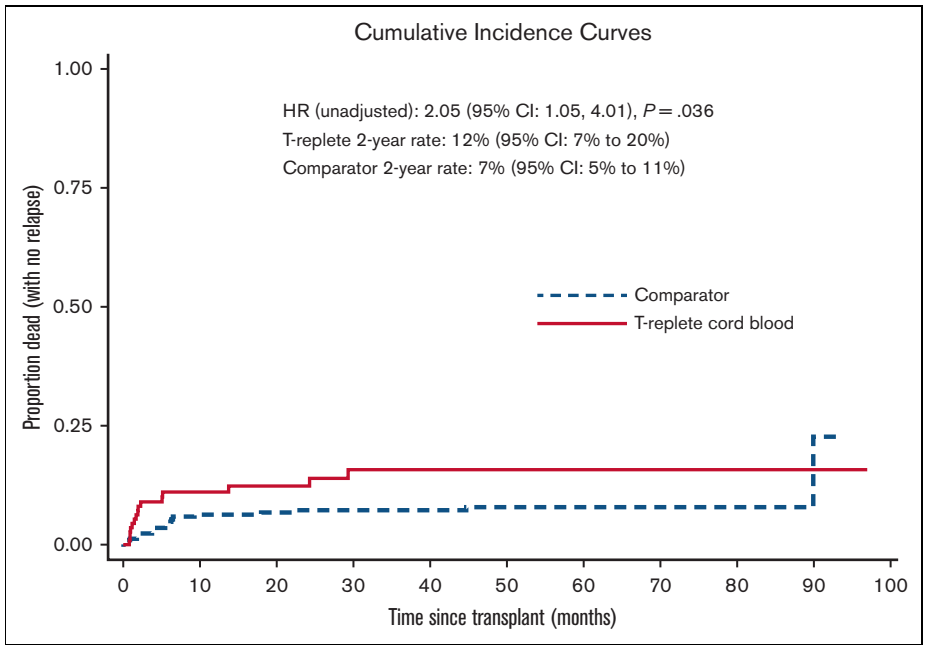

Figure 3. T-cell replete cord vs comparator cohort NRM. T-replete CB was associated with significantly higher nonrelapse mortality (HR, 2.05 [95% CI, 1.05-4.01]; P =.04) by univariable analysis with 2-year cumulative incidence of 12.3% (95% CI, 7.3-20.4) for the T-replete cord cohort vs 7.2% (95% CI, 4.6-11.2) for the comparator group.

patients, a similar trend was observed with RR of 9.9% and 27% in the TRCB and comparator groups, respectively (P = .049; HR, 0.36 [95% CI, 0.13-0.94]; P value for interaction = .67; Figure 7B).

MVA were performed for EFS, OS, and relapse (Table 2). Once adjusted for other important baseline factors, EFS and relapse showed a significant benefit for TRCB transplants; EFS HR was 0.57 (95% CI, 0.35-0.91); P = .019 and relapse HR was 0.46 (95% CI, 0.26-0.81), P = .008. This change in the treatment group effect appears to be driven by the excess of MRD positives within the T-cell replete cohort, with the HR for EFS changing from 0.76 (univariable, complete cases) to 0.54 when adjusted for MRD alone. Although not quite significant, there was also some evidence for an improvement in OS (HR, 0.65 [95% CI, 0.39-1.07]; P = .088). MRD remained significant in all analyses, with patients with MDS having a significantly better OS than AML. There was a significant interaction between age and treatment group for relapse (P value for interaction = .02); TRCB transplants appeared to be beneficial for all, but the effect may have been larger in older patients.

The number of events precluded full MVA for treatment-related mortality (33 events) and chronic GvHD (48 events), instead forward selection was performed to add in any variable significant (P < .05) to a model containing the treatment group (Table 2). The

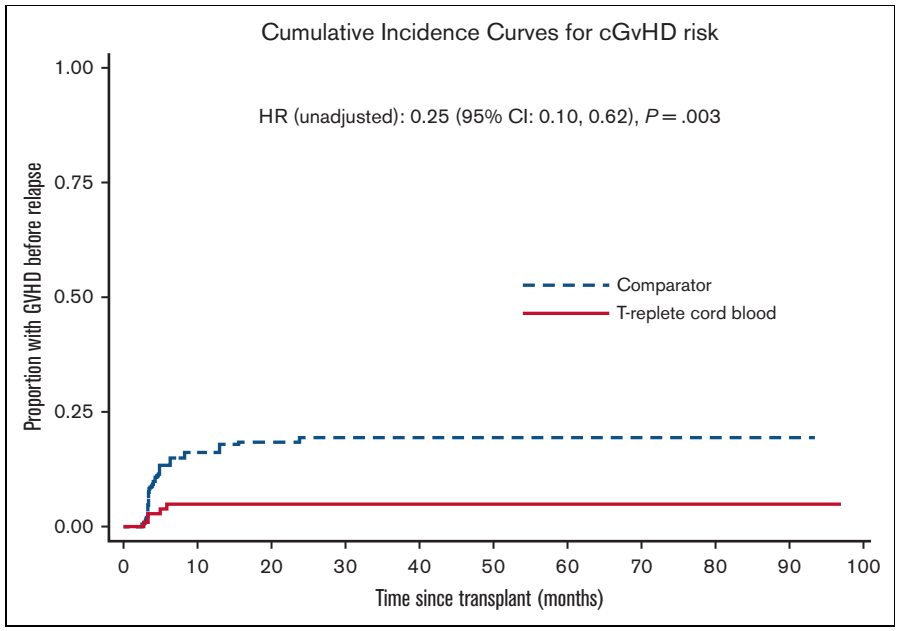

Figure 4. T-cell replete cord vs comparator cohort incidence of chronic GvHD. Univariable analysis shows a significantly lower risk of developing chronic GvHD for T-replete cord recipients compared with the patients in the comparator group (HR, 0.25 [95% CI, 0.10-0.62]; P = .003), with a cumulative incidence of 5% (95% CI, 0.02-0.11) for the T-replete cord patients compared with 19.4% (95% CI, 0.15-0.25) for the comparator. GvHD, graft versus host disease.

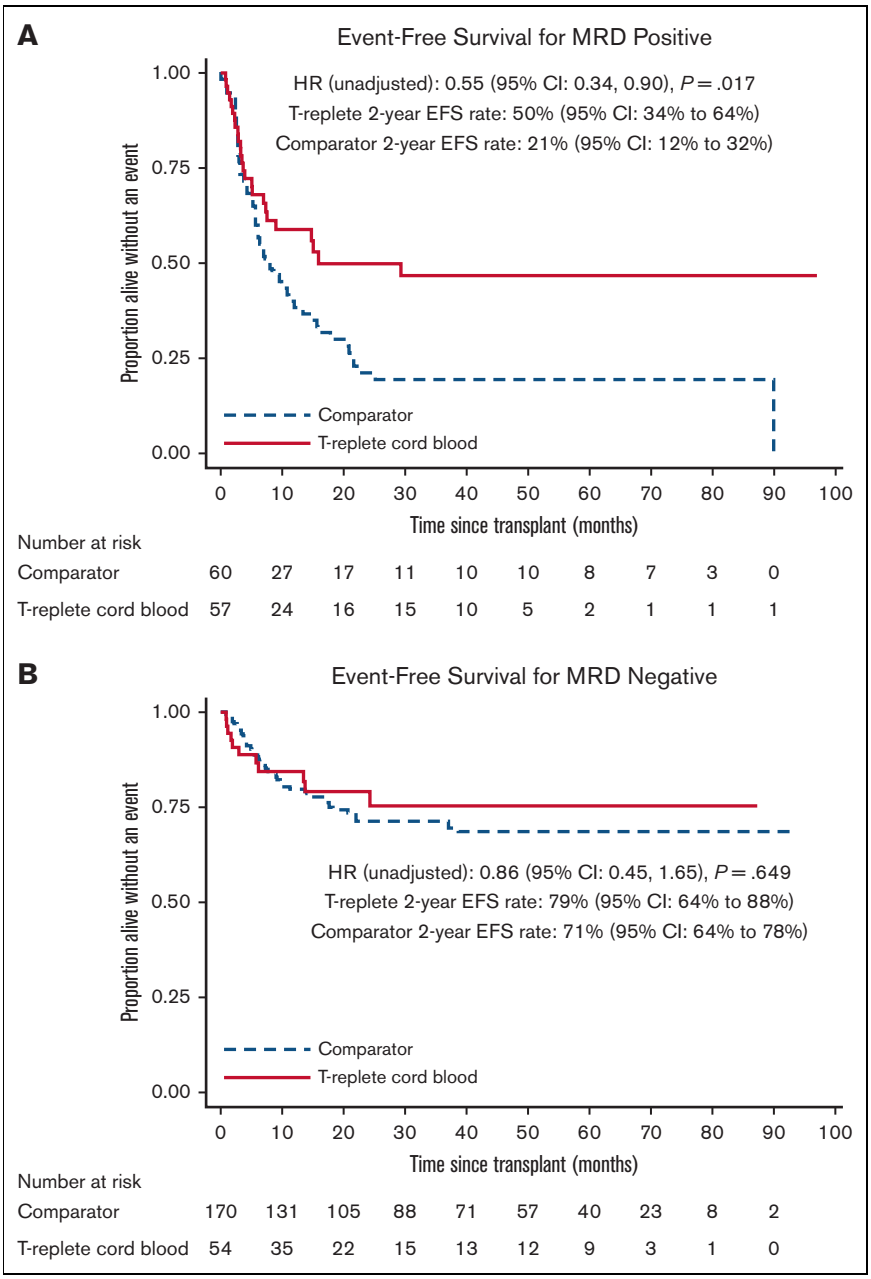

Figure 5. T-cell replete cord vs comparator cohort EFS. (A) In patients who were flow MRD positive going into transplant, T-replete CB recipients had significantly better EFS compared with recipients of other transplants, 2-year EFS 50% (95% CI, 34-64) vs 21% (95% CI, 12-32) (HR, 0.55 [95% CI, 0.34-0.90]; $P = .017$). (B) For patients who were MRD negative at transplant, there was no significant difference in EFS between patients in the T-replete cord vs comparator group, 2-year EFS was 79% (95% CI, 64-88) for T-replete cord recipients and 71% (95% CI, 64-78) for the comparator group (HR, 0.86 [95% CI, 0.45-1.65]; $P = .649$).

interactions with each variable were also explored. For TRM no other variables were significant in forward selection, though there was some evidence that the effect was greater for HLA mismatched cords (HR, 3.12 [95% CI, 0.89-10.86] vs HR, 0.43 [95% CI, 0.06-3.25]; P value for interaction = .102). Causes of death were not available for the comparator group, but within the T-cell replete cohort the most common cause of TRM was infection (n = 7), followed by GvHD (n = 5). The remaining 3 deaths were because of multiorgan failure secondary to underlying transplant-related microangiopathy (TMA).

Age was the only additional factor associated with chronic GvHD with older patients at higher risk. The effect of treatment group remained very similar (HR, 0.28 [95% CI, 0.11-0.70]; $P = .007$).

To account for the difference in follow-up, a sensitivity analysis was performed which censored all patients at 24.6 months (ie, median follow-up for the TRCB group) , these results were very similar MVA EFS (14 censored events; HR, 0.58 [95% CI, 0.35-0.93]; $P = .025$), time to relapse (4 censored events; HR, 0.48 [95% CI, 0.27-0.87]; $P = .015$), and OS (14 censored events; HR, 0.75 [95% CI, 0.44-1.26]; $P = .280$). All chronic GvHD events occurred before 2 years.

Discussion

In this large multicenter series of TRCB transplant in very HR pediatric myeloid malignancy, we demonstrated excellent outcomes, even in refractory disease, and showed how it is markedly

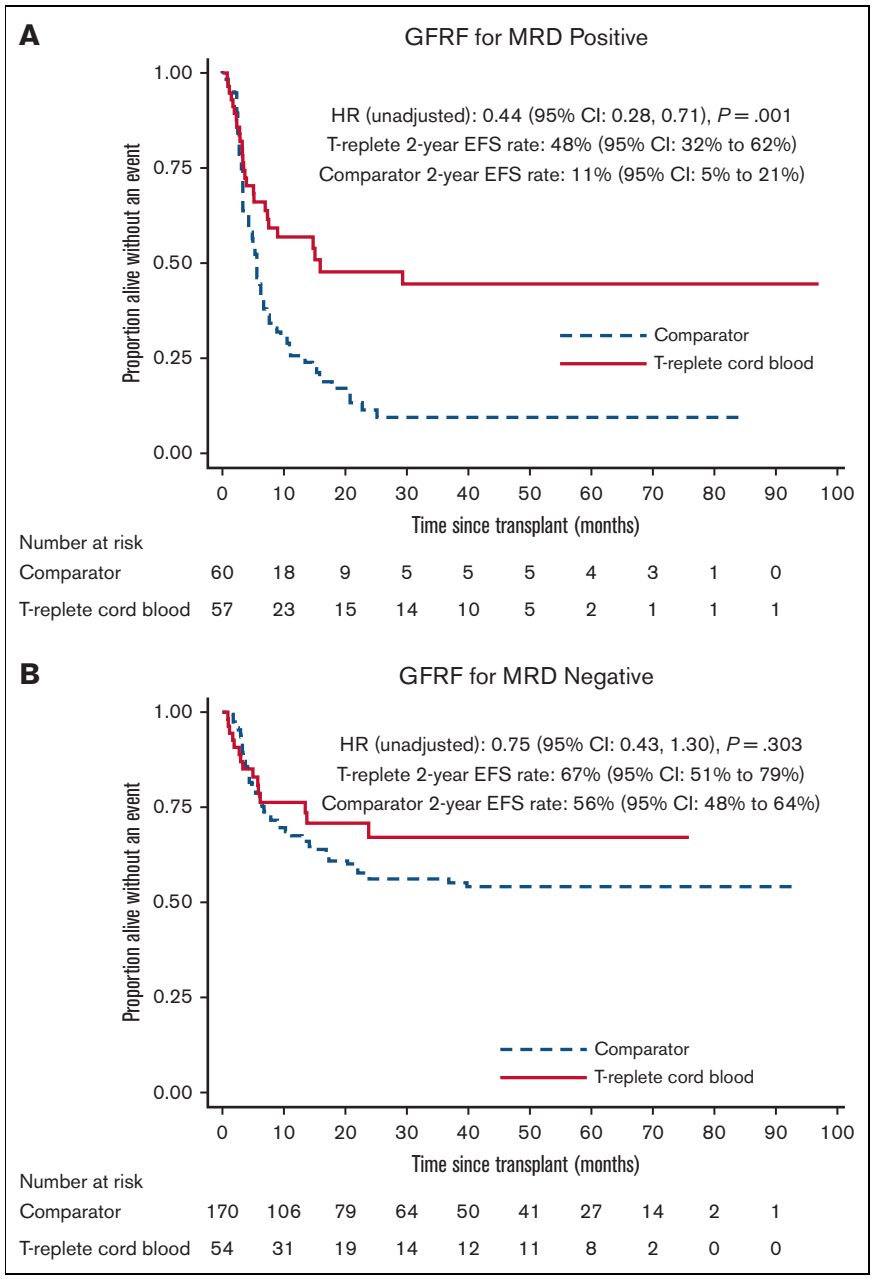

Figure 6. T-cell replete cord vs comparator cohort cGFRFS. (A) cGFRFS was significantly improved for MRD-positive recipients of a T-replete cord compared with other transplant type, 48% (95% CI, 32-62) vs 11% (95% CI, 5-21) (HR 0.44 [95% CI, 0.28-0.71]; $P = .001$). (B) In MRD-negative patients, cGFRFS was 67% (95% CI, 51-79) and 56% (95% CI, 48-64) for TRCB and comparator transplant recipients respectively, (HR, 0.75 [95% CI, 0.43-1.3]; $P = .30$), P value for interaction = .17. cGFRFS, chronic GvHD-free relapse-free survival.

superior to transplant using other cell sources. Although the TRCB transplant group had higher rates of MRD positivity, refractory disease, and second transplant, multivariable analysis showed both strikingly higher EFS and reduced RR, with a trend towards higher OS in the TRCB cohort than the comparator group, a contemporary cohort of transplants from other stem cell sources. This impact of TRCB was present at all levels of residual disease.

We recognize that there are limitations to our study; particularly that the groups were not randomly assigned, and that the follow-up of the TRCB cohort is shorter than the comparator. These imbalances, however, favored the comparator group (lower risk patients) with MVA allowing us to adjust for these for known confounders, and a sensitivity analysis showed that results held during the first 2 years, suggesting that although we cannot completely rule out a different pattern of events in the TRCB group, any later comparator events were not having an undue influence. The marked beneficial effect of TRCB in reducing relapse and promoting GvHD-free, DFS mandates a randomized clinical trial of cell source in children with myeloid malignancy requiring transplant to confirm these results. This is particularly true, given the decline in the use of CB as a cell source for transplant.

Early recognition of those with refractory disease will enable early transplant with TRCB, saving continued exposure to chemotherapy, including anthracyclines, with significant late effects. Although acute GvHD is significant after CB SCT, chronic GvHD

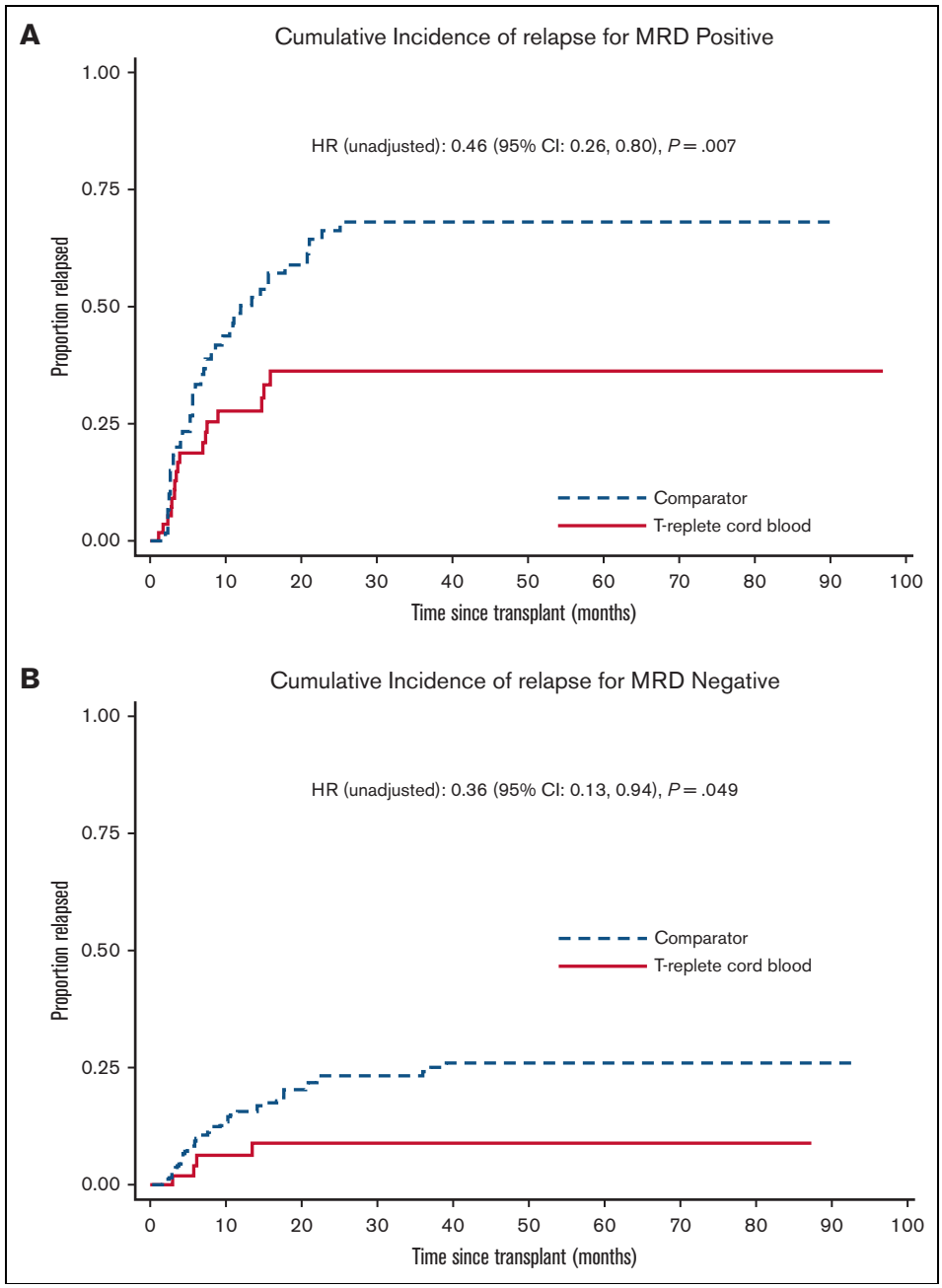

Figure 7. T-cell replete cord vs comparator relapse risk. (A) The 2-year cumulative incidence of relapse for flow MRD-positive patients was 66.2% for T-replete cord recipients compared with 36.2% for other donors (HR, 0.46 [95% CI, 0.26-0.80]; $P = .007$). (B) In MRD-negative patients a similar trend was seen with 2-year cumulative incidence of relapse of 8.9% for T-replete cord patients and 23.3% for the comparator group (HR, 0.36 [95% CI, 0.13-0.94]; $P = .049$), P-value for interaction: $P = .67$.

is much reduced compared with other cell sources, even where the HLA mismatch is greater.[15,16] The composite endpoint of GFRFS, which is the most clinically relevant outcome measure to assess in this setting, is much reduced in T-cell replete CB transplant compared with other cell sources in those with residual disease before transplant.[15,16] In those with residual disease, transplant with other cell sources may provide a cure, but this is often associated with chronic GvHD, including after donor lymphocyte infusion in those with detectable disease after transplant.

Our findings significantly extend those of Milano et al[12] which were from a single institution, and adult patients with both AML/MDS and ALL, and reported improved DFS only in those with measurable disease at the time of transplant. Similarly, Shimomura et al[13] reported a lower risk of relapse associated with CB SCT in a more limited study, comparing CB to matched family donors only, and studying only adult patients with AML not in remission. Our data are derived from a multicenter pediatric study of patients only with AML/MDS and demonstrating superior outcomes of TRCB transplant at all levels of MRD.

Table 2. Multivariable Cox regressions

	EFS		OS		Relapse		TRM*		cGvHD*	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
T-replete vs comparator	0.57 (0.35-0.91)	.019	0.65 (0.39-1.07)	.088	0.46 (0.26-0.81)	.008	2.04 (1.03-4.06)	.042	0.28 (0.11-0.70)	.007
RIC vs MAC	1.52 (0.93-2.48)	.096	1.41 (0.82-2.41)	.211	1.40 (0.80-2.47)	.241	-	-	-	-
MRD positive vs negative	3.97 (2.74-5.75)	<.001	4.46 (2.98-6.68)	<.001	4.09 (2.68-6.25)	<.001	-	-	-	-
Age at transplant (per 5 y)	0.99 (0.83-1.18)	.902	0.93 (0.77-1.31)	.483	0.90 (0.74-1.10)	.313	-	-	1.35 (1.01-1.81)	.039
MDS vs AML	0.79 (0.45-1.41)	.428	0.47 (0.23-0.97)	.040	0.96 (0.51-1.83)	.908	-	-	-	-
Previous BMT vs no previous BMT	1.36 (0.76-2.40)	.298	1.36 (0.73-2.52)	.329	1.10 (0.55-2.17)	.790	-	-	-	-
Fully matched vs mismatched cord	0.99 (0.66-1.50)	.976	0.86 (0.55-1.33)	.488	1.34 (0.81-2.22)	.251	-	-	-	-

BMT, bone marrow transplant; cGvHD, chronic graft versus host disease; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning.
*Models chosen with forward selection.

The role of pretransplant MRD in determining transplant outcome is a challenging issue with limited prospective studies.[25,26] We used multiparameter flow cytometry MRD assessment with a threshold of 0.1% in our study to reflect the methodology used in the UK pediatric AML and MDS national treatment protocol.[27] The prognostic impact of flow MRD in our data is in keeping with the recent prospective FIGARO study in adult AML which demonstrated a higher rate of relapse for patients who had a flow-determined MRD of 0.2% or above pretransplant.[28] The marked reduction in relapse for TRCB recipients in our analysis suggests that this may be the most appropriate form of transplant for patients with MRD positive disease, however, we acknowledge that prospective studies are needed to confirm this.

The higher TRM associated with CB transplantation[29] is perceived as a barrier, particularly in the era of increasing haploidentical SCT.[30] There is little doubt that other transplants, involving higher stem cell doses and graft T-cell depletion, are more straightforward, but the superior EFS for T-cell replete cord recipients, particularly those with positive MRD, shows that the loss of a GVL effect associated with such strategies is disadvantageous for these patients. The higher TRM in the cord setting arises due to a combination of high rates of acute GvHD, increased graft failure, immune cytopenia, and respiratory failure.[31]

Reduction of CB transplant TRM will accentuate the superiority of CB transplant, and likely will require collaborative working in several areas, including assistance in graft selection, optimizing GvHD prophylaxis and management, and reduction of viral infection including with newer agents.[32-35] Cord stem cell expansion technology has been investigated in several clinical trials and improves outcomes as it allows the consideration of better matched units previously not selected because of an inferior cell dose, accelerates neutrophil and platelet recovery, reduces bacterial and fungal infection, and reduces time in hospital.

Several studies have highlighted the low relapse rate for CB transplantation[21,36] and compared it with other donor sources,[29] and our data replicate these findings. The important role of T cells in enhancing the GVL effect in CB transplant has been demonstrated by data from Zheng et al,[37] where patients receiving serotherapy had significantly higher RR and inferior leukemia-free survival compared with those receiving a T-replete transplant. The significance of cord T cells in reducing relapse may also explain the findings of a recent EBMT-Eurocord acute leukemia study that failed to demonstrate a reduced relapse rate for cord compared with haploidentical SCT as most cord recipients also received T-cell depleting serotherapy.[38] Xenograft models have shown that CB T cells exhibit a superior antileukemia effect compared with that of adult T cells[22] suggesting that CB T cells have an ontogeny difference that may be implicated in the superior GVL effect observed with CB SCT.

The relapse rate for cord recipients in our cohort, although lower than recipients of other transplants, was higher than those in some previous retrospective adult studies.[12,21] The patient cohorts were different in these studies and most transplants used double-unit CB transplants while most patients in ours received single-unit CB transplants (95%). The RR has been shown in randomized studies to be reduced in double cord compared with single-cord transplants.[39] Although greater HLA disparity in CB transplants has been correlated with reduced RR, we did not show a

difference in relapse between fully matched and mismatched cord recipients in our cohort.[18,19,29,40]

Our findings suggest that CB might be considered the optimal donor cell source in children requiring transplant for AML because MVA demonstrates significantly improved DFS and RR in all patients. This should be confirmed in a prospective trial comparing RR and EFS in CB and other haematopoietic stem cell transplantation in high-risk AML/MDS, including MRD positive and refractory disease.

Authorship

Contribution: R.F.W. and P.J.A. conceived and designed the study; R.F.W., P.J.A., K.R., O.M.-D., C.F., B.J., K.P., S.L., B.G., W.R., and P.E. approved the study through the UK Pediatric BMT cooperative network; K.M., A.R., K.P., N.A.B., O.M.-D., O.O., C.F., A.D., V.B., P.E., B.G., W.R., S.A., J.J., R.D., and P.V. collected and supplied all institutional data; C.H. and R.F.W. wrote the manuscript; C.H., S.G., and A.A.K. analyzed data; S.G. and A.A.K. critically interpreted data and produced figures and tables; and all authors reviewed, edited, and approved the submitted manuscript.

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