Haplo-identical or mismatched unrelated donor hematopoietic cell transplantation for Fanconi anemia: results from the Severe Aplastic Anemia Working Party of the EBMT

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RESEARCH ARTICLE

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Haplo-identical or mismatched unrelated donor hematopoietic cell transplantation for Fanconi anemia: Results from the Severe Aplastic Anemia Working Party of the EBMT

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Abstract

Allogeneic hematopoietic cell transplantation (HCT) is the only curative option for bone marrow failure or hematopoietic malignant diseases for Fanconi anemia (FA) patients. Although results have improved over the last decades, reaching more than 90% survival when a human leukocyte antigen (HLA)-identical donor is available, alternative HCT donors are still less reported. We compared HCT outcomes using HLA-mismatched unrelated donors (MMUD; n = 123) or haplo-identical donors (HDs), either using only in vivo T cell depletion (n = 33) or T cells depleted in vivo with some type of graft manipulation ex vivo (n = 59) performed for FA between 2000 and 2018. Overall survival (OS) by 24 months was 62% (53–71%) for MMUD, versus 80% (66–95%) for HDs with only in vivo T cell depletion and 60% (47–73%) for HDs with in vivo and ex vivo T cell depletion (p = .22). Event-free survival (EFS) was better for HD-transplanted FA patients with only in vivo T cell depletion 86% (73–99%) than for those transplanted from a MMUD 58% (48–68%) or those with graft manipulation 56% (42–69%) (p = .046). Grade II-IV acute graft-versus-host disease (GVHD) was 41% (MMUD) versus 40% (HDs with no graft manipulation) versus 17% (HDs with T cell depleted graft), (p = .005). No differences were found for the other transplant related outcomes. These data suggest that HDs might be considered as an alternative option for FA patients with better EFS using unmanipulated grafts.

1 | INTRODUCTION

Fanconi anemia (FA) is a rare genetically and phenotypically heterogeneous inherited disorder, characterized by congenital malformations, progressive bone marrow failure (BMF) and a marked predisposition to malignancy.[1] Hematological abnormalities occur in at least 90% of FA patients at a median onset of 7 years and, at present, allogeneic hematopoietic cell transplantation (HCT) is the only proven curative therapy.[2-8] However, it does not prevent the occurrence of solid tumors, mostly in the head and neck.[9]

Historically, HCT outcomes were far superior in patients with FA receiving bone marrow (BM) or umbilical cord blood (UCB) hematopoietic progenitor cells (HPCs) from a human leukocyte antigen (HLA)-identical matched sibling donor (MSD) compared with HPCs from an unrelated donor.[6,7,10-13] Most FA patients do not have an HLA-identical unaffected sibling donor for HCT and therefore require an unrelated donor. Early experiences with unrelated donor HCT for the treatment of the hematological complications of FA were discouraging, with long-term survival rates of approximately 30%.[5,6] Poor outcomes were often the result of graft failure in 25% to 30% patients, graft-versus-host disease (GVHD) in 50% to 70% patients, excessive regimen-related toxicities and opportunistic infections.[5,6]

Results for HLA-matched unrelated donors have improved over the last decade, and are now comparable for survival to HLA identical siblings.[14-19] However, outcome for those with non-HLA identical donors (alternative) is significantly worse.

Since not all FA patients with an indication for HCT will have an HLA identical donor or a matched unrelated donor without HLA disparities, transplantation with an antigen mismatched donor or unrelated UCB with more than one disparity have been the most frequent donor source in these patients. However, with the improvement in survival rates with the use of haplo-identical donors (HDs) with post-HCT cyclophosphamide injections, and/or the possibility of graft engineering, this stem cell source needs to be considered as an alternative for mismatched unrelated donors.[13,21-26] To date there is no information available on the best option in this not so rare situation, therefore we have designed a study to address this question, through the EBMT registry, to help transplant units choose the best alternative option for their FA patients.

To this end, we compared outcomes after HCT in FA patients using haplo-identical or unrelated mismatched donors (UCB HCTs were excluded). To our knowledge, this is the largest reported cohort of FA patients undergoing HCT with this type of donor.

2 | METHODS

2.1 | Data collection

This is a retrospective multicenter study conducted through the Severe Aplastic Anemia and the Pediatric working parties of the European Group for Blood and Marrow Transplantation (EBMT) that collected data from 82 EBMT centers. All patients or legal guardians

provided informed consent, according to the Declaration of Helsinki. The EBMT publication rules were followed.

2.2 | Inclusion criteria

All consecutive patients with FA who underwent a first allogeneic hematopoietic cell transplantation between 2000 and 2018 from an unrelated donor with HLA disparities, or HDs who have been reported to EBMT were included. Mismatched unrelated donor (MMUD) and HD transplants were selected. This latter group was subdivided based on the type of T-cell depletion performed, where all patients received either in vivo T-cell depletion (serotherapy before and/or after stem cell infusion), or in vivo plus ex vivo T-cell depletion (graft manipulation). Centers were asked if they applied any form of ex vivo T-cell depletion (TCD) procedure. Detailed specification, on whether this was performed by depletion of CD3+ cells, CD19+ cells, alfa /beta T cells, or by positive selection of CD34+ cells by immunoselection of these antigens by specific monoclonal antibodies, was available only for a proportion of them.

Patients who received cord blood and HLA-identical related or unrelated donor transplants were not included in the study.

2.3 | Definitions

Neutrophil recovery was defined as the first of three consecutive days on which the absolute neutrophil count (ANC) was $\geq 0.5 \times 10^9$/L. Primary graft failure was defined as the failure to achieve neutrophil engraftment by Day 42, and secondary graft failure as an ANC of $<0.5 \times 10^9$/L for three consecutive days or 0% donor DNA by molecular analysis, having previously achieved neutrophil engraftment. Platelet recovery was defined as the first of three consecutive days (or laboratory measurements) on which the platelet count was $>20 \times 10^9$/L, without platelet transfusion support for 7 days before the first measurement. The donor origin of reconstituted cells was documented by molecular analysis.

Non-relapse mortality (NRM) was defined as death from any cause, without a preceding return of marrow to its status before transplant or graft failure. Acute GvHD (aGvHD) and chronic GvHD (cGvHD) were defined and graded according to previous published standard criteria.[27-29] The outcomes for aGVHD were censored after 100 days. Competing events for aGVHD and cGVHD were death, relapse, graft failure and second HSCT. The event considered in overall survival (OS) is death due to any cause. Events considered in event-free survival (EFS) are primary and secondary graft failure, second transplant, relapse and death, whichever comes first. The starting time for all outcomes was the date of transplant.

2.4 | Statistical analysis

Categorical pre-transplant risk factors are summarized as frequencies and percentages, group differences are analyzed using χ^2 tests. Continuous pre-transplant risk factors are summarized as medians with interquartile range (IQR), group differences are analyzed using Kruskal-Wallis tests. Both

OS and EFS were estimated using the Kaplan–Meier product limit estimation method and differences in subgroups until 24 months were assessed by the Log-Rank test. Median follow-up was determined using the reverse Kaplan–Meier method. Multivariable analyses of OS and EFS were conducted by means of Cox proportional hazards regression. Identical covariate constellations were used for OS and EFS: donor type (HD + in vivo TCD, HD + in vivo + ex vivo TCD vs. MMUD), interval between diagnosis and transplant (months), age at HCT (years), Karnofsky score (<90 vs. 90–100), stem cell source (peripheral blood [PB] vs. BM) and HCT year.

The cumulative incidences (CI) of grade II-IV aGvHD and limited/extensive cGvHD were estimated by 100 days and 24 months after the date of transplant, respectively. The cumulative incidences of neutrophil and platelet engraftment were estimated by 28 days and 100 days, respectively. To estimate cumulative incidences, competing risks analyses were separately applied to cGvHD, aGvHD, and neutrophil and platelet recovery. Competing events for any variable were death, relapse, primary and secondary graft failure and second transplant, whichever occurred first. Subgroup differences were assessed using Gray's test. All estimates were reported with 95% confidence intervals. All p values were two-sided and $p < 0.05$ was considered significant. Statistical analyses were performed using SPSS version 25 (SPSS Inc., Chicago, IL) and R version 3.0.3 using packages "prodlim", "survival" and "cmprsk".

3 | RESULTS

3.1 | Patients and donor characteristics

According to the inclusion criteria, 215 patients with FA were prospectively enrolled between 2000 and 2018, with a median age 9.7 years (IQR 6.8–13.2).

A MMUD was used in 123 patients (57.2%), whereas 92 were transplanted from HDs (42.7%), of which 33 received in vivo TCD, while 59 simultaneously received ex vivo TCD and in vivo TCD. A differential analysis between these three study arms was carried out.

Note, BM was the main source of stem cells (51.9% of transplants) and peripheral blood (PB) was used in 48.1% of cases.

The conditioning regimen contained cyclophosphamide in 85.6% of evaluable patients while fludarabine was used in 97.7% of instances. Total body irradiation was part of the conditioning regimen in 28.8% of cases.

Patient and transplantation characteristics are shown in Table 1. The HLA typing of the series is shown in Table S1. Most patients in the MMUD group have only one antigen mismatch (86.6%) but, we have up to 14.6% of missing data in this group of patients.

3.2 | Overall outcomes

3.2.1 | Engraftment

In the whole cohort, the CI of neutrophil engraftment was 85% by Day 28 (80–90%), with a median time to neutrophil engraftment of 14 days (14, 15).

TABLE 1 Patient characteristics table, stratified by treatment

	Group	Total N (%)	Total Missing	Mismatched unrelated N (%)	Haplo + in vivo N (%)	Haplo + in vivo + ex vivo N (%)	p
Total		215 (100%)		123 (100%)	33 (100%)	59 (100%)	
Patient sex	Male	109 (50.9%)	1 (0.5%)	65 (53.3%)	8 (24.2%)	36 (61%)	.002
	Female	105 (49.1%)		57 (46.7%)	25 (75.8%)	23 (39%)	
Age at HCT (yrs)	Median (IQR)	9.7 (6.8–13.2)	1 (0.5%)	10.6 (7.6–14.1)	9.7 (6.6–12.2)	8.5 (6–12.3)	.06
Karnofsky score	<90	39 (23.1%)	46 (21.4%)	24 (26.4%)	8 (29.6%)	7 (13.7%)	.16
	90–100	130 (76.9%)		67 (73.6%)	19 (70.4%)	44 (86.3%)	
HCT year	Median (IQR)	2013 (2010–2015)		2012 (2009–2014)	2015 (2013–2017)	2014 (2011.5–2015)	<.001
CMV donor	Negative	75 (37.5%)	15 (7%)	63 (54.3%)	4 (12.5%)	8 (15.4%)	<.001
	Positive	125 (62.5%)		53 (45.7%)	28 (87.5%)	44 (84.6%)	
CMV patient	Negative	65 (32.7%)	16 (7.4%)	37 (32.5%)	9 (28.1%)	19 (35.8%)	.8
	Positive	134 (67.3%)		77 (67.5%)	23 (71.9%)	34 (64.2%)	
TCD	In vivo alone	156 (72.6%)		123 (100%)	33 (100%)		<.001
	In vivo+ex vivo	59 (27.4%)				59 (100%)	
TBI	No	153 (71.2%)		114 (92.7%)	11 (33.3%)	28 (47.5%)	<.001
	Yes	62 (28.8%)		9 (7.3%)	22 (66.7%)	31 (52.5%)	
Stem cell source	BM	111 (51.9%)	1 (0.5%)	87 (70.7%)	21 (65.6%)	3 (5.1%)	<.001
	PB	103 (48.1%)		36 (29.3%)	11 (34.4%)	56 (94.9%)	
Interval Dx-Tx (m)	Median (IQR)	32.4 (11.5–65.2)		31.2 (11.4–63.6)	53 (17.3–77.2)	31.3 (9.8–62.9)	.19
Conditioning	Cy NO	31 (14.4%)		9 (7.3%)	14 (42.4%)	8 (13.6%)	
	Cy YES	184 (85.6%)		114 (92.7%)	19 (57.6%)	51 (86.4%)	
	Flud NO	5 (2.3%)		5 (4.1%)			
	Flud YES	210 (97.7%)		118 (95.9%)	33 (100%)	59 (100%)	
	Bu NO	190 (88.4%)		102 (82.9%)	30 (90.9%)	58 (98.3%)	
	Bu YES	25 (11.6%)		21 (17.1%)	3 (9.1%)	1 (1.7%)	

Abbreviations: BM, bone marrow; Bu, busulfan; CMV, cytomegalovirus; Cy, cyclophosphamide; Flud, fludarabine; HCT indicates hematopoietic cell transplantation; Interval Dx-HCT, the interval from diagnosis to hematopoietic cell transplantation; months; PB, peripheral blood; TBI, total body irradiation; TCD, T cell depletion.

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The CI of platelet engraftment was 68% by Day 28 (60–76%) and 75% by Day 100 (68–83%), with a median time to platelet engraftment of 19 days (17–22).

3.2.2 | Graft failure, non-relapse mortality and second transplantation

The CI of primary graft failure was 5% (2–8%), whereas that of secondary graft failure was 7% (3–10%). The CI of second transplantation was 5% (2–8%), while the total number of patients who died during the 2 year follow-up was 71. Main causes of death within the 24-month follow-up period were infection in 29 cases (40.8%), GVHD in 23 cases (32.4%), relapse or progression in five cases (7.0%), organ damage/failure in five cases (7.0%), HCT-related death in two cases (2.8%), secondary malignancy or post-transplant lymphoproliferative disease in two cases (2.8%), and other (not specified) in five cases (7.0%). Of note, GVHD and infection accounting together for 73.2% of cases. The CI of non-relapse mortality was 22% (16–28%).

3.2.3 | GVHD

The CI of aGVHD at Day 100 was 34% (28–41%). The CI of failure due to other causes (relapse, graft failure, second transplant and death) by Day 100 was 20% (14–25%).

The two-year CI of cGvHD was 13% (8–18%) and failure due to other causes (the same as above) was 36% (29–43%).
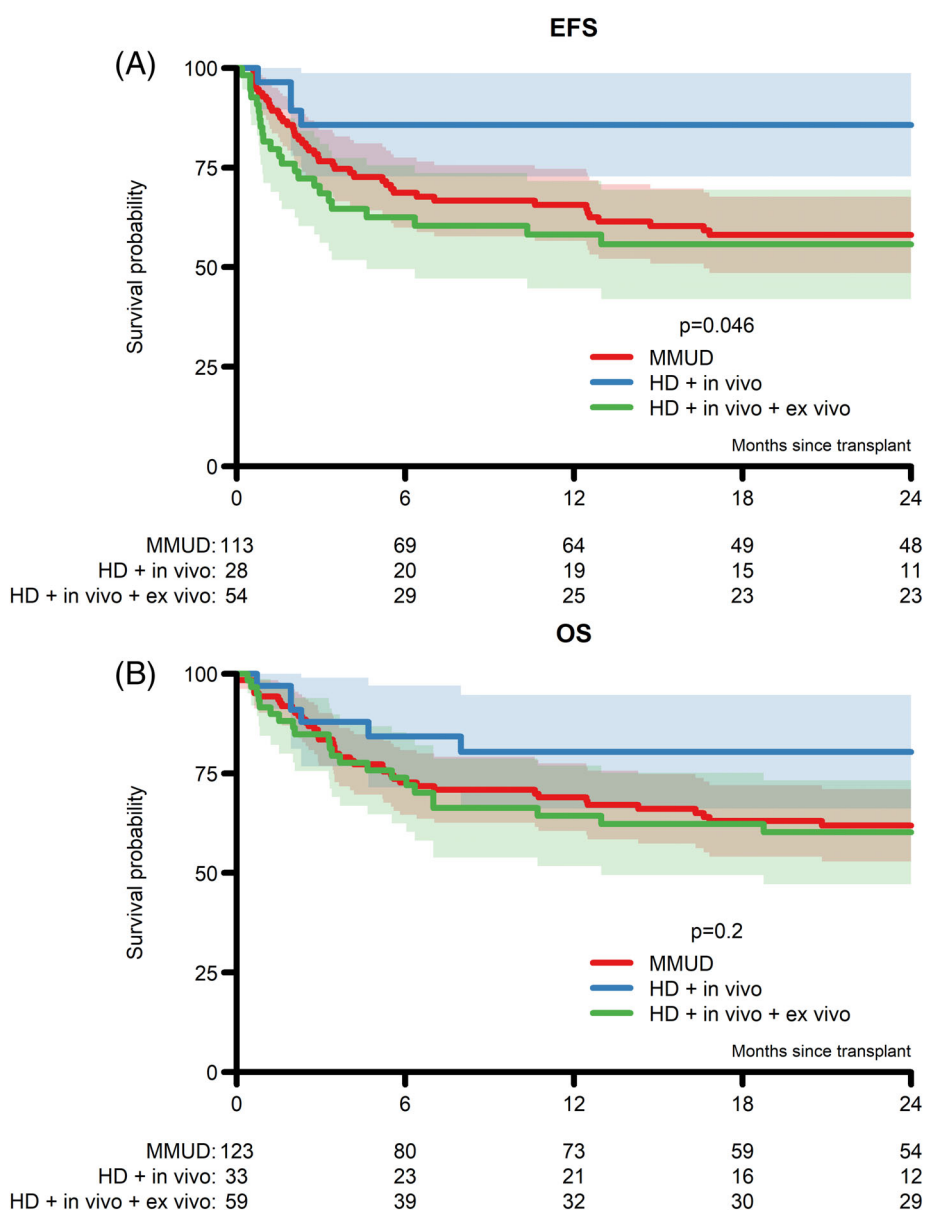

FIGURE 1 (A) Kaplan–Meier plot of event-free survival by treatment groups. (B) Kaplan–Meier plot of overall survival by treatment groups [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Multivariable Cox regression models of survival outcomes

Covariate	Group	OS		EFS	
		HR (95% CI)	p	HR (95% CI)	p
Donor	MMUD				
	HD + in vivo	0.55 (0.23–1.33)	.19	0.21 (0.05–0.89)	.03
	HD + in vivo + ex vivo	1.35 (0.68–2.68)	.4	1.39 (0.65–2.98)	.4
Interval Dx-HCT (years)		1 (0.96–1.05)	.9	0.99 (0.93–1.05)	.6
Age (decades)		1.05 (1.02–1.08)	.002	1.03 (1–1.07)	.05
Karnofsky score	90–100				
	<90	2.02 (1.11–3.65)	.02	1.09 (0.53–2.25)	.8
	Missing	1.12 (0.6–2.09)	.7	0.8 (0.41–1.54)	.5
Stem cell source	BM				
	PB	1.21 (0.69–2.14)	.5	1.04 (0.55–1.99)	.9
HCT year		0.94 (0.89–0.99)	.02	0.93 (0.88–0.99)	.02

Abbreviations: BM, bone marrow; CI, confidence interval; EFS, event-free survival; HD, haplo-identical donor; HR, hazard ratio; Interval Dx-HCT, interval from diagnosis to hematopoietic cell transplantation, MMUD, mismatched unrelated donor; OS, overall survival; PB, peripheral blood.

3.2.4 | Event-free survival and overall survival

The median follow-up time of the study group was 44.8 months (37–53.8). Two-year EFS was 61% (57–71%).

For the entire cohort, the two-year OS was 64% (95% CI, 57–71%).

3.3 | Comparison between transplant procedures

3.3.1 | Event-free survival

The MMUD group has a 58% (48–68%) probability of two-year EFS, where HDs with graft manipulation have a 54% (42–69%) probability, and HD only with in vivo T cell depletion have the best results: 86% (73–99%) (p = 0.046) (Figure 1(A)).

After multivariable analysis, most recent transplants (year of HCT) and HDs using only in vivo TCD were related to better outcomes (HR 0.21 [0.05–0.89]; p = .03) (Table 2). Neither the interval between diagnosis and transplant, nor Karnofsky score, nor age, nor stem cell source were significantly related to EFS.

3.3.2 | Overall survival

No significant differences were found between the three described groups for two-year overall survival (p = .2). The MMUD donor group had a 62% (53–71%) probability of two-year survival, where HDs with graft manipulation had a 60% (47–73%) probability and HD only with in vivo T cell depletion had 80% (66–95%) (Figure 1(B)). Older age at transplant (hazard ratio [HR] 95% CI; 1.05, 1.02–1.08; p = .002), HCT performed in the oldest times, and Karnofsky score <90 (HR 95% CI; 2.02, 1.11–3.65; p = .02) were related with poor outcomes (Table 2).

3.3.3 | Engraftment

The cumulative incidence of neutrophil engraftment was not different between the three study groups, with 86% by Day 28 (80–93%) for the MMUDs, 89% (77–100%) for the HDs with only in vivo TCD, and 81% (71–92%) for the third group (p = .3). The median time for neutrophil engraftment was Day 17 (15–17) when using MMUD, Day 14 (13–15) when using HDs only with in vivo T cell depletion, and Day 12 when using HD and graft manipulation.

The cumulative incidence of platelet engraftment by Day 100 was not significantly different either. It was 81% (72–90%) for the MMUD group, 76% (58–94%) for the HDs with only in vivo TCD, and 64% (49–79%) for the HDs with graft manipulation. The median time for platelet engraftment was Day 21 (17–23), Day 20 (19–32) and Day 13 (10–22) for the same three groups.

While HDs with graft manipulation seem to lead to faster engraftment, the cumulative incidence for both variables (neutrophils by Day 21 and platelets by Day 100) is not different between the three groups.

3.3.4 | GVHD

The cumulative incidence of aGVHD II-IV was significantly better for those patients undergoing transplantation with HD donors with in vivo and ex vivo T cell depletion 17% (7–27%) than for those with MMUD 41% (32–50%) or HDs only with in vivo T cell depletion 40% (7–27%) (p = .005).

The cumulative incidence of limited and extensive cGVHD was similar for all groups. For limited cGVHD, the cumulative incidence was 4% (0–11%) for patients undergoing transplantation with HDs with in vivo T cell depletion, 5% (1–10%) for those with MMUD donors and 4% (0–9%) when using HD donors with in vivo and

ex vivo T cell depletion (p = .914). For extensive cGVHD the cumulative incidence for the same groups was 3% (0–9%), 10% (4–16%), and 4% (0–9%) (p = .121).

3.3.5 | Graft failure, non-relapse mortality and second transplantation

No differences were found for these other transplant-related outcomes between the three groups, although there is a trend for higher primary graft failure for those transplants performed with HD donors using both modalities of T cell depletion 11% (3–19%) (p = .063). Of interest, none of the patients among the HDs in vivo TCD underwent a second transplant.

3.4 | Other variables that influence the outcome

We have also analyzed the influence of other variables on the outcomes in this series.

Younger patients and the most recent transplants (HCT year) had better EFS and OS (Table S2). However, neither year of transplant nor age did influence GVHD, primary or secondary graft failure (Table S3).

Neither patient-donor sex match, nor patients' cytomegalovirus (CMV) status or interval between diagnosis and transplantation influence the main outcomes of the series in this study. However, Karnofsky status is related to overall survival in those patients with poorer status, with an estimation of 58% (42–74%) overall survival at 2 years, and those with Karnofsky status 90–100 reaching 70% (62–78%) (p = .049) (Table S2). Bone marrow as a source of cells was only associated with increased risk of aGVHD grade II-IV 43% (34–53%) over PB 25% (16–33%) (p = .005). This is most likely due to the higher number of ex vivo manipulations in this latter group (Table S3).

4 | DISCUSSION

Two main concerns should be dealt with when considering HCT in these patients. On one hand, defects in DNA repair have been demonstrated to be related with greater toxicity following chemotherapy or radiotherapy, which requires the use of low-toxic conditioning regimens. On the other hand, defects in DNA repair seem to lead to more severe toxicities of GVHD, which, it appears, is more difficult to control and leaves greater sequelae. For instance, cGVHD is one of the factors more clearly related to the appearance of second neoplasms. These two conditions may lead to discussions if it would be better choosing one non-HLA identical unrelated donor, or if it would be more convenient to use a haplo-identical donor.

The results when an HLA-identical sibling is used as a donor demonstrate that these two obstacles have been overcome. Several studies show overall survival higher than 90%, but this is far from being resolved when no HLA-identical sibling donor is available.[10-20] In the EBMT study, which focused on transplantations performed between 1972 and 2010, the results with unrelated donors were poorer than those with family donors.[12] This is the case at most institutions, and even when survival is similar using different GVHD prophylaxes and conditioning regimens, the incidence of acute and chronic GVHD is higher for those transplants performed without HLA identical donors, most likely leading to more severe sequalae and a higher incidence of secondary neoplasia.[7,8]

We must note here the good results of a radiation-free multi-institutional study performed with graft manipulation (CD34 selected/T cell depleted) and anti-thymocyte globulin (ATG) administration.[20] In this study, OS at 3 years was 80% (±6%), with an EFS of 77.8% (±6%) at the same time point. The cumulative incidence of aGVHD was 6–7% by 100 days, without any grade III/IV, only three patients (of 45 patients included) developed limited cGVHD, and none an extensive cGVHD.[20] In this study, 19 donors were not HLA-identical, six of them being family donors with non-specifically described HLA disparities.[20]

MacMillan et al.[15] analyzed the outcomes of 130 FA patients undergoing alternative donor HCT, and more recently Ebens et al.,[17] from the same institution, updated this data for those patients transplanted with the same conditioning regimen. In that latter study, OS at 5 years was not statistically significantly different between transplants with matched sibling donors 94% (95% CI, 65–99%) and alternative donors 86% (95% CI, 74–93%).[17] However, in the latter group, these authors included an HLA-matched parental donor, as well as a non-clearly described number of unrelated donors that were 6/6 HLA-matched.

Although HLA disparity is clearly related to the results of allogeneic hematopoietic cell transplantation, haplo-identical donor transplantation has been reported over the last few years as a promising alternative for those patients without HLA compatible donors.[13,21-26] Overall survival has a wide range, from 83% at 5 years, when an ex vivo T cell depletion approach is used,[13] to a one-year overall survival for the Brazilian post-transplant cyclophosphamide T cell depletion cohort of 73%,[23] and a 68.4% overall survival, with a median follow up of 30 months, in an Indian single center study.[24]

It is in this setting where the comparison we performed may help physicians to know which is the best approach for those patients diagnosed with FA and without HLA-matched unrelated donors (10/10). According to our results, HDs give better EFS than other alternative donors, although overall survival was not significantly different. Besides, based on the results of this study, this approach should be done with only in vivo T cell depletion, since adding ex vivo T cell depletion impairs the results. Of course, better results are not only related to the donor source itself but to the protocol used for transplantation. Therefore, the use of the same ex vivo T cell depletion for HD and MMUD could lead to similar results, but with the data collected in our registry, we cannot conclude anything on this.

Our results here are slightly better than to those reported by Bonfim et al.,[23] where cyclophosphamide was used after stem cell infusion for GVHD prophylaxis. In this approach, there was no graft manipulation. One-year overall survival rate was 72.6% (95% CI 64–81%), with a median follow-up of 30 months. In this series, the

use of rabbit ATG had a clear impact on transplant outcomes, with a significant decrease of severe acute and chronic GVHD, although it continues being a relevant adverse event. Seven out of 14 patients developed mild to severe cGVHD.[23]

We can also find other small series with this approach that resulted in overall survival. The overall survival in the Uppuluri et al.[24] cohort was 13/19 (68.4%), with a median follow-up of 30 months. It is important to note that this procedure will allow a good number of patients that could not otherwise reach transplantation to undergo it. Most of them will have an immediately available potential donor (it is extremely rare not to find a HD in the family). It does not require a significant investment, as the equipment for graft manipulation is not required, and in general, it simplifies the entire process by avoiding the unrelated donor search and the ex vivo processing. The cost is also cheaper.

However, these results contrast with the results previously published,[13,21,26] most likely because the center experience in every haplo-identical approach has to be taken into account. The results of this kind of study based on data from international registries are of great help to evaluate what is being done in the field, but each center is able to recognize which approach is the most appropriate, based on its own experience in performing this type of transplantation in other much more frequent hematological diseases.

The results when using UCB for transplantation for FA patients have also improved over the last decades but again, several reports stress the relevance of HLA matching for UCB transplantation in this disease.[11,30-32] Based on all these studies, there is evidence that the use of an UCB unit with two or more HLA disparities in FA is associated with a lower probability of neutrophil recovery, decreased survival, or an unacceptable rate of GVHD.[11,30] However, UCB continues to be an acceptable source of hematopoietic progenitor cells for those patients who lack an HLA-matched unrelated BM donor when careful attention is given to HLA matching and total nucleated cells (TNC). Whether this is better or not to use HDs should be analyzed in a future study.

Our study faces some weaknesses. Firstly, there are differences between the three study groups in the year of transplant, with the group of HDs with only ex vivo T cell depletion being performed mainly in the last few years. The effect of the year of transplant was observed in OS, EFS, acute GvHD and extensive cGvHD in univariate analyses and in OS and EFS in multivariable analyses. More recent transplants tended to result in better outcomes. In order to separate the year and donor effects in EFS, OS and aGvHD, subgroup analyses by interaction were performed. After this analysis, the effect of HCT year was not significantly different in the MMUD and HD groups (results not shown), suggesting that the effect of the donor was consistent over the time period under study. Unfortunately the event rates in the other outcomes was too low to reliably separate the HCT year and donor effects. However, although the median year for each group only differs in 1 year and most of the cases were done in periods with similar supportive measures, we acknowledge that it may have impacted our findings. We should also comment that it would have been of interest to evaluate the different ex vivo TCD

procedures, but unfortunately, these data were not recorded in all cases. This is also the case for the HLA typing. These data are also missed for some patients in the series. However, some degree of missing data is inherent in all registry studies like this, and we consider that in this study this lack of detail does not undermine the study's fundamental message, since the three broad categories were clearly identifiable in the data registry by a specific field.

In conclusion, this study may help us to know the expected results in allogeneic hematopoietic cell transplantation with donors with HLA disparities in FA. However, it is very important to note that there is little experience with HDs in this disease in a large number of institutions, and although it is always advisable to refer these patients with rare diseases to referral centers, it is even more important when alternative donors are used. Many short-term and long-term issues now open up when selecting these types of donors. This study paves the way for prospective clinical trials using alternative non-HLA identical donors, with required long-term follow-up in this particular setting.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data of this study are available to investigators via the EBMT, please contact the EBMT Data Office in Leiden, the Netherlands.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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