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ARTICLE

Hematopoietic stem cell transplantation with unrelated cord blood or haploidentical donor grafts in adult patients with secondary acute myeloid leukemia, a comparative study from Eurocord and the ALWP EBMT

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Abstract

Survival of patients with secondary acute myeloid leukemia (sAML) is poor. Cord blood transplantation (UCBT) and non-T-cell-depleted stem cell transplantation from haploidentical donors (HAPLO) are both strategies that have shown encouraging results in patients who do not have an human leukocyte antigen (HLA)-matched sibling or unrelated donor. We retrospectively analyzed outcomes of 409 adults with sAML receiving either UCBT ($n = 163$) or HAPLO ($n = 246$) in EBMT centers. Myelodysplastic syndrome (MDS) or myeloproliferative disorder (MPD) was the antecedent diagnosis in 79% of UCBT and 85% of HAPLO recipients. In multivariate analysis, UCBT was associated with higher risk of grade II–IV acute GVHD (HR 1.9, $p = 0.009$) and lower GHVD-free-relapse-free-survival (GRFS) (HR 1.57, $p = 0.007$) compared to HAPLO. Chronic-GVHD, RI, NRM, LFS, and OS were not statistically different between the two. Early disease stage at transplant was independently associated with lower RI and NRM and higher OS and LFS. These results indicate that HAPLO is associated with better GRFS and lower aGvHD compared to UCBT in patients with sAML and that UCBT can be a valid alternative for sAML patients who lack a matched sibling, a proper haploidentical or an unrelated donor.

Introduction

Secondary acute myeloid leukemia (sAML) is defined as acute myeloid leukemia (AML) arising from antecedent hematological disorder or from exposure to leukemogenic agents, e.g. radiation and/or chemotherapy due to previous clonal disorders [1]. In the 2016 WHO revision, sAML are retained as distinct subgroups [2], supported also by the recent identification of a settle group of mutations in selective genes to be highly specific for sAML [3]. Patients with sAML have inferior outcomes compared to de novo AML, due to both the poor prognosis of the antecedent hematological disease, as well as the number of previous treatment received [4–7]. Allogeneic hematopoietic stem cell transplantation (HSCT) represents a potential curative therapy in this setting. For those patients lacking a matched donor [8], a volunteer matched unrelated donor (MUD) is a valid alternative. Unfortunately, a suitable MUD cannot always be identified for all patients [9]. Therefore, the use of alternative donor sources, such as unrelated cord blood (UCB) and haploidentical (HAPLO) family donors is often preferable, due to the rapid availability, which is of major importance especially in a disease with high relapse risk.

Improvements have been made in the field of allogeneic stem cell transplantation with the introduction of

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unmanipulated HAPLO and the use of post-transplant cyclophosphamide (PT-Cy) or anti-tymphocyte globulin (ATG) [10]-targeted graft vs. host disease (GvHD) prophylaxis, resulting in sweeping increase in the number of HAPLO transplants performed in recent years [11].

A previous study on patients with myelodysplastic syndromes (MDS) receiving transplantation from peripheral blood (PB) or cord blood as graft sources, reported similar inferior results in 9/10 HLA-mismatched unrelated donor and cord blood compared to 10/10 PB [12].

Recently, some studies have shown that HSCT can result in long-term outcomes in sAML supporting the use of a myeloablative-conditioning regimen (MAC) in fit patients [13]. Similarly, outcomes of sAML after HAPLO have also been reported [14]. Nevertheless, a comparison of the two available alternative donor sources, UCB and HAPLO, in sAML patients has not been described so far.

The aim of the current study is therefore to analyze and compare the outcomes of patients with sAML after UCBT and HAPLO transplants.

Methods

Study design and definitions

This is a retrospective registry-based analysis on behalf of Eurocord and the Acute Leukemia working party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). All patients or legal guardians provided informed consent according to the declaration of Helsinki. The Review Board of Eurocord/ALWP of the EBMT approved this study. Eligibility criteria for the study included all patients with sAML (secondary to hematological diseases), who underwent either a single or double UCBT or a HAPLO transplant, as first allogeneic transplant between January 2007 and December 2016. HAPLO transplants did not underwent ex vivo T-cell depletion and received either PT-Cy or ATG-based as GVHD prophylaxis.

MAC was defined as a regimen containing any of the following: total body irradiation (TBI) with a dose >6 Gy, a total dose of oral busulfan (Bu) >8 mg/kg, a total dose of intravenous Bu >6.4 mg/kg. All other regimens were defined as reduced intensity conditioning (RIC) [15].

Endpoints

The primary endpoint was leukemia-free survival (LFS), defined as the time from the date of transplant until relapse or last disease-free follow-up, with relapse and death from any cause considered as events. Secondary endpoints included overall survival (OS), relapse incidence (RI), non-relapse mortality (NRM), acute and chronic GvHD and refined GvHD-free/relapse-free survival (GRFS). OS was calculated from transplant to death of any cause or last observation alive.

GRFS was defined as previously described by our group as survival without grade 3–4 acute GvHD, extensive chronic GvHD, relapse or death, surviving patients were censored at the time of last contact [16]. NRM was defined as death without previous relapse. Neutrophil recovery was defined as achieving absolute neutrophil count (ANC) ≥ 0.5×10^9/L for 3 consecutive days. The diagnosis and grading of acute [17] and chronic GvHD [18] were performed using standard criteria by transplant centers.

Statistical analysis

Median values and ranges were used for continuous variables and percentages for categorical variables. For each continuous variable, we split the study population into quartiles and then into two groups by the median. Patient, disease, and transplant-related variables were compared using Chi-square or Fischer exact test for categorical variables and Mann–Whitney test for continuous variables. The probabilities of OS, LFS, and GRFS were calculated using the Kaplan–Meier method and the log-rank test for univariate comparisons. The probabilities of neutrophil engraftment, grade II–IV acute and chronic GvHD, relapse, and NRM were calculated with the cumulative incidence (CI) method. Multivariate analyses (MVA), adjusted for differences between the groups, were performed using Cox proportional hazards regression model for LFS and OS, and Fine and Gray's proportional hazards regression model for engraftment, GvHD, NRM, and relapse. The final model was performed adjusting for the following variables: transplant strategy (HAPLO or UCBT), diagnosis, disease status at HSCT, interval between diagnosis to HSCT, cytogenetic risk group, age at HSCT, year of HSCT, type of conditioning regimen (MAC or RIC), ATG use. In order to test for center effect, we introduced a random effect or frailty for each center into the model.

The significance level was fixed at 0.05, and p-values were two-sided. Statistical analyses were performed with the SPSS 22 (SPSS Inc./IBM, Armonk, NY, USA) and R 3.2.3 (R Development Core Team, Vienna, Austria) software packages.

Results

Patients, disease, and transplant characteristics

Patient and transplant characteristics are reported in Table 1. The median follow-up was 24 (range 3–112) months for

Table 1 Patient and transplant characteristics

	UCBT, $n = 163$	Haplo, $n = 246$	p- Value
Median follow-up, months (range)	24.3 (3–112)	16.9 (3–101)	
	9	6	
Median age at transplant, year (range)	56 (19–73)	60 (18–76)	0.003
Gender			
Male	95 (95%)	169 (69%)	0.038
Female	67 (41%)	77 (31%)	
Type of secondary AML			
To MDS/MPN	128 (79%)	210 (85%)	0.074
To other hematological malignancies	35 (22%)	36 (15%)	
Patient CMV serology			
Negative	49 (32%)	53 (22%)	0.028
Positive	105 (68%)	189 (78%)	
Missing	9	4	
Performance status at transplant			
<90%	50 (37%)	85 (38%)	0.905
Missing	29	22	
Disease status at transplant			0.037
CR1	92 (56%)	109 (44%)	
≥CR2	11 (6.8%)	15 (6%)	
Active disease	60 (37%)	122 (50%)	
Cytogenetics			
Good	2 (1%)	2 (1%)	0.024
Intermediate	36 (22%)	66 (27%)	
Poor	14 (9%)	43 (17%)	
Median year of transplant (range)	2011 (2007–2016)	2014 (2007–2016)	<0.001
Median time from diagnosis to transplant, months (range)	5.8 (0.2–243.9)	5.1 (0.3–100.3)	0.026
Previous autologous HSCT			
Yes	17 (10%)	21 (8%)	0.519
Conditioning regimen intensity			
MAC	55 (33.7%)	101 (41%)	0.136
RIC	108 (66.3%)	145 (59%)	
T-cell depletion			
In vivo TCD	69 (43%)	66 (27%)	0.002
aGvHD prophylaxis			
CsA ± MMF	144 (89%)	32 (14%)	<0.001
PT Cy	4 (3%)	156 (66%)	
CsA + MTX ± other	6 (4%)	24 (10%)	
Other	8 (5%)	24 (10%)	

UCBT umbilical cord blood transplantation, *Haplo* haploidentical transplantation, *AML* acute myeloid leukemia, *MDS* myelodysplastic syndrome, *MPN* myeloproliferative neoplasm, *IQR* interquartile range, *CR1* first complete remission, *CR2* second complete remission, *CMV* cytomegalovirus, *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning, *TCD* T cell depletion, *aGvHD* acute graft vs. host disease, *CsA* cyclosporin A, *MMF* mycophenolate mofetil, *PT Cy* post-transplant cyclophosphamide, *MTX* methotrexate

UCBT and 17 (range 3–101) months for HAPLO. MDS or myeloproliferative disorders (MPN) were the antecedent diagnosis in 79% of UCBT and 85% of HAPLO recipients ($p = 0.07$). The median age at transplant was 56 (range 19–73) and 60 (range 18–76) years for UCBT and HAPLO, respectively ($p = 0.003$). Compared to UCBT, HAPLO were performed more recently (median year 2014 vs. 2011, $p < 0.001$) and the median time from diagnosis to transplant was shorter (5 vs. 6 months, $p = 0.03$). HAPLO recipients had more advanced disease status compared to UCBT (50% vs. 36%, $p = 0.04$). Stem cell source was bone marrow in 93 (38%) and PB stem cells in 153 (62%) patients who received HAPLO. Among the 163 patients who had UCBT, 104 (64%) received a double UCBT. A RIC regimen was used in 66% of UCBT and 59% of HAPLO recipients ($p = 0.14$). The combination of thiotepa, Bu, and fludarabine (TBF) was the most frequent regimen used in both MAC and RIC setting. GVHD prophylaxis was different according to the type of transplant. The majority of patients (66%) in the HAPLO group received PT-Cy and ATG was used in the remaining 34% of patients. Cyclosporine A+mycophenolate-mofetil was the GVHD prophylaxis in 89% of UCBT. The median number of total nucleated cell and CD34 at cryopreservation was 3.3 (range 2.12–7.89) $\times 10^7$/kg and 1.97 (range 0.75–6.63) $\times 10^5$/kg, respectively, for single UCBT, and 5.1 (range 2.69–13.28) $\times 10^7$/kg and 2.09 (range 0.64–8.65) $\times 10^5$/kg, respectively, for double UCBT.

Engraftment and acute and chronic GvHD

One hundred thirty-eight patients undergoing UCBT and 214 patients receiving haploidentical graft achieved neutrophil engraftment. The CI function (CIF) of neutrophil engraftment was 88% (range 83–91%) for HAPLO and 84% (range 77–89%) for UCBT ($p = 0.003$). Patients in first complete remission (CR1) had a better engraftment compared with patients with more advanced disease (92% vs. 92% vs. 78%, $p = 0.002$). The results of the univariate analysis are reported in Supplementary Table 1.

The CIF of grade II–IV aGvHD was 27% (95% CI 23–32%). It was 23% for HAPLO and 33% for UCBT ($p = 0.02$) (Fig. 1a). Overall, the CIF of grade III–IV aGvHD was 12% (95% CI 9–15%); being 9% and 16% for Haplo and UCBT, respectively ($p = 0.04$).

The CIF of chronic GvHD was 26% for both HAPLO and UCBT ($p = 0.71$). Extensive chronic GvHD was 9% for HAPLO and 10% for UCBT ($p = 0.61$) (Fig. 1b).

In multivariable analysis (MVA) (Table 2), the use of UCBT was associated with a higher risk of aGvHD; none of the variables tested were statistically associated with an increased risk of chronic GvHD.

Relapse and NRM

Two years RI was 31% (95% CI 26–36%) at 2 years. Relapse was 30% (24–36%) for HAPLO, and 33% (25–40%) for UCBT ($p = 0.38$) (Fig. 1c). Disease status

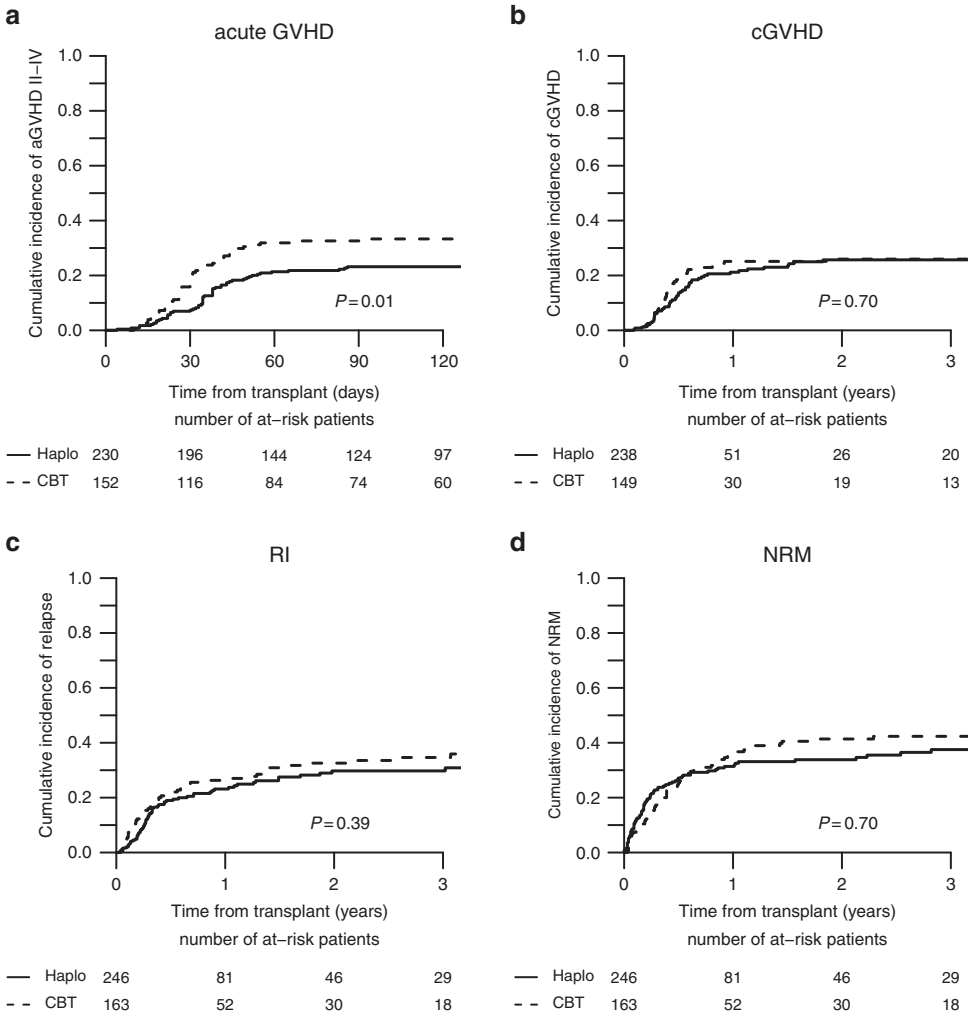

Fig. 1 CI of acute GVHD (**a**), CI of chronic GVHD (**b**), CI of RI (**c**), CI of NRM ((**d**) by donor

was associated with an increased incidence of relapse ($p = 0.03$).

In MVA (Table 2), the donor source did not have a statistically significant impact on relapse (HAPLO vs. UCBT HR 1.17, 95% CI 0.76–1.80, $p = 0.47$). Disease status at transplant (HR 2.46, 95% CI 1.63–3.71, $p < 0.001$) and older age at transplantation (HR 0.84, 95% CI 0.73–0.98, $p = 0.02$) were associated with an increased risk of relapse.

The CIF of NRM was 37% (32–42%) at 2 years. NRM was 34% and 41% for HAPLO and UCBT, respectively ($p = 0.71$). (Fig. 1d) RI was not different for patients with a previous diagnosis of MDS/MPD (29%) vs. other hematological malignancies (37%), $p = 0.20$. In MVA (Table 2), active disease was significantly associated with an increased risk of NRM (HR 1.84 95% CI 1.21–2.80, $p = 0.005$).

Disease recurrence was the most common cause of death in both groups, being 38% in UCB recipients and 40% in HAPLO. Infections and GvHD were the most common causes of transplant-related deaths in both groups (infections 32% and 33%, GvHD 15% and 12%, after UCBT and HAPLO, respectively). Thus, causes of death were quite similar for both graft sources.

OS, GRFS, and LFS

OS for the whole cohort was 36% (31–41%) at 2 years. OS was 41% (34–48%) for HAPLO and 29% (22–37%) for UCBT ($p = 0.25$). OS was significantly lower for patients with active disease (26%) or ≥CR2 (40%) compared to patients in CR1 (45%) ($p < 0.001$). Overall 2-year LFS was 32% (27–37%) and it was 36% for HAPLO and 26% for UCBT recipients ($p = 0.24$) (Fig. 2a, b). LFS was significantly lower for patients with active disease (HR 2.17; 95% CI 1.67–2.92, $p < 0.001$) (Table 2).

GRFS was 23% (19–28%) at 2 years. Compared to HAPLO, UCBT patients had a significant lower GRFS (17% vs. 28%, $p = 0.02$). Moreover, having an active disease at transplant (17% vs. 28% vs. 29%, $p < 0.001$) and receiving a graft with a female to male gender mismatch (18% vs. 25%, $p = 0.01$) were associated with lower GRFS. In MVA, UCBT (HR 1.57; 95% CI 1.13–2.18, $p = 0.007$),

Table 2 Multivariate analysis

		HR	95% CI	*p*-value
aGvHD II–IV	UCBT vs. Haplo	1.93	1.18–3.17	0.009
	Female D→male R	1.65	1.06–2.58	0.03
NRM	Disease status at Tx			
	CR1	ref		
	Active disease	1.84	1.21–2.80	0.005
	Center (frailty)			0.006
Relapse	Age (per 10 year)	0.85	0.73–0.98	0.03
	Disease status at Tx			
	CR1	ref		
	CR2/CR3	1.98	0.95–4.12	0.07
	Active disease	2.46	1.63–3.71	<0.001
OS	UCBT vs. Haplo	1.36	0.96–1.91	0.08
	Disease status at Tx			
	CR1	ref		
	Active disease	1.99	1.47–2.70	<0.001
	Center (frailty)			0.04
GRFS	UCBT vs. Haplo	1.57	1.13–2.18	0.007
	Disease status at Tx			
	CR1	ref		
	Active disease	1.97	1.48–2.63	<0.001
	Female D→male R	1.54	1.14–2.08	0.006
	Center (frailty)			0.04
LFS	Disease status at Tx			
	CR1	ref		
	Active disease	2.17	1.67–2.92	<0.001
	Center (frailty)			0.04

UCBT umbilical cord blood transplantation, *Haplo* haploidentical transplantation, *HR* hazard ratio, *CI* confidence interval, *Tx* transplantation, *CR1* first complete remission, *CR2* second complete remission, *CR3* third complete remission, *D* donor, *R* recipient, *CMV* cytomegalovirus, *aGvHD* acute graft vs. host disease, *NRM* non-relapse mortality, OS overall survival, *LFS* leukemia-free survival, *GRFS* graft vs. host disease-free relapse-free survival

active disease at transplant (HR 1.97; 95% CI 1.48–2.63, $p < 0.001$) and female to male gender mismatch (HR 1.54; 95% CI 1.14–2.08, $p = 0.005$) were associated with lower GRFS (Table 2).

Center effect, entered as a frailty variable in multivariate model, was significantly associated with the risk of NRM, LFS, GRFS, and OS (Table 2).

The above results were also confirmed in a subgroup analysis comparing UCBT with recipients of HAPLO with PTCy only as GVHD prophylaxis (data not shown).

Discussion

We retrospectively analyzed outcomes of 409 patients with AML secondary to antecedent hematological malignancies undergoing unmanipulated HAPLO or UCBT (single or double) in EBMT centers. Our results indicate that UCBT and HAPLO are both transplant strategies suitable for sAML patients who lack an HLA-matched related or unrelated donor. Those options are important in patients with sAML, who have a poorer prognosis compared to de novo AML when transplantation cannot be deferred [5].

We observed a higher incidence of acute GVHD and an inferior GRFS in patients who underwent UCBT. The majority of patients who received UCBT underwent a double UCBT ($n = 104$), which has been shown to be associated with an increased risk of acute GvHD when compared to single-unit UCBT recipients [19, 20].

The current study includes patients transplanted over 10 years, characterized by marked improvements in UCBT practices. Of note, the selection of CBU including HLA C typing [21] and the allelic level typing at the 4 loci [22], or the use of preparative regimen without ATG [23] could have had an impact on transplant outcomes. Due to the retrospective nature of our study, CBU were selected according to transplant centers experience and ~43% of UCBT received ATG before.

The use of PTCY as GvHD prophylaxis in HAPLO may have resulted in better prevention and faster engraftment, which may have led to a better GRFS. Furthermore, the shorter time for T-cell reconstitution and, subsequently, the lower risk of infection for patients undergoing HAPLO transplants [24, 25], have possibly contributed to the improved GRFS observed when compared to UCBT recipients.

In the current study CIF of cGVHD, RI, NRM, LFS, and OS were not statistically different between CBT and HAPLO transplants, a finding that is of important clinical relevance.

To improve outcomes of UCBT and HAPLO by decreasing the incidence of graft failure and NRM, is important to avoid the selection of donor with specific anti-HLA antibodies (DSA) [26, 27]. To date, there is a consensus for selecting a different donor when a patient is positive for DSA, or to proceed with strategies of desensitization to decrease the antibody load before starting conditioning regimen, in case of limitation in donor availability and urgent need to proceed to transplant.

The observed RI of 31% is similar to previous reports [14, 28] and comparable for UCBT and HAPLO, supporting the evidence that both HAPLO and UCBT may be considered early for patients with sAML, given the dismal prognosis and the high incidence of disease recurrence after transplantation. Recently, we performed a large comprehensive survey on HSCT for sAML, confirming the high incidence of relapse, especially after RIC regimen regardless of the type of donor [28].

In MVA, active disease was the only factor associated with a higher risk of relapse and NRM, which is in line with

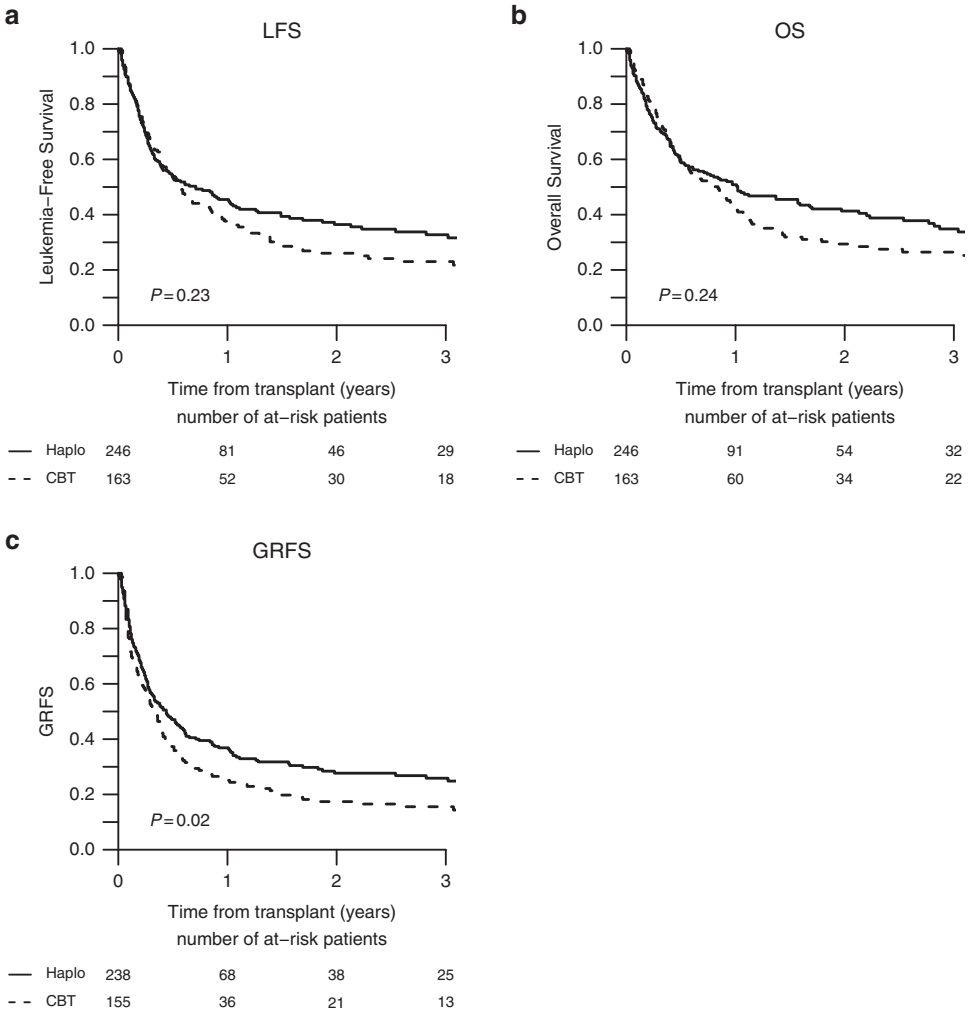

Fig. 2 Probability of LFS (**a**), and probability of OS (**b**), by donor

prior publications [29, 30]. These data emphasize the importance of achieving a disease response before transplantation in order to reduce disease burden prior to transplant. Recent findings highlight the efficacy of sequential regimen in patients with advanced disease, especially in the HAPLO setting [31]. The application of this type of regimen in patients receiving an UCBT need to be investigated.

Both UCBT and HAPLO have been used before in clinical trials in adults and children with other hematological malignancies. Brunstein et al. reported the results of a parallel trial of RIC-TBI based for unmanipulated HAPLO or double UCBT in patients with de novo acute leukemia. In both phase 2 trials, double UCBT was associated with 25% NRM and 31% of relapse, while relapse was 45% for HAPLO counterbalanced by a very low incidence of NRM [32]. This study was the basis for a formal prospective randomized phase 3 trial that is currently ongoing by the Blood and Marrow Transplantation Clinical Trials Network (BMT CTN Protocol 1101, ClinicalTrials.gov).

In the setting of de novo acute leukemia, we previously performed a large retrospective study in adults with de novo AML ($n = 918$) and ALL ($n = 528$), who received either UCBT or unmanipulated HAPLO. A delayed engraftment was observed in UCBT recipients, and no statistically significant differences were observed in main outcomes, except for a lower incidence of chronic GVHD in the UCBT group [33]. HAPLO and single UCBT have been compared in the pediatric setting, with results showing a significantly lower NRM in HAPLO recipients, but no statistically significant differences in OS, RI, and disease-free survival [34].

This study has relevant limitations, including the heterogeneity of previous hematological diseases, conditioning regimens, and GVHD prophylaxis. Furthermore, due to the retrospective nature of the study, data on platelet engraftment are lacking and some potential risk factors could not have been included in the analysis. Nevertheless, in the absence of formal prospective comparative studies between UCBT and HAPLO, our study is of clinical importance and

may help physicians to promptly consider the use of such donors.

In conclusion, both HAPLO and UCBT are feasible and valid for sAML patients with an indication for HSCT. Longer follow-up is needed to focus on the most appropriate conditioning regimen and the best GVHD prophylaxis and stem cell source for this indication.

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Author contributions AR, ML, and AN designed the study. AR and AP wrote the paper. AR and ML performed the statistical analysis. AP and FV helped with data and manuscript preparation. BS, DB, FC, AB, JT, PC, YK, JJC, GS, ED, VR, FB, MM, EG provided cases for the study. All authors edited and approved the manuscript.

Compliance with ethical standards

Conflict of interest Frederic Baron has received travel grants from Celgene, Abbvie, Novartis and Sanofi. The remaining authors declare that they have no conflict of interest.

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