Alternative donors provide comparable results to matched unrelated donors in patients with acute lymphoblastic leukemia undergoing allogeneic stem cell transplantation in second complete remission: a report from the EBMT Acute Leukemia Working Party

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ARTICLE

Alternative donors provide comparable results to matched unrelated donors in patients with acute lymphoblastic leukemia undergoing allogeneic stem cell transplantation in second complete remission: a report from the EBMT Acute Leukemia Working Party

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Abstract

Relapse of acute lymphoblastic leukemia (ALL) remains a major therapeutic challenge. Despite the consensus for proceeding to allogeneic stem cell transplantation (HSCT) in relapsing patients with ALL who achieve second complete remission (CR2) with salvage therapy, most patients lack a suitable matched-related histocompatible donor. The present multicenter retrospective study compared, for ALL patients in CR2, the HSCT outcome from all four possible alternative hematopoietic stem cell sources, namely matched unrelated 10/10 ($n = 281$), mismatched unrelated 9/10 ($n = 125$), haploidentical ($n = 105$), and cord blood ($n = 104$) donors. The 2-year outcomes were not statistically different between the four donor sources with respect to overall survival (38.3–47.2%), leukemia-free survival (30.5–39.6%), relapse incidence (32.6–37.6%), nonrelapse mortality (27.5–34.6%), and graft-versus-host disease-free relapse survival (21.4–33.1%). Donor choices for ALL patients achieving CR2 post first relapse are broad, ensuring that most patient in need secures a graft. Therefore, in practice, the donor choice should depend on timely availability and policy center.

Introduction

Treatment for adult acute lymphoblastic leukemia (ALL) has improved over the past decade with complete remission

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rates increasing to 90% and long-term remission to 52% [1, 2]. However, after first line therapy, 40–50% will continue to relapse. A second remission (CR2) may be achieved and allogeneic stem cell transplantation (HSCT) is considered to be one of the best treatment options after the achievement of CR2 [3–5]. In the MRC/ECOG 2993 study, the group who received a matched-sibling donor (MSD) demonstrated the highest overall survival (OS) (23%) compared with those patients that underwent transplantation from an unrelated donor (UD) (16%), or those receiving chemotherapy alone without HSCT (4%) [3]. Recently, in a cohort of 229 Philadelphia chromosome negative ALL (Ph-ALL) adult patients who relapsed after the first line of chemotherapy, receiving an HSCT while in CR2 were found to be a favorable prognostic factor for leukemia-free survival (LFS) [6]. However, there is very limited data for HSCT from mismatched UD 9/10 (UD 9/10), cord blood donor (CB) and haploidentical donor (Haplo) in ALL CR2 and furthermore there is no good comparison between alternative versus UD transplant in ALL CR2. A comparison of the outcomes of UD 10/10 versus alternative donors is therefore of great importance in addressing the clinical question of who is the preferable donor when there is no MSD in ALL patients achieving CR2 post relapse. This comparison may contribute to guide our practical management of ALL patients in CR2.

Materials/subjects and methods

In order to be included in the study, patients had to fulfill all of the following criteria: age ≥18 years; diagnosed with ALL undergoing first allogeneic transplantation in CR2; from a UD 10/10 or UD 9/10 (patients and donors should have HLA A, B, C, and DRB1 and DQB1 allelic typing performed), or family donor with host/donor number of HLA mismatches ≥2 (Haplo), or from a CB donor. Graft source of stem cells for UD and family relative was peripheral blood stem cells or bone marrow or both. No ex vivo T-cell depletion was allowed. Previous autologous stem cell transplantation was allowed. All patients underwent transplantation between January 2005 and June 2015. This was a retrospective multicenter analysis. Data were provided and approved for this study by the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) group registry. The EBMT is a nonprofit, scientific society representing more than 600 transplant centers mainly in Europe (Additional file 1). The EBMT promotes all activities aiming to improve stem cell transplantation or cellular therapy, which includes registering all the information related to stem cell transplantations. Data are entered, managed, and maintained in a central database with internet access; each EBMT center is represented in this database. There are no restrictions on centers for reporting data, except for those required by the law on patient consent, data confidentiality, and accuracy. Quality control measures include several independent systems: confirmation of validity of the entered data by the reporting team, selective comparison of the survey data with minimum essential data A data sets in the EBMT registry database, cross-checking with the National Registries, and regular in-house and external data audits. Since 1990, patients have provided informed consent authorizing the use of their personal information for research purposes.

Definitions and statistical analysis

The primary endpoint of interest was LFS. The secondary endpoints were OS, engraftment, acute, and chronic graft-versus-host disease (aGVHD and cGVHD), relapse incidence (RI), nonrelapse mortality (NRM), and graft-versus-host disease relapse-free survival (GRFS) [7].

OS was calculated from the date of transplant until death or last observation alive. LFS was calculated from the date of transplant until relapse or last disease-free follow-up. Relapse and death from any cause were considered events. NRM was defined as death without prior relapse. Neutrophil recovery was defined as achieving absolute neutrophil count $\geq 0.5 \times 10^9$/l for 3 consecutive days. Acute GVHD was graded according to the modified Seattle-Glucksberg criteria [8] and cGVHD according to the revised Seattle criteria [9]. The diagnosis and grading of aGVHD [10] and cGVHD [11] were performed by transplant centers using the standard criteria. Cytogenetic abnormalities were classified according to the MRC [12]. Refined GRFS was defined as being alive with neither grade III–IV aGVHD, severe extensive cGVHD nor disease relapse at any time point [7].

Statistical analysis

Patient, disease, and transplant-related characteristics for the four cohorts were compared using χ^2 statistics for categorical variables and Kruskal–Wallis test for continuous variables. Cumulative incidence (CI) functions were used to estimate RI and NRM in a competing risk setting. To study cGVHD, we considered relapse and death to be competing events. Probabilities of LFS and OS were calculated using the Kaplan–Meier estimates. Univariate analyses were performed using Gray's test for CI functions and the log-rank test for LFS and OS. Associations of patient and graft characteristics with outcomes were evaluated by multivariate analysis, using the Cox

proportional hazards model. All variables differing significantly between the four groups or factors associated with the outcome in univariate analysis were included in the Cox model. Results are expressed as the hazard ratio (HR) with the 95% confidence interval (95% CI). All tests were two-sided. The type-1 error rate was fixed at 0.05 for determination of factors associated with time to event outcomes. Statistical analyses were performed with SPSS 22 (SPSS Inc./IBM, Armonk, NY) and R 3.4 (R Development Core Team, Vienna, Austria) software packages

Results

Patient population and transplant procedures

Six hundred and fifteen patients with ALL in CR2 were included in the study. Two hundred and eighty-one (46%) were transplanted from UD 10/10, 125 (20%) from UD 9/10, 105 (17%) from a Haplo donor, and 104 (17%) from a CB donor. Patients and transplant procedures are presented in Table 1. Haplo-HSCT was performed more recently ($p = 0.001$). Recipients of cord blood transplantation (CBT) were significantly younger at a median age of 26 years, than recipients of Haplo, UD 9/10 and UD 10/10, aged 31, 32, and 34 years, respectively ($p = 0.001$). There was no difference in time from relapse to transplantation among the four donor types. ALL subtypes (Ph-ALL), Philadelphia chromosome positive ALL (Ph+ALL) and T-cell ALL were similarly distributed between the donor types. Molecular status at transplant when available was also comparable between the four donor types. CR1 duration was significantly longer for CBT. Posttransplant cyclophosphamide as GVHD prophylaxis was mainly given in the Haplo group (supplementary Table 1).

Engraftment and GVHD

The 60-day CI of absolute neutrophil count ≥500 cells per μL was 96.4% (93.1–98.1%) in UD 10/10, 96.7% (90.9–98.8%) in UD 9/10, 94.9% (87.8–97.9%) in Haplo, and 87.8% (79.2–92.9) in CBT. Engraftment was lower in the CB group with 12% of graft failure, compared with 3.6% in UD 10/10, 3.2% in UD 9/10, and 4.9% in Haplo, respectively ($p = 0.009$).

The CI of grades II–IV aGvHD was 33.4% (27.8–39.1%), 36.6% (28–45.3%), 44% (32.1–51.7%), and 37.4% (27.9–46.9) for UD 10/10, UD 9/10, Haplo, and CBT, respectively. The CI of grades III–IV aGvHD was 12.8% (9.1–17.1%) for UD 10/10, 13.7% (8.2–20.6%) for UD 9/10, 14.3% (8.2–22%) for Haplo and 14.1% (8.1–21.8) for CBT ($p = 0.95$). There was no difference in the CI of cGVHD between the donor type groups ($p = 0.78$) (Table 2). The incidences of grades II–IV aGvHD, grade III–IV aGvHD, and cGVHD did not differ between donor types in Cox analysis (Table 3).

LFS, OS, and GRFS

There was no statistically significant difference between the four donor type groups of patients with respect to LFS ($p = 0.77$) on univariate analysis (Fig. 1a), as shown in Table 2. These results were confirmed in multivariate analysis (Table 4). A time between diagnosis and HSCT of >24 months (median), Karnofsky performans status (KPS) ≥ 90, and year of transplantation were the three factors associated with a better LFS (HR = 0.7, 95% CI, 0.5–0.9, $p = 0.003$, HR = 0.8, 95% CI, 0.6–0.9, $p = 0.03$, HR = 0.9, 95% CI, 0.91–0.99, $p = 0.01$, respectively) while increasing age was inversely associated with LFS (HR = 1.1, 95% CI, 1–1.2, $p = 0.03$) (Table 4). The 2-year OS did not vary significantly between the donor type groups and was 43%, 47.2%, 39.1%, and 38.3% for UD 10/10, UD 9/10, Haplo, and CBT, respectively (Table 2 and Fig. 1b) and donor type was not a prognostic factor for OS on multivariate analysis (Table 4). Finally, the 2-year GRFS were not significantly different between the donor type groups ($p = 0.86$) (Fig. 1e). On multivariate analysis, with the UD 10/10 group as the reference group, we did not find any significant difference in GRFS in comparison with the other three types of donor (Table 4). Female patient gender, time between diagnosis and HSCT > 24 months, and year of transplant were associated with better GRFS whereas a myeloabative conditioning (MAC) regimen chemotherapy and a CMV positive donor were associated with lower GRFS (Table 4).

Relapse incidence and nonrelapse mortality

The RI was also not significantly affected by donor source (Table 2 and Fig. 1c). The time between diagnosis and HSCT > 24 months and a KPS ≥ 90 were favorable prognostic factors while both chemotherapy at myeloablative doses and reduced intensity conditioning (RIC) were associated with higher relapse when compared with the referent group of MAC with total body irradiation (TBI) (Table 4).

No difference in 2-year NRM was noted between the four groups on univariate analysis (Table 2 and Fig. 1d). Likewise, in multivariate analysis, with the UD 10/10 donor group as the reference, there was no impact of donor type. Patient age was associated with higher NRM (HR = 1.3, 95% CI, 1.1–1.5, $p \le 0.001$), while year of HSCT and a RIC regimen was associated with lower NRM (HR = 0.91, 95% CI, 0.85–0.96, $p = 0.0015$ and HR = 0.61, 95% CI, 0.37–0.99, $p = 0.05$, respectively) (Table 4).

Table 1 Baseline characteristics of patients.

	UD 10/10	UD 9/10	HAPLO	CBT	*P* value
N	281	125	105	104	
Reverse KM FU median, months (range)	35.9 (0.6–144)	36.6 (1.1–109)	20.5 (0.7–94)	36.8 (3.2–112)	0.001
Age at Tx, median (range)	33.6 (18–76)	32 (18–67)	30.9 (19–66)	26.3 (18.6–66)	0.001
Time from diag to Tx, months (range)	20.4 (3–255)	30.9 (7–323)	19.8 (3.4–141)	31 (7.4–263)	0.001
CR1 duration, days (range)	440 (5–7538)	756 (54–9654)	454.5 (23–3999)	939 (23–4191)	0.007
Time relapse to Tx, days (range)	131.5 (−1 to 383)	136.5 (−1 to 301)	140.5 (−1 to 368)	135 (−1 to 325)	0.65
Year of Tx (range)	2011 (2005–2016)	2012 (2005–2016)	2014 (2006–2016)	2009 (2005–2016)	$<10^{-3}$
ALL phenotype, *n* (%)					
B Ph negative	121 (43)	58 (46.4)	46 (43.8)	43 (41.4)	0.98
B Ph positive	65 (23.1)	24 (19.2)	24 (22.9)	25 (24)	
T ALL	95 (33.8)	43 (34.4)	35 (33.3)	36 (34.6)	
Patient sex, *n* (%)					
Male	184 (65.5)	77 (61.6)	69 (65.7)	64 (61.5)	0.80
Female	97 (34.5)	48 (38.4)	36 (34.3)	40 (38.5)	
Donor sex, *n* (%)					0.001
Male	196 (72.1)	82 (65.6)	62 (59)	51 (51.5)	
Female	76 (27.9)	43 (34.4)	43 (41)	48 (48.5)	
Female D to male R, *n* (%)					
No	232 (84.7)	101 (80.8)	75 (71.4)	70 (69.3)	0.002
Yes	42 (15.3)	24 (19.2)	30 (28.6)	31 (30.7)	
Conditioning regimen, *n* (%)					
MAC chemotherapy	54 (19.3)	18 (14.4)	47 (44.8)	26 (25.5)	$<10^{-3}$
MAC TBI	175 (62.5)	75 (60)	29 (27.6)	53 (52)	
RIC	51 (18.2)	32 (25.6)	29 (27.6)	23 (22.6)	
CMV patient, *n* (%)					
Negative	115 (42.6)	57 (46.3)	30 (28.6)	38 (39.6)	0.04
Positive	155 (57.4)	66 (53.7)	75 (71.4)	58 (60.4)	
CMV donor, *n* (%)					
Negative	164 (59.2)	77 (62.6)	33 (31.7)	47 (56)	$<10^{-3}$
Positive	113 (40.8)	46 (37.4)	71 (68.3)	37 (44.1)	
CMV status donor/recipient, *n* (%)					
CMV D−/R−	85 (31.7)	40 (32.8)	22 (21.2)	17 (20.5)	$<10^{-3}$
CMV D+/R−	30 (11.2)	16 (13.1)	8 (7.7)	15 (18.1)	
CMV D−/R+	74 (27.6)	37 (30.3)	11 (10.6)	29 (34.9)	
CMV D +/R+	79 (29.5)	29 (23.8)	63 (60.6)	22 (26.5)	
Status disease, *n* (%)					
No molecular CR	42 (37.8)	23 (38.3)	20 (40.8)	14 (42.4)	0.96
Molecular CR	69 (62.2)	37 (61.7)	29 (59.2)	19 (57.6)	
Missing	170	65	56	71	
KPS, *n* (%)					
KPS < 90	75 (30)	29 (25.4)	31 (32.3)	19 (23.2)	0.45
KPS ≥ 90	175 (70)	85 (74.6)	65 (67.7)	63 (76.8)	
In vivo T depletion, *n* (%)					
No	89 (31.9)	22 (17.9)	72 (68.6)	66 (67.4)	$<10^{-3}$
Yes	190 (68.1)	101 (82.1)	33 (31.4)	32 (32.7)	

BM bone marrow, *CBT* cord blood transplantation, *CR* complete remission, *D* donor, *FU* follow-up, *Haplo* haploidentical donor, *KM* Kaplan–Meier, *KPS* Karnovsky Performance Status, *MAC* myeloablative conditioning regimen, *PBSC* peripheral blood stem cell, *R* recipient, *RIC* reduced intensity conditioning regimen, *TBI* total body irradiation, *Tx* transplantation, *UD* unrelated donor GVHD.

Discussion

The objective of the current study was to assess the impact of donor type in ALL patients in CR2 undergoing HSCT in the absence of a MSD. We did not find any difference in terms of transplantation outcomes between the four types of donors namely UD 10/10, UD 9/10, Haplo, and CB. These data are in accordance with several reports that mostly analyzed ALL in first CR (CR1). Marks et al. compared CBT and UD and showed equivalent adjusted survival [13]. Similarly, Terakura et al. found no significant difference for ALL adults treated with either CBT, UD 8/8 or UD 7/8 [14].

Table 2 Transplantation outcomes.

	UD 10/10	UD 9/10	Haplo	CBT	*P* value
Engraftment	96.4% (93.1–98.1)	96.7% (90.9–98.8)	94.9% (87.8–97.9)	87.8% (79.2–92.9)	$<10^{-3}$
Acute GVHD Grade II–IV	33.4% (27.8–39.1)	36.6% (28–45.3)	42% (32.1–51.7)	37.4% (27.9–46.9)	0.33
Outcome at 2 years					
Leukemia-free survival	34.7% (28.5–40.8)	39.6% (30.4–48.9)	30.5% (20.3–40.8)	32.1% (22.8–41.5)	0.77
Overall survival	43% (36.4–49.5)	47.2% (37.6–56.8)	39.1% (28.3–50)	38.3% (28.4–48.3)	0.52
Relapse	37.6% (31.5–43.8)	32.6% (24–41.5)	35.5% (25.2–45.9)	33.3% (24.1–42.7)	0.93
Nonrelapse mortality	27.5% (22.1–33.2)	27.8% (19.8–36.3)	34% (24.2–44)	34.6% (25.4–44)	0.63
GRFS	26% (20.3–31.8)	33.1% (24.4–41.9)	21.4% (11.8–31.1)	28.8% (19.8–37.7)	0.86
Chronic GVHD	29.4% (23.5–35.6)	31.1% (22.2–40.4)	29.4% (19.4–40.1)	25.1% (16.3–34.9)	0.78
Ext chronic GVHD	11.9% (8–16.6)	11% (5.8–18.1)	9.3% (3.9–17.5)	10.6% (5.2–18.2)	0.70

Data are *n* (%), or *n* (%; 95% CI).

CBT cord blood transplantation, *GVHD* graft-versus-host disease, *GRFS* graft-versus-host disease-free, relapse-free survival, *Haplo* haploidentical donor, *UD* unrelated donors.

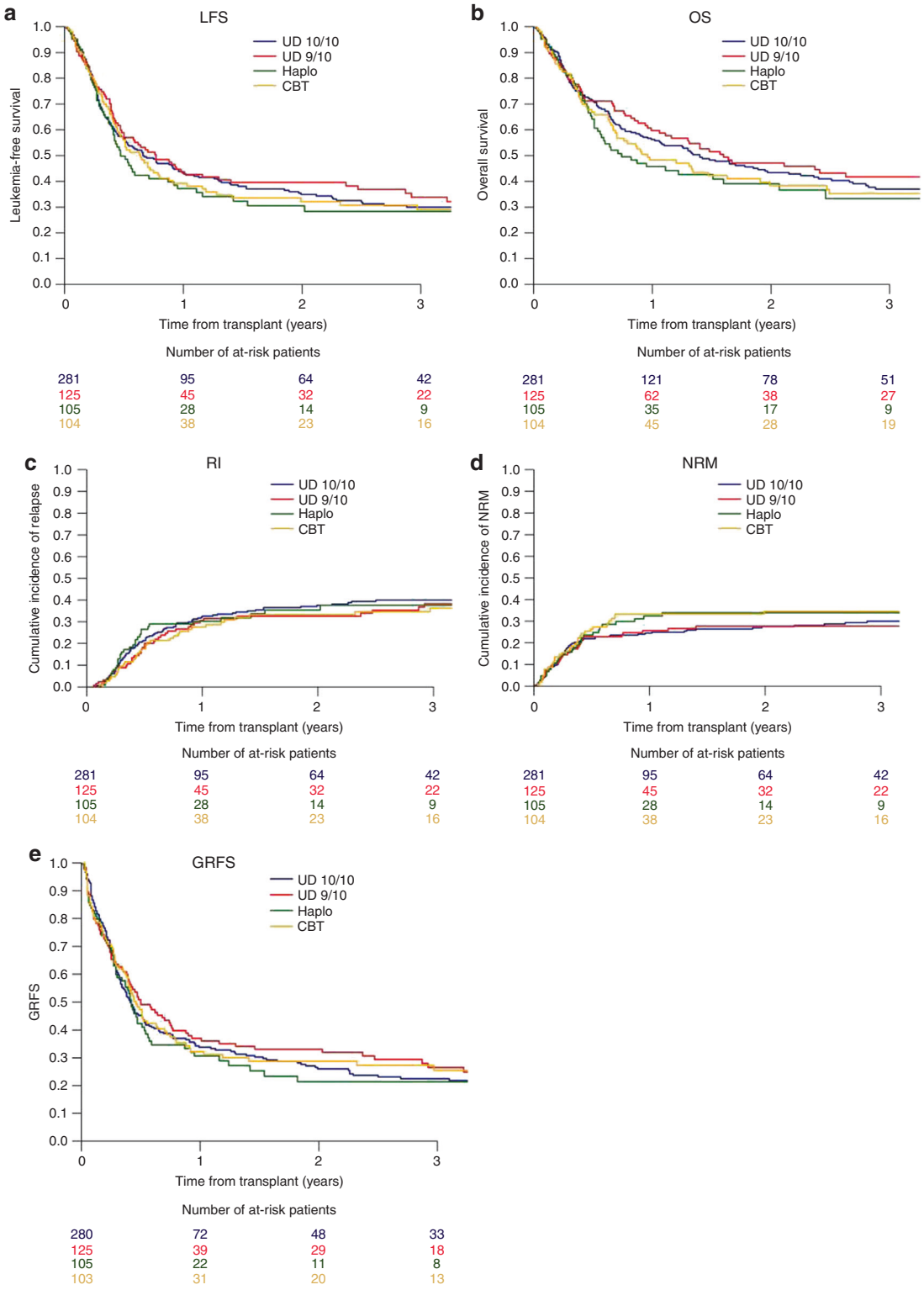
Table 3 Multivariate analysis for LFS, OS, RI, NRM, and GRFS.

	LFS			OS			Relapse			NRM			GRFS		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
UD 10/10 (reference)															
UD 9/10	0.9	0.7–1.2	NS	0.9	0.6–1.2	NS	0.8	06–1.2	NS	0.9	0.6–1.6	NS	0.9	0.7–1.2	NS
Haplo	1.1	0.7–1.5	NS	1.3	0.9–1.8	NS	0.9	0.6–1.5	NS	1.3	0.8–2.1	NS	0.9	0.6–1.3	NS
CBT	0.9	0.6–1.3	NS	1	0.7–1.5	NS	0.6	0.4–1.1	NS	1.2	0.7–2.1	NS	0.7	0.5–1.1	NS
Age (per 10 years)	1.1	1–1.2	**0.03**	1.2	1–1.3	**0.008**	1	0.9–1.1	NS	1.3	1.1–1.5	**≤10–3**	1.1	1–1.2	NS
B-ALL Ph negative (reference)															
B-ALL Ph positive	0.9	0.7–1.3	NS	0.7	0.5–1.1	NS	0.9	0.6–1.4	NS	1	0.6–1.6	NS	0.9	0.6–1.2	NS
T ALL	1.1	0.8–1.4	NS	1	0.8–1.3	NS	1.2	0.8–1.6	NS	1	0.7–1.5	NS	0.9	0.7–1.2	NS
Female vs. male	0.9	0.7–1.1	NS	0.8	0.6–1.1	NS	0.8	0.6–1.2	NS	0.9	0.7–1.4	NS	0.8	0.6–1	**0.04**
Female D vs. male D	0.9	0.8–1.2	NS	0.9	0.7–1.2	NS	0.9	0.7–1.3	NS	1	0.7–1.5	NS	1	0.8–1.3	NS
Time diag to Tx > median	0.7	0.5–0.9	**0.003**	0.7	0.5–0.9	**0.005**	0.6	0.4–0.8	**≤10–3**	0.9	0.6–1.3	NS	0.7	0.5–0.9	**0.003**
Karnofsky ≥ 90	0.8	0.6–0.9	**0.03**	0.8	0.6–1	NS	0.7	0.5–0.9	**0.02**	0.9	0.6–1.3	NS	0.9	0.7–1.2	NS
MAC TBI (reference)															
MAC chemotherapy	1.5	1.1–1.9	**0.01**	1.2	0.9–1.7	NS	1.6	1.1–2.4	**0.02**	1.3	0.9–2	NS	1.4	1–1.9	**0.009**
RIC	1.3	1–1.8	NS	1.1	0.8–1.5	NS	2.4	1.6–3.5	**≤10–3**	0.6	0.4–0.99	**0.04**	1.3	0.9–1.7	NS
Patient CMV positive	1.1	0.9–1.4	NS	1.28	1–1.7	NS	0.9	0.6–1.2	NS	1.5	0.9–2.2	NS	1.1	0.9–1.4	NS
Donor CMV positive	1.3	1–1.6	NS	1.25	1–1.6	NS	1.2	0.9–1.7	NS	1.3	0.9–1.9	NS	1.3	1–1.6	**0.02**
In vivo TCD	1.2	0.9–1.5	NS	1.2	0.9–1.6	NS	1.1	0.8–1.7	NS	1.2	0.8–1.7	NS	0.9	0.8–1.2	NS
Year of Tx	0.9	0.91–0.99	**0.01**	0.92	0.88–0.96	**≤10–3**	1	0.9–1.04	NS	0.9	0.8–0.9	**≤10–3**	0.9	0.9–0.98	**0.003**

ALL acute lymphoblastic leukemia, *BM* bone marrow, *CBT* cord blood transplantation, *CI* confidence interval, *CMV* cytomegalovirus, *D* donor, *diag* diagnostic, *GRFS* graft-versus-host disease-free, relapse-free survival, *Haplo* haploidentical, *HR* hazard ratio, *KPS* Karnofsky Performance Status, *LFS* leukemia-free survival, *MAC* myeloablative conditioning regimen, *NRM* non-relpase mortality, *NS* nonsignificant, *Ph* Philadelphia chromosome, *PBSC* peripheral blood stem cell, *R* recipient, *RIC* reduced intensity conditioning regimen, *TBI* total body irradiation, *TCD* T-cell depletion, *Tx* transplantation, *UD* unrelated donor.

Bold values indicate statistical significance $p < 0.05$.

Han et al. concluded that the outcomes of Haplo transplants were equivalent to those of matched sibling and UD 10/10 for patients treated for ALL in CR1 [15]. As for Haplo transplants in ALL, the report by Srour et al. included 109 adults with ALL treated with haplo-HSCT with PT-Cy post transplant; 36 patients were treated in CR2, with an



estimated 3-year LFS of 30% [16]. Santoro et al. on behalf of the ALWP, analyzed 208 patients (44% in CR1) who received a haplo-HSCT for ALL and reported a probability of a 3-year LFS of 33% for patients in ≥CR2 [17]. Our current finding with a LFS of 30.5% fits well with the above mentioned studies, confirming the feasibility and efficacy of the procedure in this group of high-risk patients.

A significant association of older age with increased NRM and poorer survival was found in our analysis, in agreement with many published studies [3, 18–21]. In our

◀ **Fig. 1 Leukemia-free survival (LFS), overall survival (OS), relapse incidence (RI) and nonrelapse mortality (NRM), graft-versus-host disease-free, relapse-free survival (GRFS) in allograft patients with acute lymphoblastic leukemia in second complete remission. a** The 2-year probability of LFS was 34.7.8% (95% CI: 28.5–40.8) in the UD 10/10 versus 39.6% (95% CI: 30.4–48.6) in the UD 9/10 group, 30.5% (95% CI: 20.3–40.8) in the Haplo group and 32.1% (95% CI: 22.8–41.5) in CBT group ($p = 0.77$). **b** The 2-year probability of OS was 43% (95% CI: 36.4–49.5) in the UD 10/10 versus 47.2% (95% CI: 37.6–56.8) in the UD 9/10 group, 39.1% (95% CI: 28.3–50) in the Haplo group and 38.3% (95% CI: 28.4–48.3) in CBT group ($p = 0.52$). **c** The 2-year cumulative incidence of relapse was 37.6% (95% CI: 31.5–43.8) in the UD 10/10 versus 32.6% (95% CI: 24–41.5) in the UD 9/10 group, 35.5% (95% CI: 25.2–45.9) in the Haplo group and 33.3% (95% CI: 24.1–42.7) in CBT group ($p = 0.93$). **d** The 2-year cumulative incidence of NRM was 27.5% (95% CI: 22.1–33.2) in the UD 10/10 versus 27.8% (95% CI: 19.8–36.3) in the UD 9/10 group, 34% (95% CI: 24.2–44) in the Haplo group and 34.6% (95% CI: 25.4–44) in CBT group ($p = 0.63$). **e** The 2-year GRFS was 26% (95% CI: 20.3–31.8) in the UD 10/10 versus 33.1% (95% CI: 24.4–41.9) in the UD 9/10 group, 21.4% (95% CI: 11.8–31.1) in the Haplo group and 28.8% (95% CI: 19.8–37.7) in CBT group ($p = 0.86$).

study, with MAC TBI as the reference, chemotherapy in myeloablative doses was associated with higher relapse and lower LFS, translating into a lower GRFS. TBI is considered a standard backbone for MAC in adults with ALL, reducing the risk of relapse, as was previously demonstrated in numerous retrospective analyses that indicated the advantage of radiotherapy over chemotherapy-based regimens [21–25].

A RIC regimen was associated with higher risk of relapse but lower NRM, results that are in accordance with the well-known impact of RIC, especially in patients who have been heavily pretreated as patients in CR2. In our study, we observed improvements in transplantation outcomes over time, in agreement with our previous publication [25].

As previously reported, CBT recipients had a higher incidence of graft failure [26–28], which is obviously of importance when choosing the type of stem cell source for the ALL patient and is one of the known limitations of CBT [29]. Importantly, an interval from diagnosis to transplant longer than the median was a positive prognostic factor for

Table 4 Multivariate analysis for GVHD.

	Grades II–IV aGVHD			Grades III–IV aGVHD			CGVHD			EXT CGVHD		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
UD 10/10 (reference)												
UD 9/10	1.3	0.9–1.9	NS	1.4	0.7–2.7	NS	1	0.6–1.6	NS	0.9	0.4–1.8	NS
Haplo	1.3	0.8–2.1	NS	0.9	0.4–2	NS	0.9	0.6–1.7	NS	0.5	0.2–1.2	NS
CBT	1.2	0.7–1.9	NS	0.8	0.4–1.9	NS	0.7	0.4–1.4	NS	0.5	0.2–1.4	NS
Age(per 10 years)	0.9	0.8–1.1	NS	1	0.8–1.3	NS	1.1	0.9- 1.3	NS	1.2	0.9–1.5	NS
B-ALL Ph negative (reference)												
B-ALL Ph positive	1.1	0.7–1.6	NS	1.1	0.5–2.2	NS	0.6	0.4–1	NS	0.9	0.4–1.9	NS
T ALL	0.7	0.5–1	NS	0.9	0.5–1.6	NS	0.6	0.4–0.9	**0.04**	0.7	0.4–1.4	NS
Female vs. male	0.9	0.6–1.2	NS	0.6	0.3–1.1	NS	0.8	0.5–1.2	NS	0.6	0.3–1	NS
Female D vs. male D	1	0.7–1.4	NS	0.9	0.6–1.6	NS	1.3	0.9–1.9	NS	1.6	0.9- 2.8	NS
Time diag to Tx > median	0.9	0.6–1.2	NS	0.6	0.4–1	NS	0.8	0.5–1.2	NS	0.7	0.4–1.2	NS
Karnofsky ≥ 90	1.4	0.9–1.9	NS	2	1.1–3.9	**0.03**	1.1	0.7–1.6	NS	0.9	0.4–1.7	NS
MAC TBI (reference)												
MAC chemotherapy	0.9	0.6–1.4	NS	1.2	0.6–2.1	NS	1.2	0.7–2	NS	1.1	0.5–2.4	NS
RIC	0.8	0.6–1.3	NS	0.7	0.3–1.4	NS	1.3	0.8–2	NS	1.3	0.6–2.6	NS
Patient CMV positive	1.3	0.9–1.7	NS	1.6	0.9–2.7	NS	1.2	0.8–1.7	NS	1.1	0.6–2	NS
Donor CMV positive	0.9	0.7–1.2	NS	1	0.6–1.7	NS	0.9	0.6–1.3	NS	1.5	0.9–2.8	NS
In vivo TCD	0.8	0.6–1.1	NS	0.6	0.4–1	NS	0.9	0.6–1.4	NS	0.6	0.3–1.1	NS
Year of Tx	0.9	0.9–1	NS	0.9	0.9–1	NS	0.9	0.8–0.99	**0.03**	0.8	0.7–0.9	**0.01**

aGVHD acute graft-versus-host disease, *ALL* acute lymphoblastic leukemia, *BM* bone marrow, *CBT* cord blood transplantation, *CI* confidence interval, *CMV* cytomegalovirus, *cGVHD* chronic graft-versus-host disease, *D* donor, *Haplo* haploidentical, *EXT* extensive, *HR* hazard ratio, *KPS* Karnofsky Performance Status, *LFS* leukemia-free survival, *MAC* myeloablative conditioning regimen, *NRM* non-relpase mortality, *NS* nonsignificant, *Ph* Philadelphia chromosome, *PBSC* peripheral blood stem cell, *R* recipient, *RIC* reduced intensity conditioning regimen, *TBI* total body irradiation, *TCD* T-cell depletion, *Tx* transplantation, *UD* unrelated donor.

Bold values indicate statistical significance $p < 0.05$.

LFS, OS, RI, and GRFS on multivariate analysis. These data are consistent with previous studies [5, 19], emphasizing that duration of CR1 is a strong prognostic factor for achievement of a subsequent response to salvage therapy and for survival outcomes [3, 19, 30–34]. In accordance with these results, it was demonstrated that patients with very late relapse, more than 24 months after diagnosis, represent a favorable subgroup with a better chance of achieving CR and long-term survival. The reason for the poor prognosis of an early relapse probably lies in differences in disease biology [35]. Early relapse may arise from selected, chemotherapy-resistant subclones that proliferate despite ongoing standard chemotherapy [36, 37]. Particularly in this case, there may be an urgent need for searching for a donor for ALL patients in CR2 who lack a MSD. The duration of CR2 in adults is brief and patients must proceed rapidly to transplantation [4]. Haploidentical donors are available for the majority of patients, providing access to further stem cell donations or donor lymphocyte infusions as needed [38]. Furthermore, it is a factor on which the physicians can have an influence, unlike many other factors.

Being retrospective and registry-based, our study has several limitations including the possibility of unavailable data that have not been considered, missing MRD data as well as pre HSCT lines of therapy and incomplete cytogenetics data. However, MRD and cytogenetics were relatively equally distributed among the four groups. One limitation is related to a low statistical power of the study. The 2-year probabilities must also be taken with caution as the number of patients at risk is low, especially for Haplo, and results are not adjusted for potential confounders.

Significant progress has been made recently in treating ALL, thanks especially to the outstanding progress of immunotherapy. The use of blinatumomab and inotuzumab ozogamicine has made it possible to achieve CR in most patients with relapsed or refractory B-ALL [39, 40]. However, in the TOWER study, the median OS for patients on the blinatumomab arm was 7.7 months (95% CI, 5.6–9.6) [40] and in the final report of the phase III INO-VATE study, CR/complete remission with incomplete hematologic recovery was 73.8% in the inotuzumab group versus 30.9% in the standard of care group (1-sided $P < 0.0001$), the median OS was also 7.7 months with inotuzumab with a 2-year OS rate of 22.8% [41]. Recently, Marks et al. showed that in patients with relapsed or refractory ALL, inotuzumab followed by allogeneic HSCT provided an optimal long-term survival benefit among those with no previous HSCT who went directly to first transplant after two or more remissions. Indeed, median posttransplant OS was not reached with a 2-year survival probability (95% CI) of 51% (39–62%) [42]. In addition, the US Food and Drug Administration and European Medicines Agency approved tisagenlecleucel for young adult patients up to 25 years of age with refractory B-ALL, in relapse post transplant or in second or later relapse. With a median follow-up of 13 months, RFS and OS at 12 months were 59% and 76%, respectively, and the median duration of response has not been reached (8 patients receiving HSCT following tisagenlecleucel). The place of HSCT in the "targeted" immunotherapy landscape is evolving and the role of second transplant and the allogeneic effect of HSCT namely the graft-versus-leukemia effect in ALL [43] is probably as consolidation. However, the impact of alternative donors in this setting needed to be evaluated.

In our study, one third of patients who underwent first HSCT for ALL in CR2, relapsed. These data raise the role of maintenance in the posttransplant setting. In Ph+ALL, introduction of TKI post transplant has significantly improved the outcome of the patients. However, maintenance in Ph negative B-ALL is not part of the routine practice. Introduction of bispecific T-cell engagers could be of great interest in this setting, although blinatumomab is currently being tested in this setting (NCT03114865, NCT02807883). Considering the results of our study but also its limitations, we propose that, in the absence of a match-related donor, three parameters should be considered for choosing a given donor: (1) the delay to identify one type of donor and availability of such donor: indeed, the timing of the HSCT procedure should be first determined by the urgency of the medical condition of the patient, furthermore, delaying the HSCT because of donor impediment could impact the patient outcome; (2) the presence of a high titre of donor HLA-specific antibodies that could induce primary graft rejection, which is particularly true for haplo donors and CBT HSCT; and (3) center experience: indeed most studies report a center effect reflecting the fact that each type of HSCT has its own specificities that require appropriate expertise.

Conclusions

In our study, one third of the ALL patients first transplanted in CR2 attained a 2-year LFS following transplant with comparable outcomes between UD 10/10, UD 9/10, Haplo, and CB donors indicating that transplant may rescue a selected group of relapsing ALL patients with comparable outcomes using various stem cell sources. Considering the recent profound change in the ALL therapeutic armamentarium, these results should be taken into account in the management of adult B-ALL patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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