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ORIGINAL ARTICLE

Reduced-intensity and non-myeloablative allogeneic stem cell transplantation from alternative HLA-mismatched donors for Hodgkin lymphoma: a study by the French Society of Bone Marrow Transplantation and Cellular Therapy

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Allogeneic stem cell transplantation (allo-SCT) following a non-myeloablative (NMA) or reduced-intensity conditioning (RIC) is considered a valid approach to treat patients with refractory/relapsed Hodgkin lymphoma (HL). When an HLA-matched donor is lacking a graft from a familial haploidentical (HAPLO) donor, a mismatched unrelated donor (MMUD) or cord blood (CB) might be considered. In this retrospective study, we compared the outcome of patients with HL undergoing a RIC or NMA allo-SCT from HAPLO, MMUD or CB. Ninety-eight patients were included. Median follow-up was 31 months for the whole cohort. All patients in the HAPLO group ($N = 34$) received a T-cell replete allo-SCT after a NMA (FLU-CY-TBI, $N = 31$, 91%) or a RIC ($N = 3$, 9%) followed by post-transplant cyclophosphamide. After adjustment for significant covariates, MMUD and CB were associated with significantly lower GvHD-free relapse-free survival (GRFS; hazard ratio (HR) = 2.02, $P = 0.03$ and HR = 2.43, $P = 0.009$, respectively) compared with HAPLO donors. In conclusion, higher GRFS was observed in Hodgkin lymphoma patients receiving a RIC or NMA allo-SCT with post-transplant cyclophosphamide from HAPLO donors. Our findings suggest they should be favoured over MMUD and CB in this setting.

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INTRODUCTION

Although Hodgkin's lymphoma (HL) can be cured in a majority of cases with first-line chemotherapy, prognosis remains poor when patients relapse or progress after intensive chemotherapy followed by autologous stem cell transplantation. On the basis of some retrospective data[1] such patients may benefit from an allogeneic stem cell transplantation (allo-SCT) with reduced-intensity conditioning (RIC) from an HLA-matched donor.

When no HLA-compatible sibling can be identified—in about 75% of cases—an HLA-matched unrelated donor is usually available in 50 to 60% of patients. There are today limited data regarding the use of alternative HLA-mismatched donors in HL patients undergoing allo-SCT.

After cord blood (CB) allo-SCT for HL, high relapse rates (30–40% at 1 year) have been reported[2–4] in line with a retrospective study from our group that observed poorer outcome compared with HLA-matched related and unrelated donors.[5] Although some other studies[6–9] included patients transplanted from mismatched unrelated donors (MMUD), most numbers were limited, which precluded further analysis. Those studies showed not only high relapse rates after RIC allo-SCT from a MMUD but also high treatment-related mortality (TRM).

More promising results have been reported by the Seattle group[8] and more recently by Raiola *et al.*[10] with T-cell replete, non-myeloablative (NMA) haploidentical (HAPLO) allo-SCT with post-transplant cyclophosphamide (PT CY). Using this approach, low TRM, low incidence of chronic GvHD (cGvHD), as well as acceptable relapse rates were reported. Some preliminary

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data might even favour HAPLO over unrelated HLA-matched donors in advanced non-Hodgkin lymphomas.[11]

Because of the lack of comparative data regarding allo-SCT from alternative HLA-mismatched donors for HL patients, we designed this retrospective, multicentre study to evaluate the outcome of HL patients receiving an allo-SCT prepared with RIC or NMA conditioning from one of the three types of alternative donors: HAPLO, mismatched unrelated donors (MMUD) and CB grafts.

MATERIALS AND METHODS

This study was approved by the French Society of Bone Marrow Transplantation and Cell Therapies (SFGM-TC) board and conducted in agreement with the declaration of Helsinki. Informed consent was obtained from all subjects.

Patient selection

After detailed review of the database, we found 98 consecutive patients with HL who underwent a RIC or NMA allo-SCT from an alternative HLA-mismatched donor at 24 French and Belgian centers between January 2009 and December 2014. Histological diagnosis was based on local review. Disease status at transplant, progression and relapse after allo-SCT were reviewed and assessed by PET-scan and/or CT scan, according to the criteria published by Cheson *et al.*[12,13] Although detailed Deauville classification was not systematically applied, PET negativity was defined as a fludeoxyglucose uptake below or equal to the uptake measured in the liver.

Statistical analyses

Patient characteristics were displayed as numbers and percentages or as medians and ranges. CMV risk was defined as a CMV-seropositive in recipient and/or in donor. Sex mismatch was defined as the association of a male recipient with a female donor. ABO mismatch was defined as any difference in blood type between donor and recipient. We evaluated differences between groups using the χ^2-test or the Fisher's exact test when appropriate. Overall survival (OS) was defined as the interval from allo-SCT to death, regardless of its cause. Progression and relapse post-transplant were determined by applying Cheson's criteria.[12,13] Non-relapse mortality (NRM) was defined as death resulting from the transplant procedure without evidence of relapse or progression. Event-Free Survival (EFS) was defined as the probability of being alive without evidence of relapse or treatment-related death. Because no data regarding systemic therapy-requiring chronic GvHD were available in our database we slightly altered the definition published by Holtan *et al.*[14] regarding GvHD-free relapse-free survival (GRFS). We defined GRFS as the probability of being alive without evidence of relapse, grade 3–4 acute GvHD or chronic GvHD (cGvHD). All censored criteria were calculated from the time of allo-SCT. The probabilities of OS, EFS and GRFS were estimated using the Kaplan–Meier method. The Log rank test was used to determine the prognostic value of patient characteristics on OS, EFS and GRFS. The cumulative incidences of relapse (CIR), NRM and cGvHD were studied using a competing risk methodology. For the event of relapse, NRM was considered as the competing event and vice versa. For cGvHD, death was the competing event. For aGvHD all patients who died before day 100 were excluded from the analysis. The cumulative incidence of each event was estimated using the Kalbfleish and Prentice method.[15] The individual prognostic value on the CIR and NRM of each variable was assessed by the Gray's test. Backward selection of variables having a significance level < 0.15 in univariate analysis were introduced in a multivariate Cox regression model for OS, EFS and GRFS. The proportional hazard assumption for Cox regression models was tested using the cox.zph function in the R software. No multivariate analysis was performed for CIR and NRM as only one variable was at a P level < 0.15. All statistical analyses were performed using the R software program.[16]

HLA typing and stem cell source

All the data regarding HLA-typing and stem cell source were cross-checked with the data from the French Biomedical Agency (Agence Nationale de la Biomédecine) and from the PRoMISE SFGM-TC database. Follow-up data were updated by local investigators when needed. For unrelated donors, mismatch was defined as a difference in at least one HLA-A, -B, -Cw, DR or DQ locus. In the MMUD group two mismatches (8/10 HLA-compatible) were reported in three patients, while one mismatch (9/10 HLA-compatible) was reported in 24 patients. Siblings were considered haploidentical when they exhibited two to three HLA mismatches on the unshared haplotype. For all CB grafts ($N = 37$), HLA-A and HLA-B low-resolution typing was obtained, as well as allelic, high-resolution typing for the DR locus. HLA matching for CB patients was 3/6, 4/6, 5/6 and 6/6 in 2 (5%), 22 (60%), 11 (30%) and 2 (5%) patients, respectively. Eight patients (22%) received a single CB graft while 29 (78%) received two units.

Conditioning and transplantation modalities

Conditioning intensity was defined as previously described.[17] All patients received a RIC or a NMAC. A variety of conditioning regimen was used. In the HAPLO group, 31 patients (88%) received the following NMA conditioning regimen, previously described by the Baltimore group:[18] Cy 14.5 mg/kg on day −6 and day −5, fludarabine 30 mg/m^2 on day −6 to day −2 and low-dose TBI (2 Gy) on day −1. The other patients ($N = 3$) in the HAPLO group received a RIC. One patient received thiotepa 5 mg/kg on day −6, busulfan 3.2 mg/kg on day −5 and day −4, fludarabine 40 mg/m^2 on day −5 to day −2. One patient was conditioned with a total dose of fludarabine of 180 mg/m^2 and a total dose of IV busulfan of 260 mg/m^2. One patient was conditioned with Cy 29 mg/kg associated with a total dose of fludarabine of 150 mg/m^2 and a total dose of IV busulfan of 260 mg/m^2. All patients in the HAPLO group received PT CY. All but one patient ($N = 33$) in the HAPLO group received the following GvHD prophylaxis: Cy 50 mg/kg on day +3 and day +4, tacrolimus or CsA and mycophenolate mofetil started on day +5. One patient received only one day of PT CY 50 mg/kg at day+3 and also received ATG on day −2 and day −1 for a total dose of 5 mg/kg, CsA and mycophenolate mofetil started on day +5. Donor type in the HAPLO group was offspring ($N = 2$), sibling ($N = 17$) or parent ($N = 15$). T-cell replete grafts were used in all HAPLO patients ($N = 34$).

In patients who received an allo-SCT from a MMUD ($N = 27$) the following conditioning regimens were used: fludarabine 150 mg/m^2 with IV busulfan 6.4 mg/kg in 16 patients (57%), fludarabine 90 mg/m^2 with TBI 2 Gy in 6 patients (21%), fludarabine 125 mg/m^2 with melphalan 140 mg/m^2 in 4 patients (14%). One patient underwent TLI of 12 Gy (120 cGy/day) on day −11 to day −7, then on day –4 to day −1 associated with ATG 1.5 mg/kg on day −11 to day −7. Twenty-two patients in the MMUD group (81%) were administered rabbit anti-thymocyte globulin (ATG) at 5 to 10 mg/kg over 1 to 3 days according to local practice. GvHD prophylaxis consisted of CsA or tacrolimus, on day −3 or day −1 in all patients according to local practice with either mycophenolate mofetil ($N = 25$, 89%) or methotrexate 15 mg/m^2 at day +1, 10 mg/m^2 at day+3 and day +6 ($N = 3$, 11%).

In the CB group, 36 patients (97%) were conditioned with a RIC consisting of fludarabine (120–200 mg/m^2), Cy 50 mg/kg and TBI (2-4 Gy). One patient (3%) received fludarabine 200 mg/m^2, Cy (2500 mg total dose) and melphalan 120 mg/m^2. GvHD prophylaxis consisted of CsA and mycophenolate mofetil started on day -3 for all CB patients. After their publication in 2014, haploidentical transplantation procedures were carried out according to the SFGM-TC guidelines.[19,20]

RESULTS

Patient and transplant characteristics

A total of 98 patients was included. Donor type was HAPLO, CB and MMUD for 34 (35%), 27 (28%) and 37 patients (37%), respectively. Statistically significant differences between the three groups were observed regarding prior exposure to Brentuximab, prior auto-SCT, conditioning regimens, ATG administration, TBI, stem cell source as well as day-100 chimerism (Table 1). Median age at allo-SCT was 28 years (range: 16–68 years). The median number of treatments before allo-SCT was 4 (range: 3 to 6). Median time between diagnosis and transplant was 33 months (range: 9–176). Median follow-up was 31 months for our whole cohort (range: 3–79). Median follow-up was 21 (range: 9–52), 32 (range: 7–69) and 36 months (range: 3–79) in the HAPLO, MMUD and CB groups, respectively. Chimerism at day +100 was full donor in 72 patients (73%), mixed in 15 patients (15%), full recipient in 3 patients (3%), whereas no

Table 1. Patient characteristics

Patients characteristics	N = *98*	*HAPLO*	*MMUD*	*CB*	P-*value*[a]
		N = *34 (35%)*	N = *27 (28%)*	N = *37 (37%)*	
Age at diagnosis (years)					
< 25	52 (53%)	19 (56%)	13 (48%)	20 (54%)	0.82
⩾ 25	46 (47%)	15 (44%)	14 (52%)	17 (46%)	
Age at transplant (years)					
< 28	46 (47%)	15 (44%)	12 (44%)	19 (52%)	0.79
⩾28	52 (53%)	19 (56%)	15 (56%)	18 (48%)	
Sex					
Female	39 (40%)	16 (47%)	11 (41%)	12 (32%)	0.45
Male	59 (60%)	18 (53%)	16 (59%)	25 (68%)	
Prior exposure to bendamustine					
No	93 (95%)	30 (88%)	26 (96%)	37 (100%)	0.07
Yes	5 (5%)	4 (12%)	1 (4%)	0	
Prior exposure to brentuximab					
No	77 (79%)	20 (59%)	22 (82%)	35 (95%)	0.001
Yes	21 (21%)	14 (41%)	5 (18%)	2 (21%)	
Treatment lines prior to allo-SCT					
⩽4	77 (79%)	24 (71%)	20 (74%)	33 (89%)	0.13
> 4	21 (21%)	10 (29%)	7 (26%)	4 (11%)	
Disease status per Cheson 1999 criteria					
CR	51 (52%)	15 (44%)	12 (45%)	24 (65%)	0.36
PR	31 (32%)	13 (38%)	9 (33%)	9 (24%)	
SD/PD	11 (11%)	6 (18%)	2 (7%)	3 (8%)	
Missing data	5 (5%)	0	4 (15%)	1 (3%)	
PET status					
PET-negative	44 (45%)	14 (41%)	9 (33%)	21 (57%)	0.2
PET-positive	42 (43%)	19 (56%)	11 (41%)	12 (32%)	
Missing data	12 (12%)	1 (3%)	7 (26%)	4 (11%)	

Abbreviations: allo-SCT = allogeneic stem cell transplantation; CB = cord blood; HAPLO = haploidentical donor; MMUD = mismatch unrelated donor; PET = positron emission tomography. [a]χ^2-test or Fisher's exact test when appropriate.

data were available for 8 patients (8%). Details regarding patient and transplant characteristics according to donor type are available in Table 1 and 2, respectively.

Outcome analysis

A total of 29 patients (29%) relapsed after allo-SCT and 22 patients (22%) died. Among the latter, 10 passed away because of disease relapse or progression. Twelve patients (12%) died due to NRM. Adverse events leading to NRM were as follows: acute GvHD ($N = 2$), idiopathic pneumonia syndrome ($N = 1$), fungal infection ($N = 2$), sinusoidal obstruction syndrome ($N = 1$), haemorrhage ($N = 1$). No specific cause of toxic death was reported for five patients. Kaplan–Meier curves for OS and EFS are displayed for the whole cohort and according to donor type in Figures 1 and 2, respectively.

GvHD analysis

Overall, 43 patients (43%) presented with acute GvHD (aGvHD). Grade 2–4 aGvHD and grade 3–4 aGvHD were reported in 32 (32%) and 10 (10%) patients, respectively. The day-100 CI of grade 2–4 aGvHD was 34% in the whole cohort, 28%, 27% and 45% in the HAPLO, MMUD and CB groups, respectively ($P = 0.16$). The day-100 CI of grade 3–4 aGvHD was 11% in the whole cohort, 3, 9 and 21% in the HAPLO, MMUD and CB groups, respectively ($P = 0.06$, Figure 3a).

Chronic GvHD (cGvHD) was diagnosed in 31 patients (32%) while extensive cGvHD was reported in 9 patients (9%). The CI of cGvHD at 2 years was 33% for the whole cohort; 15, 48 and 39% in the HAPLO, MMUD and CB groups, respectively ($P = 0.006$). The 2-year CI of extensive cGvHD was 9, 19 and 3% in the HAPLO, MMUD and CB groups, respectively ($P = 0.07$, Figure 3b).

Univariate analysis on outcome

Disease status at allo-SCT significantly impacted OS ($P < 0.001$), CIR ($P = 0.02$), EFS ($P < 0.001$) and GRFS ($P = 0.002$). As shown in Figure 4, we observed a significantly higher probability of GRFS in patients who received a HAPLO allo-SCT (52% versus 22% and 31% in the CB and MMUD groups at 3 years, respectively, $P = 0.02$). Higher GRFS was also observed in patients receiving a NMA conditioning compared with a RIC (50% versus 27% at 3 years, $P = 0.009$). We noted no difference in OS (83% versus 83% at 3 years, $P = 0.66$), CIR (24% versus 28% at 3 years, $P = 0.98$), NRM (12% versus 6% at 3 years, $P = 0.43$), EFS (64% versus 65% at 3 years, $P = 0.55$) and GRFS (42% versus 35% at 3 years, $P = 0.93$) between patients in CR and PR at transplant for the whole cohort. In the HAPLO group, we observed no difference in OS (78% versus 91% at 3 years, $P = 0.32$), EFS (80% versus 75% at 3 years, $P = 0.93$) and GRFS (67% versus 60% at 3 years, $P = 0.83$) between patients in CR ($N = 15$) and PR ($N = 9$) at transplant. In this subgroup, we observed a trend towards lower CIR (7% versus 25% at 3 years,

Table 2. Transplant characteristics

Transplant characteristics	N = *98*	*HAPLO*	*MMUD*	*CB*	P-*value*[a]
		N = 34 (35%)	*N = 27 (28%)*	*N = 37 (37%)*	
Prior ASCT					
No	8 (8%)	8 (23%)	0	0	0.001
Yes	89 (91%)	26 (77%)	27 (100%)	36 (100%)	
Missing data	1 (1%)	0	0	1	
Time to allo-SCT					
< 33 months	49 (50%)	16 (47%)	12 (44%)	21 (57%)	0.57
⩾ 33 months	49 (50%)	18 (53%)	15 (56%)	16 (43%)	
Conditioning regimen					
NMA	38 (39%)	31 (91%)	7 (26%)	0	< 0.001
RIC	60 (61%)	3 (9%)	20 (74%)	37 (100%)	
ATG					
No	75 (76%)	33 (97%)	5 (18%)	37 (100%)	< 0.001
Yes	23 (24%)	1 (3%)	22 (82%)	0	
TBI					
No	25 (24%)	3 (9%)	20 (74%)	1 (3%)	< 0.001
Yes	73 (76%)	31 (91%)	7 (26%)	36 (97%)	
Stem cell source					
BM	19 (34%)	17 (50%)	2 (3%)	CB	< 0.001
PBSC	37 (66%)	17 (50%)	25 (97%)		
CMV risk					
No	30 (31%)	9 (26%)	9 (33%)	12 (32%)	0.81
Yes	68 (69%)	25 (74%)	18 (67%)	25 (68%)	
Sex mismatch					
No	81 (83%)	31 (91%)	21 (78%)	29 (78%)	0.27
Yes	17 (17%)	3 (9%)	6 (22%)	8 (12%)	
ABO mismatch					
No	48 (50%)	23 (68%)	10 (37%)	15 (43%)	0.03
Yes	48 (50%)	11 (32%)	17 (63%)	20 (57%)	
Missing data	2 (2%)	0	0	2	
Day-100 chimerism					
Full donor	72 (73%)	21 (62%)	22 (81%)	29 (78%)	0.001
Mixed	15 (15%)	12 (35%)	0	3 (8%)	
Full recipient	3 (3%)	0	2 (7%)	1 (3%)	
Missing data	8 (8%)	1 (3%)	3 (11%)	4 (11%)	

Abbreviations: allo-SCT = allogeneic stem cell transplantation; ASCT = autologous stem cell transplantation; ATG = anti-thymocyte globulin; BM = bone marrow; CB = cord blood; HAPLO = haploidentical donor; MMUD = mismatch unrelated donor; NMA = non-myeloablative; RIC = reduced-intensity conditioning. [a]χ^2-test or Fisher's exact test when appropriate.

$P = 0.25$) and higher NRM (13% versus 0% at 3 years, $P = 0.18$) associated with CR, but this did not reach statistical significance. In the MMUD group, we observed no difference in OS (83% versus 89% at 3 years, $P = 0.77$), EFS (75% versus 62% at 3 years, $P = 0.93$), NRM (17% versus 11% at 3 years, $P = 0.77$) between patients in CR ($N = 12$) and PR ($N = 9$) at transplant. In this subgroup, we observed a trend towards lower CIR (8% versus 27% at 3 years, $P = 0.47$) and higher GRFS (42% versus 11% at 3 years, $P = 0.52$) associated with CR, although this did not reach statistical significance. In the CB group, probabilities of EFS (50% versus 56% at 3 years, $P = 0.58$), GRFS (28% versus 22% at 3 years, $P = 0.54$), CIR (42% versus 33% at 3 years, $P = 0.55$) and NRM (8% versus 11%, $P = 0.83$) were similar between CR ($N = 24$) and PR ($N = 9$) patients. In this subgroup, we observed a trend towards higher OS (86% versus 66% at 3 years, $P = 0.55$) in CR patients, but this did not reach statistical significance. All results from univariate analyses are displayed in Table 3.

Multivariate analysis on outcome

After adjustment for significant covariates, MMUD and CB were associated with significantly lower GRFS (HR = 2.02, $P = 0.03$ and HR = 2.43, $P = 0.009$, respectively, Cox model) compared with HAPLO donors. Disease status at allo-SCT was the only independent risk factor that correlated with lower OS (HR = 6.5, $P < 0.001$, Cox model) and lower EFS (HR = 3.42, $P = 0.002$, Cox model). All multivariate analyses are displayed in Table 4.

DISCUSSION

To our knowledge, this is the first study comparing patients who received a RIC allo-SCT from all three types of alternative HLA-mismatched donors, including CB, over the same time period and including only HL patients. Standard end points such as OS, EFS, CIR, NRM and EFS did not differ between the 3 groups. However, lower CI of cGvHD and grade 3–4 aGvHD was observed

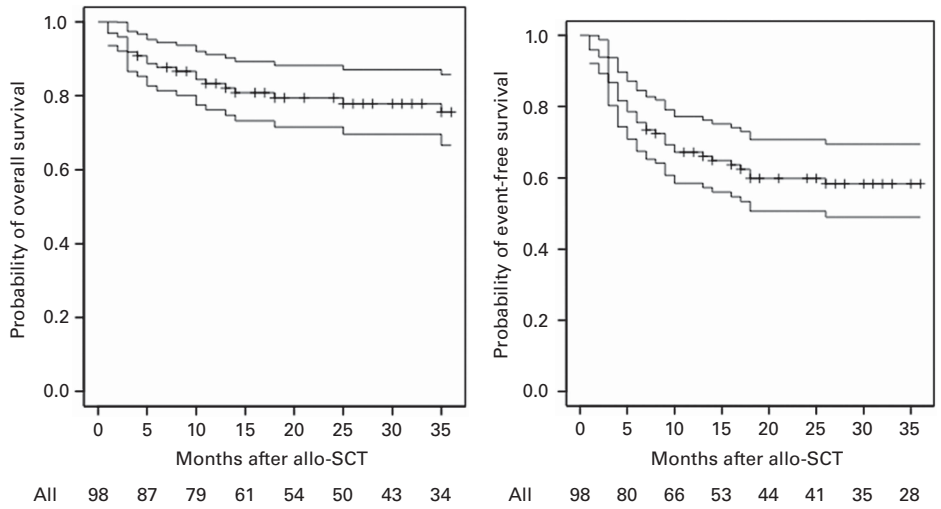

Figure 1. Kaplan–Meier probability curves of overall and event-free survival after allo-SCT in the whole cohort. allo-SCT, allogeneic stem cell transplantation.

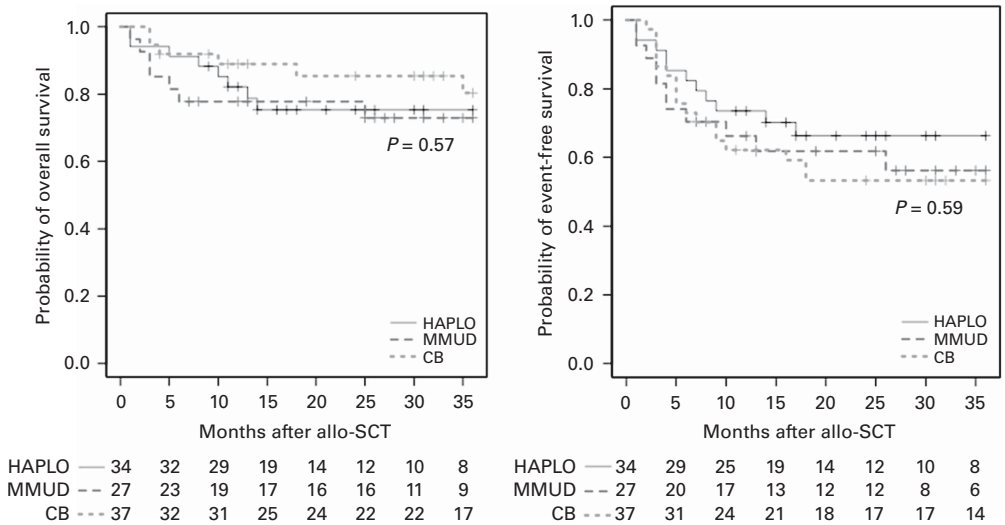

Figure 2. Kaplan–Meier probability curves of overall and event-free-survival after allo-SCT according to donor type. allo-SCT, allogeneic stem cell transplantation; CB, cord blood; HAPLO, haploidentical donor; MMUD, mismatch unrelated donor. The Log rank test was used to compare survival probabilities. A full color version of this figure is available at the *Bone Marrow Transplantation* journal online.

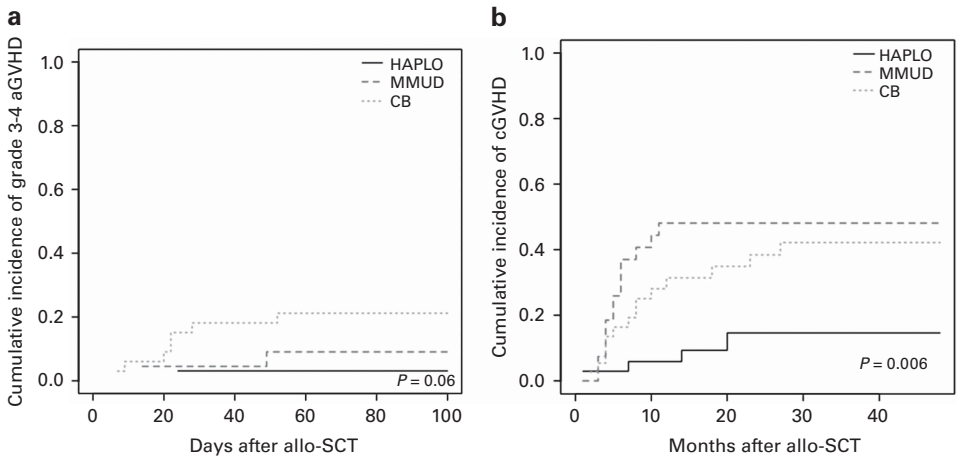

Figure 3. Cumulative incidence of (**a**) grade 3-4 aGVHD and (**b**) cGVHD according to donor type. allo-SCT, allogeneic stem cell transplantation; CB, cord blood; HAPLO, haploidentical donor; MMUD, mismatch unrelated donor. Cumulative incidences were compared using Gray's test. A full color version of this figure is available at the *Bone Marrow Transplantation* journal online.

Table 3. Univariate analysis

	3-year OS	P-*value*[a]	*3-year CIR*	P-*value*[b]	*3-year NRM*	P-*value*[b]	*3-year EFS*	P-*value*[a]	*3-year GRFS*	P-*value*[a]
Whole cohort	76%		29%		12%		58%		36%	
Donor type										
HAPLO	75%		25%		9%		66%		52%	
MMUD	73%	0.57	25%	0.52	18%	0.45	56%	0.59	22%	0.02
CB	80%		36%		11%		53%		31%	
Disease status at transplant										
CR/PR	83%	< 0.001	26%	0.02	10%	0.38	64%	0.001	38%	0.26
SD/PD	30%		54%		18%		27%		27%	
PET status at transplant										
PET-negative	80%	0.44	23%	0.36	14%	0.56	63%	0.69	32%	0.65
PET-positive	70%		35%		9%		55%		43%	
Conditioning type										
NMA	75%	0.93	24%	0.58	6%	0.17	70%	0.11	50%	0.009
RIC	76%		32%		15%		52%		27%	
Age at diagnosis										
< 25	80%	0.31	27%	0.41	11%	0.88	61%	0.42	41%	0.29
⩾ 25	71%		31%		13%		55%		31%	
Age at transplant										
< 28	75%	0.9	28%	0.61	15%	0.37	57%	0.81	37%	0.89
⩾ 28	76%		30%		10%		60%		35%	
Prior exposure to bendamustine										
No	76%	0.98	29%	0.88	13%	0.39	57%	0.48	37%	0.39
Yes	75%		20%		0%		80%		0%	
Prior exposure to brentuximab										
No	72%	0.16	32%	0.29	13%	0.67	55%	0.21	32%	0.09
Yes	90%		21%		9%		69%		51%	
Treatment lines prior to alloSCT										
< 4	72%	0.16	30%	0.85	14%	0.26	56%	0.36	35%	0.67
⩾ 4	89%		26%		5%		70%		39%	
Prior auto-SCT										
No	100%		27%	0.86	0%	0.27	73%	0.36	45%	0.36
Yes	73%	0.17	30%		13%		57%		35%	
Time to allo-SCT										
< 33 months	79%	0.24	35%	0.31	10%	0.49	54%	0.67	35%	0.97
⩾ 33 months	72%		23%		14%		62%		37%	
ABO mismatch										
No	72%	0.61	32%	0.74	12%	0.77	55%	0.66	39%	0.32
Yes	80%		26%		10%		63%		34%	
Sex mismatch										
No	75%	0.58	30%	0.65	13%	0.45	56%	0.32	35%	0.84
Yes	79%		24%		6%		70%		41%	
CMV risk										
No	89%	0.09	29%	0.88	7%	0.34	64%	0.33	35%	0.94
Yes	70%		29%		14%		55%		36%	

Abbreviations: allo-SCT = allogeneic stem cell transplantation; ASCT = autologous stem cell transplantation; ATG = anti-thymocyte globulin; BM = bone marrow; CB = cord blood; CIR = cumulative incidence of relapse; EFS = event-free survival; GRFS = GvHD-free relapse-free survival; HAPLO = haploidentical donor; MMUD = mismatch unrelated donor; NMA = non-myeloablative; NRM = non-relapse mortality; OS = overall survival; RIC = reduced-intensity conditioning. [a]Log rank test. [b]Gray's test.

in the HAPLO resulting in significantly higher GRFS at 3 years, which was confirmed in multivariate analysis. It has been suggested by our group[21] and others[14] that this new endpoint might be more clinically relevant to assess not only disease control after allo-SCT, but also GvHD-related comorbidities. Our study is also the first to report GRFS after allo-SCT for HL. Nonetheless, in a recent retrospective study including 79 patients with advanced non-Hodgkin lymphomas, Garciaz *et al.*[11]

observed a significantly higher probability of survival without relapse or severe cGvHD after an allo-SCT from HAPLO donors compared to matched unrelated donors. Keeping in mind the retrospective nature of those studies, both our findings seem to indicate better GRFS after HAPLO allo-SCT for HL. In other terms, our results suggest that despite lower cGvHD rates, the GvL effect might be preserved after a T-cell replete, NMA/RIC HAPLO allo-SCT. Kanate *et al.*[22] as well as Ghosh *et al.*[23] recently reported similar findings in two large cohorts of lymphoma patients receiving T-cell replete RIC HAPLO allo-SCT with PT CY. The mechanisms underlying this segregation between the GVH and GVL effect in that particular setting remain poorly understood. Of note, several murine experiments have shown an important role of regulatory T cells in modulating GVH/GVL effects.[24–27]

Several authors have already shown encouraging results after T-cell replete haploidentical allo-SCT for HL patients, although limited comparative data are available. Data from the Fred Hutchinson Cancer Research Centre (FHCRC) and John Hopkins University[8] showed comparable OS between HLA-matched unrelated and HAPLO recipients, along with lower NRM (9% at two years) and higher PFS (51%) in the HAPLO group. Importantly, patients from the FHCRC received only one day of PT CY at 50 mg/kg. The Italian group investigated in several retrospective studies T-cell replete non-myeloablative haploidentical allo-SCT with post-transplant cyclophosphamide using the Baltimore approach[18] for advanced HL patients. Using this approach, Raiola *et al.*[10] reported a cumulative incidence of NRM and relapse of 4% and 31%, respectively. In another retrospective study including 49 patients with refractory lymphoma, Castagna *et al.*[28] observed 2-year PFS and OS probabilities of 74% and 85%, respectively. Comparable outcomes were observed in the present study (Table 3).

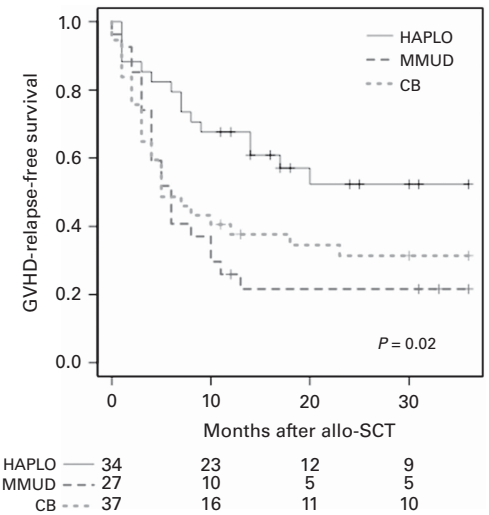

Figure 4. GvHD-free relapse-free survival (GRFS) according to donor type. allo-SCT, allogeneic stem cell transplantation; CB, cord blood; HAPLO, haploidentical donor; MMUD, mismatch unrelated donor. The Log rank test was used to compare survival probabilities. A full color version of this figure is available at the *Bone Marrow Transplantation* journal online.

Not only do we report here better outcome for patients receiving a HAPLO allo-SCT, but also the outcome was better in all subgroups compared with previously published studies. Indeed, lower OS and higher relapse rates have been reported after CB[2,3,5] HAPLO[8,10] and unrelated (matched or mismatched) donor allo-SCT[6,9] for relapsed/refractory HL. Although the definition of chemorefractoriness varies among studies, it has been reported by many to be the main adverse prognostic factor regardless of the type of donor.[1,3,5] We observed similar findings in our study, as disease status, defined as CR/PR versus SD/PD, was the only independent risk factor impacting OS, CIR and EFS. The overall better outcome reported here was likely due to a much higher proportion ($N = 51$, 52% of the whole cohort) of patients in CR in our cohort compared to other studies (14–41%).[6,8,10,29] Furthermore, 23% of the HAPLO patients had not undergone an ASCT, indicating a less heavily treated population. This may also account for the better outcome observed in the HAPLO group.

In conclusion, in the absence of an HLA-identical donor a T-cell replete, NMAC HAPLO allo-SCT with PT CY seems associated with better outcome compared with other alternative donors for patients with high-risk HL. Further studies should aim at comparing HAPLO to HLA-compatible sibling and unrelated donors in larger cohorts, ideally within prospective trials.

CONFLICT OF INTEREST

The authors declare no conflict on interest.

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Table 4. Multivariate analysis

	OS			*EFS*			*GRFS*		
	HR	*CI*	P-*value*[a]	*HR*	*CI*	P-*value*[a]	*HR*	*CI*	P-*value*[a]
Donor type									
HAPLO							1	1.06–3.84	0.03
MMUD							2.02		
CB							2.43	1.24–4.75	0.009
Disease status at allo-SCT									
CR/PR	1			1					
SD/PD	6.5	2.54–16.70	< 0.001	3.42	1.55–7.55	0.002			

Abbreviations: allo-SCT = allogeneic stem cell transplantation; CB = cord blood; CI = confidence interval; CR = complete response; EFS = event-free survival; GRFS = GvHD-free relapse-free survival; HAPLO = haploidentical donor; HR = hazard ratio; MMUD = mismatch unrelated donor; OS = overall survival; PD = progressive disease; PR = partial response; SD = stable disease. [a]Cox regression model.

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