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ARTICLE

Better outcome with haploidentical over HLA-matched related donors in patients with Hodgkin's lymphoma undergoing allogeneic haematopoietic cell transplantation—a study by the Francophone Society of Bone Marrow Transplantation and Cellular Therapy

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Abstract

The question of the best donor type between haploidentical (HAPLO) and matched-related donors (MRD) for patients with advanced HL receiving an allogeneic hematopoietic cell transplantation (allo-HCT) is still debated. Given the lack of data comparing these two types of donor in the setting of non-myeloablative (NMA) or reduced-intensity (RIC) allo-HCT, we performed a multicentre retrospective study using graft-vs.-host disease-free relapse-free survival (GRFS) as our primary endpoint. We analysed the data of 151 consecutive HL patients who underwent NMA or RIC allo-HCT from a HAPLO ($N = 61$) or MRD ($N = 90$) between January 2011 and January 2016. GRFS was defined as the probability of being alive without evidence of relapse, grade 3–4 acute GVHD or chronic GVHD. In multivariable analysis, MRD donors were independently associated with lower GRFS compared to HAPLO donors (HR = 2.95, $P < 0.001$). Disease status at transplant other than CR was also associated with lower GRFS in multivariable analysis (HR = 1.74, $P = 0.01$). In addition, the administration of ATG was independently linked to higher GRFS (HR = 0.52, $P = 0.009$). In summary, we observed significantly higher GRFS in HL patients receiving an allo-HCT using the HAPLO PT-Cy platform compared to MRD.

Introduction

While standard treatment of Hodgkin's lymphoma (HL) leads to cure in most cases, about 10% of patients still develop refractory disease. In such cases, and particularly in patients relapsing after an autologous stem cell transplantation, dismal prognosis has been reported [1]. Beside non-transplant approaches, such as brentuximab and immune checkpoint inhibitors, non-myeloablative (NMA) or reduced-intensity conditioned (RIC) allogeneic hematopoietic cell transplantation (allo-HCT) remains today the mainstay to achieve long-term responses with acceptable toxicity in patients with advanced HL. The encouraging results [2–4] reported with haploidentical (HAPLO) donors using post-transplant cyclophosphamide (HAPLO PT-Cy) initially described by Luznik et al. [5], have led to challenge the use of matched-related donors (MRD) in the setting of NMA/RIC allo-HCT for advanced HL. Nonetheless, comparative data supporting that HAPLO donors should be favoured over MRD in this specific setting remain very limited [6].

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Table 1 Patient characteristics according to donor type

Patients characteristics	Whole cohort $N = 151$	HAPLO $N = 61$	MRD $N = 90$	P*
Time to allo-HCT				
Median, in months (range)	27 (7–214)	39 (8–176)	23 (7–214)	0.02
Age at transplant				
Median, in years (range)	30 (12–68)	29 (17–68)	32 (12–67)	0.32
Sex, *N* (%)				
Female	61 (40%)	28 (46%)	33 (37%)	0.36
Male	90 (60%)	33 (54%)	57 (63%)	
Prior exposure to brentuximab, *N* (%)				
No	95 (63%)	32 (52%)	63 (70%)	0.05
Yes	56 (37%)	29 (48%)	27 (30%)	
Treatment lines prior to allo-HCT (including ASCT), *N* (%)				
≤4	111 (73%)	39 (64%)	72 (80%	0.04
>4	40 (27%)	22 (36%)	18 (20%)	
Disease status per Cheson 1999 criteria, *N* (%)				
CR	91 (60%)	32 (52%)	59 (66%)	
PR	29 (19%)	11 (18%)	18 (20%)	0.10
SD/PD	30 (20%)	18 (30%)	12 (13%)	
Missing data	1 (1%)	0	1 (1%)	
PET status, *N* (%)				
PET-negative	68 (45%)	29 (48%)	39 (43%)	0.22
PET-positive	68 (45%)	31 (51%)	37 (41%)	
Missing data	15 (10%)	1 (1%)	14 (16%)	

HAPLO haploidentical donor, *MRD* matched related donor, *allo-HCT* allogeneic haematopoietic cell transplantation, *ASCT* autologous stem cell transplantation, *CR* complete remission, *PR* partial remission, *SD* stable disease, *PD* progressive disease, *PET* positron emission tomography

*χ^2-test or Fisher's exact test when appropriate was performed to compare the MRD to the HAPLO group

To address this question, we analysed the outcome of 151 HL patients undergoing a NMA/RIC allo-HCT from a MRD or using the HAPLO PT-Cy platform, considering graft-vs.-host-disease (GVHD)-free relapse-free survival (GRFS) as our primary endpoint.

Methods

Patient selection

This study was conducted in accordance with the declaration of Helsinki and informed consent was obtained from all subjects. After detailed review of the database, we found 151 consecutive patients with HL who underwent a RIC or NMA allo-HCT from a HAPLO ($N = 61$) or MRD ($N = 90$) at 31 SFGM-TC centres between January 2011 and January 2016. Histological diagnosis was based on local review. Disease status at transplant, progression and relapse after allo-HCT were reviewed and assessed by PET-scan and/or CT scan, according to the criteria published by Cheson et al. [7, 8]. While 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.

HLA typing and donor–recipient familial relationship

Related donors were considered HAPLO when they exhibited at least two HLA mismatches on the unshared haplotype with the recipient. Related donors were considered HLA-matched when they exhibited compatibility with the recipient for the HLA-A, HLA-B, HLA-Cw, HLA-DR and HLA-DQ loci at the allelic level (10/10). Among HAPLO donors, we identified 30 siblings (49%), 4 offsprings (6%) and 21 parents (34%); familial relationship was unknown for six recipients (10%).

Conditioning and transplantation modalities

Conditioning intensity was defined as previously described [9]. HAPLO transplantation procedures were carried out according to the SFGM-TC guidelines [10–12]. Detailed information regarding conditioning and transplantation modalities can be found in the online Supplementary Information section.

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-HCT to death, regardless of its cause. Progression and relapse post-transplant were determined by applying Cheson's criteria [7, 8]. Neutrophil recovery was defined as a stable absolute neutrophil count ≥0.5 G/L. Platelet recovery was defined as a stable platelet count ≥20 G/L. Because no data regarding systemic therapy-requiring chronic GVHD was available in our database we slightly altered the definition published by Holtan et al. [13] 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

(aGVHD) or chronic GVHD (cGVHD). All censored criteria were calculated from the time of allo-HCT. The probabilities of OS and GRFS were estimated using the Kaplan–Meier method. The Logrank test was used to determine the prognostic value of patient characteristics on OS and GRFS. The cumulative incidences of relapse (CIR), non-relapse mortality (NRM), aGVHD 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 aGVHD and cGVHD, death was the competing event. The cumulative incidence of each event was estimated using the Kalbfleish and Prentice method [14]. The individual effect of each variable on the CIR and on NRM was assessed with Gray's test. Bayesian model averaging was used to select the best multivariable model based on the Bayesian Information Criteria. The proportional hazard assumption for Cox regression models was tested using the cox.zph function and by plotting Schoenfeld residuals. A Fine and Gray model was used to perform multivariable analysis for CIR. No multivariable analysis was performed for OS and NRM. All statistical analyses were performed using the R software programme. The following R packages were used: survival, cmprsk, BMA.

Results

Patient and transplant characteristics

A total of 151 patients were included. Donor type was HAPLO and MRD in 61 (40%) and 90 patients (60%), respectively. Characteristics were unbalanced between these two groups in terms of age at diagnosis, exposure to brentuximab, number of treatment lines, time to allo-HCT, conditioning intensity, ATG administration, use of TBI and stem cell source (Tables 1 and 2).

Outcomes and haematological recovery

Thirty-one deaths and 43 relapses were observed. The cause of death was relapse in 15 patients (45%) and attributed to allo-HCT in 16 patients (65%). The following specific events leading to death were reported: GVHD ($N = 5$), bacterial ($N = 2$), viral ($N = 3$), fungal infection ($N = 1$), cardiac toxicity ($N = 3$), pulmonary toxicity ($N = 2$), CNS toxicity ($N = 1$), gastrointestinal toxicity ($N = 1$), renal failure ($N = 1$), cutaneous toxicity ($N = 2$) and unknown ($N = 1$). Of note, several events could be reported in a single patient. Number and specific causes for mortality according to donor type are detailed in Table 3.

The day-30 cumulative incidence of neutrophil recovery was 98% (95% CI: 93–99) for the whole cohort and no statistical difference was noted between the HAPLO and MRD group (98% [95% CI: 93–100] vs. 99% [95% CI: 94–100], respectively; $P = 0.17$). Data regarding neutrophil recovery was missing in one patient. Median time to neutrophil engraftment was 19 days and 18 days in the HAPLO and MRD groups, respectively.

The day-30 cumulative incidence of platelet recovery was 85% [95% CI: 78–90] for the whole cohort. The day-30

Table 2 Transplant characteristics

Transplant characteristics	Whole cohort $N = 151$	HAPLO $N = 61$	MRD $N = 90$	P*
Prior ASCT, *N* (%)				
No	18 (12%)	8 (13%)	10 (11%)	0.81
Yes	133 (88%)	53 (87%)	80 (89%)	
Conditioning intensity, *N* (%)				
NMA	62 (41%)	57 (93%)	5 (6%)	<0.001
RIC	89 (59%)	4 (7%)	85 (94%)	
ATG, *N* (%)				
No	99 (65%)	61 (100%)	38 (42%)	<0.001
Yes	52 (35%)	0	52 (58%)	
TBI, *N* (%)				
No	89 (59%)	6 (10%)	83 (92%)	<0.001
Yes	62 (41%)	55 (90%)	7 (8%)	
Stem cell source, *N* (%)				
BM	44 (29%)	31 (51%)	13 (14%)	<0.001
PBSC	107 (71%)	30 (49%)	77 (86%)	
CMV risk[a], *N* (%)				
No	25 (16%)	7 (11%)	18 (20%)	0.31
Yes	126 (84%)	54 (89%)	72 (80%)	
Sex mismatch[b], *N* (%)				
No	111 (73%)	47 (77%)	64 (71%)	0.55
Yes	40 (27%)	14 (23%)	26 (29%)	
ABO mismatch[c], *N* (%)				
No	102 (67%)	39 (64%)	63 (70%)	0.59
Yes	46 (30%)	20 (33%)	26 (29%)	
Missing data	3 (3%)	2 (3%)	1 (1%)	
Follow-up duration in patients alive				
Median, in months (range)	25 (3–70)	24 (3–58)	24 (3–70)	0.06

HAPLO haploidentical donor, *MRD* matched related donor, *ASCT* autologous stem cell transplantation, *allo-HCT* allogeneic haematopoietic cell transplantation, *NMA* non-myeloablative, *RIC* reduced-intensity conditioning, *ATG* antithymocyte globulin, *TBI* total body irradiation, *BM* bone marrow, *PBSC* peripheral blood stem cell, *CMV* cytomegalovirus

*χ^2-test or Fisher's exact test when appropriate

[a] CMV risk was defined as a CMV-seropositive in recipient and/or in donor

[b] Sex mismatch was defined as the association of a male recipient with a female donor

[c] ABO mismatch was defined as any difference in blood type between donor and recipient

Table 3 Number of deaths and specific causes of mortality according to the type of donor

	HAPLO	MRD
Number of deaths, *N*	10	21
Main causes of mortality, *N* (%)		
Relapse	5	10
Transplant-related	5	11
Specific causes of mortality,[a] *N*		
GVHD	2	3
Bacterial infection	1	1
Viral infection	1	2
Fungal infection	1	0
Cardiac toxicity	1	2
Pulmonary toxicity	1	1
CNS toxicity	0	1
GI toxicity	1	1
Renal failure	0	1
Cutaneous toxicity	1	1
Unknown	0	1

HAPLO haploidentical donors, *MRD* matched-related donors, *GVHD* graft-vs.-host disease, *CNS* central nervous system, *GI* gastrointestinal

[a] More than one cause could be reported in a single patient

cumulative incidence of platelet recovery was significantly lower in the HAPLO group compared to the MRD group (71% [95% CI: 59–82] vs. 94% [95% CI: 88–98], respectively; $P < 0.001$). Data regarding platelet recovery was missing in eight patients.

In the HAPLO group, day + 100 chimaerism was full, mixed or unknown in 39 (64%), 14 (23%) and 8 (13%) patients, respectively. In the MRD group, day + 100 chimaerism was full, mixed or unknown in 54 (61%), 14 (16%) and 21 patients (23%), respectively.

Univariable analysis

CIR was significantly influenced by disease status at transplant (10% vs. 28% at 2 years for the complete remission (CR) and Other groups, respectively; $P = 0.03$), PET status at transplant (11 vs. 24% at 2 years for the PET-positive and PET-negative groups, respectively; $P = 0.03$) and median age at diagnosis (24 vs. 11% at 2 years for patients ≥ 28 years old and patients < 28 years old, respectively; $P = 0.04$). ABO mismatch was associated with a trend towards higher NRM (16 vs. 4% at 2 years, $P = 0.09$). As shown in Fig. 1, no difference was found between the HAPLO and MRD group in terms of OS, CIR and NRM (Table 4).

Donor type (58 vs. 42% at 2 years in the HAPLO and MRD groups, respectively, $P = 0.03$) and conditioning intensity (58 vs. 41% at 2 years in the NMA and RIC groups, respectively, $P = 0.03$) had a significant impact on GRFS (Fig. 2). There was a trend towards higher GRFS in patients who received TBI (58 vs. 42%, $P = 0.07$).

Multivariable analysis

Using Bayesian model averaging considering all available variables, the following variables were selected and included in a Cox regression model: donor type, administration of ATG and disease status at transplant. As shown in Table 5, receiving an allo-HCT from a MRD donor was independently associated with lower GRFS compared to HAPLO donors (HR = 2.95, 95% CI: 1.72–5.10, $P < 0.001$). Disease status at transplant other than CR was also associated with lower GRFS in multivariable analysis (HR = 1.74, 95% CI: 1.12–2.68, $P = 0.01$). In addition, the administration of ATG was independently linked to higher GRFS (HR: 0.52, 95% CI: 0.32–0.85, $P = 0.009$).

In a Fine and Gray model including disease status at transplant and age at diagnostic, absence of CR at transplant was the only independent variable negatively influencing CIR (HR = 4.55, 95% CI: 2.28–9.10, $P < 0.001$).

Univariable analysis for acute and chronic GVHD

The day-100 cumulative incidence of grade 2–4 and grade 3–4 aGVHD in the whole cohort was 25% (95% CI: 19–33) and 7% (95% CI: 4–12), respectively. The day-100 cumulative incidence estimates of grade 2–4 (29% [95% CI: 20–43] vs. 22% [95% CI: 15–32], $P = 0.29$) and grade 3–4 aGVHD (6% [95% CI: 2–16] vs. 7% [95% CI: 3–14], $P = 0.98$) in the HAPLO and MRD group, respectively, were not statistically different.

Among patients with cGVHD ($N = 41$), it was qualified as limited in 49% ($N = 20$) and extensive in 34% of cases ($N = 14$). No data regarding the extent or severity of cGVHD could be obtained in 17% of cases ($N = 6$). The 2-year cumulative incidence of cGVHD in the whole cohort was estimated at 29% (95% CI: 22–38). We observed a significantly lower 2-year cumulative incidence of cGVHD in the HAPLO group compared to the MRD group (15% [95% CI: 7–31] vs. 37% [95% CI: 27–49], respectively, $P = 0.01$).

The estimated cumulative incidences of grade 2–4 aGVHD and cGVHD are shown in Fig. 3.

Univariable analysis in subgroups

We performed four additional analyses to assess whether any subgroup could benefit from the use of a certain type of donor.

To investigate the impact of donor type according to disease status at transplant we started by analysing a

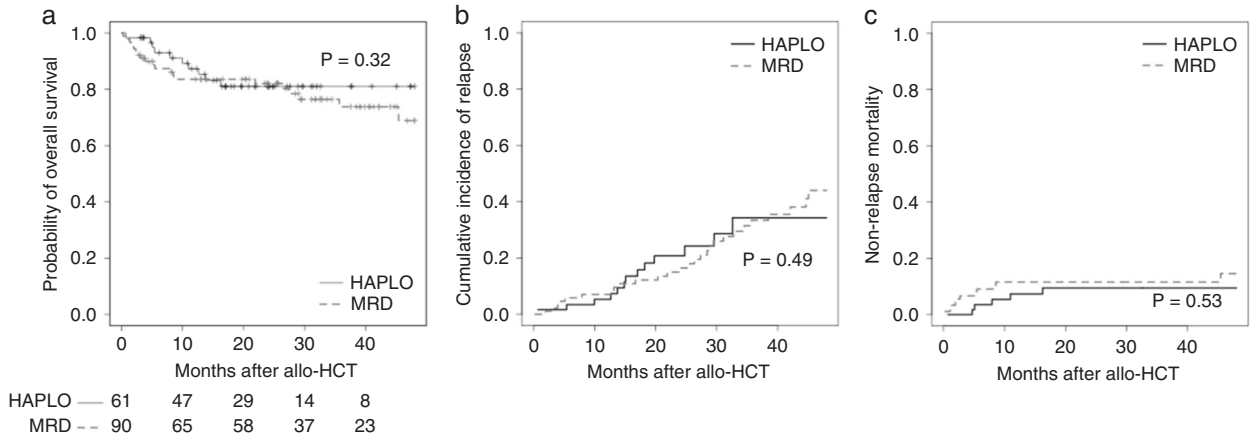

Fig. 1 Standard endpoints according to donor type. HAPLO haploidentical donor, MRD matched-related donor, allo-HCT allogeneic hematopoietic cell transplantation. **a** *P*-value determined with Logrank test. **b** *P*-value determined with Gray's test. (Color figure online)

subgroup of patients in CR or PR per Cheson 1999 criteria in association with a positive PET at restaging. The number of patients with PET data available was too limited to restrict our analysis to CR patients with a positive PET ($N = 9$). In the CR/PR PET-positive subgroup ($N = 38$), we did not observe statistically significant differences between the HAPLO and MRD groups in terms of OS (89 vs. 83% at 2 years, respectively, $P = 0.52$), CIR (24 vs. 25% at 2 years, respectively, $P = 0.74$), NRM (0 vs. 12%, respectively, $P = 0.13$). There was a trend towards higher GRFS in the HAPLO compared to the MRD group (56 vs. 39%, respectively), although it did not reach statistical significance ($P = 0.40$). Based simply on Cheson 99 criteria, we divided our cohort into two subgroups: patients in CR and patients not in CR at transplant. In patients not in CR at transplant ($N = 59$), we did not observe statistically significant differences according to donor type in OS ($P = 0.47$), CIR ($P = 0.83$). We noted a trend towards higher 2-year NRM in the MRD group (14 vs. 3% in the HAPLO group, $P = 0.17$), and somewhat higher 2-year GRFS was observed in the HAPLO group, not reaching statistical significance (57 vs. 42% in the MRD group, $P = 0.10$). In patients in CR at transplant ($N = 91$), we did not observe any statistical difference between the HAPLO and MRD groups in terms of OS ($P = 0.73$), CIR ($P = 0.43$) or NRM ($P = 0.42$). We noted a trend towards higher GRFS in the HAPLO compared to the MRD group (58 vs. 42% at 2 years, respectively; $P = 0.07$).

To further evaluate the influence of ATG, we first restricted our analysis to patients receiving an allo-HCT from a MRD ($N = 90$). In this subgroup, ATG was associated with significantly better GRFS (48 vs. 32% at 2 years, $P = 0.028$). After excluding MRD patients who did not receive ATG we compared the HAPLO group to the MRD ATG group ($N = 52$). We observed a trend towards higher GRFS in the HAPLO group (58 vs. 48% at 2 years, for the HAPLO and MRD with ATG groups, respectively), although this did not reach statistical significance ($P = 0.33$).

Discussion

The question of the best donor type between HAPLO and MRD for HL patients selected for an allo-HCT is still debated. This is the first report assessing GRFS to compare outcomes after NMA/RIC allo-HCT from a MRD with the HAPLO PT-Cy platform in the specific setting of advanced HL. Our main finding is that we observed better outcome with the HAPLO PT-Cy approach, reflected by a significantly higher GRFS probability in this group (58 vs. 42% at 2 years in the MRD group, $P = 0.03$), which was confirmed in multivariable analysis. This gain in GRFS was largely due to significantly lower incidence of cGVHD in the HAPLO PT-Cy group compared to patients transplanted from MRD (15 vs. 37% at 2 years, respectively, $P = 0.01$). Our secondary endpoints (OS, CIR and NRM) were comparable between the HAPLO and MRD groups.

A few studies compared the different types of donor but none specifically assessed GRFS nor specifically included patients with HL. Nonetheless, data favoring the use of NMA/RIC allo-HCT with the HAPLO PT-Cy platform have already been reported in patients with non-Hodgkin and HL. Burroughs et al. were the first to report the outcome after NMA/RIC allo-HCT for HL according to different donor types [6]. In this study, it was noted lower NRM and CIR in patients receiving HAPLO PT-Cy NMA/RIC, in contrast with our findings and more recent reports [15]. It is to be pointed out that the curves of CIR and progression-free survival estimates in all groups seemed to merge after 3 years [6]. In addition, PT-Cy dosage differed between patients transplanted at Fred Hutchinson and those at

Table 4 Univariable analysis

	2-year OS (CI)	*P**	2-year CIR (CI)	*P**	2-year NRM (CI)	*P***	2-year GRFS (CI)	*P**
Whole cohort	82% (75–88)		17% (11–25)		11% (6–17)		45% (40–57)	
Donor type								
HAPLO	81% (71–92)	0.91	21% (12–35)	0.49	9% (4–21)	0.53	58% (45–73)	0.03
MRD	82% (74–91)		15% (9–25)		12% (6 - 21)		42% (32–53)	
Disease status at transplant per Cheson 1999 criteria								
CR	84% (76–92)	0.32	10% (7–13)	0.004	12% (8–16)	0.59	53% (43–65)	0.27
PR/SD/PD	78% (68–90)		28% (22–34)		9% (5–13)		41% (30–57)	
PET status at transplant								
PET-negative	83% (74–93)	0.42	11% (5–23)	0.03	13% (6–24)	0.58	52% (41–67)	0.29
PET-positive	79% (70–90)		24% (15–37)		9% (4–19)		44% (33–58)	
Conditioning intensity								
NMA	82% (73–93)	0.80	18% (9–31)	0.98	11% (5–22)	0.87	58% (46–73))	0.03
RIC	81% (73–90)		17% (10–27)		11% (6–20)		41% (31–53	
ATG								
No	81% (73–90)	0.80	15% (9–25)	0.57	12% (7–21)	0.53	48% (38–60)	0.71
Yes	83% (73–95)		20% (11–34)		8% (3–20)		48% (36–65)	
TBI								
No	83% (75–91)	0.75	16% (10–28)	0.90	9% (5–18)	0.64	42% (32–54)	0.07
Yes	80% (70–91)		18% (10–32)		12% (6–25)		58% (46–73)	
Stem cell source								
BM	81% (69–94)	0.73	22% (12–40)	0.40	12% (5–27)	0.68	50% (36–69)	0.91
PBSC	82% (75–90)		15% (9–24)		10% (5–18)		47% (38–58)	
Age at diagnosis								
<28	81% (72 - 91)	0.89	24% (15–36)	0.04	7% (3–17)	0.18	51% (40–65)	0.17
≥28	82% (74–91)		11% (5–21)		14% (8–24)		45% (43–58)	
Age at transplant								
<30	84% (75–94)	0.52	20% (12–32)	0.31	8% (3–18)	0.27	53% (42–68)	0.16
≥30	80% (71–90)		15% (8–26)		13% (7–23)		43% (33–56)	
Prior exposure to brentuximab								
No	79% (71–88)	0.40	20% (13–31)	0.17	10% (5–18)	0.71	46% (37–58)	0.86
Yes	86% (76–96)		11% (5–25)		12% (5–24)		51% (39–67)	
Treatment lines prior to allo-HCT								
<4	82% (75–90)	0.84	16% (10–25)	0.64	10% (5–17)	0.50	50% (41–61)	0.76
≥4	80% (67–94)		21% (10–39)		13% (6–29)		42% (29–62)	
Time to allo-HCT								
<33 months	84% (76–93)	0.53	14% (7–25)	0.33	11% (6–21)	0.79	48% (37–62)	0.97
≥33 months	79% (69–89)		20% (12–32)		10% (5–20)		48% (37–62)	
CMV risk[a]								
No	92% (82–100)	0.22	14% (5–38)	0.68	4% (1–25)	0.28	49% (32–77)	0.65
Yes	79% (72–87)		18% (12–26)		12% (7–19)		48% (39–58)	
Sex mismatch[b]								
No	84% (77–91)	0.20	17% (11–27)	0.79	10% (5–17)	0.49	50% (41–61)	0.26
Yes	75% (62–91)		15% (7–34)		13% (6–28)		42% (28–63)	
ABO mismatch[c]								

Table 4 (continued)

	2-year OS (CI)	*P**	2-year CIR (CI)	*P**	2-year NRM (CI)	*P***	2-year GRFS (CI)	*P**
No	85% (77–92)	0.15	16% (10–26)	0.69	7% (4–15)	0.09	50% (40–61)	0.66
Yes	75% (63–90)		17% (9–33)		16% (8–31)		48% (35–66)	

OS overall survival, *CIR* cumulative incidence of relapse, *NRM* non-relapse mortality, *GRFS* graft-vs.-host disease-free relapse-free survival, *HAPLO* haploidentical donor, *MRD* matched-related donor, *ASCT* autologous stem cell transplantation, *allo-HCT* allogeneic haematopoietic cell transplantation, *NMA* non-myeloablative, *RIC* reduced-intensity conditioning, *ATG* antithymocyte globulin, *TBI* total body irradiation, *BM* bone marrow, *PBSC* peripheral blood stem cell, *CMV* cytomegalovirus

*Log rank test; **Gray's test

[a] CMV risk was defined as a CMV-seropositive in recipient and/or in donor

[b] Sex mismatch was defined as the association of a male recipient with a female donor

[c] ABO mismatch was defined as any difference in blood type between donor and recipient

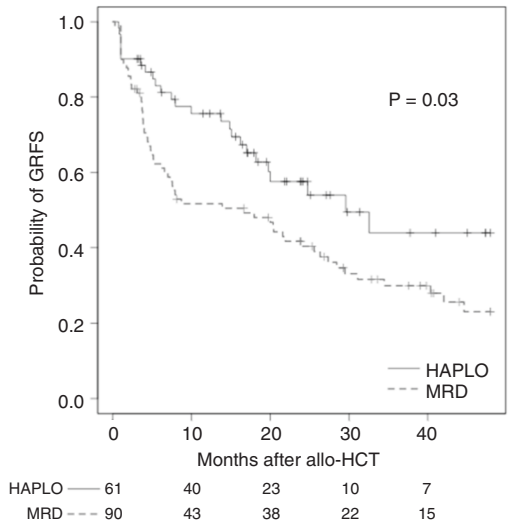

Fig. 2 Graft-vs.-host disease-free relapse-free survival according to donor type. HAPLO haploidentical donor, MRD matched-related donor, allo-HCT allogeneic hematopoietic cell transplantation. *P*-value determined with Logrank test. (Color figure online)

Table 5 Multivariable analysis for GRFS

	Number of events	HR	CI	*P**
Donor type				
HAPLO	24	1		
MRD	63	2.95	1.72–5.10	<0.001
Disease status at transplant per Cheson 99				
CR	45	1		
Other[a]	42	1.74	1.12–2.68	0.01
ATG				
No	56	1		
Yes	31	0.52	0.32–0.85	0.009

GRFS graft-vs.-host disease-free relapse-free survival, *HR* hazard ratio, *CI* confidence interval, *HAPLO* haploidentical donor, *MRD* mismatch related donor, *CR* complete response, *ATG* antithymocyte globulin

*Cox regression model

[a]Other disease statuses include: partial remission, stable disease and progressive disease

Memorial Sloan Kettering Cancer Centre (25 and 50 mg/kg, respectively), which may have also interfered with the observed outcomes. A similar composite endpoint was evaluated by Garciaz et al. [16] who reported better survival without relapse and severe cGVHD using HAPLO NMA/RIC allo-HCT with PT-Cy in 79 patients with non-Hodgkin lymphoma. More recently, Ghosh et al. observed in a large cohort of patients with a variety of lymphoma subtypes significantly lower incidence of cGVHD in patients undergoing HAPLO PT-Cy NMA/RIC allo-HCT along with similar relapse rates. These findings were confirmed in a subgroup analysis for HL patients ($N = 222$) available in the supplementary data section [15].

Given the limited availability of data, one may only speculate as to the mechanisms explaining the more favourable GVHD/GVL balance provided by the HAPLO PT-Cy platform. Data suggest that immune reconstitution of T-cell subsets is dramatically impacted after PT-Cy [17]. Some authors have correlated the expansion of regulatory T-cells with protection against GVHD in the mouse [18–20] and more specifically after PT-Cy [21]. It is also difficult to distinguish the effect of PT-Cy itself from the effect provided by the HLA disparity. Indeed, some authors have described very promising results using PT-Cy also in the HLA-matched setting [22–24]. We acknowledge that the difference in GVHD prophylaxis between the HAPLO and MRD groups is an important confounding factor, as well as difference in ATG use within the MRD group. The results of several on-going prospective trials (NCT02345850, NCT02876679) comparing different GVHD prophylaxis regimens with HLA-matched donors, including PT-Cy, should clarify this question. Finally, to better assess the

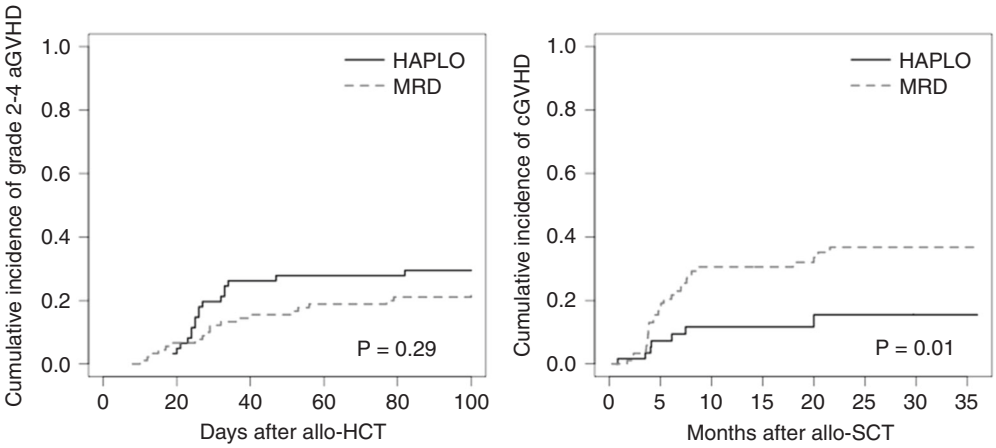

Fig. 3 Cumulative incidences of acute and chronic GVHD according to donor type. aGVHD acute graft-vs.-host disease, cGVHD chronic graft-vs.-host disease, HAPLO haploidentical donor, MRD matched-related donor, allo-HCT allogeneic hematopoietic cell transplantation. *P*-values determined with Gray's test. (Color figure online)

impact of donor type, MRD and HAPLO donor should be compared using the same PT-Cy RIC platform.

Another interesting finding in this study was the beneficial effect of ATG in patients transplanted from a MRD. Although tightly linked to MRD and the use of peripheral blood stem cells, ATG administration still favourably impacted GRFS in multivariable analysis (HR = 0.52, $P = 0.009$). In a subgroup analysis restricted to patients in the MRD group, ATG was correlated with significantly better GRFS (48 vs. 32% at 2 years, $P = 0.028$, Logrank test). A substantial body of research supports the use of ATG as part of the conditioning regimen before allo-HCT [25–27]. Our data are also in favour of the administration of ATG in the specific setting of NMA/RIC allo-HCT with MRD for HL. On the other hand, this finding means that the beneficial effect of the HAPLO PT-Cy platform might not be as significant when compared to MRD allografts in patients conditioned with ATG. Indeed, in another subgroup analysis comparing HAPLO to MRD with ATG, we observed a trend towards higher GRFS in the HAPLO group (58 vs. 48% at two years, for the HAPLO and MRD with ATG groups, respectively), yet not reaching statistical significance ($P = 0.33$, Logrank test).

Bearing in mind the differences in GVHD prophylaxis between the HAPLO and MRD group, and particularly differences in ATG use within the MRD group; our results suggest the superiority of the HAPLO PT-Cy platform over MRD in patients receiving a NMA/RIC allo-HCT for HL. Importantly, the use of PT-Cy should be evaluated in all donor types and our study could lay the groundwork for a prospective trial randomising MRD vs. HAPLO donors using uniform GVHD prophylaxis with PT Cy for patients with advanced HL.

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Author contributions JG and IYA designed the study. JG wrote the manuscript and performed all statistical analyses. All authors reviewed and approved the manuscript.

Competing interests The authors declare that they have no competing interests.

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