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Lower Graft-versus-Host Disease and Relapse Risk in Post-Transplant Cyclophosphamide–Based Haploidentical versus Matched Sibling Donor Reduced-Intensity Conditioning Transplant for Hodgkin Lymphoma

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A B S T R A C T

Classic Hodgkin lymphoma (cHL) patients with relapsed or refractory disease may benefit from allogeneic hematopoietic cell transplantation (allo-HCT), but many lack a matched sibling donor (MSD). Herein, we compare outcomes of 2 reduced-intensity conditioning (RIC) HCT platforms in cHL: T cell–replete related donor haploidentical (haplo) HCT

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with a post-transplant cyclophosphamide (PTCy)-based approach versus an MSD/calcineurin inhibitor (CNI)-based approach. The study included 596 adult patients who underwent a first RIC allo-HCT for cHL between 2008 and 2016 using either a haplo-PTCy (n = 139) or MSD/CNI-based (n = 457) approach. Overall survival (OS) was the primary endpoint. Secondary endpoints included acute graft-versus-host disease (aGVHD) and chronic GVHD (cGVHD), nonrelapse mortality (NRM), relapse/progression, and progression-free survival (PFS). On multivariate analysis, there was no significant difference between haplo/PTCy and MDS/CNI-based approaches in terms of OS (hazard ratio [HR], 1.07; 95% confidence interval [CI], .79 to 1.45; $P = .66$) or PFS (HR, .86; 95% CI, .68 to 1.10; $P = .22$). Haplo/PTCy was associated with a significantly higher risk of grades II to IV aGVHD (odds ratio [OR], 1.73, 95% CI, 1.16 to 2.59; $P = .007$), but the risk of grades III to IV aGVHD was not significantly different between the 2 cohorts (OR, .61; 95% CI, .29 to 1.27; $P = .19$). The haplo/PTCy platform provided a significant reduction in cGVHD risk (HR, .45; 95% CI, .32 to .64; $P < .001$), and a significant reduction in relapse risk (HR, .74; 95% CI, .56 to .97; $P = .03$). There was a statistically nonsignificant trend toward higher NRM with a haplo/PTCy approach (HR, 1.65; 95% CI, .99 to 2.77; $P = .06$). Haplo/PTCy-based approaches are associated with lower incidences of cGVHD and relapse, with PFS and OS outcomes comparable with MSD/CNI-based approaches. There was a leaning toward higher NRM with a haplo/PTCy-based platform. These data show that haplo/PTCy allo-HCT in cHL results in survival comparable with MSD/CNI-based allo-HCT.

INTRODUCTION

Classic Hodgkin lymphoma (cHL) patients with relapsed/refractory disease may benefit from allogeneic hematopoietic cell transplantation (allo-HCT). cHL patients who relapse after an autologous HCT have poor outcomes, with a 5-year overall survival (OS) of ~30% [1,2]. Although in theory myeloablative conditioning could improve disease control going into allo-HCT, these higher intensity approaches in allo-HCT for cHL have generally been associated with higher rates of nonrelapse mortality (NRM) [3–5]. Reduced-intensity conditioning (RIC) regimens have extended the use of allo-HCT to those who relapse after autologous HCT, older patients, and those with significant comorbidities [6–8]. In a disease for which immunotherapy has shown great promise, the application of cellular immunotherapy in the form of allo-HCT will likely remain a critical component of cHL therapeutics for the foreseeable future. Currently, there remains an ongoing risk of relapse in patients treated with programmed cell death protein 1 (PD-1) blockade as monotherapy, and there are no conclusive data that such immunotherapy is curative for most relapsed/refractory cHL. In addition, there are concerns for increased toxicity with allo-HCT in those treated with PD-1 inhibitors, with most patients who will go on to allo-HCT in the future likely to have exposure to such agents. Thus, comparing outcomes across different RIC HCT approaches will serve to better inform how to maximize the curative potential of allo-HCT while also assessing the impact of NRM and graft-versus-host disease (GVHD).

In a significant proportion of patients requiring an allo-HCT, a conventional matched donor is not available, and several reports now show that T cell–replete related donor haploidentical (haplo) HCT with post-transplant cyclophosphamide (PTCy) is a suitable option for patients with relapsed/refractory cHL with similar survival outcomes and lower rates of chronic GVHD (cGVHD) compared with matched sibling donors (MSDs) and matched unrelated donors (MUDs) [5,9–12]. Intriguingly, some small studies have suggested that haplo HCT may be associated with lower risk of relapse and improved progression-free survival (PFS) when compared with MSD HCT [5,13].

In this study we used a large registry dataset to examine the outcomes of 2 RIC platforms for HCT: the haplo PTCy-based approach compared with MSD/calcineurin inhibitor (CNI)-based approach in patients with cHL.

METHODS

Data Source

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a working group of more than 500 transplant centers worldwide that contribute detailed data on HCT to a statistical center at the Medical College of Wisconsin. Participating centers are required to report all transplants consecutively; patients are followed longitudinally, and compliance is monitored by on-site audits. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. The CIBMTR collects data at 2 levels, transplant essential data in all patients and more comprehensive data (Comprehensive Report Forms) in a subset of patients selected by a weighted randomization scheme. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule. The Institutional Review Boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

Patients

Included in this analysis were adult (≥18 years) cHL patients undergoing their first nonmyeloablative or RIC (NMA/RIC) allo-HCT between 2008 and 2016. This was a comparison of 2 HCT approaches, with eligible patients either receiving a T cell–replete related donor PTCy-based haplo graft (haplo/PTCy-based) (± CNI and mycophenolate mofetil) or MSD grafts with CNI-based GVHD prophylaxis (MSD/CNI-based). MSD recipients could have received antithymocyte globulin (ATG) or alemtuzumab. Patients receiving ex vivo graft manipulation were not included.

Definitions and Study Endpoints

The intensity of allo-HCT conditioning regimens was categorized as NMA/RIC using consensus criteria [14]. Disease response at the time of HCT was determined using the International Working Group criteria in use during the era of this analysis [15]. The primary endpoint was OS; death from any cause was considered an event, and surviving patients were censored at last follow-up. Secondary outcomes included NRM, progression/relapse, and PFS. NRM was defined as death without evidence of lymphoma progression/relapse; relapse was considered a competing risk. Progression/relapse was defined as progressive lymphoma after HCT or lymphoma recurrence after a complete remission; NRM was considered a competing risk. For PFS, a patient was considered a treatment failure at time of progression/relapse or death from any cause. Patients alive without evidence of disease relapse or progression were censored at last follow-up. Acute GVHD (aGVHD) and cGVHD were graded using established clinical criteria [16,17]. Probabilities of PFS and OS were calculated using the Kaplan-Meier estimates. Neutrophil recovery was defined as the first of 3 successive days with an absolute neutrophil count ≥ 500/μL after post-transplant nadir. Platelet recovery was considered to have occurred on the first of 3 consecutive days with a platelet count of 20,000/μL or higher in the absence of platelet transfusion for 7 consecutive days. For neutrophil and platelet recovery, death without the event was considered a competing risk.

Statistical Analysis

The haplo/PTCy cohort was compared against the MSD/CNI cohort. Cumulative incidences of hematopoietic recovery, GVHD, relapse, and NRM were calculated to accommodate for competing risks. Associations among patient-, disease-, and transplant-related variables and outcomes of interest were evaluated using Cox proportional hazards regression for cGVHD, relapse, NRM, PFS, and OS and logistic regression for aGVHD. Forward stepwise selection was used to identify covariates that influenced outcomes. Covariates with a $P < .05$ were considered significant. The proportional hazards assumption for Cox regression was tested by adding a time-dependent covariate for each risk factor and each outcome. Interactions between the main effect and significant covariates were examined. The center effect was tested using the score test for cGVHD, relapse, NRM, PFS, and OS and the

generalized linear mixed model for aGVHD [18]. Results are expressed as odds ratio (OR) for aGVHD and hazard ratio (HR) for cGVHD, relapse, NRM, PFS, and OS. The variables considered in multivariate analysis are shown in Supplementary Table 1. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

Five hundred ninety-six adult cHL patients undergoing their first NMA/RIC allo-HCT between 2008 and 2016 and reported to the CIBMTR were included. Among these, 139 received a RIC haplo/PTCy-based approach and 457 a RIC MSD/CNI-based approach. A higher proportion of recipients in the haplo/PTCy group received bone marrow as a graft source (70% versus 4%) and were of African American ethnicity (19% versus 5%). A higher proportion of the MSD/CNI cohort received a prior autologous HCT compared with the haplo/PTCy cohort (84% versus 73%). Fourteen percent of the MSD/CNI group received ATG or alemtuzumab compared with less than 1% in the haplo/PTCy group. Baseline patient-, disease-, and transplant-related characteristics are shown in Table 1.

Hematopoietic Recovery

The day 28 cumulative incidence of neutrophil recovery for the MSD/CNI platform patients was 98% (95% confidence interval [CI], 96 to 99) compared with 96% (95% CI, 92 to 98) for the haplo/PTCy platform ($P = .25$). The day 100 cumulative incidence of platelet recovery in the same order was 97% (95% CI, 95 to 98) and 91% (95% CI, 85 to 95; $P = .04$) (Table 2), respectively. Median days from HCT to neutrophil and platelet recovery for MSD patients was 14 (range, 3 to 132) and 17 (range, 8 to 89), respectively, compared with 17 (range, 5 to 64) and 26 (range, 11 to 103) for haplo patients, respectively. ($P < .001$; Table 2).

Graft-versus-Host Disease

On univariable analysis the day 180 cumulative incidence of grades II to IV aGVHD after haplo/PTCy was higher at 45% (95% CI, 37 to 53) compared 30% in the MSD/CNI cohort (95% CI, 26 to 35; $P = .003$) (Table 2). The cumulative incidence of grades III to IV aGVHD was not significantly different between the 2 groups: 7% (95% CI, 3 to 12) and 11% (95% CI, 8 to 14; $P = .14$). Multivariable analysis showed that the risk of grades II to IV aGVHD after haplo/PTCy was significantly higher (OR, 1.73; 95% CI, 1.16 to 2.59; $P = .01$) (Table 3); however, the risk of grades III to IV aGVHD was not significantly different between the 2 groups (OR, .61; 95% CI, .29 to 1.27; $P = .19$) Other variables predictive of aGVHD risk are shown in Table 3.

The 1-year cumulative incidence of cGVHD was significantly higher in the MSD/CNI platform compared with the haplo/PTCy platform at 46% (95% CI, 41 to 51) versus 23% (95% CI, 16 to 31; $P < .001$) (Table 2 and Figure 1A). Accordingly, extensive cGVHD was also higher in the MSD/CNI cohort compared with haplo/PTCy at both 1 and 3 years (Table 2). Multivariable analysis confirmed a lower risk of cGVHD for the haplo/PTCy platform (HR, .45; 95% CI, .32 to .64; $P < .001$) (Table 3).

Nonrelapse Mortality

The cumulative incidence of NRM at 1 year in the haplo/PTCy group was 11% (95% CI, 6 to 17) compared with 6% (95% CI, 4 to 8) in the MSD/CNI group ($P = .07$) (Table 2 and Figure 1B). On multivariable analysis, there was a trend toward a higher risk of NRM with the haplo/PTCy approach (HR, 1.65; 95% CI, .99 to 2.77; $P = .06$) (Table 3); however, this did not attain statistical significance. Other variables independently associated with NRM risk were age ≥ 50 years (HR, 3.55; 95%

Table 1
Baseline Characteristics of NMA/RIC MSD or Haplo Donor Patients with HL Registered to the CIBMTR from 2008 to 2016

	MSD (n = 457)	Haplo Donor (n = 139)	*P*
Number of centers	131	44	
Median patient age, yr (range)	33 (18-66)	33 (19-69)	.92
Male gender	257 (56)	81 (58)	.67
Patient race			<.001
White	371 (81)	102 (73)	
African American	23 (5)	27 (19)	
Other*	61 (13)	9 (6)	
Missing	2 (<1)	1 (<1)	
Karnofsky performance score ≥ 90	343 (75)	103 (74)	.63
Missing	15 (3)	7 (5)	
HCT-CI			.01
0	194 (42)	44 (32)	
1-2	101 (22)	45 (32)	
≥ 3	133 (29)	46 (33)	
Missing	29 (6)	4 (3)	
Previous autologous HCT	382 (84)	102 (73)	.007
Median time from diagnosis to transplant, mo (range)	34 (4-338)	32 (8-236)	.02
Remission at HCT			.72
Complete remission	178 (39)	45 (32)	
Partial remission	195 (43)	65 (47)	
Resistant disease	74 (16)	26 (19)	
Untreated relapse	6 (1)	2 (1)	
Unknown	4 (<1)	1 (<1)	
Conditioning regimens†			<.001
Flu/Mel	187 (41)	7 (5)	
Flu/Cy/TBI	21 (5)	122 (88)	
Others	249 (54)	10 (7)	
Conditioning intensity			<.001
NMA	137 (30)	125 (90)	
RIC	320 (70)	14 (10)	
TBI dose			<.001
200 cGy	60 (13)	123 (88)	
> 200 cGy	18 (4)	1 (<1)	
No TBI given	379 (82)	15 (11)	
Graft type			<.001
Bone marrow	18 (4)	97 (70)	
Peripheral blood	439 (96)	42 (30)	
GVHD prophylaxis			<.001
Post-CY ± other(s)	0	139‡	
CNI + MMF based	142 (31)	0	
CNI + MTX based	219 (48)	0	
CNI ± other(s) (except MMF, MTX, PTCy)	96 (21)	0	
ATG or alemtuzumab use	66 (14)	1 (<1)	<.001
Donor–recipient gender			.090
Female → male	111 (24)	38 (27)	
Others	346 (76)	101 (73)	
CMV status D+/R–			.025
+/–	65 (14)	29 (21)	
Other	397 (83)	109 (79)	
Missing	13 (3)	1 (<1)	
Year of transplant			.001
2008-2010	162 (35)	38 (27)	

(*continued*)

Table 1 (*Continued*)

	MSD (n = 457)	Haplo Donor (n = 139)	*P*
2011-2013	187 (41)	40 (29)	
2014-2016	108 (24)	61 (44)	
Median follow-up of survivors, mo (range)	52 (2-101)	37 (5-109)	

Values are n (%) unless otherwise defined. CMV indicates cytomegalovirus; Flu, fludarabine; HCT-CI, HCT-specific comorbidity index; Mel, melphalan; MMF, mycophenolate mofetil; MTX, methotrexate; TBI, total body irradiation.

* Other: MSD: 18 Asian; 12 Hispanic, race NOS; 2 Native Pacific Islander; 2 Native American unspecified; Race not reported: 4 USA; 1 UK; 2 France; 9 Saudi Arabia; 1 Sweden; 6 Australia; 1 Brazil; 3 Canada. Haplo: 6 Asian; 2 Hispanic, race NOS; 1 race NOS, Canada.

† Details of conditioning regimens are given in Supplementary Table 2.

‡ GVHD prophylaxis: haplo donor: 133 CNI + MMF + Cytoxan; 2 CNI + Cytoxan; 2 Cytoxan alone; 1 MMF + Cytoxan; 1 CNI + MTX+ Cytoxan.

CI, 1.81 to 6.95; $P < .001$) and HCT-specific comorbidity index of 1 to 2 relative to 3 (HR, .39; $P = .01$) (Table 3).

Relapse/Progression

The 1-year cumulative incidence of relapse was significantly higher in the MSD/CNI group at 42% (95% CI, 37 to 46) compared with 32% (95% CI, 24 to 40) in the haplo/PTCy group ($P = .04$) (Table 2, Figure 1C). In multivariable analysis, haplo-HCT was associated with a significantly reduced risk of relapse (HR, .74; 95% CI, .56 to .97; $P = .03$). Additional factors predictive of relapse/progression risk included performance status and disease status, as shown in Table 3.

Progression-Free Survival

PFS was not significantly different between the 2 groups on univariate analysis, with 1-year and 3-year PFS in the MSD/CNI group of 53% (95% CI, 48 to 57) and 34% (95% CI, 30 to 39), respectively, whereas the haplo/PTCy group had 1-year and 3-year PFS of 57% (95% CI, 49 to 65) and 38% (95% CI, 29 to 47), respectively (Table 2, Figure 1D). Similarly, on multivariable analysis there was no significant difference between the 2 groups (Table 3). Factors impacting PFS were performance status and disease status at time of transplant, as shown in Table 3.

Overall Survival

The median follow-up for surviving patients was 37 months (range, 5 to 109) for the haplo/PTCy cohort and 52 months (range, 2 to 101) for the MSD/CNI recipients. There was no significant difference in OS between the 2 platforms at either 1 or 3 years. MSD/CNI OS at 1 and 3 years was 84% (95% CI, 80 to 87) and 63% (95% CI, 58 to 67), respectively, whereas haplo/PTCy OS at 1 and 3 years was 78% (95% CI, 71 to 85) and 63% (95% CI, 54 to 71), respectively (Table 2, Figure 1E). These results were confirmed in multivariable analysis (Table 3). Other predictors of worse OS were age ≥ 50 years, poor performance status, and cHL not in complete remission at the time of allo-HCT, as shown in Table 3. Postrelapse survival (clock starting at relapse post-HCT) for MSD/CNI versus haplo/PTCy patients was not significantly different (at 3 years, 42% versus 44%; $P = .78$, respectively). No center effect was found for any outcomes.

Table 2
Univariate Outcomes

	MSD (n = 457)		Haplo Donor (n = 139)		
Outcomes	No. Assessed	Probability (95% CI) (%)	No. Assessed	Probability (95% CI) (%)	*P*
Neutrophil recovery	449		137		
28 days		98 (96-99)		96 (92-98)	.25
Median time from HCT to neutrophil engraftment, days (range)		14 (3-132)		17 (5-64)	<.001
Platelet recovery	415		108		
100 day		97 (95-98)		91 (85-95)	.04
Median time from HCT to platelet recovery, days (range)		17 (8-89)		26 (11-103)	<.001
Grades II to IV aGVHD	447		136		
180 days		30 (26-35)		45 (37-53)	.003
Grades III to IV aGVHD	420		127		
180 days		11 (8-14)		7 (3-12)	.14
cGVHD	444		133		
1 yr		46 (41-51)		23 (16-31)	<.001
3 yr		56 (51-61)		28 (21-36)	<.001
Extensive cGVHD	434		132		
1 yr		38 (34-43)		16 (10-23)	<.001
3 yr		45 (40-50)		18 (12-26)	<.001
NRM	457		139		
1 yr		6 (4-8)		11 (6-17)	.07
3 yr		10 (7-13)		14 (9-21)	.19
Relapse/progression	457		139		
1 yr		42 (37-46)		32 (24-40)	.04
3 yr		56 (51-61)		48 (39-57)	.14
PFS	457		139		
1 yr		53 (48-57)		57 (49-65)	.35
3 yr		34 (30-39)		38 (29-47)	.53
OS	457		139		
1 yr		84 (80-87)		78 (71-85)	.14
3 yr		63 (58-67)		63 (54-71)	.99

Table 3
Multivariate Analysis

	No. of Cases	HR	HR Lower CL	HR Upper CL	*P*	Overall *P*
aGVHD grades II-IV						
MSD	447	1.00*				.01
Haplo donor	136	1.73*	1.16	2.59	.01	
HCT-CI						
0	232	1.00				.01
1-2	142	1.47	.95	2.28	.08	
3+	176	1.09	.72	1.66	.68	
Missing	33	.14	.03	.61	.01	
aGVHD grades III-IV						
MSD	420	1.00*				.19
Haplo donor	127	.61*	.29	1.27		
cGVHD						
MSD	445	1.00				<.001
Haplo donor	133	.45	.32	.64	<.001	
KPS						
≥90%	433	1.00				.05
<90%	123	1.36	1.03	1.79	.03	
Missing	22	.70	.34	1.41	.32	
Relapse						
MSD	457	1.00				.03
Haplo donor	139	.74	.56	.97	.03	
KPS						
≥90%	446	1.00				.001
<90%	128	1.53	1.19	1.97	.001	
Missing	22	1.08	.61	1.89	.80	
Disease status						
CR	223	1.00				<.001
PR	260	2.06	1.58	2.69	<.001	
Resistant	100	2.77	2.01	3.82	<.001	
Untreated/missing	13	2.34	1.08	5.07	.03	
NRM						
MSD	457	1.00				.06
Haplo donor	139	1.65	.99	2.77	.06	
Age, yr						
18-29	238	1.00				.001
30-39	188	1.59	.82	3.07	.17	
40-49	94	2.13	1.01	4.49	.05	
≥ 50	76	3.55	1.81	6.95	<.001	
HCT-CI						
0	238	1.00				.05
1-2	146	.60	.29	1.24	.17	
3+	179	1.56	.90	2.70	.12	
Missing	33	1.49	.51	4.31	.47	
Contrast						
1-2 vs. 3		.39	.19	.78	.01	
PFS						
MSD	457	1.00				.22
Haplo donor	139	.86	.68	1.10	.22	
KPS						
≥90%	446	1.00				<.001
<90%	128	1.57	1.25	1.98	<.001	
Missing	22	.93	.54	1.60	.80	
Disease status						
CR	223	1.00				<.001
PR	260	1.83	1.45	2.32	<.001	
Resistant	100	2.49	1.87	3.32	<.001	
Untreated/missing	13	2.35	1.19	4.66	.01	

(*continued*)

Table 3 (*Continued*)

	No. of Cases	HR	HR Lower CL	HR Upper CL	*P*	Overall *P*
OS						
MSD	457	1.00				.66
Haplo donor	139	1.07	.79	1.45	.66	
Age, yr						
18-29	238	1.00				.03
30-39	188	.94	.69	1.30	.72	
40-49	94	1.23	.85	1.78	.27	
≥50	76	1.64	1.13	2.39	.01	
KPS						
≥90	446	1.00				.001
<90	128	1.63	1.22	2.17	<.001	
Missing	22	1.13	.61	2.11	.70	
Disease status						
CR	223	1.00				<.001
PR	260	1.69	1.24	2.31	<.001	
Resistant	100	2.54	1.76	3.65	<.001	
Untreated/missing	13	1.12	.40	3.11	.83	

CL indicates confidence limit; CR, complete remission; KPS, Karnofsky performance score; PR, partial remission.
* Represent OR.

Multivariable Analysis with ATG/Alemtuzumab Patients Excluded

Sixty-six (14%) MSD cohort patients received ATG or alemtuzumab as part of their conditioning regimen. Because ATG/alemtuzumab administration can influence risk of GVHD, relapse, and NRM, we repeated the multivariate analysis after excluding these patients. As shown in Supplementary Table 3, results of this multivariate model were concordant with the overall study population (Table 3).

Subgroup Analysis of Patients Receiving Peripheral Blood Grafts

Forty-two patients who had a haplo donor received a peripheral blood stem cell graft source and PTCy. When

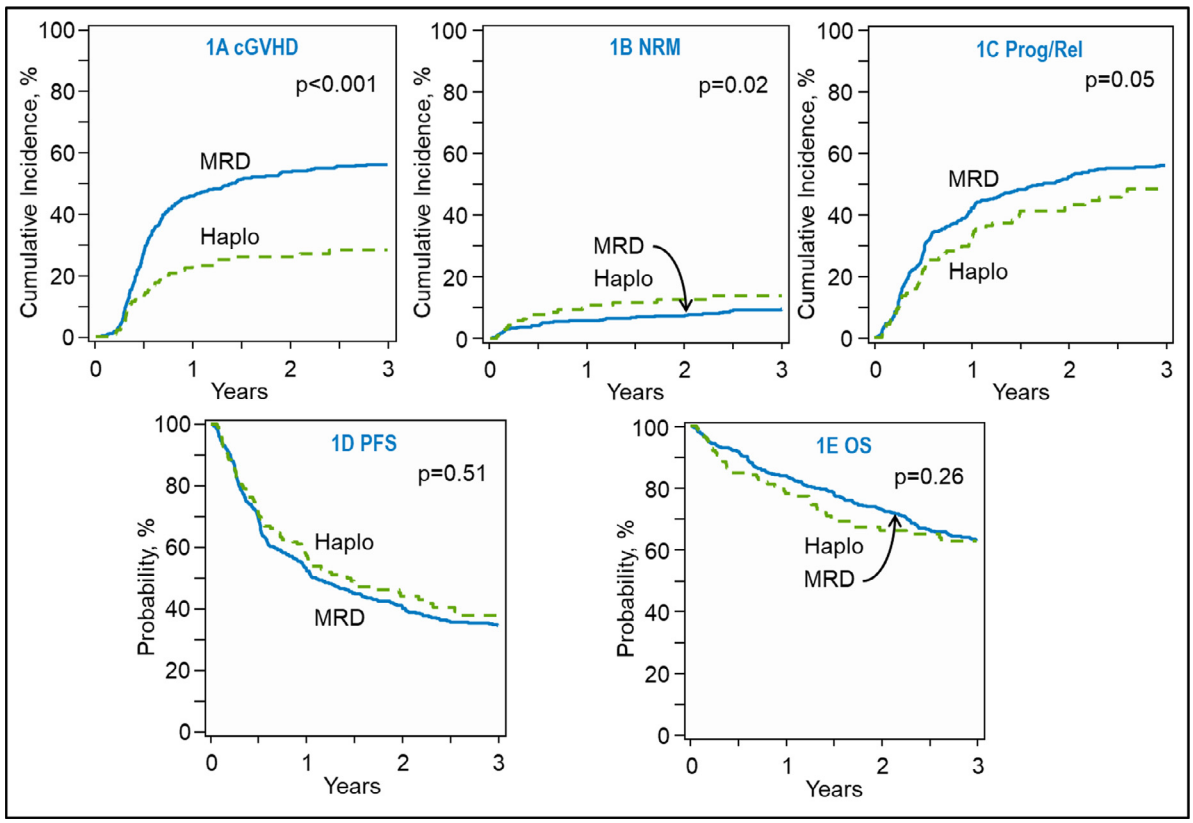

Figure 1. (A) Cumulative incidence of cGVHD in recipients of MSD and haplo donor (HAPLO) transplantations (overall $P < .001$). (B) Cumulative incidence of NRM in recipients of MSD and haplo transplants (overall $P = .02$). (C) Cumulative incidence of relapse and/or progression in recipients of MSD and haplo transplants (overall $P = .05$). (D) Kaplan-Meier estimate of PFS in recipients of MSD and haplo transplants (overall $P = .51$). (E) Kaplan-Meier estimate of OS in recipients of MSD and haplo transplants (overall $P = .26$).

Table 4
Subgroup Analysis of Patients Receiving Peripheral Blood as Graft Type

Outcomes	MSD (n = 439)		Haplo Donor (n = 42)		
	No. Assessed	Probability (95% CI)(%)	No. Assessed	Probability (95% CI)(%)	*P*
Grades III to IV a GVHD	404		40		.21
6 mo		11 (8-15)		5 (0-14)	.09
cGVHD	427		39		.16
1 yr		46 (41-51)		35 (20-50)	.15
2 yr		54 (49-59)		42 (26-59)	.18
3 yr		56 (51-61)		42 (26-59)	.11
NRM	439		42		<.001
1 yr		6 (4-8)		22 (11-35)	.02
2 yr		8 (5-10)		22 (11-35)	.03
3 yr		10 (7-13)		22 (11-35)	.07
Relapse/progression	439		42		.16
1 yr		42 (37-47)		26 (14-41)	.03
2 yr		53 (48-58)		45 (28-62)	.40
3 yr		57 (52-61)		45 (28-62)	.21
PFS	439		42		.51
1 yr		52 (47-57)		52 (37-67)	1.00
2 yr		40 (35-44)		33 (18-51)	.48
3 yr		34 (29-39)		33 (18-51)	.97
OS	439		42		.02
1 yr		84 (80-87)		68 (54-82)	.04
2 yr		72 (68-77)		57 (40-73)	.08
3 yr		62 (57-67)		49 (30-69)	.23

comparing their outcomes with the MSD/CNI cohort (receiving peripheral blood stem cells) there was no difference in the incidence of aGVHD, cGVHD, or PFS. Similar to the overall analysis, NRM was higher in the haplo/PTCy group, whereas the 1-year cumulative incidence of relapse was also comparable with the overall analysis, with the MSD/CNI group at 42% (95% CI, 37 to 47) compared with 26% (95% CI, 14 to 41) in the haplo/PTCy group ($P = .03$). Corresponding to the main analysis, MSD/CNI OS at 3 years was 62% (95% CI, 57 to 67), whereas haplo/PTCy was 49% (95% CI, 30 to 69; $P = .23$). Details of the subgroup analysis are listed in Table 4.

Outcomes of Transplant According to Remission Status at HCT

At the time of transplant 223 patients were in complete remission, 260 were in a partial remission, and 100 were deemed to have resistant disease. The NRM between these groups was not different however; not surprisingly, those who were in a complete remission had a statistically significant lower rate of relapse and superior PFS and OS when compared with the partial remission and resistant disease groups. Details of relapse, PFS, and OS based on remission status are found in Table 5.

Causes of Death

Relapse was the leading cause of death for both groups, affecting 110 (58%) MSD/CNI-based recipients and 24 (41%) haplo/PTCy-based recipients. The next most common cause of death, after primary disease, in the haplo/PTCy group was infections, 20% compared with 9% in the MSD/CNI group. GVHD was the main cause of death in 6% of the MSD/CNI group and in 2% of the haplo/PTCy group. Detailed information about causes of death is shown in Supplementary Table 4.

DISCUSSION

Donor selection for allo-HCT is based on many factors inclusive of donor availability, HLA-compatibility, and importantly outcomes associated with transplant, specifically risk of severe GVHD, relapse, and NRM. In this large registry-based study, we analyzed specifically 2 distinct platforms of donor type and GVHD prophylaxis: MSD grafts with CNI-based prophylaxis compared with haplo grafts with PTCy-based prophylaxis. The main findings of our study are as follows: (1) OS and PFS were similar for the 2 platforms, (2) the risk of cGVHD was significantly lower in recipients of haplo/PTCy-based approaches, (3) a lower incidence of relapse was observed for patients who received a haplo/PTCy-based platform, and (4) there was a nonsignificant trend toward higher NRM with haplo/PTCy-based allo-HCT, seemingly related to higher fatal infectious complications. This analysis demonstrates that haplo/PTCy allo-HCT provides similar survival outcomes to MSD/CNI allo-HCT across multiple centers with a meaningful decrease in the risk of cGVHD and relapse.

Presently, several studies are reporting the comparison of haplo HCT with conventional MSD or MUD HCT. Our study is the largest analysis to focus solely on the comparison of an MSD/CNI platform versus a haplo/PTCy-based approach to ascertain the risk-to-benefit profile of a haplo graft relative to the historical gold standard donor option (ie, HLA-identical sibling).

The European Society for Blood and Marrow Transplantation published their registry analysis [5] comparing cHL patients who received PTCy-based haplo HCT(n = 98) with outcomes of patients who received MSD (n = 338) or MUD (n = 273) HCT and reported a 1-year NRM of 13%, 21%, and 17% after alloHCT in MSD, MUD, and haplo transplants, respectively, with a difference seen in the NRM risk between the MSD and MUD groups. Similarly, Gauthier et al. [19]

Table 5
Univariate Outcomes by Remission Status at HCT

	CR (n = 223)		PR (n = 260)		Resistant (n = 100)		
Outcomes	No. Assessed	Probability (95% CI)(%)	No. Assessed	Probability (95% CI)(%)	No. Assessed	Probability (95% CI)(%)	*P*
NRM	223		260		100		.76
1 yr		7 (4-10)		6 (3-9)		9 (4-16)	.58
2 yr		8 (5-12)		8 (5-12)		10 (5-17)	.78
3 yr		12 (7-17)		10 (6-14)		10 (5-17)	.86
Relapse/progression	223		260		100		<.001
1 yr		24 (18-30)		46 (40-52)		58 (48-67)	<.001
2 yr		33 (27-40)		57 (51-63)		66 (56-75)	<.001
3 yr		37 (31-44)		61 (55-67)		69 (60-78)	<.001
PFS	223		260		100		<.001
1 yr		70 (63-75)		48 (42-55)		33 (24-43)	<.001
2 yr		59 (52-66)		35 (29-41)		24 (16-33)	<.001
3 yr		51 (44-58)		29 (23-35)		20 (13-29)	<.001
OS	223		260		100		<.001
1 yr		90 (85-93)		82 (77-86)		68 (59-77)	<.001
2 yr		83 (78-88)		68 (62-74)		56 (46-66)	<.001
3 yr		76 (69-82)		59 (52-65)		44 (33-54)	<.001

retrospectively compared MSD (n = 90) and haplo (n = 61) recipients of NMA/RIC allo-HCT for cHL and reported a 2-year NRM of 9% and 12% for haplo and MSD HCT, respectively. Mariotti et al. [2] compared outcomes between HLA-identical donors (MSD, 29; MUD, 5) and haplo (n = 30) donors for cHL patients who relapsed after an autologous transplant, with a 1-year NRM rate of 17%, with a tendency toward higher NRM after haplo relative to HLA-identical donors (26% versus 9% *P* = .09). Death was due mainly to cHL progression in the HLA-identical donor recipients (12 versus 4), whereas more patients died of complications after haplo-HCT (9 versus 6). Our study found a trend toward higher NRM with haplo/PTCy, possibly due to increased rate of fatal infections. Although no difference was observed in neutrophil engraftment between the 2 approaches, we do not have access to kinetics of immune reconstitution in the CIBMTR registry. There was also an increase in organ failure in the haplo/PTCy group (n = 7; 12%) versus the MSD/CNI group (n = 14; 7%). It is also important to highlight that the 1-year NRM of only 6% in the MSD/CNI group in our study is lower than historically reported rates at 1 year (~10% to 15%) for such patients [5,9–12], whereas the NRM rates of haplo/PTCy (1 year, 11%) are consistent with recently published data [5]. Given the time period of the current study, it contained cHL patients included in the 2016 CIBMTR [11,12] analyses of lymphoma patients who received either a haplo donor or MSD between 2008 and 2013. However, there is no overlap between patients who received in vivo T cell depletion or the subsequent years of transplant.

Relapse was the primary cause of death after allo-HCT for cHL patients in our and other studies. In the retrospective study by Burroughs et al. [13], 90 patients with cHL were treated with a NMA conditioning regimen followed by allo-HCT from MSDs (n = 38), MUDs (n = 24), or haplo donors (n = 28), and relapse was lowest among haplo recipients. Gauthier et al. [19] did not find any difference in cumulative incidence of relapse between haplo and MSD groups. In the current analysis, our findings reveal a lower relapse rate for patients receiving a haplo/PTCy-based HCT compared with MSD/CNI-based HCT, which is analogous with the findings of Mariotti et al. [5], who also reported a 3-year cumulative incidence of disease relapse of 13% for haplo HCT versus 62% for HLA-identical donor HCT. Globally, despite the curative possibility of allo-HCT, the relapse rate remains disappointingly high; therefore, studies evaluating post-transplant maintenance and consolidation are needed to address this important unmet need for this population.

Despite a higher risk of grades II to IV aGVHD with the haplo/PTCy platform in our study, the risk of severe (grades III to IV) aGVHD was not higher with this approach, whereas the risk of cGVHD was significantly lower (Table 3). The higher rate of grade II aGVHD in the haplo/PTCy cohort is line with results reported by European Society for Blood and Marrow Transplantation recently, and this mirrors other data supporting that PTCy appears to be effective at preventing grades III to IV aGVHD but is associated with grade II aGVHD in one-third to one-half of patients [5]. A higher proportion of patients in the MSD cohort received ATG/alemtuzumab, which could certainly generate the finding of decreased aGVHD; however, it is interesting that in the separate multivariate analysis with ATG/alemtuzumab excluded, the MSD arm continued to have a lower rate of aGVHD. The higher risk of cGVHD for the MSD/CNI platform was seen on both univariate and multivariable analyses. GVHD-free relapse-free survival was an endpoint we were not able to analyze given that systemic immunosuppression requiring cGVHD (a defined event for GVHD-free relapse-free survival) is not captured in our registry. Moreover, the striking difference in cGVHD seen across the 2 groups in our analysis (HR, .45) essentially means that evaluation of GVHD-free relapse-free survival will show a significant difference in similar direction and serve as a surrogate for cGVHD incidence difference. The distinct contrast between the rates of cGVHD could be related to the use of PTCy in the haplo group; however, we cannot discount that the graft source overwhelmingly was bone marrow, which has been proven to decrease the risk of cGVHD across disease states and conditioning regimens [20]. The subgroup analysis of patients receiving peripheral blood stem cell grafts would support the latter argument given that the differences in aGVHD and cGVHD are not seen; however, the numbers are small, and firm conclusions cannot be drawn. Recent data suggest that patients with exposure to checkpoint inhibitors both before and after allo-HCT may have an increased risk of aGVHD [21–23]. Consensus guidelines by

Herbaux et al. [24] highlight that there is no unanimity regarding optimal transplant strategy for patients previously treated with checkpoint inhibitors; however, there is agreement in that the goal should be to reduce the risk of GVHD and veno-occlusive disease. Furthermore, the recommendation is to preferentially use a bone marrow graft and PTCy for GVHD prophylaxis for those who have received prior checkpoint inhibitors in an effort to decrease the risk of GVHD. In the CIBMTR registry, detailed information about pretransplant treatments is available only for patients reported at the Comprehensive Report Forms level. Among the 80 subjects with available Comprehensive Report Forms data (MSD, 47; haplo, 33) in the current study, only 1 MSD and 5 haplo patients had prior checkpoint inhibitor exposure. An ongoing prospective observational CIBMTR study will be evaluating the impact of prior checkpoint inhibitor exposure in cHL patients undergoing allo-HCT.

Targeted immunotherapy approaches can achieve high rates of response in relapsed/refractory cHL, including after relapse from autologous HCT [25,26]. In current practice, allo-HCT is generally reserved for cHL with both a prior autologous HCT and brentuximab vedotin failure. In such very-high-risk patients, PD-1 blockade is also an important salvage option. ALthough PD-1 inhibitors have undoubtedly shown remarkable activity in cHL, unfortunately in high-risk subsets of patients failing both an autologous HCT and brentuximab vedotin, the results of PD-1 blockade are modest, with a median duration of response in the range of 7.8 to 11.9 months [26,27]. This obviously is suboptimal for relapsed/refractory cHL patients (with a median age in the early 30s in most published data). Considering these data, it is important to recognize that allo-HCT remains an integral option in the management and cure of relapsed cHL.

In this series we did not include myeloablative conditioning because only a small number of cHL patients in the CIBMTR registry received haplo grafts with myeloablative conditioning (n = 19). This analysis has the limitations that are fundamentally associated with registry-based studies, and although we performed a careful comparison adjusting for factors associated with transplant outcomes, differences that could likely affect our results are not readily identifiable. The higher NRM in the haplo group may be associated with infections; however, we do not have data on immune reconstitution, a limitation of our analysis. A higher percentage of patients in the MSD/CNI group had a prior autologous transplant, which may infer a more aggressive disease pattern, partially explaining the higher relapse rate in that group. The nature of data captured in the registry does not allow us to adequately assess pretransplant salvage regimens or therapy for cGVHD and therefore the ability to quantify GVHD-free relapse-free survival. Because most haplo/PTCy patients received bone marrow grafts, we cannot speculate whether similar results could be expected if most haplo/PTCy recipients underwent a peripheral blood HCT. In conclusion, our findings suggest that the haplo/PTCy package provides survival outcomes comparable with MSD/CNI HCT, with an improvement in cGVHD rates and decrease in relapse risk.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2019.05.025.

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