Reduced-Intensity Transplantation for Lymphomas Using Haploidentical Related Donors Versus HLA-Matched Sibling Donors: A Center for International Blood and Marrow Transplant Research Analysis

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ORIGINAL REPORT

Reduced-Intensity Transplantation for Lymphomas Using Haploidentical Related Donors Versus HLA-Matched Sibling Donors: A Center for International Blood and Marrow Transplant Research Analysis

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ABSTRACT

Purpose

Related donor haploidentical hematopoietic cell transplantation (Haplo-HCT) using post-transplantation cyclophosphamide (PT-Cy) is increasingly used in patients lacking HLA-matched sibling donors (MSD). We compared outcomes after Haplo-HCT using PT-Cy with MSD-HCT in patients with lymphoma, using the Center for International Blood and Marrow Transplant Research registry.

Materials and Methods

We evaluated 987 adult patients undergoing either Haplo-HCT (n = 180) or MSD-HCT (n = 807) following reduced-intensity conditioning regimens. The haploidentical group received graft-versus-host disease (GVHD) prophylaxis with PT-Cy with or without a calcineurin inhibitor and mycophenolate. The MSD group received calcineurin inhibitor–based GVHD prophylaxis.

Results

Median follow-up of survivors was 3 years. The 28-day neutrophil recovery was similar in the two groups (95% *v* 97%; $P = .31$). The 28-day platelet recovery was delayed in the haploidentical group compared with the MSD group (63% *v* 91%; $P = .001$). Cumulative incidence of grade II to IV acute GVHD at day 100 was similar between the two groups (27% *v* 25%; $P = .84$). Cumulative incidence of chronic GVHD at 1 year was significantly lower after Haplo-HCT (12% *v* 45%; $P < .001$), and this benefit was confirmed on multivariate analysis (relative risk, 0.21; 95% CI, 0.14 to 0.31; $P < .001$). For Haplo-HCT *v* MSD-HCT, 3-year rates of nonrelapse mortality (15% *v* 13%; $P = .41$), relapse/progression (37% *v* 40%; $P = .51$), progression-free survival (48% *v* 48%; $P = .96$), and overall survival (61% *v* 62%; $P = .82$) were similar. Multivariate analysis showed no significant difference between Haplo-HCT and MSD-HCT in terms of nonrelapse mortality ($P = .06$), progression/relapse ($P = .10$), progression-free survival ($P = .83$), and overall survival ($P = .34$).

Conclusion

Haplo-HCT with PT-Cy provides survival outcomes comparable to MSD-HCT, with a significantly lower risk of chronic GVHD.

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INTRODUCTION

Despite remarkable advances in lymphoma therapeutics, allogeneic hematopoietic cell transplantation (allo-HCT) remains the only potentially curative treatment for patients with high-risk relapsed or refractory lymphomas, including Hodgkin and aggressive non-Hodgkin lymphomas (NHL) failing a prior autograft.[1-4] However, the inability to identify an HLA-matched sibling donor (MSD) and sometimes the prohibitive delays in matched unrelated donor (URD) availability have been major barriers.[5,6] Nearly all patients have an available related HLA-haploidentical donor (ie, a donor with whom they share a single HLA

haplotype). Historically, attempts to perform T-cell–replete allografts from haploidentical donors were associated with unacceptable rates of graft-versus-host disease (GVHD), nonrelapse mortality (NRM), and graft rejection.[7-9]

However, contemporary GVHD prophylactic approaches, especially post-transplantation cyclophosphamide (PT-Cy), have reduced the morbidity of T-cell–replete haploidentical HCT (Haplo-HCT).[10] PT-Cy promotes immune tolerance by depleting rapidly proliferating alloreactive host and donor T cells, while sparing nonalloreactive memory T cells, regulatory T cells, and hematopoietic progenitor cells.[11] Although single-institution studies[12,13] have shown encouraging results of Haplo-HCT with PT-Cy in lymphoma, and although a recent registry analysis has reported comparable outcomes of Haplo-HCT versus matched URD allo-HCT in patients with lymphoma,[14] it remains unclear whether the greater degree of HLA disparity associated with haploidentical allografts results in higher NRM and inferior survival when compared with MSD-HCT, the established standard for allo-HCT. To address this question, we compared the outcomes of Haplo-HCT against MSD-HCT in patients with lymphoma, using the observational database of the Center for International Blood and Marrow Transplant Research.

MATERIALS AND METHODS

Patients

Included in this analysis are adult (18 years or older) patients with Hodgkin lymphoma and NHL undergoing their first reduced-intensity or nonmyeloablative conditioning (RIC/NMA) allo-HCT between 2008 and 2013. Eligible donors included either an MSD or a haploidentical related donor (mismatched for at least two or more HLA loci). Recipients of Haplo-HCT were limited to those receiving GVHD prophylaxis with PT-Cy (with or without a calcineurin inhibitor [CNI] and mycophenolate mofetil). GVHD prophylaxis in the MSD-HCT group was limited to CNI-based approaches. Patients receiving ex vivo or in vivo graft manipulation (T-cell–depleted or CD34 selected grafts) or those undergoing a planned tandem autologous–allo-HCT were excluded (Data Supplement).

Definitions

The intensity of conditioning regimens was determined using consensus criteria.[15] Complete remission (CR) before HCT was defined as complete resolution of all known areas of disease on radiographic assessments, whereas partial remission (PR) was defined as $\geq$ 50% reduction in the greatest diameter of all sites of known disease and no new sites of disease. Resistant disease was defined as $<$ 50% reduction in the diameter of all disease sites or development of new disease sites. Disease risk index (DRI) was defined as reported previously.[16]

Study End Points

The primary end point was overall survival (OS); death from any cause was considered an event, and surviving patients were censored at last contact. NRM was defined as death without evidence of lymphoma relapse/progression; relapse was considered a competing risk. Progression/relapse was defined as progressive lymphoma after HCT or lymphoma recurrence after a CR; NRM was considered a competing risk. For progression-free survival (PFS), a patient was considered to have treatment failure at the 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[17] and chronic GVHD were graded as previously described.[18,19] Neutrophil recovery was defined as the first of 3 successive days with absolute neutrophil count $\geq$ 500/μL after post-transplantation nadir. Platelet recovery was defined as achieving platelet counts $\geq$ 20,000/μL for at least 3 consecutive days, unsupported by transfusion for the preceding 7 days. For neutrophil and platelet recovery, death without the event was considered a competing risk.

Statistical Analysis

The Haplo-HCT cohort was compared with an MSD-HCT group. Probabilities of PFS and OS were calculated as described previously.[20] Cumulative incidence of NRM, lymphoma progression/relapse, and hematopoietic recovery were calculated to accommodate for competing risks.[21] Associations among patient-, disease-, and transplantation-related variables and outcomes of interest were evaluated using Cox proportional hazards regression. Backward elimination 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. Covariates violating the proportional hazards assumption were added as time-dependent covariates in the Cox regression model. Interactions between the main effect and significant covariates were examined. Center effect was examined using the random effect score test[22] for OS, PFS, relapse, and NRM. Results are expressed as relative risks (RR). The variables considered in multivariate analysis (MVA) are shown in the Data Supplement. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

Baseline patient-, disease- and transplantation-related characteristics of the 987 patients receiving MSD-HCT (n = 807) or Haplo-HCT (n = 180) are shown in Table 1. There was no significant difference between the MSD-HCT and Haplo-HCT cohorts in terms of sex, number of prior therapy lines, bone marrow or extranodal involvement at HCT, presence of bulky disease, HCT comorbidity index, chemotherapy sensitivity at HCT, and interval between diagnosis and allo-HCT. Compared with the MSD cohort, the Haplo-HCT group included a higher proportion of patients with advanced age (age $\geq$ 60 years, 24% *v* 35%; $P < .001$), African American ethnicity (4% *v* 15%; $P < .001$), and Karnofsky performance score (KPS) $\geq$ 90 (68% *v* 79%; $P < .001$). Although the proportion of patients with stage III and IV disease at diagnosis was higher in the MSD cohort (67% *v* 47%; $P = .001$), at the time of allo-HCT, significantly more Haplo-HCT cohort patients had intermediate or high DRI (75% *v* 63%; $P < .001$). The most common lymphoma histology in the Haplo-HCT and MSD-HCT groups was diffuse large B-cell lymphoma and follicular lymphoma (FL), respectively. All patients undergoing Haplo-HCT received conditioning with fludarabine, cyclophosphamide, and 200 cGy total body irradiation (TBI), whereas those in the MSD-HCT group received conditioning with fludarabine plus either an alkylator and/or 200-cGy TBI. The graft source was an unmanipulated bone marrow (BM) in 93% of Haplo-HCT and peripheral blood (PB) in 98% of MSD-HCT.

Hematopoietic Recovery

The cumulative incidence of neutrophil recovery at day 28 in Haplo-HCT and MSD-HCT groups was 95% versus 97%, respectively ($P = .31$; Table 2). The cumulative incidence of platelet

Table 1. Baseline Characteristics of Patients With Lymphoma Reported to the Center for International Blood and Marrow Transplant Research From 2008 to 2013

Variable	Haploidentical Donors	HLA-Identical Siblings	*P*
No. of patients	180	807	
No. of centers[a]	21	112	
No. of CRF-level data patients	51	104	
Age at HCT, median (range), years	55 (18-75)	54 (18-77)	< .001
18-30	22 (12)	72 (9)	
31-40	20 (11)	98 (12)	
41-50	24 (13)	136 (17)	
51-60	51 (28)	309 (38)	
61-70	51 (28)	184 (23)	
> 70	12 (7)	8 (< 1)	
Male sex	115 (64)	496 (61)	.54
Race			< .001
White	146 (81)	689 (85)	
Black	27 (15)	36 (4)	
Other[b]	6 (3)	29 (4)	
Missing	1 (< 1)	53 (7)	
Karnofsky performance score ≥ 90	142 (79)	548 (68)	< .001
HCT comorbidity index			.008
0	77 (43)	327 (41)	
1-2	50 (27)	195 (24)	
≥ 3	53 (29)	236 (29)	
Missing	0	49 (6)	
Histology			.002
Follicular lymphoma[c]	28 (16)	204 (25)	
Diffuse large B-cell lymphoma[d]	65 (36)	189 (23)	
Mantle cell lymphoma	21 (12)	113 (14)	
Mature T- and NK-cell lymphomas	22 (12)	123 (15)	
Hodgkin lymphoma	44 (24)	178 (22)	
Advanced stage (III/IV) at diagnosis	*23 (47)*	*70 (67)*	*.001*
Interval from diagnosis to HCT, months			.12
Median (range)	31 (< 1-255)	34 (1-386)	
Elevated lactate dehydrogenase at HCT	*16 (31)*	*26 (25)*	*.007*
Unknown	*14 (27)*	*11 (11)*	
Bulky disease (> 5 cm) at HCT	*5 (10)*	*8 (8)*	*.86*
Bone marrow involved at HCT	*6 (12)*	*6 (6)*	*.31*
Active extranodal involvement at HCT	*18 (35)*	*26 (25)*	*.28*
Lines of prior therapies, median (range)	*3 (1-7)*	*3 (1-9)*	*.10*
Radiation therapy before HCT	*12 (24)*	*23 (22)*	*.03*
Missing	*8 (16)*	*4 (4)*	
Remission status at HCT			.08
Complete remission	70 (39)	327 (41)	
Partial remission	97 (54)	366 (45)	
Chemotherapy-refractory	10 (6)	98 (12)	
Untreated	2 (1)	9 (1)	
Unknown	1 (< 1)	7 (< 1)	
Disease risk index at HCT			< .001
Low	45 (25)	302 (37)	
Intermediate	122 (68)	417 (52)	
High	12 (7)	88 (11)	
Missing	1 (< 1)	0	
History of prior autologous HCT	69 (38)	397 (49)	.008
Conditioning regimen			< .001
Flu/Bu	0	221 (27)	
Flu/Cy with or without rituximab	0	204 (25)	
Flu/Cy/200 cGy TBI	180	34 (4)	
Flu/Mel with or without rituximab	0	237 (29)	
Flu/200 cGy TBI with or without rituximab	0	111 (14)	
TBI in conditioning	180	145 (18)	< .001
Graft type			< .001
Bone marrow	168 (93)	15 (2)	
Peripheral blood	12 (7)	792 (98)	
Female donor to male recipient	50 (28)	224 (28)	.76
Donor/recipient CMV status			.001
−/+	39 (22)	162 (20)	
Other	140 (77)	629 (78)	
Missing	1 (< 1)	16 (2)	
GVHD prophylaxis			< .001
Post-transplant Cy[f]	180 (100)	0	
CNI + MMF with or without others[g]	0	247 (31)	
CNI + MTX with or without others (except MMF)[h]	0	444 (55)	
CNI ± others (except MMF/MTX)[i]	0	116 (14)	
Follow-up of survivors, median (range), months	37 (6-73)	36 (3-76)	

NOTE. Italicized text indicates variables available in CRF-level data patients.

Abbreviations: Bu, busulfan; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CRF, comprehensive report form; Cy, cyclophosphamide; Flu, fludarabine; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; Mel, melphalan; MMF, mycophenolate mofetil; MSD, HLA-matched sibling donor; MTX, methotrexate; NK, natural killer; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; TBI, total body irradiation; URD, unrelated donor.

[a]Twenty centers reported performing both haploidentical and HLA-identical sibling HCT. Ninety-two centers only reported HLA-identical sibling HCTs. Only one center reported only haploidentical HCT. This center contributed only one haploidentical HCT case.

[b]Haploidentical: Asian (n = 5), Native American (n = 1). HLA-identical siblings: Asian (n = 24), Pacific Islander (n = 2), Native American (n = 3).

[c]In the haploidentical versus HLA-identical sibling groups, the proportion of patients with grade 1 and 2 follicular lymphoma was 15 (54%) versus 143 (70%); grade 3 follicular lymphoma was eight (28%) versus 37 (18%), and unknown grade 5 (18%) versus 24 (12%), respectively (overall *P* = .33).

[d]Transformed from indolent lymphoma: haploidentical group: n = 5, HLA-identical siblings: n = 8.

[e]Details of mature T-cell and NK-cell neoplasms included in the analysis. For haploidentical group: PTCL-NOS = 7, angioimmunoblastic T-cell lymphoma = 3, extranodal NK/T-cell lymphoma = 4, anaplastic large cell lymphoma = 3, others = 5. For MSD group: PTCL-NOS = 42, angioimmunoblastic T-cell lymphoma = 24, extranodal NK/T-cell lymphoma = 11, anaplastic large cell lymphoma = 20, others = 26.

[f]CNI/MMF/Cy (n = 172), Cy alone (n = 3), Cy/CNI (n = 4), MMF/Cy (n = 1).

[g]CNI/MMF (n = 240), CNI/MMF/MTX (n = 7).

[h]CNI/MTX/steroids (n = 8), CNI/MTX (n = 380), CNI/MTX/sirolimus (n = 56).

[i]CNI/sirolimus (n = 95), CNI alone (n = 21).

recovery in Haplo-HCT and MSD-HCT groups at day 28 and day 100 was 63% versus 91% ($P < .001$) and 94% versus 96% ($P = .33$), respectively.

The median day 100 donor-cell chimerism in haplo-HCT versus MSD cohorts on unsorted assays was 100% (range, 77 to 100) versus 99% (range, 28 to 100; $P = .002$). The respective values for myeloid-cell–specific assays were 100% (range, 0 to 100) versus 99% (range, 13 to 100; $P = .41$), whereas those for T-cell–specific assay were 100% (range, 0 to 100) versus 94% (range, 15 to 100; $P < .001$). The proportion of patients achieving complete donor-cell chimerism (ie, ≥ 95% donor cells) by day 100 in haplo-HCT versus MSD cohorts on unsorted, myeloid-cell–specific and T-cell–specific assays was 94% versus 66% ($P = .003$), 80% versus 58% ($P = .35$), and 95% versus 48% ($P = .001$), respectively.

GVHD

The cumulative incidence of grade II to IV acute GVHD at day 100 (Table 2) in the Haplo-HCT cohort was 27% (95% CI, 15 to 40), compared with 25% (95% CI, 17 to 34) in the MSD group ($P = .84$). The rates of grades III and IV acute GVHD at day 100 were 8% in both groups (Table 2; Fig 1A). On MVA, there was no significant difference in the risk of grade II to IV and grade III and IV acute GVHD between the two groups (Table 3).

The cumulative incidence of chronic GVHD at 1 year (Table 2; Fig 1B) after Haplo-HCT was 12% (95% CI, 8 to 18) compared with 45% (95% CI, 41 to 48) in the MSD cohort ($P < .001$). MVA showed a significantly reduced risk of any chronic GVHD (RR, 0.21; 95% CI, 0.14 to 0.31; $P < .001$), as well as moderate/severe chronic GVHD (RR, 0.06; $P = .005$) after Haplo-HCT relative to MSD-HCT (Table 3).

NRM and Relapse

Among recipients of Haplo-HCT, 1-year NRM was 10% (95% CI, 6 to 15) compared with 9% (95% CI, 7 to 11) in MSD allografts ($P = .57$; Table 2; Fig 1C). On MVA, compared with MSD-HCT, there was no significant difference in the risk of NRM with Haplo-HCT (RR, 1.52; 95% CI, 0.99 to 2.34; $P = .06$; Table 3). Independent of the transplant type, KPS < 90 (RR, 2.07; 95% CI, 1.4 to 3.05; $P = .002$) and HCT comorbidity index ≥ 3 (RR, 1.88; 95% CI, 1.22 to 2.90; $P = .004$) were associated with higher risk of NRM (Data Supplement).

The cumulative incidence of disease progression/relapse at 3 years was 37% (95% CI, 30 to 44) and 40% (95% CI, 36 to 43) in the haploidentical and MSD groups, respectively ($P = .51$; Table 2; Fig 1D). On MVA, relative to the MSD-HCT group, there was no significant difference in the risk of progression/relapse after Haplo-HCT (RR, 0.80; 95% CI, 0.61 to 1.04; $P = .10$; Table 3). Other factors associated with higher risk of disease progression/relapse were lymphoma histology other than FL, not being in CR at allo-HCT, presence of bulky or extranodal disease at HCT, HCT performed before 2010, and intermediate or high DRI (Data Supplement).

PFS and OS

With a median follow-up of 3 years for surviving patients, the 3-year PFS was not significantly different between the Haplo-HCT (48%; 95% CI, 40 to 56) and MSD-HCT (48%; 95% CI, 44 to 51) groups ($P = .96$; Table 2; Fig 1E), and this was confirmed by MVA (RR of treatment failure, 0.98; 95% CI, 0.77 to 1.23; $P = .83$; Table 3). Independent of the transplant type, other predictors of higher risk of therapy failure included lymphoma histology other than FL, KPS < 90, not being in CR at allo-HCT, presence of extranodal or bulky disease, HCT performed before 2010, and intermediate or high DRI (Data Supplement).

The 3-year OS was not significantly different in the Haplo-HCT and MSD-HCT groups at 61% (95% CI, 54 to 69) and 62% (95% CI, 59 to 66), respectively ($P = .82$; Table 2; Fig 1F), and this was confirmed by MVA (RR of mortality, 1.14; 95% CI, 0.87 to 1.49; $P = .34$; Table 3). Independent of the transplant type, other predictors of higher risk of mortality included lymphoma histology other than FL or T-cell NHL, KPS < 90, not being in CR at allo-HCT, presence of bulky disease, HCT performed before 2010, and intermediate or high DRI (Data Supplement). PFS and OS stratified according to lymphoma histologies are provided in the Data Supplement.

Causes of Death

The most common cause of death in both cohorts was recurrent/progressive lymphoma: 47% (n = 34) and 52% (n = 151) in the Haplo-HCT and MSD-HCT groups, respectively (Data Supplement). Although GVHD was the cause of death in 5% (n = 13) of MSD-HCT recipients, only one death in the haploidentical group was attributed to this.

Center Effect

Haplo-HCT was performed at 21 transplant centers compared with 112 centers performing MSD-HCT. To ensure that outcomes reported in the current analysis were not driven by institutional expertise, transplant center effect was examined. We found no center effect on the hazard of OS ($P = .06$) and PFS ($P = .15$), and the cause-specific hazard of relapse ($P = .77$) and NRM ($P = .24$), using the random effect score test (Data Supplement).

Subset Analysis

Because the predominant graft source differed between the haploidentical and MSD cohorts, subset MVA of transplantation outcomes was performed in Haplo-HCT receiving BM grafts (n = 163) and MSD-HCT receiving PB grafts (n = 774). The results were in line with the outcomes of entire study population (Data Supplement).

DISCUSSION

The success of allo-HCT has historically depended on grafts from donors matched with the recipient at the HLA loci with high-resolution techniques. Approximately 30% of patients have an HLA-matched sibling donor, and, in spite of millions of donors enrolled in transplant registries, HLA-matched URD availability is driven by ethnicity[6] and varies widely across countries. The URD search process is also prone to logistical challenges, delays,[23,24] and occasionally disease progression before transplantation, especially in aggressive malignancies.[25] The use of haploidentical related donors can overcome these limitations, but in lymphoma no

Table 2. Hematopoietic Recovery, GVHD, and Unadjusted Survival Outcomes

Outcome	Haploidentical		HLA-Identical Siblings		*P*
	No. Evaluated	Probability (95% CI; %)	No. Evaluated	Probability (95% CI; %)	
Neutrophil recovery > 500/uL	179		803		
28-day		95 (90 to 98)		97 (95 to 98)	.31
100-day		99 (98 to 100)		98 (97 to 99)	.07
Platelet recovery ≥ 20/uL	180		778		
28-day		63 (56 to 70)		91 (89 to 93)	< .001
100-day		94 (90 to 97)		96 (94 to 97)	.33
Acute GVHD (II-IV)*	49		104		
100-day		27 (15 to 40)		25 (17 to 34)	.84
Acute GVHD (III-IV)*	49		104		
100-day		8 (2 to 17)		8 (3 to 14)	.92
Acute GVHD (II-IV)	175		789		
180-day		51 (43 to 60)		44 (40 to 49)	.15
Acute GVHD (III and IV)	175		789		
180-day		10 (5 to 17)		18 (15 to 21)	.03
Chronic GVHD	178		767		
6-month		5 (2 to 9)		24 (21 to 27)	< .001
1-year		12 (8 to 18)		45 (41 to 48)	< .001
2-year		15 (10 to 21)		52 (49 to 56)	< .001
Mild chronic GVHD	47		99		
6-month		6 (1 to 15)		5 (2 to 11)	.77
1-year		13 (5 to 24)		17 (10 to 25)	.56
2-year		13 (5 to 24)		20 (13 to 29)	.27
Moderate/severe chronic GVHD	47		99		
6-month		2 (0 to 9)		13 (7 to 20)	.01
1-year		2 (0 to 9)		26 (18 to 36)	< .001
2-year		2 (0 to 9)		33 (24 to 43)	< .001
Nonrelapse mortality	180		804		
1-year		10 (6 to 15)		9 (7 to 11)	.57
2-year		14 (10 to 20)		11 (9 to 14)	.27
3-year		15 (10 to 21)		13 (10 to 15)	.41
Relapse/progression	180		804		
1-year		31 (25 to 38)		30 (27 to 33)	.78
2-year		35 (28 to 42)		37 (34 to 41)	.61
3-year		37 (30 to 44)		40 (36 to 43)	.51
Progression-free survival	180		804		
1-year		59 (51 to 66)		61 (58 to 64)	.55
2-year		51 (43 to 58)		52 (48 to 55)	.78
3-year		48 (40 to 56)		48 (44 to 51)	.96
Overall survival	180		807		
1-year		77 (70 to 82)		78 (75 to 81)	.64
2-year		65 (57 to 72)		68 (65 to 72)	.39
3-year		61 (54 to 69)		62 (59 to 66)	.82

NOTE. Probabilities of neutrophil and platelet recovery, platelet recovery, acute GVHD, chronic GVHD, treatment-related mortality, and progression/relapse were calculated using the cumulative incidence estimate. Progression-free survival and overall survival were calculated using the Kaplan-Meier product limit estimate.
Abbreviations: GVHD, graft-versus-host disease.
*Calculated from comprehensive report form–level data only.

studies have compared this approach with the established gold standard donor source (ie, MSD-HCT). Here, we performed a registry analysis comparing outcomes of patients with lymphoma undergoing Haplo-HCT using PT-Cy–based GVHD prophylaxis with patients undergoing MSD-HCT. Our analysis suggests that survival, risk of relapse/progression, and NRM were virtually identical for Haplo-HCT and MSD-HCT cohorts. Second, Haplo-HCT with PT-Cy was associated with significantly lower rates of chronic GVHD, and mortality secondary to GVHD was rare. Finally, nonengraftment was not a concern with similar neutrophil recovery kinetics in the Haplo-HCT and MSD-HCT cohorts.

The Haplo-HCT cohort in this study received uniform conditioning (fludarabine/cyclophosphamide/200-cGy TBI) and PT-Cy–based GVHD prophylaxis. To ensure a valid comparison, the eligibility in the MSD-HCT group was limited to conditioning with fludarabine plus an alkylator and/or 200 cGy TBI and GVHD prophylaxis to CNI-based approaches. Additional MVA restricted to the MSD-HCT cohort did not show any differences between individual conditioning and GVHD prophylactic regimens in terms of NRM, progression/relapse, therapy failure, and mortality risk (data not shown). This step ensured that survival outcomes among MSD-HCT recipients were not influenced by the heterogeneity of conditioning and GVHD prophylaxis approaches. Although more patients in the MSD group had chemorefractory disease and KPS < 90, significantly more patients undergoing Haplo-HCT had intermediate or high DRI, indicating that the Haplo-HCT cohort

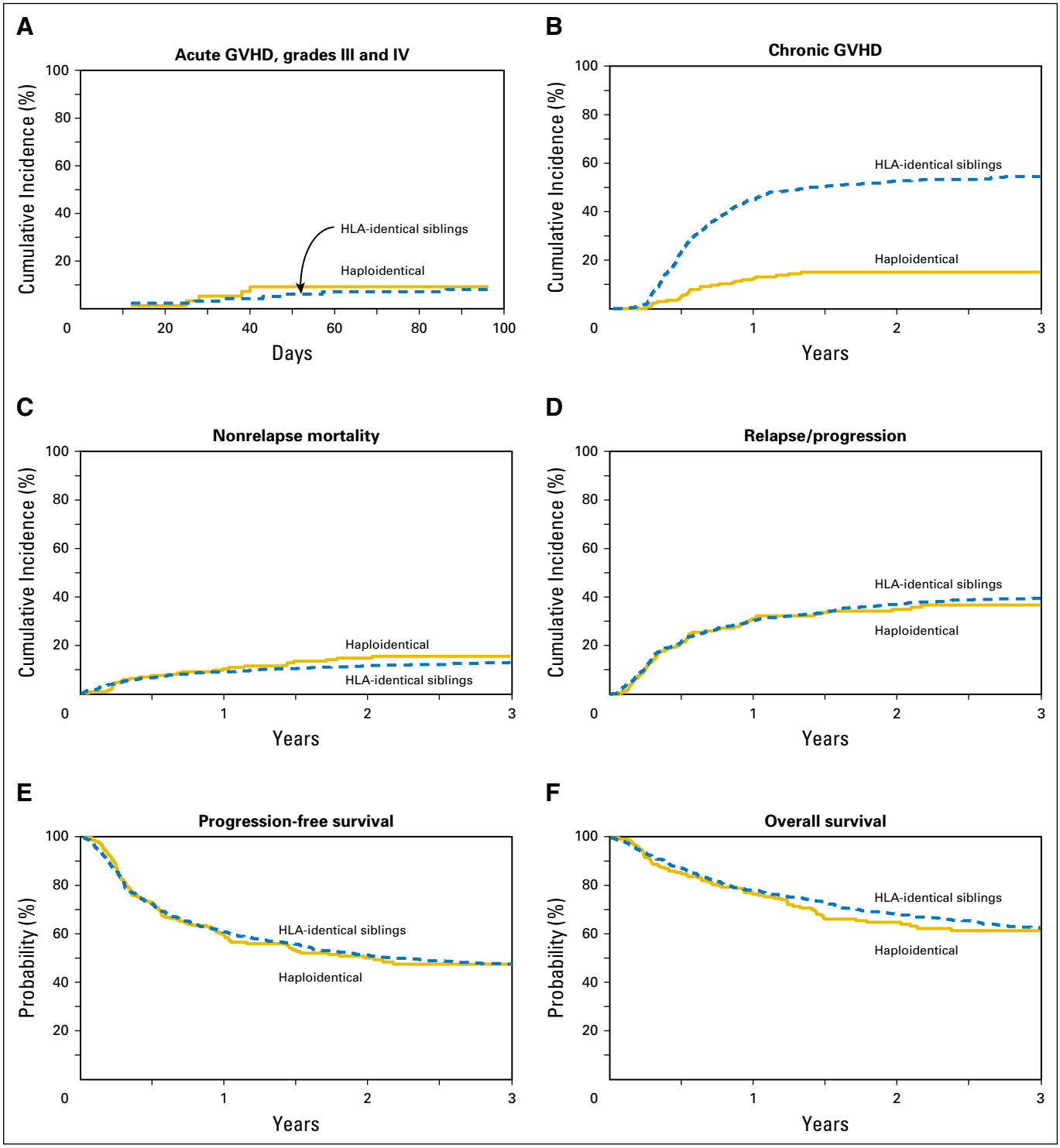

Fig 1. (A) Cumulative incidence of grade III and IV acute graft-versus-host disease (GVHD) in recipients of haploidentical donor versus HLA-identical sibling donor allogeneic hematopoietic cell transplantation. (B) Cumulative incidence of chronic GVHD in recipients of haploidentical donor versus HLA-identical sibling donor allogeneic hematopoietic cell transplantation. (C) Cumulative incidence of nonrelapse mortality in recipients of haploidentical donor versus HLA-identical sibling donor allogeneic hematopoietic cell transplantation. (D) Cumulative incidence of lymphoma relapse/progression in recipients of haploidentical donor versus HLA-identical sibling donor allogeneic hematopoietic cell transplantation. (E) Progression-free survival in recipients of haploidentical donor versus HLA-identical sibling donor allogeneic hematopoietic cell transplantation. (F) Overall survival in recipients of haploidentical donor versus HLA-identical sibling donor allogeneic hematopoietic cell transplantation.

possibly had more biologically higher-risk patients. The DRI is a validated tool that stratifies patients into risk groups using type and status of disease at the time of transplantation.[16,26] The delay in platelet recovery in the Haplo-HCT cohort is likely due to the application of PT-Cy and has been observed in other recent reports.[27]

Table 3. Results of Multivariate Analysis for Outcomes After Haplo-HCT or MSD-HCT

Outcome	No.	RR	95% CI		*P*
			Lower Limit	Upper Limit	
Grade II-IV acute GVHD*					
HLA-identical siblings	789	1			
Haploidentical	175	1.40	0.99	1.99	.06
Grade III and IV acute GVHD*					
HLA-identical siblings	789	1			
Haploidentical	175	0.50	0.25	0.98	.45
Chronic GVHD					
HLA-identical siblings	712	1			
Haploidentical	177	0.21	0.14	0.31	< .001
Moderate/severe chronic GVHD					
HLA-identical siblings	99	1			
Haploidentical	47	0.06	0.01	0.42	.005
Nonrelapse mortality					
HLA-identical siblings	755	1			
Haploidentical	180	1.52	0.99	2.34	.06
Progression/relapse					
HLA-identical siblings	804	1			
Haploidentical	180	0.80	0.61	1.04	.10
Progression-free survival					
HLA-identical siblings	804	1			
Haploidentical	180	0.98	0.77	1.23	.83
Overall survival					
HLA-identical siblings	807	1			
Haploidentical	180	1.14	0.87	1.49	.34

Abbreviations: GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; MSD, HLA-matched sibling donor; RR, relative risk; URD, unrelated donor.
*Acute GVHD models used logistic regression.

The low incidence of chronic GVHD with Haplo-HCT using the PT-Cy platform in our analysis (12% at 1 year) is in line with published data.[28] Although it is plausible that the low chronic GVHD rates observed with Haplo-HCT are in part due to the frequent use of BM as graft source in this cohort, it is important to point out that unlike myeloablative allografts, in the setting of RIC transplantation BM grafts have not been consistently shown to be associated with reduced chronic GVHD risk.[29,30] Effective depletion of alloreactive donor T cells by PT-Cy along with the use of BM as the predominant graft source are likely major drivers of reduced chronic GVHD risk after Haplo-HCT in our study. However, the relative contribution of the graft source (BM *v* PB) and PT-Cy in reducing the risk of chronic GVHD cannot be dissected by the current analysis. The ongoing Novel Approaches for Graft-versus-Host Disease Prevention Compared to Contemporary Controls trial (BMT CTN 1203; NCT02208037) is evaluating the role of PT-Cy as GVHD prophylaxis in RIC allo-HCT recipients. On its completion, we may better understand the impact of the PT-Cy for GVHD prophylaxis relative to the standard CNI-based prophylaxis. Although our analysis did not examine quality of life and other correlates that translate the reduced chronic GVHD risk to patient-reported outcomes, such analyses are imperative given the impact of chronic GVHD on long-term survivorship and will need to be examined in the prospective setting. Despite lower chronic GVHD in the haploidentical cohort, the risk of relapse was not higher, suggesting that any graft-versus-lymphoma effects in the Haplo-HCT setting are similar to MSD-HCT and independent of clinical chronic GVHD. Data on the kinetics of post–allo-HCT immune reconstitution are not captured in the registry; however, there was no difference in terms of fatal infections between the two groups (Data Supplement).

To date, no large prospective or registry data are available to suggest that alternative donor HCT for hematologic malignancies in general and lymphoma in particular could provide outcomes comparable to MSD-HCT. Although survival and NRM rates after mismatched URD or cord blood allografts have in general been either inferior or comparable to those after matched URD,[31,32] no large studies suggest that such alternative donor sources could provide outcomes comparable to MSD-HCT. The 3-year NRM and OS rates (15% and 61%, respectively) after Haplo-HCT in the current analysis not only compare favorably against prior Center for International Blood and Marrow Transplant Research data[33] for patients with lymphoma undergoing mismatched URD (3-year NRM, 44%; OS, 37%) or cord blood (3-year NRM, 37%; OS, 41%) allo-HCT, but these data for the first time demonstrate that RIC/NMA Haplo-HCT using the PT-Cy platform provides early post-HCT survival outcomes comparable to MSD-HCT, while significantly reducing the burden of chronic GVHD. It is important to note that the 3-year OS of NHL-only patients in our study (58%) seems higher than estimates reported by Kasamon et al[12] (47% at 3 years). Possible reasons for this difference include older HCT era (2003 to 2013), exclusion of young patients, and inclusion of chronic lymphocytic leukemia and aggressive lymphomas besides diffuse large B-cell lymphoma in the prior publication.

Similar to other registry-based analyses, there are some caveats to be considered. Any observational study comparing different interventions is subject to preferences of the treating centers/physicians owing to the complex criteria for selection that underlie the choice of intervention. More frequent history of autografts in

the MSD-HCT group could be reflective of institutional practice differences; however, the similar time interval between diagnosis and allo-HCT and median lines of prior therapies between the two groups suggest that no one group was overrepresented by lymphomas earlier in the disease course. Patients in this study had various histologies, and although outcomes reported here were adjusted for lymphoma subtypes, a potential benefit or lack thereof of one donor source over another for any specific lymphoma subtype cannot be confirmed. In addition, with the available data in the registry we cannot evaluate potential differences between the two cohorts in terms of health care cost effectiveness and resource use (eg secondary to infectious complications).

In summary, compared with RIC MSD-HCT, Haplo-HCT with PT-Cy significantly reduces the risk of chronic GVHD without compromising relapse and survival. RIC/NMA conditioning followed by Haplo-HCT with PT-Cy should be considered an acceptable option for patients with lymphoma without MSDs. As such, this strategy can broaden the timely applicability of allo-HCT without compromising efficacy and limit the racial barriers for receiving this potentially curative treatment option. Additional analyses in collaboration with European Group for Blood and Marrow Transplantation are being planned to validate these results in a larger international patient cohort. The results of our study warrant confirmation in prospective, randomized, controlled trials.

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Disclosures provided by the authors are available with this article at www.jco.org.

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Reduced-Intensity Transplantation for Lymphomas Using Haploidentical Related Donors Versus HLA-Matched Sibling Donors: A Center for International Blood and Marrow Transplant Research Analysis

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