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ORIGINAL REPORT

Post-Transplantation Cyclophosphamide-Based Haploidentical Transplantation as Alternative to Matched Sibling or Unrelated Donor Transplantation for Hodgkin Lymphoma: A Registry Study of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation

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A B S T R A C T

Purpose

To compare the outcome of patients with Hodgkin lymphoma who received post-transplantation cyclophosphamide–based haploidentical (HAPLO) allogeneic hematopoietic cell transplantation with the outcome of patients who received conventional HLA-matched sibling donor (SIB) and HLA-matched unrelated donor (MUD).

Patients and Methods

We retrospectively evaluated 709 adult patients with Hodgkin lymphoma who were registered in the European Society for Blood and Marrow Transplantation database who received HAPLO (n = 98), SIB (n = 338), or MUD (n = 273) transplantation.

Results

Median follow-up of survivors was 29 months. No differences were observed between groups in the incidence of acute graft-versus-host disease (GVHD). HAPLO was associated with a lower risk of chronic GVHD (26%) compared with MUD (41%; $P = .04$). Cumulative incidence of nonrelapse mortality at 1 year was 17%, 13%, and 21% in HAPLO, SIB, and MUD, respectively, and corresponding 2-year cumulative incidence of relapse or progression was 39%, 49%, and 32%, respectively. On multivariable analysis, relative to SIB, nonrelapse mortality was similar in HAPLO ($P = .26$) and higher in MUD ($P = .003$), and risk of relapse was lower in both HAPLO ($P = .047$) and MUD ($P < .001$). Two-year overall survival and progression-free survival were 67% and 43% for HAPLO, 71% and 38% for SIB, and 62% and 45% for MUD, respectively. There were no significant differences in overall survival or progression-free survival between HAPLO and SIB or MUD. The rate of the composite end point of extensive chronic GVHD and relapse-free survival was significantly better for HAPLO (40%) compared with SIB (28%; $P = .049$) and similar to MUD (38%; $P = .59$).

Conclusion

Post-transplantation cyclophosphamide–based HAPLO transplantation results in similar survival outcomes compared with SIB and MUD, which confirms its suitability when no conventional donor is available. Our results also suggest that HAPLO results in a lower risk of chronic GVHD than MUD transplantation.

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ASSOCIATED CONTENT

Appendix

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INTRODUCTION

The number of patients with Hodgkin lymphoma (HL) who are treated with allogeneic hematopoietic cell transplantation (alloHCT) has significantly increased over the last decade.[1,2] Several retrospective studies and one prospective clinical trial have demonstrated that young patients with chemosensitive disease can clearly benefit from alloHCT using reduced-intensity conditioning (RIC) regimens.[3-9] According to the current recommendations of the European Society for Blood and Marrow Transplantation (EBMT), alloHCT is considered the standard treatment option in eligible patients who experience sensitive relapse after autologous hematopoietic cell transplantation and with a sibling (SIB) or a matched unrelated (MUD) donor[2]; however, there is a significant proportion of patients for whom a conventional donor is not available. To address this issue, other options, such as HLA-haploidentical transplantation (HAPLO) or cord blood transplantation, have been explored.

HAPLO transplantation with extensive in vivo or ex vivo T-cell depletion that has been used to reduce the risk of severe graft-versus-host disease (GVHD) was historically associated with poor outcome, mainly because of a high risk of nonrelapse mortality (NRM), disease relapse, and delayed immune reconstitution[10,11]; however, encouraging results have been reported with HAPLO after a nonmyeloablative regimen and post-transplantation cyclophosphamide (PTCy) as GVHD prophylaxis.[12-18] Three recent registry studies (two from the Center for International Blood and Marrow Transplant Research and another from EBMT, including patients with lymphoid malignancies) suggest similar survival outcomes with lower incidence of chronic GVHD for HAPLO using PTCy compared with SIB and MUD transplantations.[18-20]

NRM, disease relapse, survival, and GVHD incidence have been historically recognized as the main single end points with which to evaluate the effectiveness of novel alloHCT strategies; however, as a result of the complexity of the alloHCT procedure in which decreases in NRM and GVHD often come at the cost of increased relapse, no one factor is sufficient when examining post-transplantation outcomes. Recently, novel composite end points that encompass not only mortality and relapse, but other clinically meaningful post-transplant events, such as GVHD, are being increasingly used to quantify survival without significant morbidity after alloHCT.[21-24] GVHD-free/relapse-free survival (GRFS) has developed as a novel composite end point that may be more indicative of clinical success when comparing traditional alloHCT procedures with new platforms, such as HAPLO using PTCy.

The objective of the current study was to compare the outcomes of alloHCT, including GRFS, using HAPLO donors with the PTCy approach with the outcomes of conventional HLA-identical SIB donors and MUD donors for patients with HL.

PATIENTS AND METHODS

Data Source

EBMT is a voluntary organization that comprises more than 500 transplant centers, mainly from Europe. Accreditation as a member center requires submission of the minimal essential data form A from all consecutive patients to a central registry from which patients can be identified by diagnosis of underlying disease and type of transplantation. Minimal essential data form A data are annually updated. Informed consent for transplantation and data collection was obtained locally according to regulations that were applicable at the time of transplantation. Since January 1, 2003, all transplantation centers have been required to obtain written informed consent before data registration with the EBMT in accordance with the 1975 Helsinki Declaration.

Patient Eligibility

Eligible patients were age $\geq$ 18 years and had undergone alloHCT for HL between January 2010 and December 2013. Transplantations from mismatched related donors—two or more mismatches—were identified as haploidentical transplantations. Baseline information and transplantation characteristics of eligible patients were downloaded and centers were contacted to provide additional information about post-transplant outcomes. Outcomes of patients who received PTCy-based HAPLO was compared with those of patients who were identified in the EBMT database as having received transplantation from a matched SIB donor or MUD (matched at the allele-level at HLA-A, -B, -C, and -DRB1) but otherwise meeting the eligibility criteria described above. Patients who received ex vivo graft manipulation were not eligible.

Statistical Analysis

Patient characteristics were compared by using a Kruskall-Wallis test for quantitative variables, and χ^2 or Fisher's exact test for categorical variables. NRM was defined as the time from alloHCT to death in the absence of prior relapse and/or progression. Relapse rate was calculated as the time from alloHCT to relapse and/or progression. NRM and relapse rate events were considered as competing risks. Chronic GVHD (cGVHD) was also analyzed in a competing-risks setting, with death and relapse as competing events. Progression-free survival (PFS) was defined as the time from alloHCT to relapse and/or progression or death from any cause, and overall survival (OS) was defined as the time from alloHCT to death from any cause. A composite end point defined as extensive cGVHD-free, relapse-free survival (cGRFS) after transplantation was also studied. This end point was calculated as the time from alloHCT to relapse and/or progression, to the onset of extensive cGVHD, or to death from any cause.

Probabilities of OS, PFS, and cGRFS were estimated by using the Kaplan-Meier product limit method and compared by using the log-rank test. Estimates of NRM, relapse rate, and cGVHD were calculated by using cumulative incidence curves to accommodate competing risks, and were compared by using Gray's test. The effect of donor type on NRM, relapse rate, PFS, and OS was assessed by multivariable analyses (Cox proportional hazards regression models or competing risk proportional subdistribution hazards regression models) adjusting by potential prognostic factors. The effect of donor type was investigated by multivariable models, adjusting for time from HL diagnosis to alloHCT, sex, age at transplantation, previous autologous hematopoietic cell transplantation, disease status at transplantation, performance status at transplantation, type of conditioning regimen, patient and donor cytomegalovirus status, and donor sex. Several models were constructed that explored different cutoff values for continuous variables or classifying disease status in different groups or in two categories (sensitive *v* refractory disease). The proportionality assumption was tested for each covariate factor. All variables met the proportionality assumption. A backward stepwise method was used that included the type of donor as the main factor-of-interest in all steps of model building. Survival and cumulative incidence results are presented as estimates and 95% CIs. Association of factors with end points is presented as relative risk (RR) and 95% CI. All tests were two-sided and P values $< .05$ were considered as indicating significant associations. Analyses were performed by using the SPSS for Windows version 20.0 (SPSS, Chicago, IL) and R Project software, version 2.15.2.

RESULTS

Baseline Characteristics

Baseline patient-, disease- and transplantation-related characteristics are listed in Table 1. A significantly higher number of patients in the HAPLO group received RIC regimens, bone marrow stem-cells (BMSC), and had female donors. Patients in the SIB and MUD groups received calcineurin inhibitor–based prophylaxis plus antithymocyte globulin (ATG; 14% and 51%, respectively) or campath (23% and 23%, respectively).

Hematopoietic Recovery

The cumulative incidence of neutrophil recovery at day 28 for patients who received BMSC was 96% (95% CI, 91 to 100) in the HAPLO group compared with 94% (95% CI, 86 to 100) and 93% (95% CI, 84 to 100) in the SIB and MUD groups, respectively ($P = .82$). The day 28 cumulative incidence of platelet recovery in similar order was 67% (95% CI, 48 to 92), 87% (95% CI, 75 to 100), and 79% (95% CI, 63 to 99) ($P = .79$). For peripheral blood stem-cell (PBSC) transplantations, the cumulative incidence of neutrophil recovery was 97% (95% CI, 92 to 100) in the HAPLO group compared with 96% (95% CI, 94 to 98) and 94% (95% CI, 91 to 97) in the SIB and MUD groups, respectively ($P = .02$). The cumulative incidence of platelet recovery in similar order was 72% (95% CI, 54 to 96), 90% (95% CI, 85 to 95), and 89% (95% CI, 84 to 95; $P = .01$). Engraftment results expressed as median time and ranges to recovery are provided in the Appendix (online only).

Acute and cGVHD

The rate of grade II to IV acute GVHD after HAPLO was higher compared with that of SIB (33% *v* 18%; $P = .003$), whereas no differences were observed in comparison with MUD (30%; $P = .36$). The incidence of grade III to IV acute GVHD was similar between the three groups (HAPLO, 9%; SIB, 6%; and MUD, 9%; $P = .54$). The cumulative incidence of cGVHD at 1 year after HAPLO, SIB, and MUD was 26% (95% CI, 18 to 39), 25% (95% CI, 20 to 32), and 41% (95% CI, 34 to 48), respectively ($P = .017$). In univariable analysis, MUD was associated with a higher risk of cGVHD compared with SIB ($P = .012$) and HAPLO ($P = .04$; Table 2 and Fig 1). Results were

Table 1. Characteristics of Patients and alloHCT According to the Type of Donor

Characteristic	HAPLO (n = 98)	SIB (n = 338)	MUD (n = 273)	*P*
Median age at alloHCT, years (range)	31 (18-68)	32 (18-67)	32 (18-68)	.37
Sex, No. (%)				.18
Male	56 (57)	193 (57)	175 (64)	
Female	42 (43)	145 (43)	98 (36)	
Performance status, No. (%)				.84
Good (> 80% KS)	81 (95)	301 (95)	240 (96)	
Poor (< 80% KS)	4 (5)	16 (5)	10 (4)	
HL status, No. (%)				.1
Chemosensitive	83 (85)	264 (78)	230 (84)	
Refractory	15 (15)	74 (22)	43 (16)	
Yes for previous autoHCT, No. (%)	75 (77)	236 (70)	206 (76)	.2
Median time from HL diagnosis to alloHCT, months (range)	30 (11-179)	28 (6-343)	35 (3-269)	.01
Source of stem cells, No. (%)				< .001
Bone marrow	60 (61)	33 (10)	31 (11)	
Peripheral blood	38 (39)	302 (89)	241 (88)	
Female donor, No. (%)	54 (55)	152 (45)	61 (23)	< .001
Reduced intensity conditioning regimen, No. (%)	84 (90)	218 (69)	172 (69)	< .001
TBI in conditioning, No. (%)	61 (62)	42 (13)	28 (10)	< .001
Conditioning regimen, No. (%)				< .001
Flu +Cy + 2 Gy TBI	57 (58)	4 (1)	3 (1)	
Flu +Cy + Bu	22 (22)	1 (0.3)	0	
Flu + Mel	2 (2)	112 (33)	82 (30)	
Flu + Bu	2 (2)	51 (15)	41 (15)	
Other Flu-based regimen	10 (10)	88 (26)	73 (27)	
BEAM	0	36 (11)	28 (10)	
Cy +TBI or Bu	1 (1)	20 (6)	9 (3)	
Other	4 (4)	26 (8)	37 (13)	
GVHD prophylaxis, No. (%)				< .001
Post-transplantation Cy	98 (100)	—	—	
CNI + MTX ± others	2 (2)	132 (39)	90 (33)	
CNI + MMF ± others (except MTX)	92 (94)	90 (27)	90 (34)	
CNI ± others (except MTX/MMF)	0	88 (26)	64 (23)	
ATG as part of GVHD profilaxis	0	48 (14)	139 (51)	
Campath as part of GVHD profilaxis	0	79 (23)	64 (23)	

Abbreviations: alloHCT, allogeneic hematopoietic stem cell transplantation; ATG, antithymocyte globuline; autoHCT, autologous hematopoietic stem cell transplantation; BEAM, carmustine, etoposide, arabinoside of cytosine, melphalan; Bu, busulfan; CNI, calcineurine inhibitors; Cy, cyclophosphamide; Flu, fludarabine; GVHD, graft-versus-host disease; HAPLO, haploidentical donor; HL, Hodgkin lymphoma; KS, Karnofsky status; Mel, melphalan; MMF, mofetil mycophenolate; MTX, methotrexate; MUD, match-unrelated donor; SIB, sibling donor; TBI, total-body irradiation.

Table 2. Univariable Analysis for Survival Outcomes, Nonrelapse Mortality, and Relapse by Donor Type

Outcomes	HAPLO (n = 98)	SIB (n = 338)	MUD (n = 273)	*P*
NRM				.023
1-year cumulative incidence	17%	13%	21%	HAPLO *v* SIB, .37
95% CI	11 to 27	10 to 17	16 to 26	HAPLO *v* MUD, .30
				SIB *v* MUD, .006
Relapse rate				< .001
2-year cumulative incidence	39%	49%	32%	HAPLO *v* SIB, .039
95% CI	30 to 51	43 to 55	26 to 38	HAPLO *v* MUD, .31
				SIB *v* MUD, < .001
PFS				.086
2-year cumulative incidence	43%	38%	45%	HAPLO *v* SIB, .18
95% CI	33 to 54	31 to 43	39 to 51	HAPLO *v* MUD, .91
				SIB *v* MUD, .038
OS				.118
2-year cumulative incidence	67%	71%	62%	HAPLO *v* SIB, .51
95% CI	57 to 76	66 to 76	56 to 68	HAPLO *v* MUD, .44
				SIB *v* MUD, .039
Chronic GVHD				.017
1-year cumulative incidence	26%	25%	41%	HAPLO *v* SIB, .90
95% CI	18 to 39	20 to 32	34 to 49	HAPLO *v* MUD, .040
				SIB *v* MUD, .012
Extensive cGVHD and PFS				.04
2-year cumulative incidence	40%	28%	38%	HAPLO *v* SIB, .049
95% CI	29 to 51	23 to 34	32 to 44	HAPLO *v* MUD, .59
				SIB *v* MUD, .038

Abbreviations: cGVHD, chronic graft-versus-host disease; HAPLO, haploidentical donor; MUD, match-unrelated donor; NRM, nonrelapse mortality; OS, overall survival; PFS, progression-free survival; SIB, sibling donor.

similar when we analyzed the cumulative incidence of cGVHD according to BMSC or PBSC.

NRM and Relapse

One hundred twenty-nine (18%) patients died without experiencing disease relapse and/or progression. No differences in the cumulative incidence of NRM at 1 year were observed between HAPLO and SIB (17% *v* 13%; *P* = .37), whereas MUD had a significantly higher NRM compared with SIB (21% *v* 13%; *P* = .006; Table 2 and Fig 2A). In multivariable analysis, the variables associated with a higher NRM were MUD (RR, 1.78; 95% CI, 1.21 to 2.60; *P* = .003), age ≥ 40 years (RR, 1.78; 95% CI, 1.24 to 2.55; *P* = .002), poor performance status (RR, 2.39; 95% CI, 1.22 to 1.68; *P* = .011), and refractory HL (RR, 1.62; 95% CI, 1.05 to 2.50; *P* = .03; Table 3).

A total of 280 (39%) patients experienced relapse. The cumulative incidence of disease progression and/or relapse at 2 years was 39% (95% CI, 30 to 51), 49% (95% CI, 43 to 55), and 32% (95% CI, 26 to 38) after HAPLO, SIB, and MUD, respectively (Fig 2B). In multivariable analysis, SIB was associated with a higher relapse risk compared with MUD (RR, 0.57; 95% CI, 0.43 to 0.74; *P* < .001) and HAPLO (RR, 0.69; 95% CI, 0.48 to 0.99; *P* = .047; Table 3). Other factors associated with a higher relapse rate were male gender (RR, 1.28; 95% CI, 1.01 to 1.63; *P* = .049), poor performance status (RR, 1.88; 95% CI, 1.1 to 3.2; *P* = .02), and refractory HL (RR, 2.67; 95% CI, 2.04 to 3.48; *P* < .001; Table 3).

Survival

Four hundred forty-eight (63%) of 709 patients are currently alive, with a median follow-up for surviving patients of 27 months (range, 1.1 to 64 months) for HAPLO, 27 months (range, 1 to 76 months) for SIB, and 31 months (range, 0.9 to 70 months) for MUD. The 2-year OS was not significantly different between HAPLO (67%; 95% CI, 57 to 76) and SIB (71%; 95% CI, 66 to

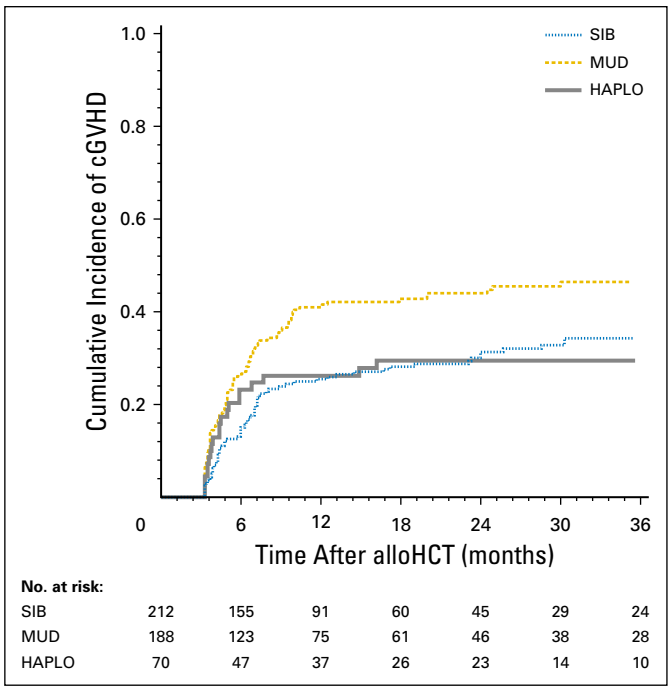

Fig 1. Cumulative incidence of chronic graft-versus-host-disease (cGVHD; overall, *P* = .017). alloHCT, allogeneic hematopoietic stem cell transplantation; HAPLO, haploidentical donor; MUD, match-unrelated donor; SIB, sibling donor.

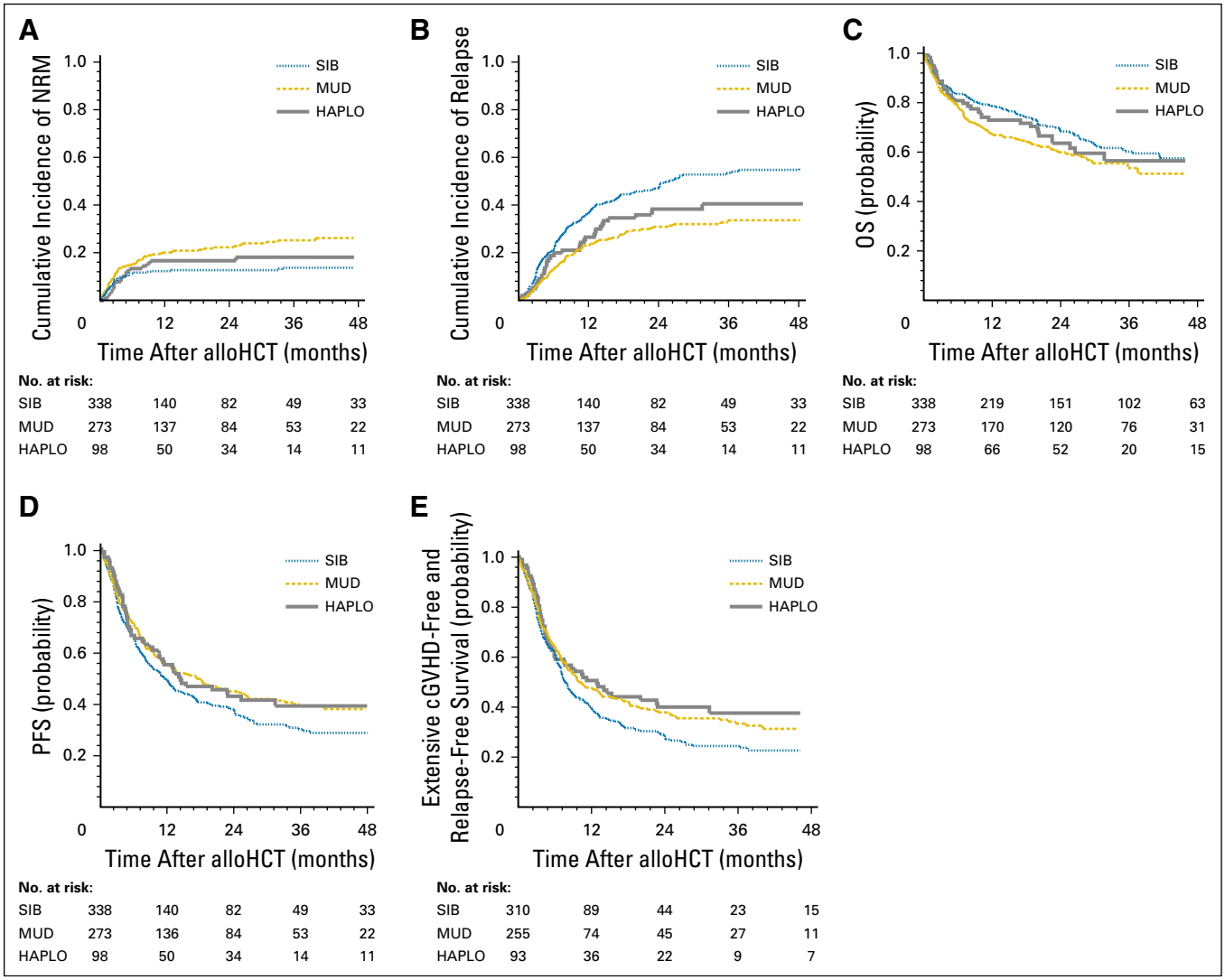

Fig 2. (A) Cumulative incidence of nonrelapse mortality (NRM) in recipients of sibling donor (SIB), match-unrelated donor (MUD), and haploidentical donor (HAPLO) transplantations (overall, $P = .23$). (B) Cumulative incidence of relapse and/or progression in recipients of SIB, MUD, and HAPLO transplantations (overall, $P < .001$). (C) Kaplan-Meier estimate of overall survival (OS) in recipients of SIB, MUD, and HAPLO transplantations (overall, $P = .118$). (D) Kaplan-Meier estimate of progression-free survival (PFS) in recipients of SIB, MUD, and HAPLO transplantations (overall, $P = .086$). (E) Kaplan-Meier estimate of combined incidence of extensive chronic graft-versus-host-disease (cGVHD)–free and relapse-free survival in recipients of SIB, MUD, and HAPLO transplantations (overall, $P = .04$).

76; $P = .51$), whereas patients who underwent MUD transplantation had a lower OS (62%; 95% CI, 56 to 68; $P = .039$) than those who received an SIB alloHCT (Fig 2C). These results were confirmed in multivariable analysis (Table 3). Other predictors for a worse OS were age ≥ 40 years (RR, 1.62; 95% CI, 1.25 to 2.11; $P < .001$), poor performance status (RR, 2.4; 95% CI, 1.51 to 3.83; $P < .001$), and refractory HL (RR, 2.15; 95% CI, 1.62 to 2.85; $P < .001$; Table 3).

The 2-year PFS was similar between HAPLO and SIB (43%; 95% CI, 33 to 54; and 38%; 95% CI, 31 to 43, respectively; P .18), but significantly better after MUD (45%; 95% CI, 39 to 51; $P = .038$) than after an SIB alloHCT (Fig 2D). Multivariable analysis did not demonstrate significant differences in PFS after HAPLO or MUD in relation to SIB (Table 3). Factors associated with a worse PFS were age ≥ 40 years (RR, 1.31; 95% CI, 1.06 to 1.63; $P = .014$), poor performance status (RR, 2.05; 95% CI, 1.35 to 3.11; $P = .001$), and refractory HL (RR, 2.22; 95% CI, 1.76 to 2.79; $P < .001$). The rate of the composite end point of 2-year cGRFS was significantly better for HAPLO (40%; 95% CI, 29 to 51) compared with SIB (28%; 95% CI, 23 to 34; $P = .049$) and similar to MUD (38%; 95% CI, 32 to 44; $P = .59$; Fig 2E).

A multivariable subanalysis that included HAPLO, SIB, MUD with ATG, and MUD without ATG indicated that HAPLO was associated with a lower relapse rate than SIB (hazard ratio, 0.69; 95% CI, 0.48 to 1.0; $P = .047$) with no significant differences in NRM, OS, or PFS. No differences were observed between HAPLO and MUD with or without ATG (Appendix and Appendix Table A1, online only). These results were in line with the outcomes shown in the main analysis.

Table 3. Multivariable Cox Proportional Hazards Models With Donor Type as a Covariate

Factor	HR	95% CI	*P*
Cox model on NRM			
Donor type			
SIB			
MUD	1.78	1.21 to 2.60	.003
HAPLO	1.38	0.79 to 2.39	.26
Age, years			
≤ 39			
≥ 40	1.78	1.24 to 2.55	.002
Performance status			
Good			
Poor	2.39	1.22 to 4.68	.011
Refractory HL			
Nonrefractory			
Refractory	1.62	1.05 to 2.50	.03
Cox model on relapse rate			
Donor type			
SIB			
MUD	0.57	0.43 to 0.74	< .001
HAPLO	0.69	0.48 to 0.99	.047
Sex			
Female			
Male	1.28	1.01 to 1.63	.049
Performance status			
Good			
Poor	1.88	1.1 to 3.2	.02
Refractory HL			
Nonrefractory			
Refractory	2.67	2.04 to 3.48	< .001
Cox model on OS			
Donor type			
SIB			
MUD	1.47	1.13 to 1.92	.004
HAPLO	1.24	0.84 to 1.82	.27
Age, years			
≤ 39			
≥ 40	1.62	1.25 to 2.11	< .001
Performance status			
Good			
Poor	2.4	1.51 to 3.83	< .001
Refractory HL			
Nonrefractory			
Refractory	2.15	1.62 to 2.85	< .001
Cox model on PFS			
Donor type			
SIB			
MUD	0.86	0.69 to 1.06	.17
HAPLO	0.82	0.61 to 1.12	.22
Age, years			
≤ 39			
≥ 40	1.31	1.06 to 1.63	.014
Performance status			
Good			
Poor	2.05	1.35 to 3.11	.001
Refractory HL			
Nonrefractory			
Refractory	2.22	1.76 to 2.79	< .001

Abbreviations: HAPLO, haploidentical donor; HL, Hodgkin lymphoma; HR, hazard ratio; MUD, match-unrelated donor; NRM, nonrelapse mortality; OS, overall survival; PFS, progression-free survival; SIB, sibling donor.

DISCUSSION

Here, we describe the largest series of patients with HL who underwent HAPLO alloHCT that used PTCy-based GVHD prophylaxis compared with transplantations that used either a MUD or an SIB donor. This registry analysis demonstrates that the survival outcomes of HAPLO transplantation are comparable with that of conventional SIB and MUD transplantations across multiple centers and conditioning regimens. Moreover, HAPLO alloHCT seems to be associated with significantly lower rates of cGVHD compared with MUD transplantations.

Thus far, there is only one nonrandomized study that compared HAPLO transplantations with SIB and MUD in patients with HL.[25] In that retrospective study by Burroughs et al, 90 patients with HL were treated with a nonmyeloablative conditioning regimen followed by alloHCT from an SIB (n = 38), an MUD (n = 24), or a HAPLO (n = 28) donor. HAPLO transplantation was performed by using unmanipulated bone marrow as a graft source and PTCy as GVHD prophylaxis. The authors did not find significant differences in OS among the three groups; however, significantly improved PFS was observed for HAPLO compared with SIB and MUD. NRM and relapse were lowest among HAPLO recipients. In our study, HAPLO compares favorably with SIB in terms of relapse rate and without differences in OS. In contrast to this series, we found no significant differences in post-transplantation outcomes between HAPLO and MUD, except for a lower incidence of cGVHD for HAPLO transplantation. It should be noted that in the study by Burroughs et al, NRM reported after MUD transplantation was unexpectedly low (8%). We found a 2-year NRM of 13% and 23% after SIB and MUD alloHCT, respectively, which are in line with previous nonrandomized studies that compared SIB and MUD transplantations in patients with HL.[3,5,26,27] In the current study, 2-year OS (71% and 62% after SIB and MUD, respectively) and 2-year PFS (38% and 45% after SIB and MUD, respectively) also compare similarly with those reported by other groups.[3,5,21,26-28]

Recently, two retrospective studies from the Center for International Blood and Marrow Transplant Research compared outcomes after HAPLO with MUD and SIB transplantations.[18,19] Only 22% of patients who were included in these large series had HL. Both studies—the first comparing HAPLO with MUD with and without ATG, and the second comparing HAPLO with SIB—reported similar survival outcomes with a lower risk of cGVHD for those patients who received HAPLO.

In the current study, no differences between groups in the incidence of acute grade II to IV GVHD were observed; however, the 1-year cumulative incidence of cGVHD was higher for MUD (41%) compared with SIB (25%; $P = .012$) and HAPLO (26%; $P = .04$). The lower cGVHD rate with HAPLO is in line with recent reports in patients with lymphoma and acute myeloid leukemia. The incidence of acute and cGVHD in our study seems to be lower for all groups than that reported by Burroughs et al[25] despite the fact that most patients in our study received PBSC. This could be explained by the use of ATG or alemtuzumab in a significant proportion of patients in the SIB (14% and 23%, respectively) and MUD (51% and 23%, respectively) groups. In our study, the low incidence of cGVHD after HAPLO resulted in a lower rate of cGFRS at 2 years (40%) compared with SIB (28%; $P = .049$) and similar to MUD (38%; $P = .59$).

In support of the role of HAPLO for the treatment of relapsed HL, three recently published series report encouraging results.[28-30] In a retrospective study, Raiola et al[28] reproduced the Burroughs et al data, which confirmed the reproducibility of the PTCy HAPLO

procedure in terms of toxicity and efficacy. In this series, the cumulative incidence of NRM was low (4%) and the relapse rate (31%) was the major cause of treatment failure. Three-year OS and PFS were 77% and 63%, respectively, in this small series of 26 patients. Gayoso et al[29] reported a series of 43 patients who received HAPLO with an RIC approach that substituted total-body irradiation with busulfan in the conditioning regimen in an attempt to reduce the relapse rate. In contrast to the study by Raiola et al, most patients received PBSC graft instead of BMSC. NRM at 1 year (21%) was similar to that observed in our study (17%) and higher than that previously reported, likely as a result of the use of more intensive conditioning regimens.[21,25] Relapse was also the main problem in this series, with a cumulative incidence of 24% at 2 years. Estimated 2-year PFS and OS were 48% and 58%, respectively, and these results compare similarly with our experience. Finally, Castagna et al[30] have recently reported similar results (3-year OS, 63%; and PFS, 59%) in a series of 62 patients with HL.

This study has some inherent limitations as with other registry-based analyses. The decision to perform an MUD versus a HAPLO transplantation was not an intent-to-treat one; a shorter time from diagnosis to alloHCT for the HAPLO group may suggest that some patients have been offered HAPLO on the basis of institutional preferences, but it may also indicate a shorter time to make the necessary arrangements to perform HAPLO transplantation compared with MUD. Second, the nature of the data captured by the registry does not allow us to evaluate the effect of different types of conditioning regimens on transplant outcome. Thus, although a significantly higher proportion of HAPLO transplantations were performed using RIC regimens compared with SIB and MUD, recent data indicate that, at least for those alloHCTs performed more recently, outcomes after transplantation are similar after myeloablative conditioning regimens and RIC.[31] Finally, differences in GVHD prophylaxis approaches between SIB and MUD, and the use of BMSC for most HAPLO transplantations versus PBSC for most SIB and MUD transplantations, prevents us from being able to segregate the effect of donor versus GVHD prophylaxis and type of graft source. Nevertheless, this is the largest reported series that compared HAPLO, SIB, and MUD in HL; all HAPLO transplantations were performed by using PTCy as GVHD prophylaxis; and median follow-up for HAPLO transplantations was similar to SIB and MUD.

In the absence of randomized data, our study suggests that PTCy-based HAPLO alloHCT is associated with comparable results with respect to NRM, OS, and PFS with those of conventional transplantations. Moreover, our results indicate that HAPLO results in a lower incidence of extensive cGVHD compared with MUD transplantations and higher cGFRS compared with SIB. Despite the lower cGVHD incidence in the HAPLO group, the risk of relapse was lower than that in the SIB group and similar to that for MUD transplantation group, which suggests that the graft-versus-lymphoma effect in the HAPLO setting might be independent of a clinically significant cGVHD. These results support the use of HAPLO as an alternative for patients with advanced HL who lack an SIB donor. Use of HAPLO donors may allow patients to proceed more rapidly to transplantation, avoiding the time needed to complete a formal MUD search and arrange for graft collection at a remote center. Whether HAPLO transplantation is the first choice instead of MUD transplantation and whether it can eventually substitute SIB transplantation in specific subgroups of patients must be assessed within the context of a randomized prospective clinical trial.

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

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Post-Transplantation Cyclophosphamide-Based Haploidentical Transplantation as Alternative to Matched Sibling or Unrelated Donor Transplantation for Hodgkin Lymphoma: A Registry Study of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation

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Appendix

Hematopoietic Recovery

Median time to an absolute neutrophil count of $\geq 500/mm^3$ for patients who received bone marrow stem-cells was 18 days for haploidentical (HAPLO), 20 days for sibling (SIB), and 20 days for HLA-matched unrelated donor (MUD; $P = .23$) transplantation. Platelet recovery was not significantly different among groups (median time to a platelet count of $\geq 20{,}000/mm^3$ was 20, 18, and 16 days for HAPLO, SIB, and MUD, respectively; $P = .45$). For those patients who received peripheral blood stem-cell transplantation, median time for absolute neutrophil count of $\geq 500/mm^3$ was 18, 14, and 14 days for HAPLO, SIB, and MUD, respectively ($P < .001$). Platelet recovery was significantly faster for SIB and MUD recipients compared with patients in the HAPLO group (13 and 12 days *v* 25 days, respectively; $P < .001$).

Effect of Antithymocyte Globulin or Campath Use on SIB and MUD alloHCT Outcomes

Because there was a tight correlation between donor type and the type of graft-versus-host-disease prophylaxis, we performed a subset analysis of allogeneic hematopoietic cell transplantation (alloHCT) outcomes to assess the potential effect of antithymocyte globulin (ATG) or campath on SIB and MUD alloHCT outcomes. Two separate multivariable analyses were performed, one that was restricted to SIB with and without ATG or campath and another restricted to MUD with and without ATG or campath. Use of ATG or campath did not have any effect on nonrelapse mortality (NRM), relapse, overall survival (OS), or progression-free survival (PFS) in the SIB setting. Whereas the use of campath did not have any effect on alloHCT outcomes in the MUD group, use of ATG was associated with a lower PFS (hazard ratio, 1.51; 95% CI, 1.1 to 2.1; $P = .02$), with no differences in the risk of NRM, relapse, and OS. A subsequent multivariable analysis that included HAPLO, SIB, MUD with ATG, and MUD without ATG indicated that HAPLO was associated with a lower relapse rate than SIB (hazard ratio, 0.69; 95% CI, 0.48 to 1.0; $P = .047$) with no significant differences in NRM, OS, or PFS (Appendix Table A1). No differences were observed between HAPLO and MUD with or without ATG. These results were in line with the outcomes shown in the main analysis.

Table A1. Multivariable Cox Proportional Hazards Models With Donor Type as a Covariate: Analysis of Four Groups (HAPLO, SIB, MUD with ATG, and MUD without ATG)

Factor	HR	95% CI	*P*
Cox model on NRM			
Donor type			
SIB			
HAPLO	1.38	0.79 to 2.39	.25
MUD with ATG	2.31	1.50 to 3.54	< .001
MUD without ATG	1.31	0.81 to 2.12	.28
Age, years			
≤ 39			
≥ 40	1.83	1.28 to 2.63	< .001
Performance status			
Good			
Poor	2.39	1.22 to 4.68	.011
Refractory HL			
Nonrefractory			
Refractory	1.60	1.03 to 2.47	.037
Cox model on relapse rate			
Donor type			
SIB			
HAPLO	0.69	0.48 to 1.0	.047
MUD with ATG	0.67	0.48 to 0.94	.019
MUD without ATG	0.48	0.34 to 0.68	< .001
Sex			
Female			
Male	1.28	1.01 to 1.64	.045
Performance status			
Good			
Poor	1.84	1.08 to 3.13	.026
Refractory HL			
Nonrefractory			
Refractory	2.68	2.98 to 6.37	< .001
Cox model on OS			
Donor type			
SIB			
HAPLO	1.27	0.86 to 1.86	.22
MUD with ATG	1.71	1.25 to 2.36	.001
MUD without ATG	1.27	0.91 to 1.78	.16
Age, years			
≤ 39			
≥ 40	1.58	1.22 to 2.06	.001
Performance status			
Good			
Poor	2.37	1.48 to 3.80	< .001
Refractory HL			
Nonrefractory			
Refractory	2.13	1.61 to 2.83	< .001
Cox model on PFS			
Donor type			
SIB			
HAPLO	0.87	0.64 to 1.17	.36
MUD with ATG	1.03	0.80 to 1.33	.80
MUD without ATG	0.67	0.51 to 0.89	.005
Age, years			
≤ 39			
≥ 40	1.29	1.04 to 1.60	.021
Performance status			
Good			
Poor	2.0	1.32 to 3.03	.001
Refractory HL			
Nonrefractory			
Refractory	2.22	1.76 to 2.80	< .001

Abbreviations: ATG, antithymocyte globulin; HAPLO, haploidentical donor; HL, Hodgkin lymphoma; HR, hazard ratio; MUD, match-unrelated donor; NRM, nonrelapse mortality; OS, overall survival; PFS, progression-free survival; SIB, sibling donor.