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blood advances

PTCy-based haploidentical vs matched related or unrelated donor reduced-intensity conditioning transplant for DLBCL

Peter Dreger,[1,*] Anna Sureda,[2,*] Kwang Woo Ahn,[3,4] Mary Eapen,[4] Carlos Litovich,[4] Herve Finel,[5] Ariane Boumendil,[5] Ajay Gopal,[6] Alex F. Herrera,[7] Christoph Schmid,[8] José Luis Diez-Martin,[9] Ephraim Fuchs,[10] Javier Bolaños-Meade,[10] Mahasweta Gooptu,[11] Monzr M. Al Malki,[7] Luca Castagna,[12] Stefan O. Ciurea,[13] Alida Dominietto,[14] Didier Blaise,[15] Fabio Ciceri,[16] Johanna Tischer,[17] Paolo Corradini,[18] Silvia Montoto,[5,19] Stephen Robinson,[5,20] Zafer Gülbas,[21] and Mehdi Hamadani[4]

[1]Department Medicine V, University of Heidelberg, Heidelberg, Germany; [2]Hematology Department, Institut Català d'Oncologia–Hospitalet, Barcelona, Spain; [3]Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, WI; [4]Center for International Blood and Marrow Transplant Research, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI; [5]European Society for Blood and Marrow Transplantation, Paris, France; [6]Division of Medical Oncology, Clinical Research Division, Department of Medicine, University of Washington, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, Seattle, WA; [7]City of Hope, Duarte, CA; [8]Klinikum Augsburg, Augsburg, Germany; [9]Hospital Gregorio Marañón, Madrid, Spain; [10]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [11]Dana-Farber Cancer Institute, Boston, MA; [12]Istituto Clinico Humanitas, Rozzano Milan, Italy; [13]University of Texas, MD Anderson Cancer Center, Houston, TX; [14]Divisione Ematologia e Trapianto di Midollo, Istituto di Ricovero e Cura a Carattere Scientifico San Martino, Genoa, Italy; [15]Programme de Transplantation and Thérapie Cellulaire–Centre de Recherche en Cancérologie de Marseille, Institut Paoli Calmettes, Marseille, France; [16]Hematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, Milan, Italy; [17]Department of Internal Medicine III, Campus Großhadern, University of Munich, Munich, Germany; [18]Department of Oncology and Hematology, University of Milan, Milan, Italy; [19]Department of Haemato-oncology, St Bartholomew's Hospital, Barts Health NHS Trust, London, United Kingdom; [20]BMT Unit, University Hospital Bristol NHS Foundation Trust, Bristol, United Kingdom; and [21]Anadolu Medical Center Hospital, Kocaeli, Turkey

Key Points

- PTCy-based haplo-HCT provides lower chronic GVHD rates compared with matched sibling or unrelated donor HCT in DLBCL.
- Three-year OS and PFS after haplo-HCT was 46% and 38%, respectively, in DLBCL.

This study retrospectively compared long-term outcomes of nonmyeloablative/reduced intensity conditioning (NMC/RIC) allogeneic hematopoietic cell transplantation (allo-HCT) from a haploidentical family donor (haplo-HCT) using posttransplant cyclophosphamide (PTCy) with those of matched sibling donor (MSD) and matched unrelated donor (MUD) with or without T-cell depletion (TCD+/TCD−) in patients with relapsed diffuse large B-cell lymphoma (DLBCL). Adult patients with DLBCL who had undergone their first NMC/RIC allo-HCT between 2008 and 2015 were included. Recipients of haplo-HCT were limited to those receiving graft-versus-host disease (GVHD) prophylaxis with PTCy. GVHD prophylaxis in MSD was limited to calcineurin inhibitor (CNI)–based approaches without in vivo TCD, while MUD recipients received CNI-based prophylaxis with or without TCD. Outcome analyses for overall survival (OS) and progression-free survival (PFS), nonrelapse mortality (NRM), and disease relapse/progression were calculated. A total of 1438 patients (haplo, 132; MSD, 525; MUD TCD+, 403; and MUD TCD−, 378) were included. Patients with haplo donors were significantly older, had a better performance status and had more frequently received total body irradiation-based conditioning regimens and bone marrow grafts than MSD and MUD TCD+ or TCD−. 3-year OS, PFS, NRM and relapse/progression incidence after haplo-HCT was 46%, 38%, 22%, and 41%, respectively, and not significantly different from outcomes of matched donor transplants on multivariate analyses. Haplo-HCT was associated with a lower cumulative incidence of chronic GVHD compared with MSD, MUD TCD+/TCD−. NMC/RIC haplo-HCT with PTCy seems to be a valuable alternative for patients with DLBCL considered for allo-HCT but lacking a matched donor.

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*P.D. and A.S. contributed equally to this study.

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Introduction

Although rituximab-based chemoimmunotherapy (CIT) is highly effective in diffuse large B-cell lymphoma (DLBCL), 20% to 40% of patients with DLBCL do not respond to standard first-line CIT or experience disease recurrence within 1 year after diagnosis. Only a minority of these early failures can be durably rescued by high-dose chemotherapy with autologous hematopoietic cell transplantation (auto-HCT), while the majority will be chemotherapy resistant.[1,2] Although chimeric antigen receptor–engineered T cells (CAR-T cells) have been recently approved for patients with DLBCL who have failed second-line CIT,[3,4] an accepted alternative salvage strategy in this poor-risk setting in eligible patients is cellular immunotherapy by allogeneic hematopoietic cell transplantation (allo-HCT).[5-7] Using well-matched sibling donors (MSDs) or unrelated donors (MUDs), allo-HCT can result in sustained disease control in 30% to 45% of patients with DLBCL who have early disease recurrence after standard CIT or have failed auto-HCT.[8-12] However, the search for a well-matched unrelated donor could be time-consuming and unsuccessful in up to 50% of the patients in need.[13]

With the introduction of posttransplant cyclophosphamide-based immunosuppression (PTCy), allo-HCT using haploidentical related donors (haplo-HCT) has emerged as a valuable alternative for patients without an available MSD or MUD.[14-16] Similar to other allo-HCT standard indications, PTCy haplo-HCT seems to provide disease control and survival rates comparable to MSD/MUD transplants (using conventional calcineurin inhibitor [CNI]–based prophylaxis) in patients with lymphoma despite a significantly reduced risk of chronic graft-versus-host disease (GVHD) compared with the traditional donor sources.[14,17-22] However, these results derive from retrospective analyses of patient samples with the global diagnoses of Hodgkin lymphoma and/or non-Hodgkin lymphoma (NHL). Since in particular the various NHL subsets are characterized by fundamental differences in biology and allo-HCT efficacy,[23] disease-specific studies on the main NHL entities are mandatory. Here, we provide the first comparison of haplo-HCT with MSD/MUD transplants in patients with DLBCL.

Materials and methods

Data sources

The study was performed through collaboration between the European Society for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR) lymphoma working committees. EBMT is a voluntary organization comprising 640 transplant centers mainly from Europe. Accreditation as a member center requires submission of minimal essential data form from all consecutive patients to a central registry. Since 1996, accredited EBMT centers are subject to on-site audits. Since January 2003, all transplant centers have been required to obtain written informed consent prior to data registration following the Declaration of Helsinki 1975.

CIBMTR is a working group of >500 transplantation 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 transplantations 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 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 Health Insurance Portability and Accountability Act of 1996 Privacy Rule. The institutional review boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

Study design

This was a collaborative retrospective registry-based analysis. Eligible were adult (≥18 years) patients with DLBCL who had undergone their first nonmyeloablative or reduced-intensity conditioning (NMC/RIC) allo-HCT between 2008 and 2015. Eligible donors included MSD, 8/8 MUD (allele-level match at HLA-A, -B, -C, and -DRB1), or haploidentical related donors (mismatched for ≥2 HLA loci). Recipients of haplo-HCT were limited to those receiving GVHD prophylaxis with PTCy (with or without CNI and mycophenolate mofetil). GVHD prophylaxis in MSD was limited to CNI-based approaches without antithymocyte globulin/alemtuzumab in-vivo T-cell depletion (TCD), while MUD recipients received CNI-based prophylaxis with or without in vivo TCD. Patients receiving ex vivo graft manipulation (eg, CD34 selection) were excluded. CIBMTR cohort was limited to patients from the United States and Canada only to avoid duplicate inclusion of European patients reported to both registries.

Definitions

The intensity of allo-HCT conditioning regimens was categorized as NMC/RIC using consensus criteria.[24] Disease response at the time of HCT was determined using the International Working Group criteria in use during the era of this analysis.[25]

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 follow-up. Secondary outcomes included nonrelapse mortality (NRM), progression/relapse, and progression-free survival (PFS). NRM was defined as death without evidence of prior lymphoma progression/relapse; relapse was considered a competing risk. Progression/relapse was defined as progressive lymphoma after HCT or lymphoma recurrence after a complete response (CR); NRM was considered a competing risk. For PFS, a patient was considered a 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 and chronic GVHD were graded using established clinical criteria.[26,27] GVHD-free, relapse-free survival (GRFS) was calculated using the modification proposed by Ruggeri et al for registry-based studies.[28] Probabilities of GRFS, PFS, and OS were calculated using the Kaplan-Meier estimates. Neutrophil recovery was defined as the first of 3 successive days with absolute neutrophil count $\geq 0.5 \times 10^9$/L after posttransplantation nadir. Platelet recovery was considered to have occurred on the first of 3 consecutive days

with platelet count 20×10^9/L 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-HCT cohort was compared against the MSD, MUD with TCD (MUD TCD+), and MUD without TCD (MUD TCD−) cohorts. Patient-, disease- and transplant-related variables were compared among the 4 cohorts using the χ^2 test for categorical variables and the Wilcoxon 2-sample test for continuous variables. Cumulative incidences of hematopoietic recovery, acute and chronic 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 chronic GVHD, relapse, NRM, PFS, and OS and logistic regression for acute GVHD. 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. 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. Results are expressed as odds ratio for acute GVHD and relative risk (RR) for chronic GVHD, relapse, NRM, PFS, and OS. The variables considered in multivariate analysis are shown in supplemental Table 1. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patient and transplant characteristics

Altogether, 1438 eligible patients (haplo, 132; MSD, 525; MUD TCD+, 403; and MUD TCD−, 378) were included. Compared with the MSD and MUD cohorts, patients with haploidentical donors were significantly older, had a better performance status (PS), and were less likely to have received a prior auto-HCT. Moreover, total body irradiation (TBI)–based conditioning and bone marrow grafts as standard elements of the original PTCy platform were predominantly used in the haplo-HCT group, while the vast majority of the MSD/MUD transplants were performed with peripheral blood grafts and TBI-free conditioning. In contrast, there were no significant differences in terms of sex, time from diagnosis to transplant, and disease status at HCT among the 4 cohorts. Details are given in Table 1.

Hematopoietic recovery

Although the proportion of patients having achieved neutrophil recovery by day +28 tended to be lower in the haplo group (90%) than in the MSD/MUD cohorts (95% to 97%), this difference was not statistically significant. Virtually all patients in all groups had reached neutrophil engraftment by day +100. In contrast, platelet recovery was significantly delayed in the haplo group, with 61% and 91% by day +28 and day +100, respectively, compared with 89% to 92% and 96% to 98%, respectively, in the MSD/MUD cohorts (Table 2).

GVDH

Acute GVHD grade 2 to 4 (grade 3 to 4) was reported in 34% (7%) of the haplo-transplanted patients and was thus not significantly different from the acute GVHD rates in the MSD group (32% [11%]) and the MUD TCD+ group (32% [13%]). In contrast, the grade 2 to 4 (42%) and grade 3 to 4 (19%) acute GVHD risk was significantly increased in patients transplanted from MUD without TCD in univariate and multivariate comparisons (Tables 2 and 3). The cumulative incidence of chronic GVHD at 1 and 2 years after haplo-HCT was 15% and 18%, respectively. This was significantly lower than the corresponding incidences in the MSD group (41% and 48%), the MUD TCD+ group (23% and 27%), and the MUD TCD− group (48% and 57%) by univariate and multivariate comparisons (Tables 2 and 3; Figure 1A). Within the MUD TCD+ cohort, compared with ATG, the use of alemtuzumab was associated with a significant reduction of grade 3 to 4 acute GVHD but did not affect any other end point (supplemental Table 3).

NRM

The 3-year cumulative incidences of NRM in the haplo-HCT, MSD, MUD TCD+, and MUD TCD− cohorts were 22%, 17%, 26%, and 30%, respectively (Table 2; Figure 1B). There was no significant difference among the 4 groups on multivariate analysis if the haplo-HCT cohort was used as reference. However, the MSD cohort had a significantly reduced NRM risk if the MUD TCD− cohort served as comparator (RR, 0.71; 95% confidence interval [CI)], 0.54-0.93; $P = .01$) (Table 3). Other significant predictors of NRM risk were increasing age and HCT-CI (supplemental Table 4).

Disease control

The 3-year cumulative incidence of relapse/progression was 41% (95% CI, 32% to 49%) in the haplo-HCT group compared with the 3-year cumulative incidence of 47%, 38%, and 34% for the MSD, MUD TCD+, and MUD TCD− cohorts, respectively. On multivariate analysis, the relapse incidence tended to be lower with MUD TCD− than with haplo-HCT (RR, 0.73; 95% CI, 0.53-1.00; $P = .05$). Compared with MUD TCD−, MSD-HCT was associated with a higher risk of relapse/progression (RR, 1.45; 95% CI, 1.17-1.80; $P = .0008$) (Tables 2 and 3). Other factors adversely affecting relapse risk are shown in supplemental Table 4. Of note, the majority of relapse/progression events occurred during the first posttransplant year in all 4 donor groups (Figure 1C).

Survival

With a median follow-up of 4.1 (1.0-6.1) years, 3-year OS in the haplo-HCT group was 46% (95% CI, 37% to 55%) and thus comparable to the matched donor groups, with 50%, 43%, and 46% for MSD, MUD TCD+, and MUD TCD−, respectively (Table 2; Figure 1E). Similarly, there were no significant differences in PFS (38%, 37%, 36%, and 37% at 3 years for haplo donors, MSD, MUD TCD+, and MUD TCD−, respectively) (Table 2; Figure 1D). Multivariate analyses confirmed the absence of significant OS and PFS differences among the 4 groups (Table 3). In contrast, disease status less than CR and decreased PS significantly reduced OS and PFS on multivariate analysis. In addition, OS was affected by increasing age and HCT-CI (supplemental Table 4).

Two-year composite end point GRFS following haplo-HCT was 36% (95% CI, 28% to 45%) compared with 23% (95%CI 19% to 27%) following MSD ($P = .007$), 19% (95% CI, 15% to 24%) following MUD TCD− ($P < .001$) and 33 (95% CI, 28% to 39%) following MUD TCD+ ($P = .60$) (Figure 1F). However, when GRFS

Table 1. Patient characteristics

	Haplo donor	MSD	MUD TCD+	MUD TCD−	*P*
Number of patients	132	525	403	378	
Number of centers	24	86	45	51	
Reporting registry					<.001
CIBMTR	97 (73)	353 (67)	166 (41)	263 (70)	
EBMT	35 (27)	172 (33)	237 (59)	115 (30)	
Patient age, median (range), y	58 (20-75)	55 (19-73)	55 (19-75)	56 (23-73)	<.001
Patients ≥60 y	59 (45)	135 (26)	121 (30)	134 (35)	
Male sex	86 (65)	323 (62)	259 (64)	218 (58)	.22
KPS ≥90	96 (73)	325 (62)	249 (62)	216 (57)	.003
KPS missing	5 (4)	24 (4)	26 (6)	10 (2)	
HCT-CI					<.001
0	33 (25)	119 (23)	54 (13)	63 (17)	
1-2	31 (23)	112 (21)	75 (19)	84 (22)	
≥3	36 (27)	137 (26)	85 (21)	125 (33)	
Missing*	33 (25)	157 (30)	189 (47)	106 (28)	
Patient race					<.001
White	91 (69)	349 (66)	258 (64)	282 (75)	
African American	15 (11)	12 (2)	2 (<1)	5 (1)	
Other	2 (2)	36 (8)	2 (<1)	7 (1)	
Missing	24 (18)	128 (24)	141 (36)	84 (22)	
Time from diagnosis to transplant, median (range), mo	22 (<1-173)	26 (2-386)	24 (2-340)	28 (2-299)	.18
Previous auto-HCT	56 (42)	288 (55)	237 (59)	229 (61)	.002
Remission status at HCT					.72
Complete	63 (48)	217 (41)	179 (44)	171 (45)	
Partial	45 (34)	181 (34)	133 (33)	133 (35)	
Refractory	23 (17)	109 (21)	74 (18)	64 (17)	
Untreated/unknown	1 (<1)	18 (4)	17 (5)	10 (3)	
TBI in conditioning†	114 (86)	109 (21)	30 (7)	121 (32)	<.001
Graft type					<.001
Bone marrow	100 (76)	10 (2)	30 (7)	20 (5)	
Peripheral blood	32 (24)	515 (98)	373 (93)	358 (95)	
CMV status					
D+/R−	11 (8)	38 (7)	21 (5)	31 (8)	<.001
Missing	64 (49)	257 (49)	240 (58)	120 (31)	
D-R sex match					<.001
Female-male	42 (32)	139 (26)	95 (24)	66 (17)	
Other	90 (68)	386 (74)	306 (75)	311 (82)	
Missing	0	2 (<1)	2 (<1)	1 (<1)	
GVHD prophylaxis					<.001
PTCy	132	N/A	N/A	N/A	
CNI + MMF ± others	N/A	191 (36)	158 (39)	159 (42)	
CNI + MTX ± others	N/A	236 (45)	154 (38)	150 (40)	
CNI + others	N/A	98 (19)	91 (23)	69 (18)	
Follow-up of survivors, median (range), mo	49 (12-73)	48 (2-97)	49 (3-100)	39 (4-96)	

Values in parentheses represent percentages if not indicated otherwise.

A/C, anti–thymocyte globulin/alemtuzumab; CMV, cytomegalovirus; D-R, donor-recipient; HCT-CI, hematopoietic cell transplant-comorbidity index; KPS, Karnofsky performance score; MMF, mycophenolate mofetil; MTX, methotrexate; N/A, not applicable; w, with; w/o, without.

*EBMT does not collect this variable for minimal essential data (MED-A) patients.

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

Table 2. Univariate outcomes

Outcomes	Haploidentical donor (n = 132)		MSD (n = 525)		MUD TCD+ (n = 403)		MUD TCD− (n = 378)		P
	Eval	Prob (95% CI), %	Eval	Prob (95% CI), %	Eval	Prob (95% CI), %	Eval	Prob (95% CI), %	
Neutrophil recovery	126		475		383		336		.004
28 d		90 (84-94)		97 (95-98)*		95 (93-97)		96 (93-98)	.10
100 d		99 (97-100)		99 (98-100)		98 (97-99)		99 (98-100)	.79
Platelet recovery	82		342		276		238		<.001
28 d		61 (50-71)		92 (89-95)*		89 (85-92)*		89 (84-92)*	<.001
100 d		91 (84-96)		99 (97-100)*		96 (93-98)		98 (96-99)	.01
Acute GVHD 2-4	123		490		377		359		.001
180 d		34 (26-43)		32 (28-36)		32 (28-38)		42 (37-47)	.01
Acute GVHD 3-4	123		456		377		359		<.001
180 d		7 (3-12)		11 (9-14)		13 (10-16)		19 (15-23)*	<.001
Chronic GVHD	124		522		403		335		<.001
1 y		15 (9-21)		41 (37-46)*		23 (19-28)		48 (42-53)*	<.001
2 y		18 (12-26)		48 (43-52)*		27 (23-32)		57 (52-63)*	<.001
NRM	132		525		403		378		.001
1 y		16 (10-23)		13 (10-16)		21 (17-26)		20 (16-24)	.007
3 y		22 (15-30)		17 (13-20)		26 (21-31)		30 (25-35)	<.001
Relapse/progression	132		525		403		378		<.001
1 y		34 (26-43)		39 (34-43)		33 (28-38)		28 (23-33)	.01
3 y		41 (32-49)		47 (42-51)		38 (33-43)		34 (29-39)	.001
PFS	132		525		403		378		.72
1 y		50 (41-58)		48 (44-53)%		46 (40-51)		52 (47-57)	.32
3 y		38 (29-47)		37 (32-41)		36 (31-41)		37 (31-42)	.99
OS	132		525		403		378		.36
1 y		66 (58-74)		65 (61-69)		56 (51-61)		63 (58-68)	.03
3 y		46 (37-55)		50 (45-55)		43 (38-49)		46 (41-52)	.32

Eval, number of evaluable patients; Prob, probability; TCD+, TCD with alemtuzumab or anti–thymocyte globulin; TCD−, TCD without alemtuzumab or anti–thymocyte globulin.
*Significant pairwise comparisons in reference to the haploidentical donor group.

of the haplo group was broken down to graft source, it seemed that the benefit was restricted to those patients who received a marrow graft (2-year GRFS 40% (95% CI, 30% to 50%) for bone marrow vs 23% (95% CI, 8% to 41%) for peripheral blood; $P = .08$).

To ensure that outcomes reported in the current analysis were not driven by institutional expertise, transplant center effect was examined using the random effect score test. No center effect on the hazard of OS ($P = .71$), PFS ($P = .89$), relapse ($P = .43$), and NRM ($P = .50$) was seen.

Causes of death

The most common cause of death in all 4 cohorts was progressive DLBCL (haplo, 44%; MSD, 53%; MUD TCD+, 47%; and MUD TCD−, 34%). GVHD was considered as main cause of death only in minority of patients, with the highest proportion in the MUD TCD− group (11%), followed by MUD TCD+ (6%) and MSD and haplo-HCT (3% each) (supplemental Table 5).

Discussion

Allo-HCT is an effective treatment strategy to rescue patients with DLBCL who relapse after auto-HCT and as a first transplant in those patients with adverse prognostic features at the time of relapse that predict poor outcomes with auto-HCT.[5] The availability of haplo donors in this setting would eventually give almost every transplant-eligible patient access to allo-HCT. The joint analysis performed by the EBMT and CIBMTR presented here indicates that with the precise inclusion criteria considered here, outcomes of haplo-HCT do not seem inferior to that of standard donor sources (MSD and MUD). Of note, the cumulative incidence of chronic GVHD after transplant was significantly lower in the haplo group compared with MSD and MUD TCD−, thus significantly improving GFRS after haplo-HCT in comparison with T-replete transplantation from matched donors (despite no differences in severe acute GVHD, relapse, and mortality).

Similar to previous retrospective analyses of unspecified pooled lymphoma populations,[8-12] this first DLBCL-specific study on haplo-HCT shows that all main survival outcomes are comparable with those of standard well-matched donor transplants. This is particularly noteworthy for the risk of relapse/progression, since DLBCL appears to be less graft-versus-leukemia (GVL) sensitive than other NHL entities, such as follicular lymphoma and mantle cell lymphoma,[23,29] and thus might rely more on intensive conditioning.[10]

Table 3. Multivariate analysis

	n	OR or RR*	Lower CL	Upper CL	*P*	Overall *P*
Acute grade 2-4 GVHD						
Haploidentical donors	123	1				.009
MSD	493	0.88	0.58	1.33	.54	
MUD TCD+	377	0.92	0.60	1.41	.70	
MUD TCD−	359	1.39	0.90	2.13	.13	
Acute grade 3-4 GVHD						
Haploidentical donors	123	1				.0007
MSD	493	1.56	0.75	3.26	.24	
MUD TCD+	377	1.84	0.88	3.89	.11	
MUD TCD−	359	3.05	1.47	6.32	.0028	
Chronic GVHD						
Haploidentical donors	127	1				<.0001
MSD	469	3.15	2.08	4.77	<.0001	
MUD TCD+	321	2.05	1.32	3.17	.001	
MUD TCD−	344	4.06	2.68	6.15	<.0001	
NRM						
Haploidentical donors	132	1				.08
MSD	522	0.90	0.60	1.36	0.62	
MUD TCD+	403	1.17	0.77	1.76	0.46	
MUD TCD−	378	1.28	0.86	1.91	0.23	
Significant contrast						
MSD vs MUD TCD−		0.71	0.54	0.93	.01	
Relapse/progression						
Haploidentical donors	132	1				.009
MSD	525	1.06	0.79	1.41	.71	
MUD TCD+	403	0.92	0.68	1.25	.60	
MUD TCD−	378	0.73	0.53	1.00	.05	
Significant contrast						
MSD vs MUD TCD−		1.45	1.17	1.80	.0008	
PFS						
Haploidentical donors	132	1				.45
MSD	522	0.94	0.74	1.19	.61	
MUD TCD+	403	0.97	0.76	1.24	.84	
MUD TCD−	378	0.86	0.67	1.09	.21	
OS						
Haploidentical donors	132	1				.52
MSD	522	0.90	0.69	1.16	.42	
MUD TCD+	403	1.02	0.78	1.33	.90	
MUD TCD−	378	0.91	0.70	1.19	.49	

The main effect of multivariate analysis is shown. Complete multivariate analysis results are provided in supplemental Table 3.
CL, confidence limit.
*Values are odds ratios (ORs) for "Acute grade 2-4 GVHD" and "Acute grade 3-4 GVHD"; all others are RR.

The fact that the vast majority of the haplo transplants in this study were performed using the nonmyeloablative Baltimore conditioning regimen (67%; supplemental Table 2) providing only modest antilymphoma activity implies that the GVL effect conferred with the bone marrow/PTCy haplo platform is potent enough to compensate for an eventually reduced contribution of the conditioning regimen to disease control. Of note, this seems to be the case despite a strongly reduced incidence of chronic GVHD, as it is the rule in PTCy-based haplotransplants.

However, unlike in indolent B-cell neoplasms,[23,30] the association between chronic GVHD and GVL is less well documented in DLBCL allotransplants.[8-10,23] Accordingly, the reduced incidence

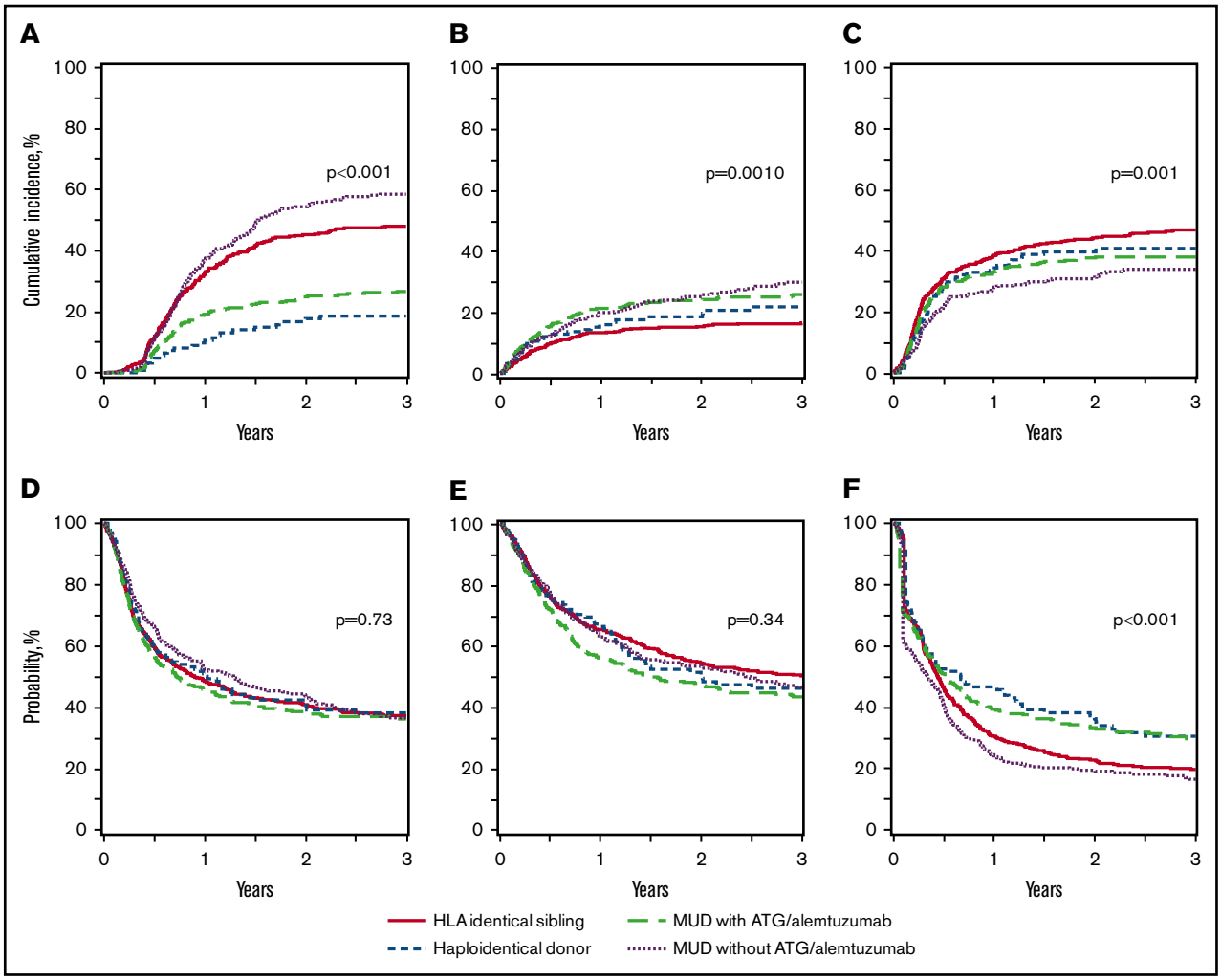

Figure 1. Transplantation outcomes. (A) Cumulative incidence of chronic GVHD. (B) Cumulative incidence of NRM. (C) Cumulative incidence of relapse. (D) PFS. (E) OS. (F) GRFS. ATG, anti–thymocyte globulin.

of chronic GVHD observed in our haplo group did not significantly increase the risk of relapse/progression, suggesting that the composite end point GRFS seems to be clinically relevant in patients with DLBCL. To this end, haplo-HCT with the PTCy platform may have advantages over CNI-based matched donor transplants in this entity, although the subset analyses of our haplo cohort suggest that the superior GRFS observed may be due to the use of bone marrow instead of peripheral blood grafts (which were used in the vast majority of the patients in the matched donor groups).[31,32] In contrast, the delayed platelet engraftment associated with haplo-HCT, as shown in this and other studies,[21] may have adverse implications in terms of quality of life and resource utilization, but a detailed analysis of this issue was beyond the scope of our study.

When interpreting the results of the present analysis, some important shortcomings inherent to the design of the study need to be taken into consideration. There are some significant differences in terms of clinical characteristics before transplant between haplo patients and patients in other groups, such as PS and rate of prior auto-HCT, which may have confounded the comparison despite Cox modeling (supplemental Tables 1 and 4). Moreover, and as expected, the transplant procedure was also different between the haplo group and the other groups; more TBI-based conditioning regimens were used in the haplo patients, and bone marrow cells were more frequently used. Most importantly, and by definition, GVHD prophylaxis was inherently different among groups. As results of allo-HCT using the PTCy bone marrow platform in HLA-compatible settings emerge,[33,34] it will be important to study how PTCy-based matched donor transplants compare with PTCy-based haplo-HCT in DLBCL. Currently, the use of PTCy in matched donor HCT remains uncommon; for example, from 2015 to 2016, only ~8% (n = 19) of DLBCL patients undergoing MSD or MUD HCT in the United States received PTCy-based GVHD prophylaxis. Data on genetic risk factors (such as *c-myc* status) are not routinely collected by the CIBMTR and EBMT registries and may have differed between groups. Finally, additional confounders that could not be compensated in the present analysis, such as center effects, may have biased the comparisons performed here.

Of note, myeloablative conditioning regimens were disregarded in this analysis. The major reason for that was to reduce the

heterogeneity in the groups, as the number of patients identified in the 2 registries who were transplanted using a myeloablative conditioning regimen was <20 in the haplo group. NMC/RIC allotransplants represent a significant proportion of this activity in patients with DLBCL; allo-HCT is most frequently used when patients fail auto-HCT, and information coming from some registry analyses indicates that the intensity of the conditioning regimen does not significantly modify the outcome of the procedure.[35,36]

With more than 1400 patients, this study is also the largest ever performed on allo-HCT for DLBCL, and survival data are in keeping with those observed in previous smaller series investigating both MSD and MUD transplants.[8-10,12,37] Moreover, the present study confirms for the first time for DLBCL earlier findings made in MUD transplants in patients with acute leukemia[38] and unspecified lymphoma[19] suggesting that in vivo TCD with ATG does not improve NRM and overall mortality despite a reduced incidence of chronic GVHD (although the latter effect was not significant in the present study). This is in contrast with the only prospective study on allo-HCT in DLBCL performed to date.[10]

In the era of novel treatment strategies, one must take into consideration the potential impact that CAR-T cells will have on the use of allogeneic strategies. The pivotal phase 2 clinical trial ZUMA-1[4] using axicabtagene ciloleucel, an anti-CD19 CAR-T-cell construct, in patients with relapsed/refractory DLBCL initially demonstrated a durable CR rate in 40% of the patients with a median follow-up of 15.4 months. Comparable results were observed in phase 2 trials using tisagenlecleucel and lisocabtagene maraleucel, respectively, in patients with multiply relapsed/refractory aggressive B-cell lymphoma, although the follow-up was still short.[39,40] Treatment-related toxicity mainly included neurological effects and cytokine release syndrome, but the NRM associated with CD19 CAR-T cells in DLBCL seems to be generally <5%. Although these compelling results will potentially compete with those of allo-HCT, the number of patients treated with CAR-T cells is still quite limited, and follow-up is too short to be meaningful for long-term outcome. For example, in the long-term follow-up of ZUMA-1 subjects, while median OS was not reached, the median PFS was a modest 5.9 months.[41] Finally, the enormous economic impact associated with this treatment strategy has to be taken into account. The currently ongoing global phase 3 trials comparing CAR-T cells with standard of care in second-line treatment will help to define the role of CAR-T cells in the treatment algorithm of DLBCL.

The transplant registry character of the current study precludes conclusions on the impact of allo-HCT on the natural history of DLBCL. For example, only a minority of those patients who had DLBCL recurrence after auto-HCT on the CORAL trial were able to proceed to salvage allo-HCT.[42] Future studies should therefore follow an intent-to-treat design, ideally comparing allo-HCT with CAR-T-cell therapies in a prospective randomized manner.

In summary, this study suggests that in DLBCL outcome after RIC haplo-HCT with PTCy may be comparable to that after RIC allo-HCT using matched donors despite a lower risk of chronic GVHD, at least if marrow is used as a haplo graft source. This might be of particular relevance in patients with highly proliferative or advanced disease who need to rapidly proceed to an allo-HCT. However, additional studies are needed before haploidentical donors can be considered as equivalent to well-matched related or unrelated donors in patients with DLBCL.

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Authorship

Contribution: P.D., A.S., and M.H. conceived and designed the study; C.L., H.F., A.B., and M.H. collected and assembled data; K.W.A., C.L., and M.H. analyzed data, and all authors interpreted data; P.D., A.S., and M.H. wrote the first draft of the manuscript; and all authors helped revise the manuscript and approved the final version of the manuscript.

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Correspondence: Mehdi Hamadani, Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, 9200 W Wisconsin Ave, Suite C5500, Milwaukee, WI 53226; e-mail: mhamadani@mcw.edu.

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