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Peripheral Blood Stem Cells versus Bone Marrow for T Cell–Replete Haploidentical Transplantation with Post-Transplant Cyclophosphamide in Hodgkin Lymphoma

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A B S T R A C T

Haploidentical stem cell transplantation (haplo-SCT) with post-transplant cyclophosphamide (PT-Cy) represents a potential curative strategy for patients with Hodgkin lymphoma (HL) when a matched related or unrelated donor is not available. The role of graft source, either bone marrow (BM) or peripheral blood stem cells (PBSCs), in this setting has not been fully elucidated. We performed a retrospective study on 91 patients with HL to compare the outcome after BM (n = 53) or PBSC (n = 38) transplant. Eighty-nine patients engrafted with no difference between BM and PBSCs in terms of median time for neutrophil (20 versus 20 days, $P = .405$) and platelet (26 versus 26.5 days, $P = .994$) engraftment. With a median follow-up of 40.2 months, 100-day cumulative incidences of grades II to IV acute graft-versus host disease (GVHD) and grades II to IV acute GVHD were 24% and 4%, respectively. Graft source was not associated with a different risk of acute GVHD both by univariate and multivariate analyses. Consistently, 1-year cumulative incidence of chronic GVHD was 7% with no differences between the 2 graft types ($P = .761$). Two-year rates of overall survival (OS), progression-free survival (PFS), nonrelapse mortality, and GVHD/relapse-free survival (GRFS) were 67%, 58%, 20%, and 52%, respectively. By univariate analysis, pretransplant disease status was the main variable affecting all outcomes. By multivariate analysis, PBSCs resulted in a protective factor for OS (hazard ratio [HR], .29; $P = .006$), PFS (HR, .38; $P = .001$), and GRFS (HR, .44; $P = .020$). The other independent variables affecting the final outcome were pretransplant disease status and hematopoietic cell transplant–specific comorbidity index. In conclusion, when planning a haplo-SCT with PT-Cy for patients with poor-risk HL, graft type is an important variable to take into account when selecting the best available donor.

INTRODUCTION

T cell–replete haploidentical transplantation (haplo-SCT) with high-dose post-transplant cyclophosphamide (PT-Cy) has recently widely spread for patients lacking a matched related or unrelated donor. Clinical registry–based retrospective studies have shown comparable outcomes between haplo-SCT and matched related or unrelated donor Allogeneic SCT both in patients with acute myeloid leukemia [1,2] or with lymphomas [3,4].

The initial design of haplo-SCT with PT-Cy comprised bone marrow (BM) cells as the stem cell source [5], but more recently peripheral blood stem cells (PBSCs) have been more frequently used as graft source because of donor convenience, logistics, and with the intent of reducing the incidence of disease relapse that is still considerable after haplo-SCT. Single-center experiences have reported relatively good outcomes using mobilized PBSCs [6–10]. In particular, we have analyzed the effect of stem

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Table 1
Characteristics of Patients with HL Undergoing Haplo-SCT

Characteristics	Haplo-HL	BM	PBSC	*P*
No. of patients	91 (100)	53 (58)	38 (42)	
Median age, yr (range)	31 (18-68)	31 (19-66)	33 (19-68)	.609
Gender				.066
Male	52 (57)	26 (49)	26 (68)	
Female	39 (43)	27 (51)	12 (32)	
Disease status preallogeneic				
CR	58 (64)	33 (62)	25 (66)	.941
PR	23 (25)	14 (26)	9 (24)	
SD/PD	10 (11)	6 (11)	4 (11)	
Conditioning regimens				
Nonmyeloablative	68 (75)	33 (62)	35 (92)	.001
Reduced Intensity	23 (25)	20 (38)	3 (8)	
HCT-CI score				
0-2	51 (56)	37 (70)	14 (37)	.002
≥3	40 (44)	16 (30)	24 (63)	
CMV serostatus				
−/−	79 (87)	44 (83)	35 (92)	.206
Others	12 (13)	9 (17)	3 (8)	
Sex mismatch				
Others	74 (81)	46 (87)	28 (74)	.114
Female → male	17 (19)	7 (13)	10 (26)	
Previous SCT				
No	12 (13)	4 (8)	8 (21)	.060
Yes	79 (79)	49 (92)	30 (79)	
Previous nivolumab				
Yes	15 (16)	11 (21)	4 (11)	.257
No	76 (84)	42 (79)	34 (89)	

Values are n (%) unless otherwise defined. Definition of conditioning intensity was based on Giralt S, et al. Biol Blood Marrow Transplant. 2009;15:367-369. HCT-CI definition was based on Sorror ML, et al. Blood 2005;106:2912. PR indicates partial remission; SD, stable disease; PD, progressive disease; CMV, cytomegalovirus.

cell source on the outcome of 69 patients with hematologic malignancies undergoing haplo-SCT with PT-Cy [10]. We were not able to detect any difference between the 2 graft sources in terms of engraftment, overall survival (OS), nonrelapse mortality (NRM), and risk of acute or chronic graft-versus-host-disease (GVHD).

Haplo-SCT with PT-Cy seems particularly effective in Hodgkin lymphoma (HL) patients [11]. In particular, the European Society for Blood and Marrow Transplantation retrospective study comparing transplantation from haplo donors versus matched related and unrelated donors confirmed the 3 groups had similar survival, but toxicity was reduced after haplo-SCT [12]. In that study 39% of haplo-SCT was supported by PBSCs, without impact on outcome by multivariate analysis. Here we analyzed the effect of stem cell source in 91 HL patients receiving haplo-SCT with PT-Cy with the aim to evaluate if the final outcome was modified by the use of PBSCs or BM.

METHODS

This is a retrospective study comprising 91 consecutive patients with poor-prognosis HL treated with an allogeneic transplant at 2 different institutions, Humanitas Cancer Center (Rozzano, Italy) and Institut Paoli Calmettes (Marseille, France). This analysis comprised all patients who were able to proceed to an allogeneic transplant according to the following criteria shared by both institutions:

- Inclusion criteria: HL relapsed after allogeneic SCT, no HLA identical matched related or unrelated donor, and availability of a haplo donor for allogeneic transplant.
- Exclusion criteria: no previous allogeneic SCT, no active uncontrolled infections, low Karnofsky performance status < 60, or severe organ dysfunction, including a left ventricular ejection fraction < 40%, DL_{CO} < 50%, or creatinine clearance < 50 mL/min.

Patients provided informed consent for the retrospective collection of their data. Results from 62 of these patients were previously published [10,13]. A haplo donor was selected only when any HLA identical donor was not available either from a matched related or matched unrelated donor.

Conditioning Regimen and GVHD Prophylaxis

Two main different conditioning regimens were used: (1) nonmyeloablative, consisting of Cy 14.5 mg/kg on days −5 and −6, fludarabine 30 mg/m^2 from days −6 to −2, and low-dose total body irradiation (2 Gy) on day −1, or (2) reduced intensity, comprising thiotepa 5 to 10 mg/kg on day −6, Cy 30 to 60 mg/kg on day −5, fludarabine 120 mg/m^2 on days −5 to −2, and low-dose total body irradiation (2 Gy) on day −1 (Table 1). GVHD prophylaxis consisted of Cy 50 mg/kg administered on days +3 and +4, tacrolimus or cyclosporine A, and mycophenolate mofetil. Tacrolimus, at a total dose of 1 mg, was administered as a continuous infusion during hospitalization and converted to an oral formulation after discharge. Cyclosporine A was dosed at 3 mg/kg as a continuous infusion until discharge and was converted to an oral formulation thereafter. Their respective dosages were adjusted based on respective range of activity (tacrolimus between 10 and 20 ng/mL and cyclosporine A between 100 and 200 ng/mL). Mycophenolate mofetil was administered at 15 mg/kg p.o. 3 times per day until day +35. Tacrolimus or cyclosporine A and mycophenolate mofetil were started on day +5. Tacrolimus and cyclosporine A were tapered by days +100 to +180. Granulocyte colony-stimulating factor was started on day +5 in all patients.

Stem Cell Sources and Donors

Potential family members were typed at the HLA-A, -B, and -DRB1 loci at high level of resolution. Selected donors were also typed at the HLA-C locus at a high-resolution level. Some donors underwent BM harvest under general anesthesia for a target dose of 3 to 4×10^8 nuclear cells/kg of recipient weight. Other donors were mobilized by the subcutaneous administration of granulocyte colony-stimulating factor for 5 to 6 days at 10 μg/kg/day. The target was a minimum of 4×10^6 CD34/kg. Unmanipulated BM and PBSCs were

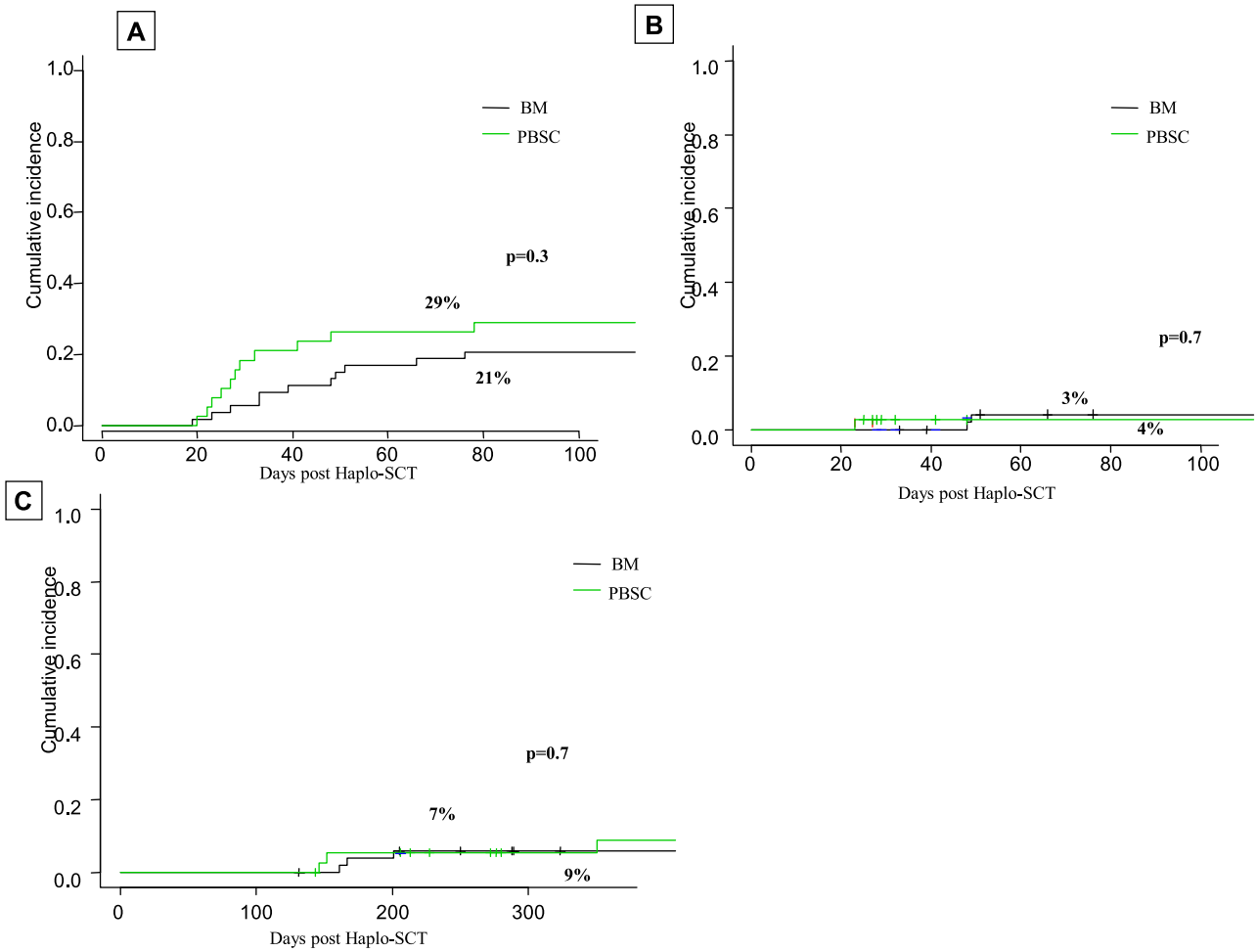

Figure 1. Cumulative incidence (CI) of aGVHD and cGVHD in patients with HL undergoing haplo-SCT with PT-Cy. (A) Six-month CI of grades II to IV aGVHD in the entire population and in patients receiving PBSC or BM grafts. (B) Six-month CI of grades III to IV aGVHD in the entire population and in patients receiving PBSC or BM grafts. (C) Two-year CI of moderate to severe cGVHD in the entire population and in patients receiving PBSC or BM grafts.

used for stem cell support on day 0. Regarding the stem source choice, initially we used BM as reported by Luznik et al. [5]. Subsequently, BM was gradually replaced by PBSCs starting from April 2012. Furthermore, the choice to donate PBSCs or BM depended on donor decision and the availability of a specific prospective protocol.

Supportive Care

Supportive care has been previously reported [13]. Briefly, patients received prophylaxis against bacterial, virus, and fungal infections. They were monitored for cytomegalovirus and Epstein-Barr virus reactivation using PCR, twice a week from days +15 to +100 and then weekly until day +180.

Engraftment and GVHD Evaluation

Neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count of $.5 \times 10^9$/L after transplantation. Platelet engraftment was defined as a platelet count of 20×10^9/L, with no transfusions during the preceding 7 days. Acute GVHD (aGVHD) was graded according to the Keystone criteria [14], and chronic GVHD (cGVHD) was retrospectively graded following the National Institutes of Health criteria [15].

Patients were tested for the presence of donor-specific antibodies. IgG anti-HLA reactivity in the sera was tested with a bead-based screening assay. Briefly, we used the LABScreen Mixed kit (One Lambda Inc., Kittridge, Canoga Park, CA), which simultaneously detects class I and class II antibodies with microbeads coated with purified class I and class II HLA antigens. Results above a cut-off value of 3.0 were considered positive. The Single Antigen kit (One Lambda) was also used to identify HLA specificities. Tests were carried out according to the manufacturer instructions, and the analysis was performed with One Lambda software (HLA Fusion, Bio-Rad, Hercules, CA, USA, version 3.0). Fluorescence intensity, measured on a Luminex analyzer, indicates the relative amount of antibody bound to the test sample. All sera with a mean fluorescence intensity value > 1000 were considered positive.

Statistical Analysis

Data were summarized as frequencies and proportions or median and range. The differences between the groups were estimated by the chi-square test (Fisher exact test when appropriate) or the median test. Outcome were defined in accordance with the European Society for Blood and Marrow Transplantation statistical guidelines, and GVHD/relapse-free survival (GRFS) was defined as reported by Holtan et al. [16] starting the observation from allogenic transplant. Survival analysis (i.e., progression-free survival [PFS], OS, GRFS) was performed using the Kaplan-Meier method [17], and differences between groups were evaluated by the log-rank test. Differences in cumulative incidence outcome (relapse incidence, NRM, aGVHD, cGVHD) were estimated by the Gray test [18]. Hazard ratios (HRs) with their corresponding 95% confidence intervals were calculated using the Cox proportional hazard model [19]. The *P* value for statistical significance was set at .05, and all analyses were performed using SAS (SAS Institute), version 9.4 and R version 3.4.1 (R project: https://www.r-project.org).

RESULTS

From April 2009 to January 2017, 91 consecutive patients with poor-prognosis HL received a haplo-SCT with PT-Cy either from PBSCs (n = 38) or BM (n = 53). Patient characteristics are summarized in Table 1. The 2 cohorts were not statistically different in terms of gender, age, pretransplant disease status, cytomegalovirus serostatus, or previous autologous or allogeneic transplant. The only differences were represented by hematopoietic cell transplant–specific comorbidity index

Table 2
Univariate Analysis of Risk Factors for aGVHD and cGVHD in Patients with HL Undergoing Haplo-SCT

Characteristics	100-Day aGVHD Grades II-IV	*P*	100-Day aGVHD Grades III-IV	*P*	1-Year cGVHD Moderate to Severe	*P*
Disease status preallogeneic						
CR	29	.253	3	.813	8	**<.001**
PR	17		4		10	
SD/PD	10		0		0	
Conditioning						
NMA	26	.378	3	.757	7	.476
RIC	17		4		11	
Graft source						
BM	21	.315	4	.775	7	.761
PBSCs	29		3		9	
Previous SCT						
No	25	.830	8	.289	17	.727
Yes	24		3		7	
CMV						
Others	20	**.034**	4	.495	8	.816
−/+	50		0		9	
Sex mismatch						
No	27	.196	3	.521	8	.874
F → M	12		6		6	
HCT-CI score						
0-2	24	.858	6	.121	4	.194
≥3	25		0		13	
Sex						
Female	28	.498	3	.746	9	.741
Male	21		4		7	
Age						
≤31 yr	24	.908	0	.077	5	.339
>31 yr	24		7		10	

NMA indicates nonmyeloablative; RIC, reduced-intensity conditioning; F→M, female donor into male recipient.
$p < 0.05$ values are in bold.

(HCT-CI), with more patients having an unfavorable score ≥ 3 within the PBSC group ($P = .002$), and the intensity of the conditioning, with more subjects receiving nonmyeloablative conditioning within the PBSC cohort ($P = .001$).

Hematopoietic Recovery

There were 2 donor-specific antibody–linked graft failures after BM and none after PBSC grafts ($P = .5$). The median time to neutrophil recovery was similar in the 2 cohorts: 20 days (range, 15 to 32) after PBSC graft versus 20 days (range, 13 to 27; $P = .405$) after BM graft. Accordingly, cumulative incidence of neutrophil engraftment at day 30 was 100% for PBSCs and 95% for BM ($P = .39$). Median time to achieve platelet engraftment did not differ between BM and PBSC transplants: 26 days (range, 0 to 185) versus 26.5 days (range, 11 to 139; $P = .994$). Consistently, cumulative incidence of platelets > 20,000/μL at day 60 was 98% after PBSC and 94% after BM transplant ($P = .9$)

Acute and Chronic GVHD

One hundred–day cumulative incidence of grades II to IV aGVHD was 24% for all patients without any difference between BM (21%) and PBSC (29%) recipients ($P = .315$; Figure 1A). Similarly, 100-day cumulative incidence of grades III to IV aGVHD was 4% versus 3% ($P = .775$; Figure 1B), respectively. One-year cumulative incidence of moderate to severe cGVHD was 7% for the entire population and was similar between patients receiving BM (7%) or PBSC graft (9%) ($P = .761$, Figure 1C). By univariate analysis, only cytomegalovirus serostatus and pretransplant disease status were associated with a higher incidence of grades II to IV aGVHD and moderate to severe cGVHD, respectively (Table 2). Of note, patients > 31 years of age had a slighter, but not statistically significant, incidence of grades III to IV aGVHD relative to younger subjects.

OS, PFS, and GRFS

With a median follow-up of 40.2 months (range, .7 to 101.8), 2-year OS and PFS rates for the whole population were 67% (Figure 2A) and 58% (Figure 2D), respectively. By univariate analysis, we did not observe any difference between PBSCs and BM in terms of OS (74% versus 62%, $P = .076$; Figure 2B) and PFS (62% versus 56%, $P = .125$; Figure 2E). As expected, pretransplant disease status was the only variable significantly affecting long-term outcomes by univariate analysis: 2-year OS in complete remission (CR) was 77% versus 63% in partial remission versus 15% in stable/progressive disease, whereas 2-year PFS in CR was 69% versus in 55% in partial remission versus 10% in stable/progressive disease (Figure 2C, F and Table 3). Two-year GRFS was 52% for the whole population with no differences between PBSCs and BM by univariate analysis ($P = .141$; Table 3).

By multivariate analysis, 3 variables remained independent predictors of outcome: pretransplant disease status, graft source, and the HCT-CI (Table 4). Patients not in CR had a worse OS (HR, 3.1; $P < .001$) and PFS (HR, 2.8; $P = .001$) relative to those in CR. PBSC graft type was associated with an

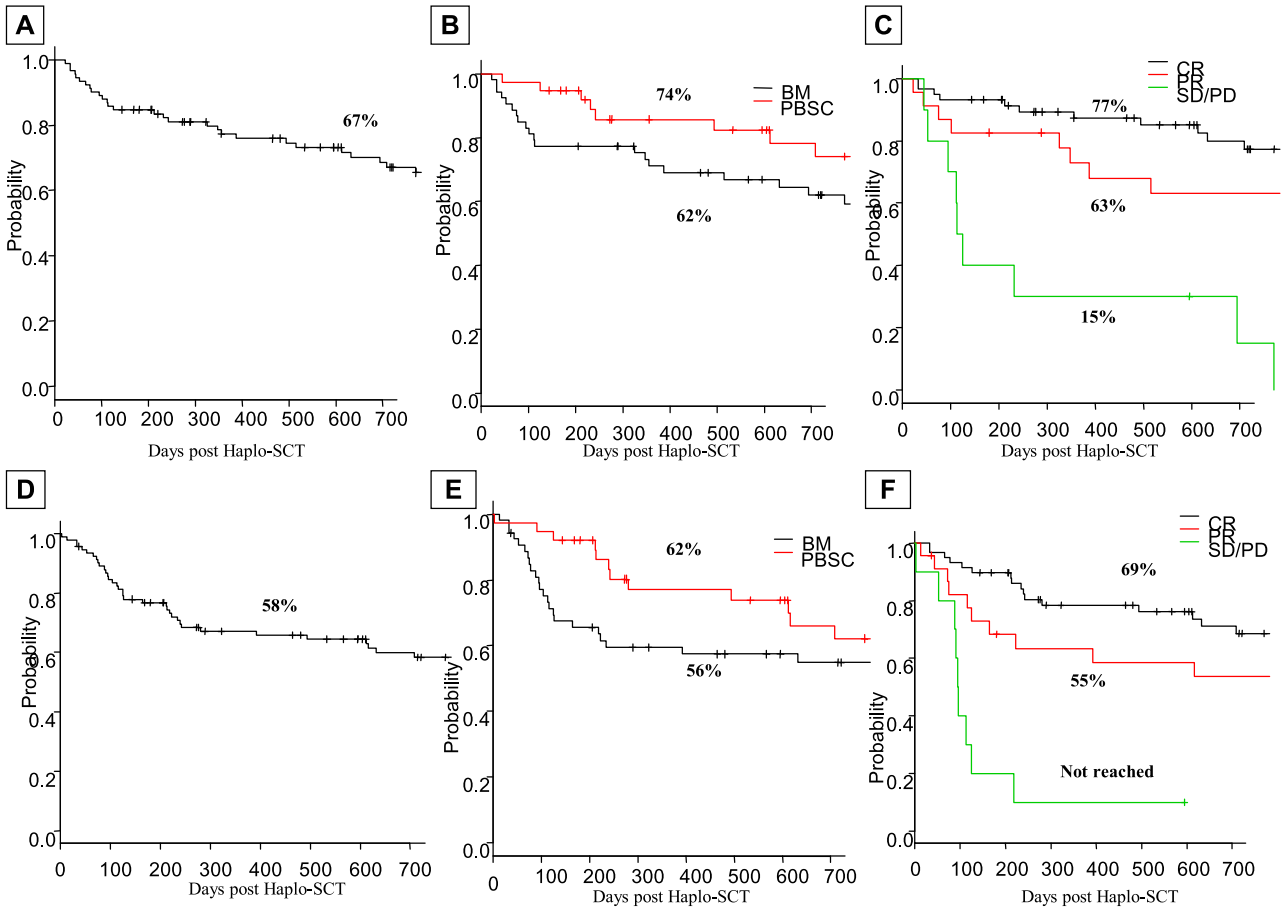

Figure 2. Two-year PFS and OS in with HL patients undergoing haplo-SCT with PT-Cy. Two-year PFS in (A) the entire population, (B) according to graft type, and (C) pretransplant disease status. Two-year OS in (D) the entire population, (E) according to graft type, and (F) pretransplant disease status.

improved OS (HR, .29; $P = .006$) and PFS (HR, .3; $P = .001$) relative to BM cells. Patients with a HCT-CI ≥ 3 had a worse OS (HR, 2.7; $P = .011$) and PFS (HR, 2.2; $P = .031$). By multivariate analysis, the composite outcome of GRFS was affected again by pretransplant disease status (patients not in CR versus CR: HR, 2.4; $P = .003$), graft source (PBSCs versus BM: HR, .4; $P = .020$), and HCT-CI (score > 3 versus 0 to 2: HR, 1.9; $P = .045$). Of note, at 1 year after haplo-SCT 65 of 89 assessable patients (data missing for 2 patients) had stopped immunosuppressants for a cumulative incidence at 1 year of 74%.

Relapse and NRM

Two-year cumulative incidence of disease relapse/progression was 22% for the entire population. When we analyzed patient outcomes according to stem cell source, relapse rate was not statistically different between patients receiving PBSC or BM grafts (18% versus 25%, $P = .333$) (Table 3). Univariate analysis showed that pretransplant disease status was the only variable associated with relapse incidence (Table 3), whereas patients aged ≤ 31 had a higher, but not statistically significant, incidence of disease relapse relative to older subjects.

Two-year NRM rate was 20% for all patients with no difference between transplants from PBSCs (20%) or BM (20%, $P = .460$). Causes of transplant-related death in the BM cohort were represented by infections (pneumonia, 5; septic shock, 2), aGVHD (n = 1), heart failure (n = 1), secondary diseases (n = 2), and thrombotic microangiopathy (n = 1). In the cohort of patients receiving PBSC transplant, causes were infections (pneumonia, 1; septic shock, 1), cGVHD (n = 1), acute myocardial infarction (n = 1), post-transplant lymphoproliferative disease (n = 1), and thrombotic microangiopathy (n = 1). Of note, only 2 patients died because of disease relapse in the PBSC cohort relative to 10 patients in the BM cohort. By univariate analysis, pretransplant disease status was the only variable affecting the risk of NRM (Table 3), whereas patients with HCT-CI ≥ 3 had a much higher, but not statistically different, NRM rate relative to those with HCT-CI < 3 (32% versus 10%, $P = .054$). By multivariable analysis, pretransplant disease status remained the only independent variable associated with the risk of disease relapse, whereas no variable retained an independent significance for NRM (data not shown).

DISCUSSION

In this retrospective study comprising 91 consecutive transplant recipients, we found that stem cell source is an important variable to take into account when choosing the best setting to perform a haplo-SCT with PT-Cy for patients with HL. With a median follow-up of 40.2 months, PBSC graft was associated with enhanced OS, PFS, and GRFS relative to BM cells add-back without enhancing the risk of toxicity, in particular the risk of aGVHD and cGVHD. Other variables affecting the final outcome were pretransplant disease status and HCT-CI score. Even with the limitation of the retrospective analysis, this represents the largest study describing the potential role of stem cell source on haplo-SCT outcome in the setting of poor-prognosis HL.

Table 3
Univariate Analysis of the Main Variables Affecting the Outcome of HL Patients Undergoing Haplo-SCT with PT-Cy

Characteristics	2-Year Relapse	*P*	2-Year OS	*P*	2-Year PFS	*P*	2-Year NRM	*P*	2-Year GRFS	*P*
Disease status preallogeneic										
CR	11	<**.001**	77	<**.001**	69	<**.001**	20	**.026**	60	<**.001**
PR	36		63		55		9		46	
SD/PD	50		15		10		40		10	
Conditioning										
NMA	23	.707	71	.160	61	.274	16	.112	53	.247
RIC	18		53		56		26		47	
Graft source										
BM	25	.333	62	.076	56	.125	20	.460	48	.141
PBSCs	18		74		62		20		54	
Previous SCT										
No	25	.461	56	.532	60	.988	15	.421	50	.780
Yes	21		69		59		20		51	
CMV										
Others	21	.696	67	.256	58	.657	21	.309	50	.634
−/+	27		83		65		8		56	
Sex mismatch										
No	21	.820	67	.583	60	.876	19	.749	52	.704
F → M	25		71		53		21		47	
Sex										
Female	24	.654	66	.757	60	.763	17	.972	52	.756
Male	21		68		57		21		50	
HCT-CI score										
0-2	25	.583	74	.173	65	.277	10	.054	57	.349
≥3	19		57		50		32		42	
Age										
≤31 yr	30	.089	67	.820	54	.643	17	.218	52	.472
>31 yr	14		67		64		23		50	

$p < 0.05$ values are in bold.

Table 4
Multivariate Analysis of the Main Variable Affecting Outcome of Patients with HL Undergoing Haplo-SCT with PT-Cy

Characteristics	OS	*P*	PFS	*P*	GRFS	*P*
Disease status preallogeneic						
CR	1		1		1	
Not in CR	3.115 (1.493-6.495)	**.0002**	2.874 (1.478-5.588)	**.0019**	2.474 (1.343-4.558)	**.0037**
Graft source						
BM	1	**.0065**	1	**.0014**	1	**.020**
PBSCs	.293 (.121-.709)		.381 (.177-.821)		.441 (.221-.88)	
HCT-CI score						
0-2	1	**.0116**	1	**.0311**	1	**.0454**
≥3	2.765 (1.255-6.091)		2.2 (1.074-4.505)		1.953 (1.014-3.765)	

$p < 0.05$ values are in bold.

Reports have provided favorable outcomes of the haplo-SCT platform in patients with HL. Studies first used BM as the graft source based on the original Hopkins' protocol. Raiola et al. [20] reported a 3-year OS and PFS of 77% and 63%, whereas Burroughs et al. [21] showed a 2-year OS and PFS of 58% and 51%, respectively. PBSCs then became the preferred method over BM graft because they were easier to collect. Gayoso et al. [22] reported the Spanish experience of 42 HL patients (11 receiving BM and 32 PBSC grafts) with a 2-year OS and PFS of 58% and 48%, respectively. Gauthier et al. [23] described the experience of the French Society of Bone Marrow Transplantation on 34 HL patients (50% received BM and PBSC grafts) and found a favorable outcome in terms of 3-year OS (75%), PFS (66%), and GRFS (52%). More recently, the European Society for Blood and Marrow Transplantation group [12] published a retrospective analysis on 98 HL patients (60 receiving BM and 38 PBSC) reporting a 2-year OS, PFS, and GRFS of 67%, 43%, and 40%, respectively. None of these studies compared the outcome of HL patients based on graft source.

Our results, even if retrospective, suggest that PBSCs are associated with a better outcome in terms of OS, PFS, and GRFS in the setting of HL. Because we did not find any difference in terms of NRM between BM and PBSC grafts, it is possible that the beneficial effect of PBSC source is related to a reduced chance of relapse and that our cohort was not sufficiently powered to detect such a difference. This phenomenon has been described in other clinical contest and is justified by the number of CD3 infused with PBSCs [24]. In this sense, O'Donnell et al. [25] and Bashey et al. [26] have reported in retrospective studies a reduced chance of relapse, with no difference in terms of OS and PFS, after PBSC haplo-SCT relative to BM transplants. Of note, the first study comprised 15 and the second 60 patients with HL. It is also possible that the slightly higher number of patients treated with nivolumab before transplant in the BM graft cohort (21% versus 11%) masked the reduced incidence of relapse associated with PBSC graft. In accordance with our recent results in a larger group of patients [27], we observed a lower relapse rate in patients receiving pretransplant nivolumab relative to those not treated with this PD1 inhibitor (7% versus 25%, $P = .1$). Further studies are needed to evaluate the effect of PBSCs and BM in the haplo-SCT setting

In the present study we did not observe any differences between PBSCs and BM in terms of aGVHD and cGVHD. This finding is an agreement with our previous observation [13] and with results from smaller series [25,28,29]. On the contrary, studies comprising a larger number of patients [26,30] documented a higher incidence of both aGVHD and cGVHD. These differences may be due to sample size and other potential bias related to the retrospective nature of these studies, such as differences in attribution of clinical finding to GVHD versus over etiologies, type of hematologic malignancies included, and heterogeneity in GVHD prophylaxis. Of note, we did not observe a statistical significant difference in grades II to IV and III to IV aGVHD incidence between the cohorts receiving or not pretransplant nivolumab (40% versus 21%, $P = .109$; 0% versus 4%, $P = .463$). Consistently, there was no difference in terms of 2-years cGVHD between the 2 categories (7% versus 7%, $P = .984$).

This study has several limits related to the retrospective nature of the analysis and to the presence of imbalances between the 2 treatment groups. However, it is important to note that our cohort of patients is homogeneous in terms of patient age, disease type, and pretransplant disease status. Moreover, the imbalances between the 2 graft types should have favored the BM source instead of PBSCs for the analyzed outcome because PBSC patients had a higher probability of receiving nonmyeloablative conditioning or having a high-risk HCT-CI (≥3). In particular, high-risk HCT-CI was associated with worse OS and NRM both in univariate and multivariate analyses. Nevertheless, OS was enhanced in the cohort receiving PBSCs.

Besides graft type, the present analysis confirms that pretransplant disease status and HCT-CI are the main predictors of the final outcome of HL patients undergoing allogeneic SCT. Several studies have shown that chemotherapy refractoriness represents the main adverse prognostic factor for patients with lymphoma receiving allogeneic transplant regardless of the type of donor [15,22,31-33]. Recipients with several comorbidities resulting in an HCT-CI ≥ 3 were at higher risk of NRM and consequently reduced OS. This effect on OS was also found in other series [34] but not in a report by the Johns Hopkins group [35].

In conclusion, haplo-SCT is an effective strategy in the treatment of HL patients leading to high OS and PFS. Our analysis study shows that 2 variables need to be carefully evaluated and fine-tuned before haplo-SCT with PT-Cy in patients with HL: pretransplant disease control and graft source. Pretransplant disease control may be optimized by the use of new drugs such as checkpoint inhibitors and monoclonal antibody that are able to achieve high rates of response that were previously unpredictable. Graft source suggests that a donor able to provide PBSC product may be preferred to BM because of the better long-term outcome. Whether this finding is characteristic of patients with HL or may be extended to other diseases needs to be confirmed by further prospective clinical trials.

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