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ARTICLE

Peripheral blood stem cell for haploidentical transplantation with post-transplant high dose cyclophosphamide: detailed analysis of 181 consecutive patients

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Abstract

While bone marrow (BM) grafts were initially used for T-replete HLA-haploidentical related donors transplantation (Haplo-SCT) with post-transplantation cyclophosphamide (PT-Cy), the use of peripheral blood stem cell (PBSC) remains debated. We thus conducted a detailed analysis evaluating the incidence, risk factors, and prevalence of GVHD after PBSC Haplo-SCT with PT-Cy. One hundred and eighty-one patients with hematological diseases were included. Median time for neutrophil and platelet recovery was 21 and 30 days, respectively. The cumulative incidence of grade 3–4 acute GVHD and severe chronic GVHD were 8% and 4%, respectively, approaching what was observed after BM Haplo-SCT. NRM at 2 years was 21%, and 41% of the non-relapse deaths were caused by GVHD. The cumulative incidence of relapse at 2 years was 17% in the whole cohort, and 13% among AML patients ($n = 54$), suggesting a high GVL effect. As surrogate markers for good quality of life, we observed a 2-year GVHD-relapse-free survival probability of 50% and found that 6% and 2% of disease-free patients at 2 years were still living with GVHD and immunosuppressive treatments, respectively. Haplo-SCT with PT-Cy using PBSC grafts results in low incidence GVHD and promising disease control, making PBSCs a valuable alternative to BM graft in this setting.

Introduction

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is a curative treatment for many hematological diseases. Donor availability and treatment related morbidity may limit its applications. In 2008, Luznik [1] et al. showed that the use of PT-Cy as GVHD prophylaxis allows for the use of T-replete grafts from HLA-haploidentical related donors (Haplo-HSCT), resulting in a low incidence of GVHD, and thus overcoming previously mentioned hurdles [2, 3]. Several retrospective studies support similar outcomes for Haplo-HSCT using PT-Cy regimen and "canonical" HLA-matched sibling or unrelated donor Allo-HSCT [4–8]. Although initially described using bone marrow as the graft source [1], the use of peripheral blood stem cells (PBSC) has grown and now exceed BM, at least in Europe [9]. In the setting of HLA-identical Allo-HSCT, prospective randomized trials showed that the use of PBSC is associated with faster engraftment kinetics but also with higher incidence of GVHD (notably cGVHD) when compared to BM

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[10–12]. However, no prospective comparison is available in the context of Haplo-HSCT so far, and it is not precisely known to which extend the use of PT-Cy may revert the anticipated higher risk of GVHD of PBSC Haplo-HSCT. Retrospective analyses report contradictory results as to the risk of an increased incidence of GVHD when transplanting PBSC rather than BM [13–15]. The heterogeneity in patient characteristics and transplantation procedures (especially in GVHD prophylaxis) in and across these studies do not support robust conclusions, and few data on GVHD prevalence are available. We here present the detailed experience of T-cell replete Haplo-HSCT with PT-Cy in a joint collaborative program at 2 European transplant centers.

Patients and methods

Selection criteria

Inclusion criteria were (1) Haplo-HSCT at the Paoli-Calmettes Institute and Humanitas Cancer Center from 2012 to 2016; (2) PBSC as a graft source; (3) PT-Cy as part of GVHD prophylaxis; and (4) patients with hematologic malignancies.

Non inclusion criteria were (1) previous Allo-HSCT; (2) sequential chemotherapy and conditioning regimen for refractory AML patients. The outcome of those patients is evaluated in other specific studies. Patients gave signed informed consent for the clinical data collection. This study is in accordance with the Helsinki declaration and was approved by the institutional review board of both insitutions.

Transplantation procedures

The Haplo-HSCT program was originally started using non-myeloablative conditioning (NMAC) regimen including fludarabine (Flu), cyclophosphamide (Cy), and 2-Gray total body irradiation (TBI) (Flu-Cy-TBI). In order to improve anti-tumor effect, low dose TBI was progressively replaced with intravenous busulfan (Bu) (at reduced [RIC, ≤260 mg/m²] or myeloablative [MAC, >260 mg/m²] doses according to EBMT criteria [16], while pre-transplant Cy was replaced with thiotepa, 5–10 mg/m² total dose). For the purpose of this study, conditioning regimens were categorized as NMAC (Flu-Cy-TBI), RIC (reduced Bu dose), and MAC (myeloablative Bu dose). All patients received GVHD prophylaxis consisting of PT-Cy 50 mg/kg on days+3 and +4, calcineurin inhibitors (CNI) and mycophenolate mofetil (MMF) starting on day+5. CNI was progressively tapered off starting on day+90 until day+180, while MMF was stopped on day +35, in the absence of GVHD. All patients were given G-CSF starting on day+5. Supportive care is detailed in (Supplemental File). Minimal targeted CD34+ cell dose was 4×10^6/kg (recipient body weight) while no maximal limit was used.

Engraftment and GVHD treatment

Neutrophil engraftment was defined as the first of three consecutive days with absolute neutrophil count (ANC) >0.5 G/L. Platelet recovery was defined as a platelet count (PLT) >20 G/L during three consecutive days, without transfusions for the preceding 7 days. Poor graft function (PGF) was defined by (1) the persistence of cytopenia in at least 2 hematopoietic lineages (ANC < 0.5 G/L, PLT < 30 G/L, Hb < 8.5 g/dL) beyond day+30 post Haplo-SCT or at any time after engraftment; (2) transfusion requirements; (3) presence of full donor chimerism (defined by donor cells >95% among CD3+ sorted PBMC); and (4) absence of GVHD, infection or evidence of hematological disease relapse [17].

Acute and chronic GVHD were classified according to Glucksberg and NIH classification [18, 19], respectively. GVHD treatments are detailed in Supplemental File.

Statistical analyses

Cumulative incidences of neutrophil and platelet recovery, GVHD, relapse, and NRM were calculated taking into account the presence of competing risk while survivals were computed using standard Kaplan–Meier methods (details in Supplemental File). In addition, we evaluated in disease-free patients the prevalence of GVHD and immunosuppressive treatment (IST) at different time points after Haplo-HSCT (months 3, 6, 9, 12, 15, 18, 21, and 24), in order to assess the quality of life of surviving patients. Multivariate Cox model was computed including age (continuous variable), disease risk index (DRI) [20] (low vs. intermediate vs. high/very-high), conditioning regimen (NMAC vs. RIC vs. MAC) [16], CD34+ cell dose (continuous variable) and HCT-CI (0–2 vs. ≥3) [21]. To take into account a potential center effect, we stratified the cox model by center. Statistics were computed using R-project 3.3.2 software (http://www.R-project.org).

Results

Patient, disease, and transplantation characteristics

We analyzed 181 consecutive patients who underwent T-cell replete PBSC Haplo-HSCT for hematologic malignancies from March 2012 to June 2016. Patients characteristics at baseline are detailed in Table 1. Median age was 60 years (range: 19–73), with 60 patients (33%) who were ≥65 years. DRI was high or very high in 47 patients

Table 1 patient, disease, and transplantation characteristics

	PBSC haplo-SCT ($N = 181$)	
	N	%
Median age, years (range)	60	(19–73)
Median CD34+cell dose, 10e6/kg (range)	5.4	(1.5–18.1)
Diagnosis		
Lymphoid	84	46%
NHL	40	22%
MM	10	6%
HL	23	13%
CLL	3	2%
ALL	8	4%
Myeloid	97	54%
AML	*54*	30%
MDS	*30*	17%
MPN	*9*	5%
CML	*4*	2%
Disease risk index		
Low	18	10%
Intermediate	116	64%
High	39	22%
Very high	8	4%
HCT-CI		
0–2	71	39%
≥ 3	110	61%
Conditioning regimens		
NMAC	92	51%
RIC	68	38%
MAC	21	12%
Median follow up, months (range)	21	(6–60)

ALL acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *CLL* chronic lymphocytic leukemia, *CML* chronic myeloid leukemia, *HCT-CI* hematopoietic cell transplant-comorbidity Index, *HL* Hodgkin lymphoma, *MDS* myelodysplastic syndrome, *MM* multiple myeloma, *MPN* myeloproliferative neoplasm, *NHL* non-Hodgkin lymphoma, *NMAC* non myeloablative conditioning, *RIC* reduced intensity conditioning, *MAC* myeloablative conditioning

(26%) and HCT-CI was ≥3 in 110 patients (60%). Median CD34+ and CD3+ cell doses were 5.4×10^6/kg (range: 1.5–18.1) and 280×10^6/kg (range: 38–704), respectively. Median follow-up was 21 months after Haplo-SCT (range: 6–60).

Hematopoietic recovery

Between 24 and 48 h after Haplo-SCT, 88% of recipients experienced fever with chills (median temperature=40.1 °C). There was no microbiological proof of infection in most patients (91%), while bacterial infection was identified in bloodstream cultures in 9% of patients. In 79% of patients,

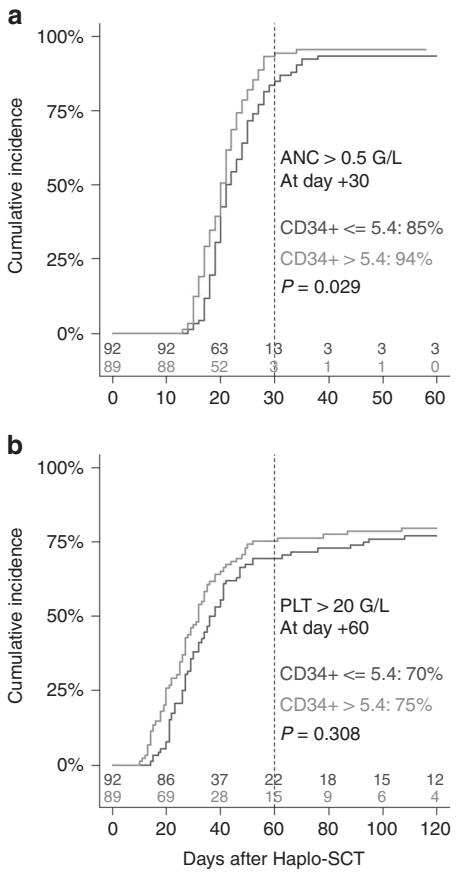

Fig. 1 Cumulative incidences of ANC > 0.5 G/L (**a**) and PLT > 20 G/L (**b**) according to CD34+ cell dose

fever completely disappeared on day+5, 24 h following the last PT-Cy infusion. All but 2 patients (1%) were engrafted. Median time to neutrophil and platelet recovery was 21 (range: 13–112) and 30 (range: 10–394) days, respectively. We observed a slightly but significantly faster ANC recovery (>0.5 G/L) in patients who received CD34+ cell dose above the median value (on D +30: ≤5.4 vs. $>5.4\times10^6$/kg: 85% vs. 94%, $p = 0.029$, Fig. 1a). No difference in platelet recovery was observed (on D +60: ≤5.4 vs. $>5.4\times10^6$/kg: 70% vs. 75%, $p = 0.308$; Fig. 1b). At day+30, 173 patients (95%) had blood CD3-sorted complete donor chimerism. Eight patients (4%) experienced PGF (primary: $n = 6$; secondary: $n = 2$), without any correlation with the infused CD34+ cell dose. They received CD34-selected stem cell boost in a median time of 197 days after Haplo-SCT (range: 44–224). All but 2 recovered within 32 (range: 20–98) days after CD34-selected stem cell boost infusion.

Acute and chronic GVHD

Acute GVHD occurred after a median time of 39 days (range: 16–167) after Haplo-SCT. The cumulative incidence of grade 2–4 and 3–4 acute GVHD at day+100 were 23%

[95% CI: 17–29] (day+180: 26% [95% CI: 19–32]) and 8% [95% CI: 4–12] (day +180: 10% [95% CI: 6–15]), respectively (3% of grade 3 and 5% of grade 4) (Table 2). Among patients who developed acute GVHD, skin, gut, and liver were involved in 35 (73%), 17 (35%), and 4 patients (8%), respectively. Forty-one patients (83%) had only 1 organ affected (skin $n = 30$, gut $n = 10$, and liver $n = 1$), whereas six patients had two organs affected and only one had three organs affected. Biopsy proven for isolated gut was given in all but one patient. No biopsy was provided for the patient with isolated acute GVHD liver involvement. We observed no significant difference in the cumulative incidence of acute GVHD, whether patients had received more or less than the median CD34+ cell dose (grade 2–4: ≤5.4 vs. >5.4×10^6/kg: 20% vs. 27%, $p = 0.129$; grade 3–4: ≤5.4 vs. >5.4: 8% vs. 9%, $p = 0.139$; Fig. 2a, b). Although the cumulative incidence of grade 2–4 acute GVHD was similar in both younger and older patients (age <60 vs. ≥60 years: 22% vs. 24%, $p = 0.575$, Fig. 3a), the severity was higher in older patients with a cumulative incidence of grade 3–4 acute GVHD of 14% compared to 2% in younger patients ($p = 0.014$, Fig. 3b).

The median time to chronic GVHD occurrence after Haplo-SCT was 172 days (range: 102–644). At 2 years after Haplo-SCT, the cumulative incidence for all grades and moderate+severe chronic GVHD were 17% (95% CI: 12–23) and 9% (95% CI: 5–13; severe=4%), respectively. In seven cases, chronic GVHD followed prophylactic donor lymphocyte infusions (pDLI) that were given in a total of 17 patients. Among patients who developed chronic GVHD,

Table 2 Outcome after PBSC haplo-SCT

	PBSC haplo-SCT ($n = 181$)	
	Estimation[a](%)	95% CI
Acute GVHD		
Grade II–IV	26	(19–32)
Grade III–IV	10	(6–15)
Chronic GVHD		
All grades	17	(12–23)
Moderate+severe	9	(5–13)
NRM	21	(15–27)
CIR	17	(11–23)
PFS	62	(54–70)
GRFS	50	(43–59)
OS	66	(59–74)

CIR cumulative incidence of relapse, *GVHD* graft-versus-host disease, *NRM* non-relapse mortality, *OS* overall survival, *GRFS* graft and relapse-free survival, *PFS* progression-free survival

[a]Estimations are given at 2 years except for acute GVHD (day 180)

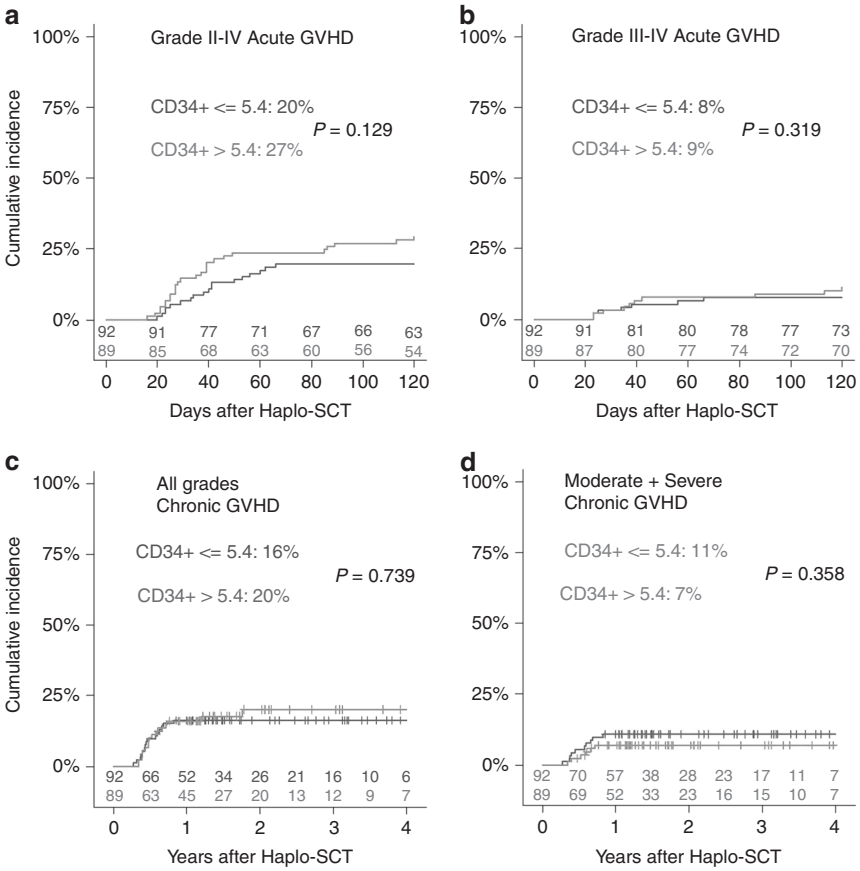

Fig. 2 Cumulative incidence of grade II–IV (**a**) grade III–IV (**b**), all grades (**c**) and moderate or severe (**d**) chronic GVHD according to CD34+ cell dose

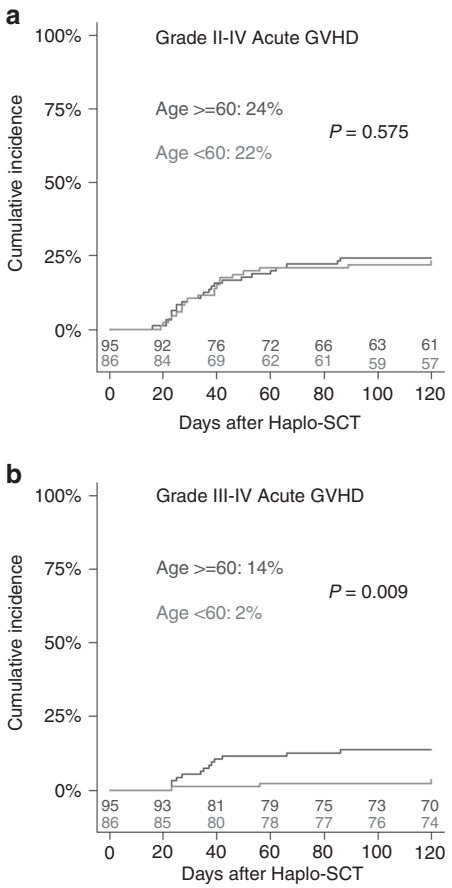

Fig. 3 Cumulative incidences of grade II–IV (**a**) and III–IV (**b**) acute GVHD according to age

Table 3 Impact of CD34+ cell dose on outcome in multivariate Cox model adjusted by age, conditioning regimen, DRI, and HCT-CI; and stratified by center

	HR	95% CI	*p*
Acute GVHD			
Grade II–IV	1.05	(0.97–1.15)	0.223
Grade III–IV	1.04	(0.92–1.18)	0.549
Chronic GVHD			
All grades	0.99	(0.89–1.10)	0.838
Moderate+severe	0.92	(0.79–1.08)	0.331
NRM	1.00	(0.90–1.10)	0.954
CIR	1.02	(0.91–1.16)	0.718
PFS	1.01	(0.93–1.09)	0.827
OS	1.01	(0.93–1.10)	0.855
GRFS	0.98	(0.92–1.05)	0.581

CIR cumulative incidence of relapse, *GVHD* graft-versus-host disease, *NRM* non-relapse mortality, *OS* overall survival, *GRFS* graft and relapse-free survival, *PFS* progression-free survival

77% had de novo chronic GVHD. The skin was the most frequently involved organ (77% of patients) before mucosae ($n = 19$, 61%). Three patients developed severe pulmonary

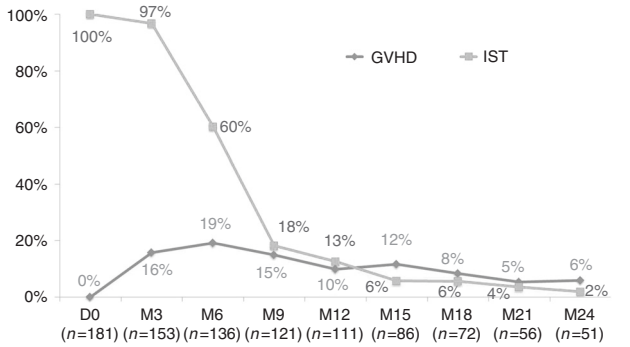

Fig. 4 Prevalences of GVHD and immunosuppressive treatment among disease-free patients

chronic GVHD. CD34+ cell dose did not influence the cumulative incidence of chronic GVHD (all grades: ≤5.4 vs. >5.4×10^6/kg: 16% vs. 20%, $p = 0.739$; moderate or severe: ≤5.4 vs. >5.4×10^6/kg: 11% vs. 7%, p = 0.358; Fig. 2c, d). Multivariate analyses confirmed that CD34+ cell dose did not significantly influence the incidence of both acute and chronic GVHD (Table 3), while age was associated with higher risk of grade 3–4 acute GVHD ($p = 0.03$). In addition, we did not observed significant impact of conditioning regimen intensity on the risk of both acute (with MAC as reference: p-NMAC = 0.558; p-RIC = 0.675) and chronic GVHD (with MAC as reference: p-NMAC = 0.462; p-RIC = 0.861).

Prevalence of GVHD, immusuppressive treatment (IST), and outcome

Among the 41 patients who developped grade 2–4 acute GVHD, 6 (15%) patients relapsed and 5 of them died from their hematological disease. Twelve (29%) patients died from acute GVHD. The 23 (56%) remaining patients responded to systemic GVHD treatement and were able to discontinue IST (median IST duration: 138 days, range: 79–456). Among the 31 patients who developed chronic GVHD, 2 (6%) patients died from hematological relapse and 3 (10%) patients died from chronic GVHD. Among the 26 (84%) remaining patients, 14 (74%) were able to stop IST at the time of analysis (median IST duration of 134 days, range: 25–475).

At 1 year after Haplo-SCT, 13 and 10% of disease-free patients were living with GVHD and IST, respectively. At 2 years after Haplo-SCT, almost all disease-free patients (>90%) had stopped IST and had no GVHD features (Fig. 4).

NRM and CIR

We observed a cumulative incidence of NRM at 100 days and 2 years of 11% (95% CI, 7–16) and 21% (95% CI, 15–27), respectively (Table 2). Causes of NRM were GVHD

($n = 15$), infections in absence of GVHD ($n = 15$), CNS hemorrhage ($n = 1$), non-well defined neurological complications ($n = 2$), and 2 hemolytic anemia. Fatal sinusoidal obstruction syndrome (SOS) was observed only in 1 heavily pre-treated patient. Three patients died before engraftment on day+4, +12, and +32.

Two-year CIR was 17% (95% CI, 11–23) (Table 2). The median time from Haplo-HSCT to relapse was 226 days (range: 14–1459). High or very high DRI was the only predictive factor associated with higher risk of relapse (HR = 2.36, 95%CI = [1.08–5.15], $p = 0.032$). Among the 54 patients transplanted for AML (25 in CR1, 29 in either CR > 1 or refractory disease at the time of Haplo-SCT), the 2-year CIR was 13% (95% CI, 4–21, 12% for patients in CR1 and 14% for those in CR > 1 or refractory disease).

PFS, OS, and GRFS

PFS and OS at 2 years were 62% (95% CI, 54–70) and 66% (95% CI, 59–74), respectively. As a surrogate to evaluate quality of life, we also analyzed the composite endpoint GRFS, which was 50% (95% CI, 43–59) at 2 years (Table 2). By multivariate analysis, high/very-high DRI was the only factor associated with significantly worse OS (HR = 2.26; 95%CI = [1.30–3.93], $p = 0.004$) and PFS (HR = 1.93; 95% CI = [1.15–3.25], $p = 0.013$), and with a trend for worse GRFS (HR = 1.48; 95% CI = [0.93–2.37], $p = 0.099$).

Discussion

The introduction of PT-Cy as GVHD prophylaxis for T-cell replete Haplo-HSCT, as developed by the Baltimore group [1] allowed for achieving good engraftment and low incidence of GVHD with minimal graft processing. Initial reports were using bone marrow grafts [1]. PT-Cy is also an effective GVHD prophylaxis for PBSC Haplo-HSCT, when administering conditioning regimen with different intensities [22, 23]. We previously reported an interim retrospective comparison of BM versus PBSC Haplo-HSCT [14] on 69 patients in which we observed no increased incidence of both acute and chronic GVHD, resulting in similar outcome. Our present study on a larger number of patients confirms the feasibility of PBSC Haplo-HSCT.

The BM versus PBSC graft comparison for Haplo-HSCT with PT-Cy, was assessed in different retrospective studies showing diverging results about the GVHD incidences [23–26]. Two more recent studies compared BM versus PBSC in the Haplo-HSCT setting. O'Donnell et al. [15] conducted a retrospective matched-pair analysis in patients undergoing PT-Cy Haplo-HSCT using a NMAC regimen (Flu-Cy-TBI). No significant increase in the incidence of acute and chronic GVHD (day-100 grades 2–4 acute GVHD: PBSC 40% vs BM 33% $P = 0.50$; 2-year all grades chronic GVHD: PBSC 23% vs BM 19% $P = 0.63$) was observed using PBSC grafts. On the other hand, Bashey et al. [13] showed in a large CIBMTR registry analysis that the use of PBSC was associated with a significantly higher incidence of grades 2–4 acute and chronic GVHD (6-month grades 2–4 acute GVHD: PBSC 42% vs BM 25% $P < 0.001$; 2-year all grades chronic GVHD: PBSC 41% vs BM 20% $P < 0.001$).

Two additional European studies on behalf of EBMT showed an increased risk of GVHD using PBSC rather than BM graft [27, 28]. These analysis, conducted on a large registry cohort from EBMT and CIBMTR, included patients from 99 and 350 centers, respectively, leading to a very heterogeneous experience in the field of Haplo-HSCT, different platforms of conditioning regimen and different approaches to GVHD prophylaxis [27, 28]. The last point is especially relevant in the study published by Rubio et al. [27], where PT-Cy as GVHD prophylaxis was used only in 25% of patient received a NMAC and 32% of patients received a MAC regimen. Also in the recent report of Ruggeri et al. [28], some patients (5% and 7% in BM and PBSC group, respectively) received ATG in association with PT-Cy.

Compared to the large registry analyses, our study allow a detailed analysis of GVHD (incidence, organ involvement, and prevalence) on a cohort of patients receiving the same GVHD prophylaxis treatment (PT-Cy+CSA+MMF). In this study, the cumulative incidence of grades 2–4 acute GVHD at 100 days as well as the moderate–severe chronic GVHD at 2 years, continues to be relatively low (23% and 9%, respectively). When compared to the literature, our results with PT-Cy seem to approach those observed after BM [6, 29–31] rather than PBSC [13, 23, 24, 28, 32] Haplo-HSCT.

Although the cumulative incidence of GVHD is a common method for evaluating this end point, the co-prevalence analysis of both GVHD and IST allows a better assessment of GVHD and of its treatment after Allo-HSCT. Indeed, we reported the proportion of patients who actually live with GHVD features and/or IST at different time points, giving a clear picture of outcome after Haplo-HSCT. Moreover, although limited by its retrospective nature, our prevalence analysis can provide information about patients' quality of life. Among the patients alive without evidence of disease progression, 90% and 87% of patients were IST and GVHD-free after 1 year, respectively (98% and 94% at 2 years, respectively).

We were not able to identify any factor associated with an increased risk of developing acute or chronic GVHD. However, we observed that the severity of acute GVHD

was higher in older (age ≥60 years) than in younger patients (grades 3–4 at day 100 ≥vs. <60 years: 14% vs. 2%, $p = 0.009$). In addition, we did not observe any impact of infused CD34+ cell dose on the incidence of GVHD, in both univariate and multivariate analysis. It was initially shown that CD34+ cell dose above 8.3×10^6/kg was associated with an increase of chronic GVHD. However, this was observed in the setting of HLA matched related Allo-HSCT prepared with MAC regimen and no ATG [33]. Our present study mostly included patients who received RIC or NMAC regimens (88%), making difficult the comparison of previous results to this different context. This was in line with our previous experience in the setting of matched related and unrelated RIC Allo-HSCT showing no impact of CD34+ cell dose [34].

Although the use of PBSC is associated with faster hematological recovery in the setting of both HLA matched related and unrelated donor, we observed a median time from Haplo-SCT to ANC and platelet recovery of 21 and 30 days, respectively. This is similar to what was observed after BM Haplo-SCT [10–12]. Also in previous reports on Haplo-SCT with PBSC and PT-Cy, neutrophil engraftment was observed after a median time between 15 and 17 days [23–25, 32]. Interestingly, we observed a better ANC recovery in patients receiving higher CD34+ cell dose (≤5.4 vs. >5.4: 85% vs. 94%, $p = 0.029$), but no effect was found on PLT recovery (≤5.4 vs. >5.4: 70% vs. 75%, $p = 0.308$).

We observed a relapse incidence of 17% in the whole cohort at 2 years. This is encouraging taking into account the baseline characteristics of the patients (i.e. high or very high DRI in 26% of patients) but the interpretation of this finding is limited by the heterogeneity of our cohort in terms of diagnoses. However, when focused on AML patients ($n = 54$), we observed a CIR of 13% although more than half of them ($n = 29$) were transplanted for advanced disease (CR ≥2 or refractory disease). This is in line with previous report from Bashey et al. showing that the use of PBSC is associated with lower CIR compared to bone marrow Haplo-SCT in the setting of AML [13]. Initial reports of bone marrow Haplo-HSCT with PT-Cy showed higher incidence of relapse [1, 30]. Taken together, these results suggest a potential benefit for disease control using PBSC.

We conclude that PT-Cy allows the use of PBSC as graft source for Haplo-HSCT without dramatically increasing the incidence of both acute and chronic GVHD. The overall outcome is promising, with most of disease-free patients (>90%) actually living without IST or GVHD features, suggesting a preserved long-term quality of life. However, severe acute GVHD in older patients remains a concern justifying the optimization of the PT-Cy platform in this specific setting. Beyond the feasibility, the use of PBSC for PT-Cy Haplo-HSCT seems associated with promising antitumor effect. This need to be prospectively evaluated in a disease specific manner.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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