Transplantation and Cellular Therapy 000 (2022) 1–10

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Post-Transplantation Cyclophosphamide After HLA Identical Compared to Haploidentical Donor Transplant in Acute Myeloid Leukemia: A Study on Behalf of GETH-TC

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Article history:
Received 11 October 2021
Accepted 21 January 2022

Key Words:
GVHD prophylaxis
Post-transplantation cyclophosphamide
Acute myeloid leukemia

A B S T R A C T

Post-transplantation cyclophosphamide (PTCY) effectively prevents graft-versus-host disease (GVHD) after unmanipulated HLA-haploidentical hematopoietic stem cell transplantation (HSCT) and achieves low rates of GVHD in HLA-identical transplantation. To compare the outcomes of haploidentical versus HLA identical HSCT in patients undergoing HSCT for acute myeloid leukemia (AML) using PTCY. We conducted a retrospective study of 229 patients undergoing first HSCT for AML using PTCY with additional immunosuppression, 99 from matched sibling or unrelated donor (MSD/MUD) performed in 3 hospitals and 130 from haploidentical donors (haplo group) performed in 20 hospitals within the Spanish Group of Hematopoietic Stem Cell Transplantation and Cellular Therapy. Peripheral blood stem cells were used as graft in 89% of patients; myeloablative conditioning was used in 56%. There were significantly more patients with active disease (5% versus 20%, $P = .001$), high/very high disease risk index (DRI) (32% versus 67%, $P = .000$) and prior auto-HSCT (2% versus 11%, $P = .010$) in the haplo group. Median follow-up was 27 and 62.5 months for MSD/MUD and haplo, respectively. At 2 years, no significant differences were observed in overall survival (OS) (72% versus 62%, $P = .07$), event-free survival (EFS) (70% versus 54%, $P = .055$), cumulative incidence of relapse (19% versus 25%, $P = .13$), non-relapse mortality (14% versus 19%, $P = .145$), and the composite endpoint of GVHD and relapse-free survival (49% versus 42%, $P = .249$). Multivariate analysis identified only age and active disease as significant risk factors for OS and EFS; reduced-intensity conditioning, high/very high DRI, and haplo donor were nearly statistically significant for these outcomes. Grade II-IV

Financial disclosure: See Acknowledgments on page XXXX.
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https://doi.org/10.1016/j.jtct.2022.01.020

acute GVHD was lower in MSD/MUD (14% versus 47%, $P = .000$). Cumulative incidences of grade III-IV acute GVHD (4% versus 9%, $P = .14$) and moderate-severe chronic GVHD (22% versus 19%, $P = .28$) were similar. Limitations of our study include limited sample size, differences between haplo and MSD/MUD groups and heterogeneous additional immunosuppression and PTCY timing in MSD/MUD. The use of an HLA-identical donor with PTCY in patients with AML showed lower incidence of clinically significant grade II-IV acute GVHD compared to haplo donors. Further studies with larger sample sizes should be performed to establish a possible benefit of HLA-identical donor on survival.

Proof of the feasibility and safety of high-dose post-transplantation cyclophosphamide (PTCY) in combination with additional immunosuppression, pioneered by Luznik et al [1]., has led to the expansion of haploidentical (haplo) hematopoietic stem cell transplantation (HSCT) worldwide and now ensures that a donor will be available for virtually all patients in need of an allogeneic transplant. The low rates of graft-versus host disease (GVHD) achieved by this prophylaxis regimen have sparked interest in the use of PTCY in the HLA-identical setting in both matched sibling donor (MSD) and matched unrelated donor (MUD) transplants [2,3]. The combination of methotrexate and calcineurin inhibitors (CNI) [4] in MSD transplants and anti-thymocyte globulin (ATG)–based regimens [5,6] in MUD transplants is still the standard of care for GVHD prophylaxis in HLA-identical HSCT in the majority of centers [7]. Recently, however, several retrospective, registry-based studies have compared these prophylaxis regimens to PTCY-based regimens in MSD, MUD, and mismatched transplants, suggesting lower rates of GVHD with PTCY [8–12]. After this, the use of PTCY has been more widely extended to the non-haplo setting, and there is growing interest in comparing its results with those obtained when haplo donors are used.

Several studies have compared haplo-HSCT with PTCY with MSD/MUD in acute leukemia using standard GVHD prophylaxis regimens in the MSD/MUD groups [13–15]. However, few studies have analyzed both donor approaches in the setting of PTCY. A first attempt by the Johns Hopkins group compared myeloablative MSD/MUD to reduced-intensity haploidentical HSCT using bone marrow and PTCY based prophylaxis including patients with acute leukemia and showing comparable results in all main outcomes [16]. More recently, 2 recent registry studies published by the European Society for Blood and Marrow Transplantation (EBMT) [17] and the Center for International Blood and Marrow Transplant research (CIBMTR) [18] compared outcomes in haploidentical versus HLA-identical transplant using PTCY in acute myeloid leukemia (AML). The first included patients with AML in first complete remission (CR1) and compared haplo and MUD to standard-of-care MSD using both myeloablative and reduced-intensity conditioning regimens; 30% of MUD recipients also received ATG. In this study, haplo HSCT showed significantly higher rates of acute GVHD (aGVHD) and nonrelapse mortality (NRM) compared to MSD, although relapse was lower. No differences were found between MUD and MSD, and overall survival (OS) was similar across groups. In the second, more recent, study the CIBMTR reported the results of a large registry cohort of haplo-HSCT versus MUD using homogeneous prophylaxis with PTCY/CNI/MMF in patients with acute leukemia and high-risk myelodysplastic syndromes (MDS). Recipients of reduced-intensity conditioning (RIC) were analyzed separately; aGVHD, graft failure, and NRM were lower after MUD, leading to better OS and event-free survival (EFS) in RIC HSCT, whereas no differences in terms of survival were observed in recipients of myeloablative regimens. Therefore, despite reports of a trend toward lower aGVHD rates in HLA-identical donors with PTCY compared to haplo, the benefit of HLA identical donors in acute leukemia in terms of OS, EFS, and graft-versus-host and relapse-free survival (GRFS) when PTCY is used has yet to be firmly established. The aim of this study was to compare the impact of donor type in AML patients receiving a first allo-HSCT from MSD/MUD versus haplo donors using PTCY as GVHD prophylaxis in hospitals associated with the Spanish Group of Hematopoietic Stem Cell Transplantation and Cellular Therapy (GETH-TC).

PATIENTS AND METHODS

Patients

The haplo group included 130 consecutive adult AML patients who underwent transplantation in 20 centers in Spain between 2013 and 2019. The MSD/MUD group included 99 consecutive patients from 3 centers, in which PTCY was the standard prophylaxis for MSD/MUD, who underwent transplantation between 2013 and 2019, 61 from 10/10 (n = 52) or 12/12 (n = 9) MUD, and 38 from MSD. HLA typing was performed using high-resolution DNA-based techniques [19]. Haplo was defined as recipient-donor number of HLA mismatches ≥ 2. Study patients were followed up for at least 6 months after transplantation. The study was approved by the ethics committee of Gregorio Marañón Hospital, and all patients signed informed consent forms. The study was performed according to the Declaration of Helsinki. Baseline data were collected from the GETH-TC database, and each hospital was asked to review the data.

GVHD prophylaxis

GVHD prophylaxis in the haplo group consisted of intravenous cyclophosphamide 50 mg/kg/d on days 3 and 4 combined with CNI (cyclosporine A [CsA] or tacrolimus [FK]) and mycophenolate mofetil (MMF) from day 5.

In the MSD/MUD group, additional immunosuppressive drugs differed depending on the center and donor, as follows:

- Center A: Cy 50 mg/kg/d on days 3 and 4, combined with either CsA or FK plus MMF from day 5 in both MSD (n = 12) and MUD (n = 18)
- Center B: Cy 50 mg/kg/d on days 3 and 5, combined with either CsA or FK from day 0 (n = 20 MSD and n = 13 MUD) or same prophylaxis as center A (n = 6 MUD)
- Center C: Cy 50 mg/kg/d on days 3 and 4, combined with sirolimus and MMF from day 5 in MUD patients (n = 30)

In all cases, MMF was withdrawn on day 35 in the absence of GVHD, and CNI or sirolimus dose was decreased from days 60 to 90 and stopped in the absence of GVHD by day 120 to 180, depending on relapse risk (active disease or high/very high disease risk index [DRI]) [20]. No patient received ATG.

Conditioning regimen and graft source

The most common myeloablative conditioning (MAC) regimens administered in all groups were intravenous busulfan (Bux) 3.2 mg/kg/d 3 or 4 doses on days −6 to −3 and fludarabine (Flu) 40 mg/m^2/day on days -6 to -3 (Flu-Bux-MAC) or thiotepa 5 mg/kg/d on days −7 to −6, Bux 3.2 mg/kg/d 3 or 4 doses on days −6 to −3, and Flu 50 mg/m^2/d on days −5 to −3 (TBF-MAC). RIC was performed with either a modified Hopkins regimen with Bux (Flu 30 mg/m^2/d on days −6 to −2, Cy 14.5 mg/kg/d on days −6 and −5 and Bux 3.2 mg/kg/d on days −3 to −2), TBF-RIC (thiotepa 5 mg/kg/d on days −7 to −6, Bu 3.2 mg/kg 1 or 2 doses on days −5 and −4, Flu 50 mg/m^2/d on days −5 to −3) or FluBux-RIC (Flu 30 mg/m^2/d on days −6 to −2 and Bu 3.2 mg/kg/d on days −4 to −3). RIC regimens were used in patients who were either over 50 to 55 years or showed a Hematopoietic Cell Transplantation–Comorbidity

Age Index (HCT–CI) ≥ 3. The most frequently used graft source was unmanipulated mobilized peripheral blood stem cells (PBSC).

Pretransplantation and post-transplantation evaluation

Pretransplantation comorbidities were recorded using the HCT–CI [21], and patients were stratified according to DRI [20]. Chimerism was determined by quantitative analysis of informative microsatellite DNA polymorphisms [22]; first determination was performed between days 14 and 60 depending on center policies. Acute GVHD was scored according to the MAGIC criteria [23]. An exception was made with a patient diagnosed with acute pulmonary GVHD (nonclassical manifestation) who did not meet MAGIC criteria and was classified as grade III-IV acute GVHD because of its severity. Chronic GVHD was scored according to the NIH Consensus Development Project [24].

Definitions

Myeloid engraftment was defined as an absolute neutrophil count of 0.5×10^9/L or greater for 3 consecutive days. Platelet engraftment was defined as a platelet count of 20×10^9/L or higher for 3 consecutive days or without transfusion support for 7 days. These definitions were used for both RIC and MAC regimens. Graft failure was defined as absence of myeloid engraftment with survival of more than 28 days after transplantation. Diagnosis of disease recurrence was based on clinical and pathological criteria.

Statistical analysis

Quantitative variables were expressed as median and range or interquartile range (IQR) (twenty-fifth and seventy-fifth percentiles). Qualitative variables were expressed as frequency and percentage. The $\chi 2$ test was used to identify correlations between qualitative variables and the non-parametric Kruskal-Wallis test was used for quantitative variables. Variables which were significantly correlated in the univariate analysis were evaluated using a forward stepwise selection method with a *P*-in value of <.05 and a *P*-out of <.1. Criteria for inclusion in multivariate Cox regression analysis was a *P* value <.1. Primary endpoints were rates of OS and EFS at 2 years. Secondary endpoints were cumulative incidence of engraftment, relapse, NRM, aGVHD, cGVHD and GRFS. Multivariate analysis performed for OS, EFS, GRFS, relapse, and NRM included donor (haplo versus HLA identical), age, sex, prior auto-HSCT, pretransplantation disease status (active disease versus complete response), DRI (low-intermediate versus high/very high), HCT-CI (0-2 versus ≥3), stem cell source, intensity of conditioning regimen, CMV serostatus and sex disparity (male recipient/female donor versus other). The same variables excluding DRI and disease status were included in the multivariate analysis performed for GVHD. GRFS was defined the first event (aGVHD grade III-IV, cGVHD requiring systemic therapy, relapse, or death) occurring at 24 months after transplantation [25]. Relapse, toxic death, and second transplant because of graft failure were considered events for EFS. Estimates of OS, EFS and GRFS were calculated using the Kaplan-Meier method with a 95% confidence interval (95% CI). Adjusted curves for OS, EFS, and GRFS were calculated adjusted by significant variables detected by multivariate analysis. Cumulative incidence curves and competing risk regression were performed as alternatives to Cox regression for survival data in the presence of competing risks using the Fine-Gray model. Events considered competing events were death and any other development that prevented the appearance of the event under study. NRM and relapse were considered competing events for each other, in addition to repeat transplantation for both. Death before month 6, second transplant, and donor lymphocyte infusion (DLI) were considered competing events for acute GVHD, and death before 1 year, second transplant and DLI for chronic GVHD. Relapse was not considered a competing event for GVHD unless it required decreasing immunosuppression. The cohort was last updated in March 2021. Data were analyzed using SPSS (SPSS Statistics for Windows, Version 21.0; IBM, Armonk, NY), multivariate analysis and Kaplan-Meier curves were performed with Stata software (Version 15.1), and cumulative incidences were calculated with R software.

RESULTS

Patient and transplant characteristics

Between 2013 and 2019, a total of 229 patients undergoing a first HSCT for AML using PTCY with additional immunosuppression were uploaded to the GETH-TC registry, 99 from a matched sibling (n = 38) or 10/10 or 12/12 unrelated donor (n = 61) (MSD/MUD group) and 130 from a haploidentical donor (haplo group). Baseline characteristics of the patients are summarized in Table 1. HCT-CI score distribution was similar in both groups (0-2 in 61% of MSD/MUD versus 56% of haplo, *P* = .442). There were more patients with active disease at transplant (5% versus 20%, *P* = .001), high/very high DRI (32% versus 67%, *P* <.001) and prior autologous HSCT (2% versus 11%, *P* = .010) in the haplo group. Among patients in complete response (CR), there were no statistically significant differences in the proportion of patients in CR1 (80% versus 75%, *P* = .343) and MRD status between the two cohorts (MRD positive 37% versus 33%, *P* = .594). Mobilized PBSC was the most frequent stem cell source in both groups (88% and 89%, *P* = .102) with no differences in graft composition and most patients underwent myeloablative conditioning (64% and 55%, *P* = .170). A significantly higher proportion of male patients received a graft from a female donor in the haplo group (12% versus 25%, *P* = .017). There were more CMV seronegative recipients in the MSD/MUD group (23% versus 19%), but a higher proportion of seronegative recipients received a seropositive graft in the haplo group (9% versus 14%, *P* = .03).

Engraftment, chimerism

One patient (0.8%) in the haplo group presented primary graft failure and died; no patient in the MSD/MUD group presented primary graft failure but there was one patient in this group who experience secondary graft failure and received a second HSCT. Five patients (3 haplo, 2 MSD/MUD) died because of infection before day 28 without engraftment.

Cumulative incidence of neutrophil recovery at day 28 was 97% in both groups (*P* = .034), within a median of 16 days (IQR 14-18) for the MSD/MUD group and 17 days (IQR 15-20 days) for the haplo group. Cumulative incidence of platelet recovery at days 28 and 100 was 69% and 92% in the MSD/MUD group and 70% and 90% in the haplo group, respectively (*P* = .19). Median time to platelet recovery was 22 days (IQR 15-30) in the MSD/MUD group and 24 days (IQR 19-29) in the haplo group.

Data on chimerism was available in 94 patients in the MSD/MUD group and 124 in the haplo group. The remaining patients died before first determination was performed between days 20 and 120. Full-donor chimerism in peripheral blood was achieved in 89 out of 94 evaluable patients (95%) by day +60 in in the MSD/MUD and 118 out of 124 (95%) in the haplo group (*P* = .872).

Overall and Event-free Survival

After a median follow-up of 27 months in the MSD/MUD group (range 7-76 months) and 62.5 months in the haplo group (range 6-104 months), 2-year OS showed a higher trend in the MSD/MUD group (72% [P = 95% CI, 61.8-80.6] versus 62% [P = 95% CI, 53.5-70.4] in the haplo group, *P* = .07) (Figure 1A). Estimated EFS at 2 years also showed an upward trend in the MSD/MUD group (70% [P = 95% CI, 60.4-79.9] versus 54% [P = 95% CI, 45.4-62.5]) the haplo group, but this difference was not statistically significant (*P* = .055, Figure 1C). Multivariate analysis showed younger age (adjusted pseudoHR [asHR] 1.02 [P = 95% CI, 1.01-1.04], *P* = .007) and complete remission (asHR 0.46 [P = 95% CI, 0.28-0.75], *P* = .002) to be the only factors significantly associated with longer OS. Disease status was the unique independent factor for EFS (asHR 0.42 [P = 95% CI, 0.26-0.69], *P* = .001) (Supplementary Table S1). Adjusted curves were calculated controlled by variables significant in the multivariate analysis for both OS and PFS (*P* = .268 and *P* = .242, respectively Figure 1;B and 1D).

Use of RIC regimen was significant in the univariate analysis for both OS and EFS (nonadjusted pseudoHR (sHR) 1.75 [P = 95% CI, 1.16-2.63], *P* = .007 and sHR 1.55 [P = 95% CI, 1.04-2.30], *P* = .033, respectively). Difference in the type of donor (MSD/MUD versus haplo) was nearly statistically significant in the univariate analysis for OS and EFS (sHR 1.51 [P = 95% CI,

Table 1
Characteristics of Patients and Transplants

	MSD/MUD n = 99	Haplo n = 130	*P* Value
Age, years, median (range)	50 (18-72)	51 (16-75)	.976
Sex, male (%)	53 (53)	77 (59)	.442
Prior transplant, n (%)			.010
Auto-HSCT	2 (2)	14 (11)	
Allo-HSCT	0	0	
Disease Risk Index, n (%)			<.001
Low	7 (7)	4 (3)	
Intermediate	60 (61)	39 (30)	
High/Very High	32 (32)	87 (67)	
Pretransplantation status, n (%)			
Active disease	5 (5)	26 (20)	.001
CR	94 (95)	104 (80)	
First CR	75 (80)	78 (75)	0.343
≥ Second CR	19 (20)	26 (25)	
MRD positive	33 (37)	36 (33)	.594
Age-adjusted HCT-CI			.795
0	17 (17)	18 (14)	
1-2	43 (44)	54 (42)	
≥3	39 (39)	58 (44)	
Donor/recipient sex, female/male (%)	12 (12)	32 (25)	.017
CMV sero-status			.030
Donor positive, recipient positive	53 (54)	85 (66)	
Donor negative, recipient negative	14 (14)	7 (5)	
Donor positive, recipient negative	9 (9)	18 (14)	
Donor negative, recipient positive	23 (23)	20 (15)	
Stem cell source, N (%)			.102
Bone marrow	12 (12)	14 (11)	
Peripheral blood	87 (88)	116 (89)	
CD34+ ($\times 10^6$/kg) graft composition, median (range)	5.2 (2-14)	5.5 (2.7-11.4)	.729
Conditioning regimen, N (%)			.170
Myeloablative	63 (64)	71 (55)	
Reduced intensity	36 (36)	59 (45)	
GVHD prophylaxis, N (%)			–
PTCy +3, +4 and CNI + MMF*	36 (37)	130 (100)	
PTCy +3, +5 and CNI†	33 (33)	0	
PTCy +3, +4 and Siro + MMF‡	30 (30)	0	

Siro indicates sirolimus.
* PTCy + CNI + MMF (n = 36; 18 MRD + 18 MUD, 4 of them with bone marrow).
† PTCy + CNI without MMF (n = 33, 20 MRD + 13 MUD; 8 of them (4 + 4) using bone marrow).
‡ PTCy + Siro + MMF in n = 30 MUD (Valencia protocol, all using PBSC).

0.96-2.35], *P* = .071 and sHR 1.49 [P = 95% CI, 0.97-2.28], *P* = .067, respectively) but not independent in the multivariate analysis. Similarly, high/very high DRI was nearly significant in the univariate analysis for OS, and significant for EFS (sHR 1.50 [P = 95% CI, 0.99-2.28], *P* = .056 and sHR 1.57 [P = 95% CI, 1.05-2.36], *P* = .030) but was not identified by the multivariant analysis as an independent factor for these endpoints.

Additionally, data were analyzed by intensity of conditioning regimen. No differences in OS were found between the MSD/MUD and haplo groups; however, EFS was longer in MSD/MUD patients as compared to haplo in the RIC conditioning setting (Supplementary Table S2). Finally, we performed a subanalysis by donor used (haplo versus MSD/MUD) excluding patients with active disease and controlling by DRI (low-intermediate versus high/very high). In this analysis, both 2-year OS and EFS showed a trend to be higher in the MSD/MUD group in patients with low or intermediate DRI as compared to haplo, whereas no differences were observed between haplo and MRD/MUD in the high-risk setting (Supplementary Table S3).

Toxicity and non-relapse mortality

Cumulative incidence of NRM at 2-years was 14% in the MSD/MUD group and 19% in the haplo group (*P* = .145, Figure 2A). Toxic causes of death are detailed in Table 2. Of note, infection was most the frequent cause of NRM in the early post-HSCT period in both groups. NRM in the MSD/MUD group was due to infection in 8 patients (52%), GVHD in 3 (20%), and other toxicities in 4 (28%). In the haplo group, causes of NRM were infection in 12 (43%) cases, GVHD in 5 (18%), and other toxicities in 11 (39%), including 5 patients who died because of other neoplasms (1 due to relapse of prior breast cancer and 4 due to second neoplasms) a median of 22 months after HSCT. In the multivariate analysis, older age and prior autologous transplants were identified as independent risk factors for NRM (asHR 1.05 [P = 95% CI, 1.02-1.08], *P* <

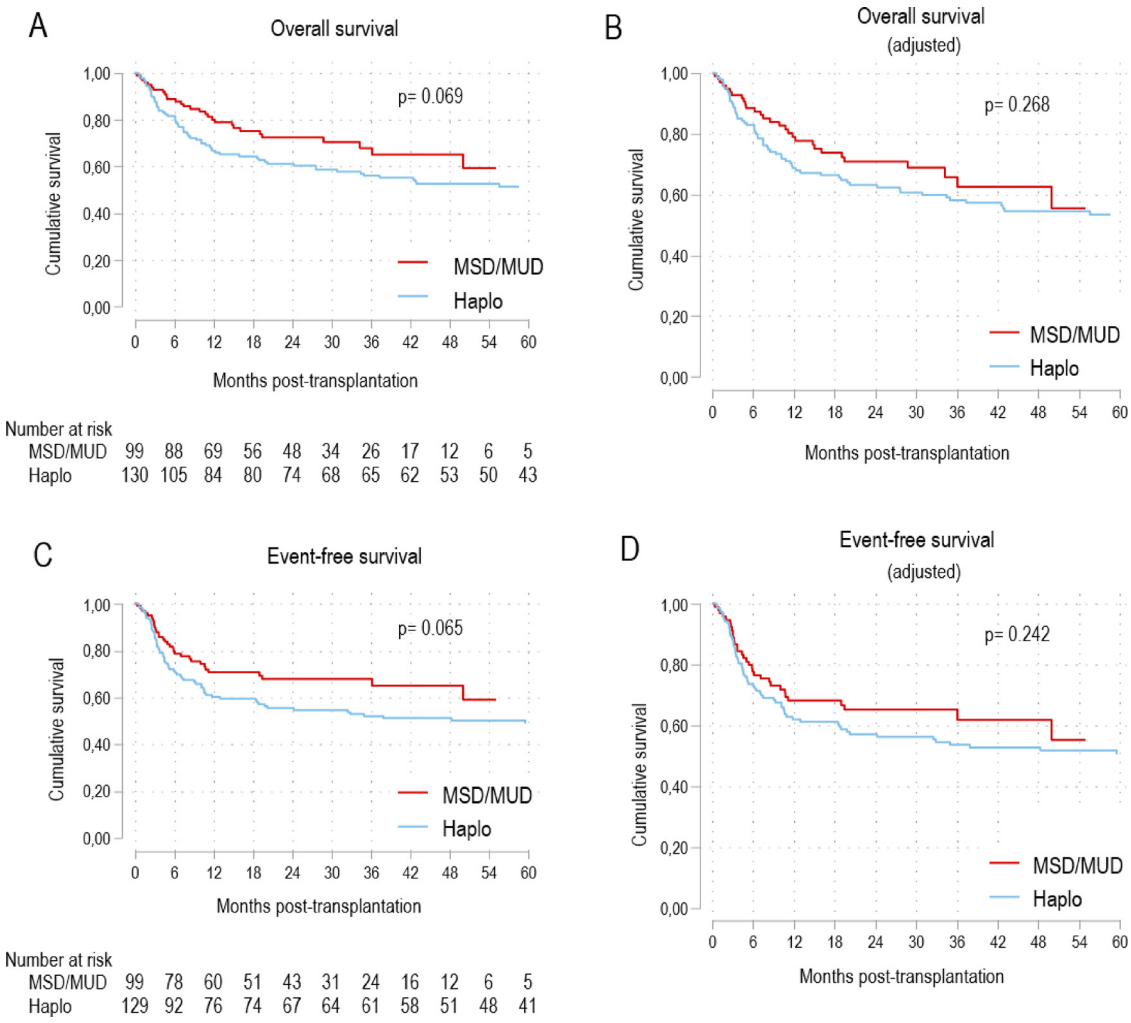

Figure 1. Overall survival (A), adjusted overall survival (B), event-free survival (C), and adjusted event-free survival (D).

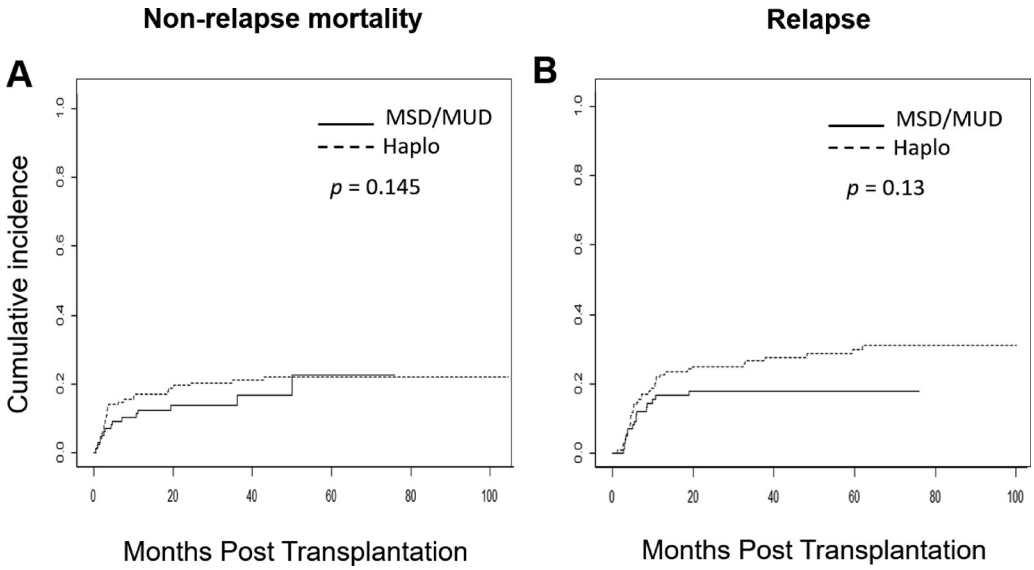

Figure 2. Non-relapse mortality (A) and relapse (B).

Table 2
Causes of Death

	MSD/MUD n = 99	Haplo n = 130
2-year NRM cumulative incidence	14%	19%
Total deaths (complete follow up), no.	15	28
Acute GVHD- related mortality		
Refractory/progressive GVHD	0	0
Infection during treatment	0	1 (3.5%)
Chronic GVHD-related mortality		
Refractory/progressive GVHD	1 (7%)	2 (7%)
Infection during treatment	2 (13%)	2 (7%)
Infection (not GVHD-related)*		
Bacterial infection	5 (33%)	8 (29%)
Fungal infection	3 (19%)	2 (7%)
Viral infection	0	2 (7%)
Other		
TA-TMA / PRESS	1 (7%)	1 (3.5%)
SOS	1 (7%)	1 (3.5%)
Other neoplasm†	1 (7%)	5 (19%)
Other pulmonary toxicity	1 (7%)	2 (7%)
Graft failure	0	1 (3.5%)
Unknown	0	1 (3.5%)

PRESS indicates posterior reversible encephalopathy syndrome; TA-TMA, transplant-associated thrombotic microangiopathy; SOS, sinusoidal obstruction syndrome.

* Most non-GVHD related infections occurred before day 100. One patient in the MSD/MUD group and 1 in the haplo group developed septic shock and died after the first year being in remission.

† In the MSD/MUD group, 1 patient developed second neoplasm (urothelial); in the haplo group, 4 patients developed second neoplasms in a median of 22 months, and 1 had a relapse of underlying breast cancer.

.001 and asHR 2.81 [P = 95% CI, 1.21-6.54], P = .017, respectively).

Relapse

No differences were observed in the 2-year cumulative incidence of relapse (19% versus 25%, P = .13 Figure 2;B). Among the 17 patients who experienced relapse in the MSD/MUD group, in 16 cases (94%) it occurred within the first 12 months after HSCT. In all cases the status at HSCT was CR. Five of the patients received DLI, and 7 received a second transplant; only 4 of those 17 patients were alive at last follow-up. In the haplo group, 39 patients relapsed, of whom 13 (33%) presented active disease at HSCT. Most patients (30, 77%) relapsed during the first 12 months after HSCT; 6 patients presented late relapse (after more than 2 years). Four relapsed patients in the haplo group received DLI, and 4 received a second transplant; only 3 patients were alive at last follow-up. Variables included in the multivariate analysis identified high/very high DRI as an independent predictive factor for relapse (asHR 2.32 [P = 95% CI, 1.32-4.07], P = .003).

GVHD and GRFS

Cumulative incidence of acute GVHD grade II-IV at 100 days was lower in the MSD/MUD group (14% vs 47%, P < .001), whereas grade III-IV aGVHD was similar between groups (4% versus 9%, P = .14) (Figure 2A and 2B). In the MSD/MUD group, 35 (35%) patients presented aGVHD, 22 of them grade I and 13 grade II-IV aGVHD, 10 met criteria for grade II aGVHD (5 with cutaneous, 6 with gastrointestinal, and 0 with hepatic involvement). After systemic steroids, all patients with grade II aGVHD achieved CR. Three patients presented grade III-IV aGVHD (1 with pulmonary, 1 gastrointestinal and 1 with hepatic involvement); all were refractory to steroids and required subsequent treatment with tocilizumab, ruxolitinib, and both ruxolitinib and extracorporeal photopheresis, respectively; 2 of them achieved response. Seven of 13 patients with grade II-IV aGVHD in the MSD/MUD group developed cGVHD, 2 of them with moderate-to-severe cGVHD.

Within the haplo group, 75 (58%) patients developed aGVHD, 20 of them grade I and 47 grade II aGVHD. Data on involvement and response to treatment were available in 29 out of 47 patients with grade II aGVHD (24 cutaneous, 13 gastrointestinal and 6 hepatic involvement). All patients achieved CR after steroid treatment. Eight patients presented grade III-IV aGVHD (5 cutaneous, 5 gastrointestinal and 1 hepatic involvement); all received a combination of steroids with either rapamycin, extracorporeal photopheresis, mesenchymal stromal cells, or basiliximab, achieving response in all cases. Twenty-five of 47 patients with grade II-IV aGVHD developed cGVHD, 12 of them moderate-to-severe cGVHD. There were no deaths related to aGVHD in the MSD/MUD group, and 1 patient in the haplo group died as a result of infection under immunosuppressive treatment.

Multivariate analysis identified haploidentical donor as a risk factor for the development of grade II-IV aGVHD (asHR 4.12 [P = 95% CI, 2.14-7.58]; P < .001), together with older age (asHR 1.02 [P = 95% CI, 1.00-1.04]; P = .017). However, in the case of grade III-IV aGVHD the only significant risk factor identified in the multivariate analysis was having received a previous autologous transplant (asHR 6.97 [P = 95% CI, 1.95-24.89]; P = .003).

A trend toward a higher 2-year cumulative incidence of chronic GVHD in the MSD/MUD group was observed (42% versus 33%, P = .051), while chronic moderate-to-severe GVHD was similar between groups (22% versus 19%, P = .28) (Figure 3C,D). In the MSD/MUD group, 41 (41%) patients developed cGVHD, 22 of them mild with cutaneous-mucosal or gastrointestinal involvement, controlled with topical treatment and/or reintroduction of systemic CNI; all achieved complete or partial response. Nineteen patients developed moderate-to-severe cGVHD requiring at least steroid treatment; 2 were refractory. There were 3 cGVHD-related deaths in this group, 1 because of refractory pulmonary GVHD and 2 because of infection under immunosuppressive treatment.

In the haplo group, 43 (33%) patients developed cGVHD, 21 of them mild and 22 moderate-to-severe; 16 responded to treatment. There were 4 cGVHD-related deaths in this group, 2 because of infection and 2 because of GVHD progression. No independently associated factors for cGVHD and moderate-to-severe cGVHD were identified in the multivariate analysis.

Because of the heterogeneity in PTCY timing and immunosuppressors added in the MSD/MUD group, a subset analysis of GVHD was performed. Both cumulative incidence of grade II-IV (P = .16) and grade III-IV acute GVHD (P = .29) were similar between the 3 subgroups (PTCY+3+4/CNI/MMF; PTCY+3+5/CNI; PTCY+3+4/Sir/MMF); no differences were detected in the 2-year cumulative incidence of chronic GVHD (P = .21). A higher incidence of moderate-severe cGVHD was observed in the group receiving PTCY/Sir/MMF (P = .017); however, this result is limited by the high proportion of patients censored for this endpoint (40%) in the PTCY/CNI/MMF group. Finally, an additional subset analysis including patients only from the 3 centers contributing to both cohorts was performed to discard a possible center effect, showing no differences in outcomes to those obtained in the complete cohort (data not shown).

The composite endpoint of GVHD and relapse-free survival (GRFS) at 2 years showed a higher trend in the MSD/MUD group (49% [P = 95% CI, 38.0-58.6] versus 42% [P = 95% CI, 33.6-

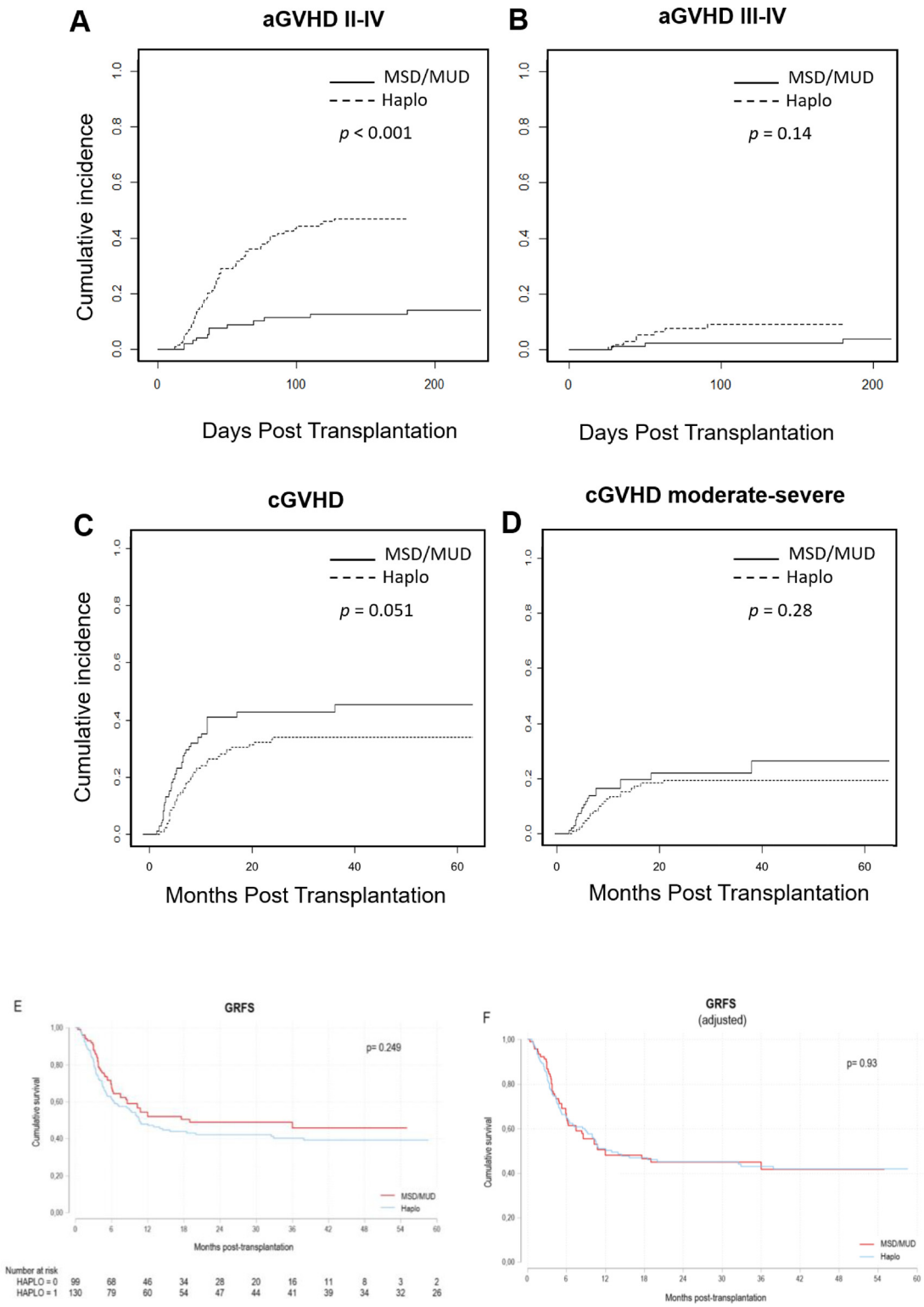

Figure 3. Acute GVHD grade II-IV cumulative incidence (A). Acute GVHD grade III-IV cumulative incidence (B). Chronic GVHD cumulative incidence (C). Chronic moderate-to-severe GVHD cumulative incidence (D). Graft-versus-host disease-free and relapse-free survival (GRFS) (E). Adjusted GRFS (F).

50.6], P = .249, Figure 3E; adjusted P = .93, Figure 3F). In the multivariate analysis, complete response as pre-HSCT status was identified as an independent protective factor (asHR 0.48 [P = 95% CI, 0.30-0.76], P = .002) and female donor/male recipient as a risk factor (asHR 1.95 [P = 95% CI, 1.35-2.83], P < .001) for GRFS.

DISCUSSION

MSD transplantation is the standard of care for patients with acute leukemia in need of an allo-HSCT, and MUD remains as the first option for patients lacking an HLA-identical sibling [26,27]. Although GVHD prophylaxis with methotrexate/CNI for MSD, adding ATG in MUD, are still the standard

regimens [7], PTCY-based platforms have shown low acute GVHD rates without impairing disease control [8–12]. The favorable results of PTCY in these donor settings have led to an increase in its use. During the conventional prophylaxis era, several studies compared the results of PTCY haplo-HSCT to MSD and MUD in AML [13–15], showing that MSD is generally more beneficial in patients with intermediate risk AML, but less so in high-risk patients. Some of these studies have reported a higher risk of NRM or relapse in haplo recipients compared to MSD/MUD, but these differences were not reflected in survival rates. These studies have been included in a meta-analysis of several transplant indications [28], which concluded that haplo showed higher all-cause mortality compared to MRD and similar mortality to MUD. However, few studies have compared haplo versus MSD/MUD when PTCY-based prophylaxis is used in all strategies. A first attempt by the Johns Hopkins group compared haplo to HLA-identical donors using PTCY but was limited to bone marrow grafts, and all haplo received RIC whereas all HLA-identical received MAC regimens [16]. Only 2 recent studies so far have compared outcomes in haplo versus MSD/MUD in acute leukemia when PTCY-based prophylaxis is used in all strategies using both peripheral blood and bone marrow and RIC and MAC regimens. These 2 studies are registry based and accomplish the intrinsic limitations of these analysis.

The first study comparing haploidentical HSCT to MSD and MUD using PTCY in all groups was reported by the EBMT registry [17]. This study included patients with AML in CR1 between 2010 and 2017: 400 from MSD/MUD and 789 from haplo donors, including both bone marrow and PBSC as graft source. The study focused on the relative risk of MUD and haplo compared to standard MSD for each transplantation outcome; haplo-HSCT showed a significantly higher risk of grade II-IV aGVHD and NRM compared to MSD, whereas relapse was lower, accounting for similar survival rates. No significant differences were found between MUD and MSD. The lower relapse rate in haplo could be justified by both higher NRM or a possibly stronger graft-versus-leukemia effect as previously reported in other platforms [29]. Significantly, 30% of MUD patients received ATG. The second study was recently published by the CIBMTR [18] and included patients with acute leukemia and high-risk MDS between 2011 and 2019. This large project compared the outcomes of haplo-HSCT (n = 2036) to MUD (n = 284) using a homogeneous prophylaxis with PTCY/CNI/MMF. PBSC was the most common graft source in the MUD group. Patients receiving RIC regimens were analyzed separately. In RIC transplants, aGVHD grades II-IV and III-IV, graft failure, and NRM were lower in the MUD group, giving longer OS and EFS. No benefit in terms of survival was observed in the myeloablative setting, in which the MUD group showed lower rates of III-IV aGVHD and chronic GVHD. Limitations of this study include different donor selection algorithms used depending on center policies together with disparities in donor availability, also limited by ethnic differences.

Considering the similar outcomes reported between MSD and MUD using PTCY, in the present analysis two groups were defined (MSD/MUD versus haplo). Our results are in line with those reported by the EBMT and CIBMTR. A trend toward higher OS and EFS was observed in the MSD/MUD group; however, a higher proportion of patients with poor disease characteristics was included in the haplo group. Haploidentical donor was not identified as a risk factor for OS and EFS in the multivariate analysis; however, the study could be underpowered because *P* value for nonadjusted pseudoHR was nearly statistically significant. Only poor disease status was identified as an independent risk factor for EFS, together with age for OS. Adjusted Kaplan-Meier curves were calculated for these endpoints controlled by these characteristics showing the same results for OS and EFS. Although not statistically significant in the multivariate analysis, both high/very high DRI and intensity of conditioning regimens were statistically significant for some of these endpoints in the univariate analysis. The impact of active disease on multivariate analysis may have excluded DRI as an independent risk factor. Because of the imbalance between groups in some of these characteristics (active disease and DRI) and the previously reported importance of conditioning regimen, 2 subset analyses were performed. A first analysis excluding patients with active disease and controlling by DRI showed a possible benefit on both OS and EFS of HLA-identical donor in patients with low/intermediate DRI. Similarly, we performed a differential analysis considering conditioning intensity that showed an advantage in terms of EFS for MSD/MUD in the RIC setting. Although consistent with the results reported by the international groups, our study was not designed to address these questions, and these findings should be considered with caution. Finally, although the cumulative incidence of relapse showed an upward trend in the haplo group, no statistically significant differences were observed in its incidence and that of NRM.

Regarding GVHD, incidence of grade II-IV aGVHD was higher in the haplo group; no differences were observed in grade III-IV aGVHD and a trend towards a higher incidence of cGVHD was observed in the MSD/MUD group. There were low rates of steroid-resistant GVHD and similar GFRS in both groups. Of note, there was one patient in the MSD/MUD group who presented a non-classical manifestation [30] (pulmonary GVHD) and was classified as grade III-IV because of its severity and outcome [31]; all remaining patients were classified by MAGIC criteria. Our results in terms of GVHD are also consistent with those previously reported by the EBMT and the CIBMTR. In the EBMT study, the haplo group showed a significantly higher risk of grade II-IV aGVHD than the MSD group. In the CIBMTR study, recipients of RIC were at less risk of both grade II-IV and III-IV aGVHD when MUD was used versus haplo. This, together with lower graft failure rates, accounted for a benefit in NRM and OS. In MAC transplants, grade III-IV aGVHD and cGVHD were also lower in the MUD compared to the haplo group. In our study, the trend toward higher cGVHD observed in the MSD/MUD groups might have been influenced by the different immunosuppressors added to PTCY. Moreover, a higher proportion of patients were censored for this endpoint in the haplo group (36% versus 24%) because of competing events, possibly contributing to lower incidence of cGVHD in the haplo group. Significantly, GVHD-related mortality was low in both groups, with non-GVHD related infection being the most frequent cause in both groups. This finding is similar to that previously reported by the GETH-TC group in PTCY haplo-HSCT [32]. These results could be related to the impact of PTCY on immune reconstitution that has largely been described in haplo-HSCT [33]; although data on immune reconstitution in the HLA-identical HSCT setting with PTCY are still scarce, a recent report has studied immune reconstitution in this setting describing the expansion dynamics of T-cells [34]. Its translation to impact on infection, however, warrants further investigation. Despite a better trend in the MSD/MUD group, no significant differences were observed in GRFS; however, this endpoint might be underpowered similarly to OS and EFS. Finally, nonrelapse mortality related to noninfectious causes, including endothelial complications, was low in both groups.

Our study has several limitations, including its retrospective nature and the relatively limited number of patients. However, to improve the quality of our data, participating centers were asked to replace missing data and review GVHD characteristics and treatment. One important limitation of our study is the heterogeneity of the immunosuppressors added to PTCY in the MSD/MUD group, with 33% of patients receiving only CNI without MMF. Moreover, the use of these 3 regimens depended on center policies introducing a possible center effect. The use of 2 additional immunosuppressors has previously been associated with a reduction in cGVHD rates [8], and this subgroup also received a different strategy, with PTCY on days 3 and 5 and CNI starting from day 0, as reported by the Italian group, without MMF [35]. This different timing of PTCY has been compared to PTCY on days 3 and 4 in murine models with no impact on GVHD development [36]. Anyway, all these differences could have impacted our results in terms of cGVHD. To better address the impact on GVHD of these differences a subset analysis was performed in the MSD/MUD group by immunosuppressive regimens used. In this analysis all endpoints were similar between subgroups and only moderate to severe cGVHD appeared to be higher with PTCY/Sir/MMF; however, this result should be taken with caution because of the high proportion of patients censored for this endpoint in the rest of subgroups. Another limitation of our study is the limited number of centers performing MSD/MUD with PTCY as compared to haplo. To discard a possible center effect, an additional subset analysis including patients only from the 3 centers contributing to both cohorts was also performed, showing similar results to that obtained in the complete cohort. Finally, the sample size could had been insufficient to detect a possible independent effect of the use of HLA-identical donor in other outcomes including survival and GRFS.

Although more data from prospective randomized studies should be waited for to better address whether HLA-identical has an advantage over haplo-HSCT in AML in the PTCY era, our results show that PTCY MSD/MUD transplant, using mostly PBSC as graft source, is superior to haplo in terms of grade II-IV aGVHD and showed a trend toward longer OS and EFS with low rates of NRM and no impact on disease control. Our results support those already reported by other international groups adding evidence in this setting. This benefit is clinically significant because of the morbidity caused by both aGVHD and its treatment. However, it should be taken into account that grade II aGVHD has previously been associated with better outcomes in both RIC haplo-HSCT and MAC HLA-identical transplantation using bone marrow as a graft source [37,38]. Nevertheless, PTCY with haplo donors offers similar survival results and should therefore be considered in urgent situations in which a readily available haplo-donor could be the best option [39]. Currently, a European randomized clinical trial (EudraCT 2017-002331-41) is recruiting patients with acute leukemia or high-risk MDS in indication for first allo-HSCT lacking a MSD to haplo versus MUD transplantation using PTCY to better address this important question.

In conclusion, in our experience, PTCY as GVHD prophylaxis in both MSD/MUD and haplo transplantation in AML using mostly PBSC effectively prevents GVHD and offers similar NRM, relapse, and survival rates. Clinically significant grade II-IV aGVHD incidence was lower in MSD/MUD transplantation, suggesting a benefit for HLA-identical donor HSCT in this context.

ACKNOWLEDGMENTS

We thank the staff and nurses of all the hematology and transplant units for their care and contributions to this study. We thank Felipe Pérez-García and José María Bellón for the data analysis. We thank Medical Science Consulting for their help with the preparation of the manuscript (financed by Jazz Pharmaceuticals as part of the “Publibecas” grant program of the GETH-TC).

Financial disclosure: None.

Conflicts of interest: There are no conflicts of interest to report.

Authorship statement: M.K. and R.B. conceived and designed the study. All authors provided study materials or patients. R. B., M.J.P.C., M.G., L.L.C., A.C., A.B., A.S., I.H., E.G.T., M.T., J.R.R., I.S. O., C.S., V.N., and K.H. collected and assembled the data. All authors analyzed and interpreted the data. R.B. and M.K. wrote the manuscript. All authors participated in revision and final approval of manuscript.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2022.01.020.

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