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Characterization of Chronic Graft-versus-host Disease After Haploidentical Stem Cell Transplantation With Posttransplant Cyclophosphamide: A Study on Behalf of GETH-TC

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Background. Chronic graft-versus-host disease (cGVHD) is a cause of late morbidity and nonrelapse mortality (NRM) after allogenic hematopoietic stem cell transplantation (allo-HSCT). Although studies evaluating haploidentical allo-HSCT (haplo-HSCT) using posttransplant cyclophosphamide (PTCy) demonstrate lower cGVHD rates, comprehensive data describing the clinical profile, risk factors, or outcomes of cGVHD within this platform are scarce. **Methods.** We conducted a retrospective multicenter analysis of 389 consecutive patients who underwent haplo-HSCT PTCy in 7 transplant centers of the Spanish Group Grupo Español de Trasplante Hematopoyético y Terapia Celular (GETH-TC) between 2008 and 2020 describing incidence, clinical profile, risk factors, and cGVHD outcomes. **Results.** Ninety-five patients of 389 developed cGVHD. Our data revealed that the incidence and severity of cGVHD are lower than those reported for HLA-identical transplantation with conventional prophylaxis and that the strongest predictor for cGVHD was previous acute GVHD ($P = 0.031$). Also, recipient age ≥60 y ($P = 0.044$) was protective against cGVHD. Moreover, patients with moderate cGVHD had longer event-free survival at 3 y than other patients ($P = 0.016$) and a lower relapse rate at 3 y ($P = 0.036$). **Conclusions.** Our results support the fact that the incidence and severity of cGVHD are lower than those reported for HLA-identical transplantation with conventional prophylaxis. In this series, patients who develop moderate cGVHD after haplo-HSCT PTCy had a higher overall survival and event-free survival, and lower relapse, suggesting higher graft-versus-leukemia effect. Although this is the largest series focused on characterizing cGVHD in haplo-HSCT PTCy, further prospective studies are needed to confirm the findings.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative option for patients who suffer malignant and nonmalignant hematological conditions. However, not all patients requiring allo-HSCT have an HLA-identical donor. In this setting, haploidentical donors allow patients the opportunity to proceed with potentially curative allo-HSCT. Initially, haploidentical allo-HSCT (haplo-HSCT) was associated with primary graft failure, acute graft-versus-host disease (aGVHD), and nonrelapse mortality (NRM).[1-3] Nowadays, haplo-HSCT with posttransplantation cyclophosphamide (PTCy) pioneered by Luznik et al[4] is widely used because haploidentical donors are usually available,[5-8] and PTCy has improved efficacy and safety, making the latter an important prophylaxis strategy for GVHD.[9-16]

Chronic GVHD (cGVHD) remains the leading cause of late morbidity and NRM after allo-HSCT, with an increasing incidence despite advances in transplantation practices.[17-19] This complication, together with the long-term immunosuppressive treatment, impacts on patient's quality of life. However, it is linked to the graft-versus-tumor effect, which reduces the risk of relapse of the underlying disease.[20]

Historically, the incidence of cGVHD in haplo-HSCT was higher than that in HLA-identical allo-HSCT.[1-3] By contrast, recent studies evaluating T cell–repleted haplo-HSCT using PTCy demonstrate lower cGVHD rates compared with historical rates for HLA-identical donor transplants.[11,15,21-24] Several risk factors for developing cGVHD after related or unrelated allo-HSCT have been described.[25,26] However, despite the increasing use of haplo-HSCT PTCy, data fully describing the clinical profile, risk factors, or outcomes of cGVHD within this platform are scarce.[27] In this setting, some studies identified different risk factors associated with cGVHD after haplo-HSCT PTCy, including white race, previous grade II–IV aGVHD, graft source (peripheral blood [PB]), and reduced intensity conditioning (RIC) using PB.[28,29]

In recent years, a new endpoint determined as disability related to cGVHD (any diagnosis of bronchiolitis obliterans [BO], grade ≥2 keratoconjunctivitis sicca, sclerotic features score 2–3, or an esophageal stricture score of 3 requiring dilatation), has been explored; patients with these characteristics show impaired recovery of pretransplantation function, poor quality of life, and a requirement for immunosuppression.[30] Fatobene et al[31] recently described that disability rates were lower in a small series of 88 patients who underwent haplo-HSCT versus unrelated single HLA-allele mismatched which may be helpful for transplant centers when considering an alternative donor in some cases.

Here, we aimed to analyze the incidence and risk factors for the development of cGVHD. In addition, we describe clinical profile, disability impact, and treatment response of cGVHD in a series of adult patients with hematologic malignancies who underwent PTCy-based haplo-HSCT within the Spanish Group of Hematopoietic Stem Cell Transplantation and Cell Therapy.

MATERIALS AND METHODS

Patients

A retrospective multicenter analysis of 389 consecutive patients who underwent haplo-HSCT PTCy at 7 Spanish transplant centers from 2008 to 2020 was conducted. Patients aged ≥18 y who were transplanted because of a hematological malignancy or aplastic anemia were included. All underwent HSCT from a haploidentical donor (defined as a donor with ≥2 antigen-level mismatches among HLA-A, -B, -C, and -DRB1). Bone marrow (BM) or PB was used as the graft source.

The institutional ethics committees of all transplant centers approved the study, and all patients provided written consent before entering the study in accordance with the Declaration of Helsinki.

Conditioning Regimens and GVHD Prophylaxis

Myeloablative conditioning (MAC) regimens included IV busulphan (Bu; 3.2 mg/kg/d for 3 or 4 d [days −5 or −4 to −2]), fludarabine (Flu; 30 mg/m^2/d from days −6 to −2 + Cy 14.5 mg/kg/d on days −6 and −5 [FluBu-MAC]), or a Raiola et al[32] conditioning regimen that includes thiotepa (Thio; 5 mg/kg/d) from days −6 to −5; Bu (3.2 mg/kg/d) from days −4 to −2, and Flu (50 mg/m^2/d) from days −4 to −2 (TBF-MAC).

RIC regimens included Bu (3.2 mg/kg/d on days −4 to −3 or −4), Cy (14.5 mg/kg/d on days −6 and −5), and Flu (30 mg/m^2/d on days −6 to −2 [FluBu-RIC]); a Hopkins conditioning regimen[4] comprising Flu (30 mg/m^2/d on days −6 to −2), Cy (14.5 mg/kg/d on days −6 to −5) and a single fraction low-dose total body irradiation of 2 Gy on day −1 (Flu-TBI-RIC), or a modified Raiola et al[32] conditioning regimen comprising Thio (5 mg/kg/d on days −6 and −5), Bu (3.2 mg/kg/d from days −4 to −3), and Flu (50 mg/m^2/d from days −4 to −2 [TBF-RIC]). RIC regimens were selected for patients >60 y, patients under poor clinical condition, patients who had received a previous transplantation, or patients diagnosed with Hodgkin lymphoma, non-Hodgkin lymphoma, or multiple myeloma.

GVHD prophylaxis comprised intravenous (IV) Cy (50 mg/kg/d on days +3 and +4) combined with a calcineurin inhibitor (CNI; cyclosporine or tacrolimus) and MMF (from day +5); for conditioning regimens that included Thio, Cy was administered on days +3 and +4 or +5, and the CNI was started at day 0 and MMF at day +1 or both on day +5. In the absence of GVHD, MMF was withdrawn on day +35 and CNI was decreased from approximately day +60 or +90, and stopped at day +120 or +180 depending on the relapse risk and the presence of GVHD.

Clinical Assessment and Study Endpoints

aGVHD was diagnosed and scored according to the Mount Sinai Acute GVHD International Consortium criteria.[33] Diagnosis of cGVHD was performed and graded according to the National Institutes of Health (NIH) criteria.[34,35]

Response of cGVHD treatment were determined according to NIH criteria.[36] Disease manifestation at 2 different points are compared, and a judgment was made as to whether the magnitude of any change qualifies as improvement or deterioration according to these NIH criteria.

Patients with evidence of engraftment were evaluable for aGVHD, whereas patients who engrafted and survived ≥100 d were evaluable for cGVHD.

Disability related to cGVHD was classified as described by Fatobene et al.[31]

Overall survival (OS) was defined as the time from transplantation to death (from any cause) or last

follow-up. Event-free survival (EFS) was defined as time from transplantation to relapse or death (whichever comes first). NRM was defined as death without previous occurrence of relapse or disease progression. Relapse incidence was calculated from the date of haplo-HSCT to the date of relapse or progression. The composite endpoint graft-versus-host-free relapse-free survival (GRFS) was defined as survival without any grades III–IV aGVHD, cGVHD that requires systemic immunosuppressive treatment, or relapse or death from any cause after haplo-HSCT.

Deaths because of infection in the context to active GVHD were considered to be related to GVHD.

Statistical Analysis

The main endpoints of this study were to analyze risk factors that influence cGVHD after haplo-HSCT and its incidence. Secondary endpoints included to analyze clinical cGVHD profile after haplo-HSCT, disability related to cGVHD, response to treatment, and the impact of cGVHD on survival after haplo-HSCT PTCy.

Quantitative variables are expressed as the median and range, and qualitative variables as frequency and percentage.

The cumulative incidence of NRM, aGVHD, and cGVHD was estimated using the Fine-Gray test, considering death not related to GVHD as a competing event for aGVHD and cGVHD, and relapse or progression for NRM. OS, EFS, and GRFS, were analyzed using the nonparametric test Kaplan–Meier estimator, including 95% confidence intervals (CIs). NRM was considered a competing risk for progression or relapse. Comparison of time to event endpoints was performed using Cox regression analysis.

Clinical variables included in the analysis of risk factors for cGVHD were patient, disease, and transplant-related variables.

Variables that correlated significantly with different endpoints in univariate analysis were entered into multivariate analysis, and only those with $P < 0.05$ were retained. For analyses related to cGVHD, a cutoff was fixed at day 100 posttransplantation. To identify variables associated with development of cGVHD, logistic regression was used.

SPSS (IBM, SPSS Statistics for Windows, version 21.0. Armonk, NY) and R software were used for all analyses.

RESULTS

Baseline features of patients, donor characteristics, and transplantation procedures are summarized in Table 1.

The median age was 48 (15–74) y, and 62.2% patients were male. Acute myeloid leukemia and Hodgkin lymphoma were the most common diagnoses (37.0%, n = 144; and 22.9%, n = 89). The HCT-CI was ≥3 in 129 patients (33.2%), and the DRI was high/very high for 54 patients (13.9%).

Among the 83 patients receiving TBF, 49.4% (n = 41) received Cy +3,+5 and CNI 0 versus 50.6% (n = 42) Cy +3,+4 and CNI +5. Overall, 58.4% of patients received a FluBu-RIC. PB was selected as the stem cell source for the majority of patients (80.4%). A median of 5.3 and 180×10^6/kg of $CD34^+$ and $CD3^+$ were infused.

Overall Outcomes Posttransplantation

The median follow-up for living patients was 35 (3–102) mo. Neutrophil and platelet recovery was reached after a median of 17 (12–48) d and 25 (5–150) d. Twelve patients (3%) had primary graft failure.

The cumulative incidence of overall aGVHD, grades II–IV, and III–IV at +180 d was 63.6% (P = 95%; 95% CI, 58.5-8.2), 21.8% (P = 95%; 95% CI, 17.6-26.1), and 10.9% (P = 95%; 95% CI, 8.0-14.3), respectively. NRM at +100 d was 11.9% (P = 95%; 95% CI, 8.9-15.42), and global NRM was 24.5% (P = 95%; 95% CI, 20.1-29.1).

The 2-y OS, EFS, and GRFS were 59.6% (P = 95%; 95% CI, 54.8-64.9), 53.2% (P = 95%; 95% CI, 48.3-58.6); and 45.2% (P = 95%; 95% CI, 40.4-50.6), respectively. The estimated 3-y OS, EFS, and GRFS were 56.1% (P = 95%; 95% CI, 51.0-61.6), 50.1% (P = 95%; 95% CI, 45.1-55.6) and 42.0% (P = 95%; 95% CI, 37.2-47.6; **Figures S1–S3, SDC**, http://links.lww.com/TP/D45).

cGVHD Incidence, Clinical Characteristics, and Risk Factors

Three hundred thirty-four patients that engrafted and survived >100 d were evaluable for cGVHD and were included in this analysis. According to NIH diagnostic criteria, 95 patients (28.4%) developed cGVHD. The cumulative incidence of cGVHD was 30.2% (P = 95%; 95% CI, 25.0-35.6) and 32.4% (P = 95%; 95% CI, 26.8-38.1) at 2 and 3 y, and that of moderate-to-severe cGVHD was 17.6% (P = 95%; 95% CI, 12.2-23.0) and 19.5% (P = 95%; 95% CI,14.2-24.8) at 2 and 3 y (Figure 1).

cGVHD characteristics, including the patterns of organ involvement, are described in Table 2. Seventy-one patients (74.7%) had classic cGVHD, and 24 (25.2%) were diagnosed with overlap syndrome. In addition, 21 patients (22.1%) had progressive cGVHD onset. Regarding NIH severity, 49.5% (n = 47), 26.3% (n = 25), and 24.2% (n = 23) of patients had mild, moderate, and severe cGVHD, respectively. The median number of affected organs was 1 (1–4), and only 17 patients (17.9%) had ≥3 organs involved. The skin, followed by the mouth, was the most common site of cGVHD. Also, 15 patients (16.0%) developed BO. In 27 patients (28.7%) and in 14 patients (14.9%), immunosuppression reduction or discontinuation within 6 previous wk was identified as a potential triggering factor, respectively.

The cumulative incidence of disability related to cGHVD manifestations was 7.2% (P = 95%; 95% CI, 3.87-10.53) and 9% (P = 95%; 95% CI, 5.28-12.72) at 2 and 3 y. Clinical manifestations of disability related to cGVHD are shown in **Table S1** (**SDC**, http://links.lww.com/TP/D45). Twenty-two patients (23%) exhibited any manifestation responsible for disability related to cGHVD. The most frequent morbidities were BO and sclerotic features, followed by keratoconjunctivitis.

When analyzing risk factors for cGVHD, univariate analysis identified female donor (hazard ratio [HR], 1.547; 95% CI, 1.032-2.318, P = 0.034), female donor and male recipient (HR, 1.548; 95% CI, 1.018-2.356, P = 0.041), low DRI (HR, 1.608; 95% CI, 1.059-2.441, P = 0.026), MAC conditioning (HR, 1.521; 95% CI, 1.005-2.301, P = 0.047), the use of Cy on days +3 and +5 along with CNI and MMF on day 0 (HR, 1.001; 95% CI, 1.001-1.002, P = 0.000) as factors that

TABLE 1.
Patients and transplant characteristics

Characteristic	N = 389
Age at transplant, y, median (range)	48 (15–74)
Donor age, y, median (range)	37 (14–75)
Male, n (%)	242 (62.2)
HCT-CI, %	
0–2	253 (65.0)
≥3	126 (32.4)
Incomplete data	10 (2.6)
Diagnosis, n (%)	
Acute myeloid leukemia	144 (37.0)
Hodgkin lymphoma	89 (22.9)
Non-Hodgkin Lymphoma	49 (12.6)
Myelodysplastic syndrome	37 (9.5)
Acute lymphocytic leukemia	34 (8.7)
Myeloproliferative syndrome	12 (3.1)
Chronic myelomonocytic leukemia	7 (1.9)
Chronic myeloid leukemia	6 (1.5)
Multiple myeloma	5 (1.3)
Others[a]	6 (1.5)
Prior treatment regimens, n (%)	
0–2	223 (57.2)
>2	166 (42.8)
Previous transplantation, n (%)	
Autologous transplantation	105 (27.0)
Allogenic transplantation	35 (9.0)
Disease risk index, n (%)	
Very high/high	7 (1.8)/47 (12.1)
Intermediate/low	230 (59.1)/105 (27)
Donor–recipient sex match, n (%)	
No mismatch	199 (51.2)
Female to male	114 (29.3)
Male to female	76 (19.5)
Donor–recipient relationship, n (%)	
Child to parent	155 (39.8)
Sibling to sibling	146 (37.6)
Mother to child	53 (13.6)
Father to child	34 (8.7)
Other (aunt)	1 (0.3)
Conditioning regimen, n (%)	
Myeloablative regimen	104 (26.7)
TBF-MAC	55 (52.9)
FluBux3-MAC	29 (27.9)
FluBux4-MAC	20 (19.2)
Reduced intensity regimen	278 (71.5)
FluBux2-RIC	167 (60.1)
FluBux1-RIC	60 (21.5)
TBF-RIC	28 (10.1)
FluBu-TBI-RIC	23 (8.3)
Sequential regimen	7 (1.8)
GVHD prophylaxis, n (%)	
Tacro + MMF + Cy	250 (64.3)
CsA + MMF + Cy	139 (35.7)
Graft source, n (%)	
Peripheral blood	313 (80.5)
Bone marrow	76 (19.5)
CD34 + ($\times 10^6$/kg) infused, median (range)	5.3 (0.65–13.68)
CD3 + ($\times 10^6$/kg) infused, median (range)	180 (2.98–3054.17)
Transplant period, n (%)	
2007–2011	19 (4.9)
2012–2016	249 (64.0)
2016–2020	121 (31.1)

[a]Others: mycosis fungoides (n = 3); dendritic cell leukemia (n = 1); and bone marrow aplasia (n = 2).
GVHD, graft-versus-host disease; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; MAC, myeloablative conditioning; MMF, mycophenolate-mofetil; RIC, reduced intensity conditioning.

increase the risk of developing cGVHD. Recipient age >60 y (HR, 0.485; 95% CI, 0.270-0.871, $P = 0.015$) had a favorable influence. Regarding the impact of previous aGVHD, it was a risk factor, as expected (HR, 1.859; 95% CI, 1.134-3.047, $P = 0.014$). In multivariate analysis including the statistically significative variables, the strongest predictive factor for cGVHD was previous aGVHD (HR, 2.218; 95% CI, 1.328-3.705, $P = 0.002$). Also, recipient age ≥60 y (HR, 0.491; 95% CI, 0.259-0.931, $P = 0.029$) showed to be protective against developing cGVHD (Table 3). Recipient age ≥60 y is still protective against cGVHD even in a multivariate model excluding aGVHD from the covariates (**Table S2, SDC,** http://links.lww.com/TP/D45).

Fifty-three patients (55.8%) were managed with supportive or topical treatment (topical CNI or corticosteroids) approaches, with a high overall response rate (ORR) (92.5%). Forty-three of 95 patients received systemic treatment (steroids, CNI, Ruxolitinib, mesenchymal cells, or extracorporeal photopheresis), with a median of 1 treatment line (1–5). Complete and partial response rate (RR) were 44.2% and 30.2%, respectively, among those who received systemic treatment. Nineteen patients required second-line therapy; nevertheless, complete RR were lower (15.8%; Table 4).

The cumulative incidence of discontinued systemic immunosuppressive therapy at 2 and 3 y was 50.3% ($P = 95\%$; 95% CI, 44.7-55.9) and 67.5% ($P = 95\%$; 95% CI, 61.8-73.2).

Risk Factors for Moderate-to-severe cGVHD

When analyzing risk factors for moderate-severe cGVHD, univariate analysis identified female donor (HR, 1.804; 95% CI, 1.016-3.204, $P = 0.044$), low DRI (HR, 1.803; 95% CI, 1.011-3.217, $P = 0.046$), and previous aGVHD (HR, 3.475; 95% CI, 1.476-8.810, $P = 0.004$) as factors that increase the risk of developing cGVHD. Recipient age >60 y (HR, 0.277; 95% CI, 0.099-0.771, $P = 0.014$) had a favorable influence on cGVHD. In multivariate analysis including the statistically significative variables, the strongest predictive factor for moderate-to-severe cGVHD was previous aGVHD (HR, 3.568; 95% CI, 1.513-8.417, $P = 0.004$). Also, recipient age ≥60 y (HR, 0.291; 95% CI, 0.0.104-0.812, $P = 0.018$) showed to be protective against developing cGVHD (**Table S6, SDC,** http://links.lww.com/TP/D45).

Survival Outcomes Examining the Impact of cGVHD and cGVHD Severity

This analysis was conducted with patients evaluable for cGVHD. The median time to onset of cGVHD

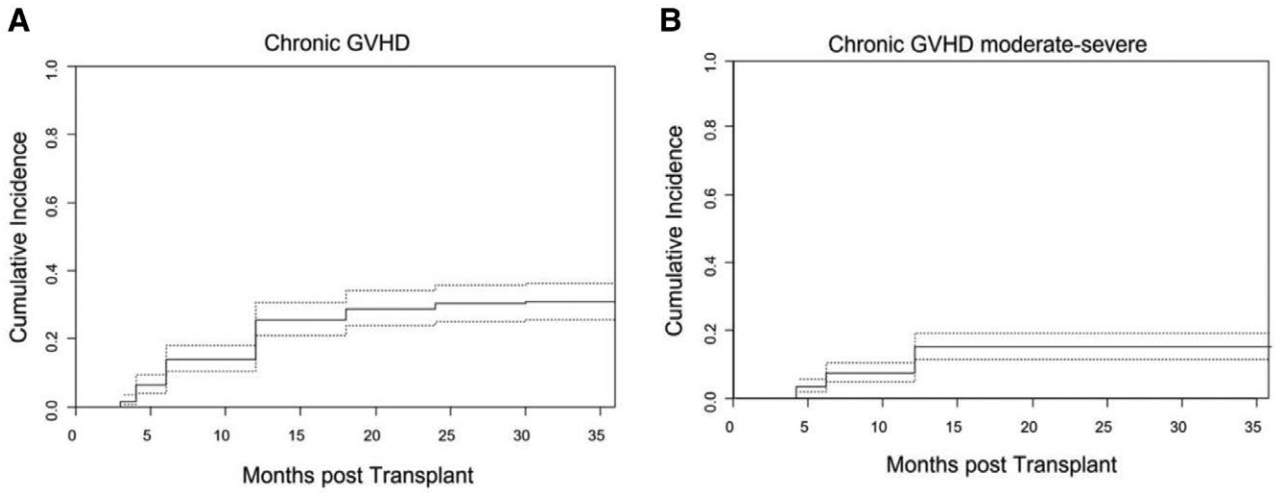

FIGURE 1. Cumulative incidence of cGVHD. A, Cumulative incidence of cGVHD at 3 y. B, Cumulative incidence of moderate-to-severe cGVHD at 3 y. cGVHD, chronic graft-versus-host disease.

TABLE 2.

Characteristics of chronic graft-versus-host disease

Chronic GVHD characteristics	n = 95
cGVHD onset, n (%)	
Progressive	21 (22.1)
Quiescent	50 (52.6)
De novo	24 (25.3)
cGVHD overlap, n (%)	24 (25.2)
Prior acute GVHD	
Prior late acute GVHD, n (%)	6 (6.3)
Prior II–IV acute GVHD, n (%)	55 (57.8)
Prior III–IV acute GVHD, n (%)	14 (14.7)
NIH severity, n (%)	
Mild	47 (49.5)
Moderate	25 (26.3)
Severe	23 (24.2)
Sites of cGVHD involved, median (range)	1 (1–4)
Sites of cGVHD involved, n (%)	78 (82.1)
1–2	17 (17.9)
≥3	
Sites of cGVHD, n (%)	
Skin	43 (45.7)
Mouth	33 (35.1)
Eyes	22 (23.4)
Gastrointestinal tract	18 (19.1)
Liver	17 (18.1)
Lung (bronchiolitis obliterans)	15 (16.0)
Joint/fasciae	5 (5.3)
Genitals	4 (4.3)
Potential triggering factors, n (%)	
IST reduction within 6 previous wk	27 (28.7)
IST discontinuation within 6 previous wk	14 (14.9)
DLI	4 (4.3)
Platelet count $<100 \times 10^9$/L	38 (40)
Eosinophils >500/μL at cGVHD onset, n (%)	7 (7.4)

cGVHD, chronic graft-versus-host disease; DLI, donor lymphocyte infusion; IST, immunosuppressive therapy.

was 189 (68–1477) d from infusion, and the median follow-up time after cGVHD diagnosis was 22 (0.5–85) mo.

The 2 and 3-y NRM in the cGVHD population was 8.6% (*P* = 95%; 95% CI, 3.5-16.8) and 10.4% (*P* = 95%; 95% CI, 4.5-19.3), respectively. OS and EFS in the cGVHD population were 80.9% (*P* = 95%; 95% CI, 72.1-90.8) and 72.2% (*P* = 95%; 95% CI, 62.8-81.6) at 2 y, and 77.4% (*P* = 95%; 95% CI, 67.9-88.2) and 67.7%, (*P* = 95%; 95% CI, 60.8-74.5) at 3 y (**Figure S4, SDC,** http://links.lww.com/TP/D45).

Nonrelapse Mortality

Patients with severe cGVHD showed a higher 3-y NRM, albeit not significantly *(P* = 0.470; severe cGVHD, 26.0%, moderate cGVHD, 13.8%, mild cGVHD, 6.5%; absence of cGVHD, 12.8%; **Figure S5, SDC,** http://links.lww.com/TP/D45). No differences according to cGVHD onset (de novo, progressive, or quiescent) were found (*P* = 0.115). However, overlap cGVHD showed a higher NRM than classic cGVHD (40.5% versus 13.3%; *P* = 0.010; Figure 2).

There were no statistically significant differences in NRM according to the affected organ, irrespective of the number of organs or whether cGVHD was classified as disability related (**Table S3, SDC,** http://links.lww.com/TP/D45). In patients with cGVHD, the most common cause of NRM was infection (n = 10, 66.7%), 6 patients died because of bacterial infection, 2 of fungal infection, 2 of viral infection. Two patients died because of a flare of gastrointestinal grade IV aGVHD, another because of pulmonary cGVHD progression, and another 2 presented a sudden death.

Overall Survival

Overall, 67 patients survived and 28 patients died during the follow-up period. The median OS was not reach. Interestingly, patients with moderate cGVHD had a longer 3-y OS than patients with mild, severe, or absence of cGVHD, although the difference was not statistically significant (*P* = .110, 3-y OS, 86.2% [*P* = 95%; 95% CI, 72.8-100] versus 71.8% [*P* = 95%; 95% CI, 59.4-86.8], 51.8% [*P* = 95%; 95% CI, 34.8-77.1], and 63.6% (*P* = 95%; 95% CI, 57.2-70.6], respectively). Moreover, patients with overlap syndrome showed a lower 3-y OS

TABLE 3.

Cox uni- and multivariate analysis of risk factors for cGVHD

	Univariate analysis			Multivariate analysis		
Risk factors	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**
Donor sex female	**0.034**	**1.547**	**1.032-2.318**	0.839	1.061	0.600-1.873
Receptor sex male	0.399	0.834	0.546-1.272			
Male receptor female donor	**0.041**	**1.548**	**1.018-2.356**	0.167	1.519	0.839-2.749
Recipient age ≥ 60 y	**0.015**	**0.485**	**0.270-0.871**	**0.047**	**0.512**	**0.265-0.991**
Donor age ≥ 37 y	0.853	1.059	0.578-1.941			
Acute hematological disease	0.503	1.151	0.763-1.736			
≥2 treatment lines	0.908	0.973	0.606-1.561			
Previous transplant	0.824	0.952	0.620-1.463			
HCT-CI ≥ 3	0.282	1.270	0.822-1.963			
DRI low	**0.026**	**1.608**	**1.059-2.441**	**0.071**	**1.524**	**0.965-2.407**
Graft source peripheral blood	0.155	1.400	0.881-2.224			
$CD34^{+} \geq 6 \times 10^{6}$/kg	0.976	0.994	0.655-1.508			
Myeloablative conditioning	**0.047**	**1.521**	**1.005-2.301**	0.710	1.110	0.639-1.930
TBF vs others	0.100	1.464	0.927-2.313			
Cy +3, +5 and CNI 0 vs Cy +3, +4 and CNI +5	**0.000**	**1.001**	**1.001-1.002**	0.078	1.734	0.939-3.203
Previous aGVHD	**0.014**	**1.859**	**1.134-3.047**	**0.011**	**1.959**	**1.164-3.298**
Transplantation period						
2007–2011	0.967	0.981	0.398-2.418			
2012–2016	0.951	1.014	0.659-1.558			
2017–2020	0.965	0.990	0.629-1.558			
CMV negative/negative	0.959	0.982	0.491-1.964			
Donor, recipient or both CMV positive	0.959	1.019	0.509-2.038			
TA-TMA	0.793	1.146	0.413-3.184			
Hemorraghic cystitis	0.871	0.955	0.551-1.658			
Venooclusive disease	0.825	0.853	0.208-3.501			

Bold values indicate variables that were statistically significant.

cGVHD, chronic graft-versus-host disease; CNI, calcineurin inhibitor; Cy, cyclophosphamide; DRI, disease risk index; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; TA-TMA, transplant-associated thrombotic microangiopathy.

TABLE 4.

cGVHD response to treatment according to NIH criteria

cGVHD treatment and response	**n = 95 (%)**
No. systemic treatment lines, median (range)	1 (1–5)
Treatment of cGVHD at first line and response, n (%)	
Supportive and topic treatment (steroids)	53 (55.8)
CR	37 (69.8)
PR	12 (22.7)
NR	4 (7.5)
Systemic treatment with steroids ± calcineurin	43 (44.2)
inhibitors	19 (44.2)
CR	13 (30.2)
PR	11 (25.6)
NR	
Treatment of cGVHD at second line and response, n (%)	
Systemic treatment with steroids, ruxolitinib, calcineurin inhibitors, mesenchymal cells or extracorporeal photopheresis	19
CR	3 (15.7)
PR	10 (52.7)
NR	6 (31.6)
Treatment of cGVHD at third line or more, n (%)	18 (18.9)

cGVHD, chronic graft-versus-host disease; CR, complete response; NIH, National Institutes of Health; NR, nonresponse; PR, partial response; SD, stable disease.

(74.4% [*P* = 95%; 95% CI, 67.9-88.2] versus 43.3% [P = 95%; 95% CI, 25.6-73.4], *P* = 0.004; HR, 2.984; 95% CI, 1.387-6.418; Figure 3).

Regarding organs involved, the mouth and eyes were protective factors (*P* = 0.008 and *P* = 0.023, respectively). No statistical difference was found in 3-y OS between patients with cGVHD classified as disability-related cGVHD from those without (*P* = 0.763; **Table S4, SDC,** http://links.lww.com/TP/D45).

EFS and Relapse

Patients with cGVHD had longer 3-y EFS than those without cGVHD (67.7% [*P* = 95%; 95% CI, 60.8-74.5] versus 55.7% [*P* = 95%; 95% CI, 48.8-62.56]; *P* = 0.016; HR, 0.526; 95% CI, 0.309-0.893). For EFS, patients with moderate cGVHD had significantly longer 3-y EFS (moderate 83.0% [*P* = 95%; 95% CI, 66.5-100] versus mild 69.6% [P = 95%; 95% CI, 60.8-74.5], severe 50.2% [*P* = 95%; 95% CI, 33.1-76.1], and absence of cGVHD 55.7% [*P* = 95%; 95% CI, 48.8-62.56], *P* = 0.022; Figure 4). There were no differences according to organ involvement, overlap syndrome, or disability related to cGVHD (**Table S5, SDC,** http://links.lww.com/TP/D45).

Regarding relapse rate, patients who developed moderate cGVHD had lower risk of relapse at 3 y (*P* = 0.036; mild, 24.9% [*P* = 95%; 95% CI, 9.8-36.7]; moderate, 8.4% [*P* = 95%; 95% CI, 0-22.8]; severe, 29.8% [*P* = 95%; 95% CI, 6.1-47.6]; absence of cGVHD, 35.2% [*P* = 95%; 95% CI, 27.8-41.8]; Figure 5).

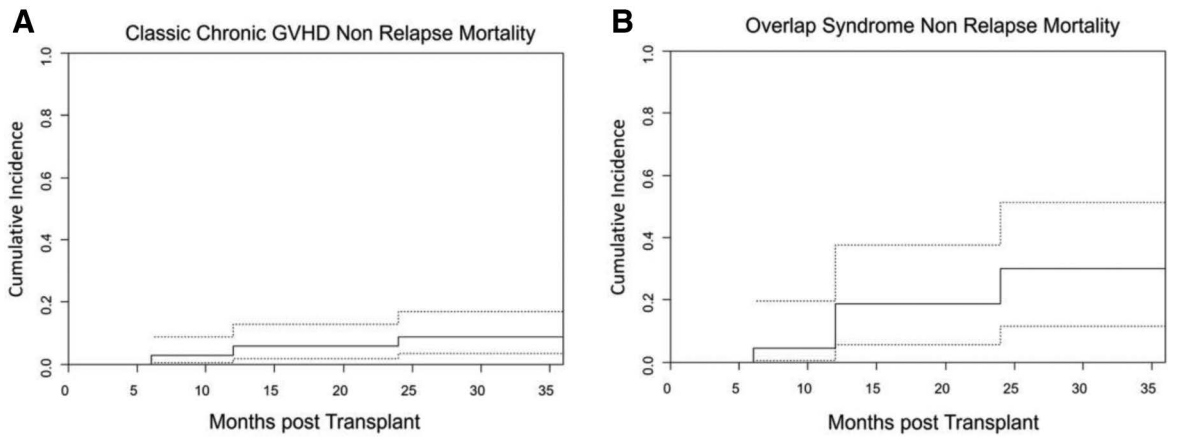

FIGURE 2. Cumulative incidence of NRM. A, Cumulative incidence of NRM according to classic cGVHD. B, Cumulative incidence of NRM according to overlap cGVHD. cGVHD, chronic graft-versus-host disease; NRM, nonrelapse mortality.

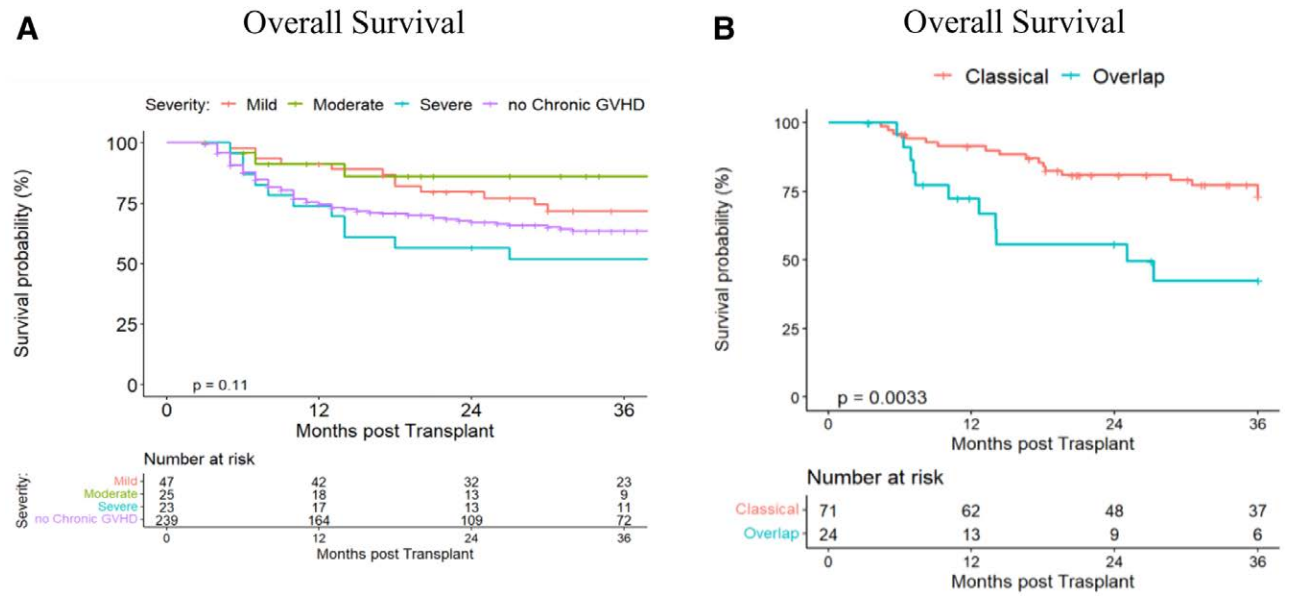

FIGURE 3. Kaplan–Meier estimate of survival outcome in haplo-HSCT patients. A, Overall survival according to cGVHD severity. B, Overall survival according to overlap or classical cGVHD. cGVHD, chronic graft-versus-host disease; haplo-HSCT, haploidentical hematopoietic stem cell transplantation.

DISCUSSION

Historically, the incidence of GVHD in haplo-HSCT was higher than in HLA-identical allo-HSCT.[1-3] However, PTCy prophylaxis effectively controls GVHD in the haplo-HSCT setting, and increases the successful use of this platform. In the current study, the cumulative incidence of grade II–IV aGVHD at day +180 was 21.8% (grade III–IV 10.9%) and a cumulative incidence of cGVHD at 3 y was 32.4% (moderate to severe, 15%). These percentages are in line with those reported previously,[10,26,37-39] and are even lower than those reported for HLA-identical transplants without PTCy prophylaxis.[13,20,24,26,28,32,40]

Several risk factors for developing cGVHD after related or unrelated allo-HSCT have been described. However, few studies to date describe risk factors, severity, spectrum of organ involvement or response to treatment of cGVHD in the setting of haplo-HSCT PTCy. A large Center for International Blood and Marrow Transplant Research analysis by Bashey et al[41] and other by Sohl et al[28] demonstrated a significantly lower incidence of aGVHD and cGVHD in BM grafts. In addition, Im et al[42] showed that PB was a risk factor for the development of cGVHD in the RIC setting. In contrast to the aforementioned studies, we did not find the receipt of PB was predictive for cGVHD.

Another classical risk factor for cGVHD is older age, but very few studies addressing this issue are available in the context of haplo-HSCT PTCy, and the study by Im et al[42] failed to confirm this association, irrespective of the intensity of the conditioning regimen. In our series, recipient age ≥60 y was a protective variable for cGVHD. Because no reason was identified for this finding in donor characteristics, it could probably be explained by the careful selection of elderly patients and the haplo-HSCT platform. In this context, recent studies have shown that allo-HSCT PTCy is very well tolerated in older patients with low rates of cGVHD.[43-45]

The consistent factor associated to cGVHD across all transplant platforms is a prior history of aGVHD; this was

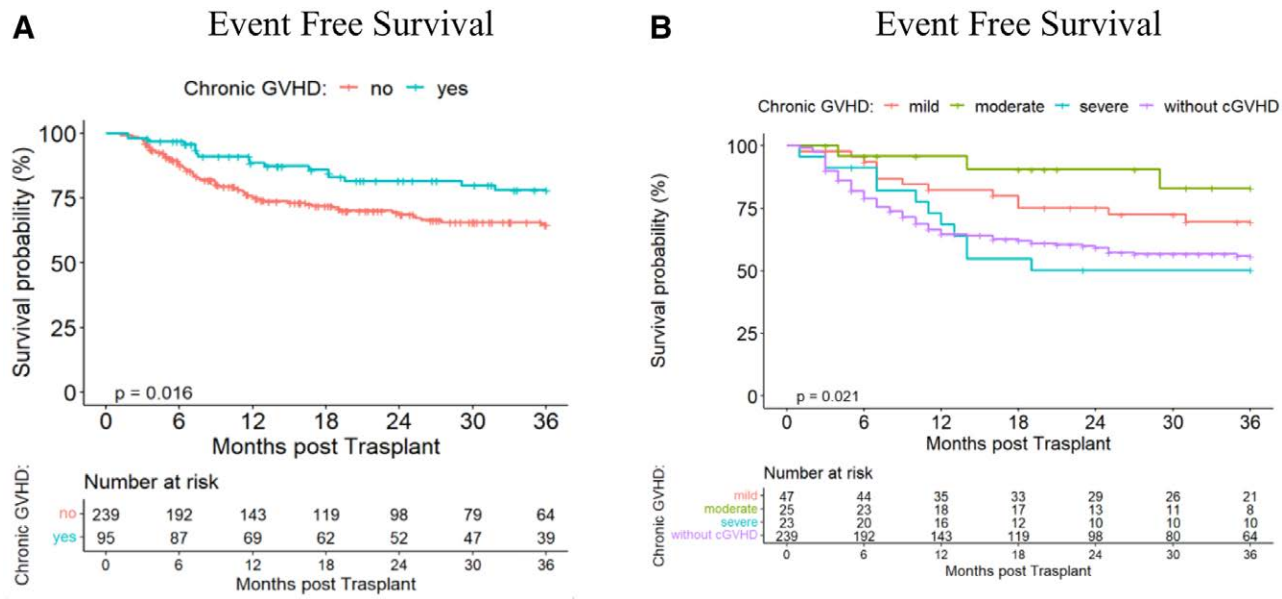

FIGURE 4. Kaplan–Meier estimate of EFS outcome in haplo-HSCT patients. A, EFS according to overlap or classical cGVHD. B, EFS according to cGVHD, and EFS according NIH cGVHD criteria. cGVHD, chronic graft-versus-host disease; EFS, event-free survival; haplo-HSCT, haploidentical hematopoietic stem cell transplantation; NIH, National Institutes of Health.

the strongest predictive factor for cGVHD in our patients, as shown also by Solh et al.[28] Of note, the overall incidence of aGVHD was high, but grade III–IV aGVHD rate was low, which was also reported previously,[46-48] suggesting that PTCy immunomodulation decreases the risk of severe aGVHD, without reduction of milder grades.[49,50]

Regarding NIH severity distribution, the proportion of mild cGVHD cases (49.5%) was higher, and the median number of affected organs (1; 1–4) was lower than those described in the literature after HLA-identical and alternative donor groups, a finding supported by other groups.[26,30,47] We also analyze whether not only the incidence and NIH severity of cGVHD was lower with haplo-PCy but also whether the response to treatment was better. In this regard, the high number of patients needing only supportive and/or topical treatment, the high ORR after first-line systemic treatment and the low incidence of second-line treatment for cGVHD in our study supports the notion that the severity of cGVHD is lower when using haplo-HSCT PTCy.[28,51] Thus, patients with moderate-to-severe cGVHD were treated with a median of 1 line of systemic treatment and achieved an ORR of 74.4% after first-line treatment. These data compare favorably with those reported in the literature of HLA-identical transplantation. In the same line, Sohl et al[28] reported that patients with cGVHD after haplo-HSCT PTCy were more likely to respond to treatment than those undergoing matched unrelated donor with CNI plus methotrexate or MMF.

Saliba et al[52] compared GVHD characteristics between haplo-HSCT PTCy and matched related donor with conventional prophylaxis and found that the spectrum of organ involvement did not differ significantly between them, being the skin, mouth, and eyes the most affected organs in both groups. In accordance, Sohl et al[28] as well as our study showed that the most common areas of cGVHD after haplo-HSCT were the mouth and skin, which is similar to cGVHD manifestation in non-haplo-HSCT scenarios.[26,30,49] In addition, 23% of our patients exhibited a manifestation related to disability, including 16% of BO, similar to the percentages reported in Saliba et al[52] and Sohl et al.[28]

The median follow-up time after cGVHD diagnosis was 22 mo. This long-term follow-up allowed us to analyze survival outcomes in the cGVHD population. In this regard, patients diagnosed with cGVHD showed a 3-y NRM of 10.4%, with a 3-y OS and EFS of 77.4% and 74.9%, data comparable with those reported in the literature.[53] Overlap syndrome had a significant impact on NRM, and as expected,[54] infections were the most common cause of NRM in cGVHD population. Interestingly, patients with moderate cGVHD had the higher OS and EFS, and the lower relapse rates at 3 y (86.2%, 83.0%, and 8.4%). Although NRM was higher in this group than in patients without or mild GVHD, the low relapse rate would explain the superior survival outcomes, probably because of a higher graft-versus-leukemia effect in this subgroup of patients.

There are several limitations that should be mentioned. First, this is a retrospective analysis based on data submitted to a national registry, and factors that could lead to pre-transplant decision making, such as donor selection, stem cell source, or conditioning regimen, are based on center experience. In addition, although all participant transplant centers have wide experience in applying NIH diagnostic and response criteria, some manifestations of cGVHD may have been underreported because of the retrospective nature of the study. Although this is, to the best of our knowledge, the largest series focused solely on characterizing cGVHD after haplo-HSCT PTCy, a larger number of patients could lead to detection of more risk factors.

To sum up, this study has shown that haplo-HSCT PTCy presents not only a lower incidence but also a more favorable profile of cGVHD in terms of the number of affected organs, severity and response to treatment than described after matched donor following conventional GVHD prophylaxis. Previous aGVHD was the most important risk factor for developing cGVHD. In addition, patients who develop moderate cGVHD had better survival outcomes

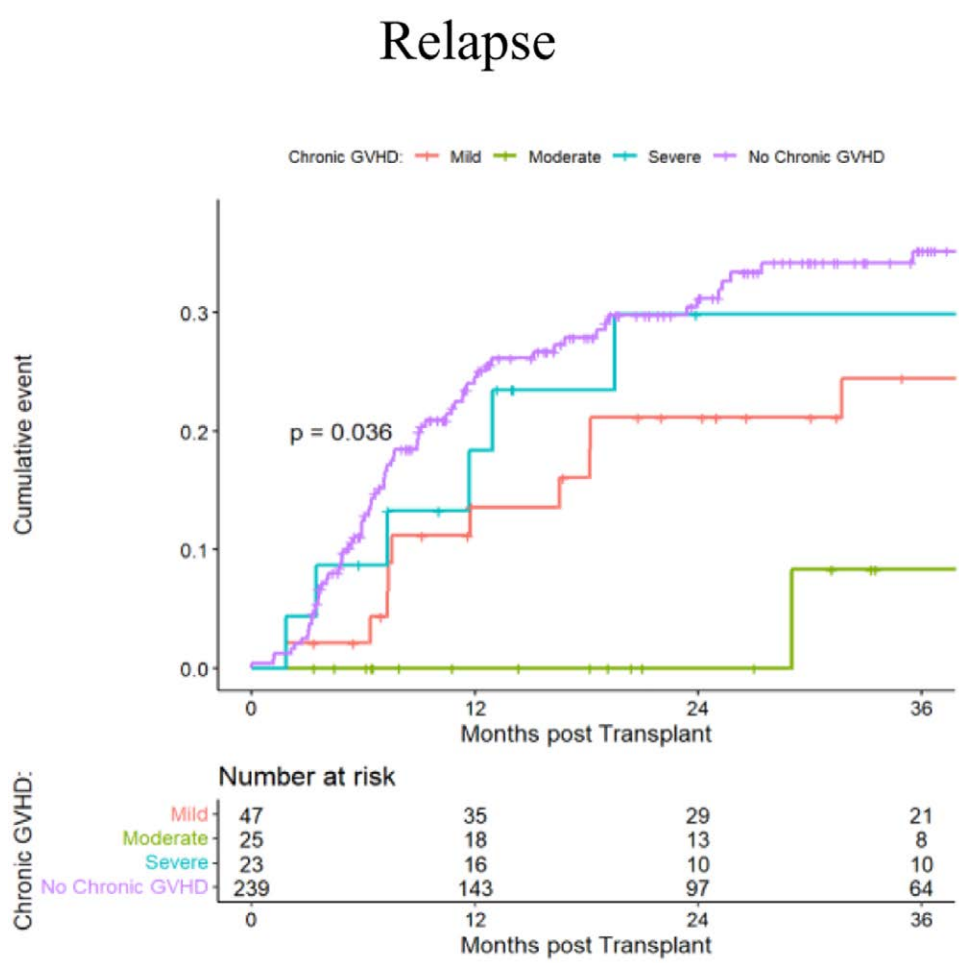

FIGURE 5. Kaplan–Meier estimate of relapse outcome in haplo-HSCT patients. Relapse stratified by cGVHD severity. cGVHD, chronic graft-versus-host disease; haplo-HSCT, haploidentical hematopoietic stem cell transplantation.

and lower relapse, suggesting higher graft-versus-leukemia Characterizing this subgroup of patients could lead the clinicians to improve haplo-HSCT outcomes.

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