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Characteristics of Graft-versus-Host Disease (GvHD) after Post-transplant Cyclophosphamide versus Conventional GvHD Prophylaxis

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CONFLICTS OF INTEREST

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Abstract

Post--transplantation cyclophosphamide (PTCy) has been shown to effectively control GvHD in haploidentical (Haplo) transplants. In this retrospective registry study, we compared GvHD organ distribution, severity, and outcomes in patients with GvHD occurring after Haplo transplantation with PTCy GvHD prophylaxis (Haplo/PTCy) versus HLA-matched unrelated donor transplantation with conventional prophylaxis (MUD/conventional). We evaluated two cohorts: patients with grade 2–4 acute GvHD (aGvHD) including 264 and 1,163 recipients of Haplo and MUD transplants; and patients with *any* chronic GvHD (cGvHD) including 206 and 1,018 recipients of Haplo and MUD transplants, respectively. In comparison with MUD/conventional transplantation +/− antithymocyte globulin (ATG), grade 3–4 aGvHD (28% vs. 39%, P=.001), stage 3–4 lower gastrointestinal (GI) tract aGvHD (14% vs 21%, P=.01), and chronic GI GvHD (21% vs. 31%, P=.006) were less common after Haplo/PTCy transplantation. In patients with grade 2–4 aGvHD, cGcHD rate after Haplo/PTCY was also lower (HR =.4, P<.001) in comparison with MUD/conventional transplantation without ATG in the non-myeloablative conditioning setting. Irrespective of the use of ATG, non-relapse mortality rate was lower (HR=.6, P =.01) after Haplo/PTCy transplantation, except for transplants that were from a female donor into a male recipient. In patients with cGvHD, irrespective of ATG use, Haplo/PTCy transplantation had lower non-relapse mortality rate (HR=.6, P=.04). Mortality rate was higher (HR=1.6, P=.03) within, but not after (HR=.9, P=.6) the first six months subsequent to cGvHD diagnosis. Our results suggest that PTCy-based GvHD prophylaxis mitigates the development of GI GvHD and may translate into lower GvHD-related non-relapse mortality rate.

Keywords

post-transplantation cyclophosphamide; graft-versus-host disease; prophylaxis; non-relapse mortality

INTRODUCTION

Graft-versus host disease (GvHD) remains a common and severe complication of allogeneic hematopoietic stem cell transplantation (alloSCT) associated with higher morbidity and mortality. Traditionally, GvHD prophylaxis has consisted of a calcineurin inhibitor (CNI), commonly tacrolimus, in combination with methotrexate or mycophenolate mofetil +/− antithymocyte globulin (ATG). Recently, post-transplant cyclophosphamide (PTCy), has demonstrated efficacy in achieving engraftment as well as reducing the incidence of severe acute and chronic GvHD [1–6]. While the incidence of severe acute and chronic GvHD has consistently been shown to be lower with the use of PTCy prophylaxis, *it is not known if the spectrum of GvHD organ involvement (including site and severity) differs with the use of PTCy versus conventional GvHD prophylaxis*. The aim of this study was to examine, in a systematic manner, whether in patients with GvHD, organ distribution and severity are different after Haplo/PTCy versus MUD/conventional transplantation with or without ATG, and how outcomes in patients diagnosed with GvHD differ across these three platforms.

We hypothesized that acute and chronic GvHD may be less severe and associated with superior outcomes in patients who had received PTCy-based versus conventional GvHD prophylaxis. We tested this hypothesis in a large, multicenter dataset provided by the Center for International Blood and Marrow Transplant Research (CIBMTR), by comparing GvHD manifestations and outcomes in haploidentical transplant patients treated with PTCy-based GvHD prophylaxis (Haplo/PTCy) versus a cohort of HLA-matched unrelated donor (MUD) transplants using conventional prophylaxis (MUD/conventional) with or without ATG.

PATIENTS AND METHODS

Data Source and Inclusion Criteria

Data for this retrospective analysis were obtained from the CIBMTR database. Detailed information on the CIBMTR has been previously described [7].

Eligible patients included recipients of a haploidentical (mismatched to recipient at two or more HLA- loci) related donor transplantation treated with PTCy, CNI, and mycophenolate mofetil, and HLA-matched (at least allele level matching at HLA-A, -B, -C, and -DRB1) unrelated donor transplantation who received conventional GvHD prophylaxis, including a CNI and methotrexate or mycophenolate mofetil, +/− ATG. Only first T-cell-replete un-manipulated bone marrow or peripheral blood stem cell transplants occurring between 2013 and 2017 and reported to CIBMTR were included. Excluded were patients <18 years of age and those with diagnoses other than acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, or myelodysplastic syndrome.

Conditioning regimens eligible for this study included myeloablative (MAC) or reduced-intensity (RIC)/non-myeloablative (NMA) conditioning, with or without total body irradiation (TBI) based on the CIBMTR operational definition.[8] The Institutional Review Boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

Endpoints

The primary endpoints of this study were: 1) GvHD organ manifestations and severity, and 2) treatment outcomes (non-relapse mortality [NRM] and overall survival [OS] rates) in patients diagnosed with grade 2–4 acute GvHD (aGvHD) or chronic GvHD (cGvHD). In addition, cGVHD was evaluated as an outcome in patients with grade 2–4 aGvHD. These endpoints were compared in the Haplo/PTCy-based versus MUD/conventional GvHD prophylaxis platforms because PTCy prophylaxis was predominantly used in the Haplo transplantation context at the time of conception of the study. GvHD was graded according to consensus criteria [9,10]. The revised Disease Risk Index[11] (DRI) was used to stratify patients into low-, intermediate-, and high- or very high-risk groups. NRM was defined as death in the absence of disease persistence, relapse or progression of the underlying malignancy. Relapse was defined on the basis of hematologic, cytogenetic, or molecular criteria. Death from any cause was considered an event for OS, and surviving patients were censored at last contact.

Statistical Methods

Patients' characteristics were compared using chi-square and Fisher's exact tests for categorical variables and Wilcoxon's rank-sum test for continuous variables. The time to event was estimated starting on the date of GvHD diagnosis. The cumulative incidence of NRM and cGvHD was estimated accounting for competing risks[12]. Relapse and relapse-related mortality were the competing risks for NRM, and death from any cause, relapse or progression of the underlying malignancy before cGvHD were the competing risks for cGvHD. Probability of OS was estimated using the Kaplan-Meier method[13]. Predictors of NRM and cGvHD were evaluated in univariate and multivariate analyses using Fine and Grey sub-distribution hazard regression[14] to accommodate competing risks. Predictors of OS were evaluated in univariate and multivariate analyses using Cox proportional hazards regression. In addition to the main effect (Haplo/PTCy vs MUD/conventional), we evaluated the following predictors: the use of ATG in the MUD cohort, grade (2 vs. 3–4) of aGvHD, recipient age (18–39 vs. 40–59 vs. ≥ 60 years), Karnofsky performance score (KPS) (90–100 vs. ≤80), Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) score, donor/recipient sex-match, donor/recipient cytomegalovirus (CMV) serostatus-match, DRI, conditioning regimen intensity, and stem cell source. Predictors that were significant in the univariate analysis were included in the multivariate analysis, with the exception of the main effect which was forced to be included in all multivariate regression models. The predictive multivariate regression models were developed using the backward selection method. The proportionality of hazards assumption was evaluated and adjusted for as indicated. First-order interactions, between the main effect and the adjusted covariates in the multivariable models, were evaluated and presented when indicated. Subset analyses were performed for patients aged ≥ 60 years using identical statistical methods. Statistical significance was set at the .05 level, and all *P* values were two-sided. Statistical analyses were performed using primarily STATA version 14 software (College Station, TX).

RESULTS

Overall Patient Population

The study population consists of two separate (but *not* mutually exclusive) cohorts: the first includes consecutive patients diagnosed with grade 2–4 aGvHD, and the second consecutive patients diagnosed with *de novo*, progressive, or relapsing cGVHD (Figure 1). These study cohorts were derived from the parent population of 758 and 2,586 patients who had received Haplo/PTCy and MUD/conventional transplants, respectively, between 2013 and 2017, and met the study's eligibility criteria. In the parent population, the 6-month cumulative incidence of grade 2–4 aGvHD after Haplo/PTCy transplantation was 35% (95% confidence interval [CI], 32%−39%). This was lower than the incidence after MUD/conventional transplantation with (42%, 95% CI, 39%−46%); hazard ratio [HR] = .8, 95% CI, .6–.9, P = .001) or without (46%, 95% CI, 44%−48%; HR=.7, 95% CI, .6–.8, P <.001) ATG. The 2-year cumulative incidence of cGvHD after Haplo/PTCy transplantation was 29% (95% CI, 25%−32%); it was equivalent (HR=0.9, 95% CI, 0.8–1.2, P = .9) to the incidence (29%, 95% CI, 26%−32%) after MUD/conventional transplantation with ATG; but significantly lower (HR=0.6, (95% CI, 0.5–0.6, P <.001) than the incidence (46%, 95% CI, 44%49%) after MUD/conventional transplantation without ATG. The grade 2–4 aGvHD

cohort evaluated in this current study included 264 and 1,163, recipients of Haplo/PTCy and MUD/conventional transplantation, respectively. The cGVHD cohort included, 206 and 1,018 recipients of Haplo/PTCy and MUD/conventional transplantation, respectively. Analyses were stratified according to the use of ATG for GvHD prophylaxis in the MUD/conventional cohort.

Acute GvHD Cohort

Patient population.—Table 1A shows the demographic, disease, and transplant characteristics of patients who developed grade 2–4 aGvHD after Haplo/PTCy or MUD/conventional transplantation. Compared with the MUD/conventional cohort, the Haplo/PTCy cohort was characterized by younger recipients, a higher DRI, a higher proportion of bone marrow grafts and grafts from female donors to male recipients, and a higher proportion of TBI-based regimens among those who received myeloablative conditioning. Acute myeloid leukemia was more likely to be the indication for transplantation in the Haplo/PTCy cohort. One third (33%) of patients in the MUD/conventional cohort received ATG for GvHD prophylaxis.

Acute GvHD characteristics.—Grade 2–4 aGvHD manifestations, including timing, organ involvement and severity, are detailed in Table 1A. The main differences between the Haplo/PTCY and MUD/conventional transplantation with or without ATG include:

Timing: The median time to aGvHD diagnosis was 35 days after Haplo/PTCy transplantation. This was comparable to the time to diagnosis after MUD/ conventional transplantation with ATG [median 34 days, (P = .1)] , but later than the time after MUD transplantation without [median 32 days, (P = .001)] ATG. There was no difference in the proportion of cases diagnosed after day 100 across the three groups.

Overall severity: Severe (grade 3–4) aGvHD was less common after Haplo/PTCy [27%, (reference)] than after MUD/ conventional transplantation with [35%, (P = .04)] or without ATG [39% (P = .0001)].

Organ involvement and severity: Skin was the most common aGvHD organ involved and was comparably prevalent (64–67%) across the three groups. Similarly, involvement of the lower gastrointestinal (LGI) tract was seen in about half (52–55%) of the patients, and the prevalence did not significantly differ across the three groups. However, severe (stage 3–4) LGI aGVHD, was less common after Haplo/PTCy [14%] than after MUD/conventional transplantation with [20%, (P = .05)] or without [22%, (P = .001)] ATG. Upper GI (UGI) and liver involvement were also less common after Haplo/PTCy, but the difference reached statistical significance [UGI: 46% vs 54%, (P = .03); liver: 11% vs 16%, (P = .04)] only in comparison with MUD/conventional transplantation without ATG. The trends described above were observed in recipients of peripheral blood or bone marrow grafts (Supplemental Table 1A), as well as in ≥60 year old patients (data not shown).

Outcomes in patients with grade 2–4 aGVHD.—The median follow-up durations in surviving patients after grade 2–4 aGvHD were 24 months (range, 2.6–62.0 months) in the

Haplo/PTCy cohort, and 34 months (range, 4.5–66 months) in the MUD/conventional cohort with (range, 4.5–66 months) and without (range, 0.7–62) ATG.

Non-relapse mortality: In univariate analysis, NRM rate was lower after Haplo/PTCy versus MUD/conventional transplantation with (HR=.6, 95% CI, .4–.8; P = .004) or without (HR=.6, 95% CI, .4–.8, P = .004) ATG. Stratified analyses showed that factors that associated with NRM were the same across the Haplo and MUD cohorts (Supplemental Figure 1A) except for donor/recipient gender. Within the Haplo/PTCy group, male patients with female donors had significantly higher (HR=2.1, 95% CI, 1.1–3.9. P = .02) NRM rate. In contrast, in the MUD/conventional cohort, male patients with female donors did not have a higher NRM rate (HR=.87, 95% CI .6–1.2, P = .4). Multivariate analysis (Table 2) adjusting for significant predictors of NRM revealed that NRM was lower (HR=.6; 95% CI, .4–.9; P=.01) in the Haplo/PTCy versus MUD/conventional in transplants that were *not* from a female donor to a male recipient. In female to male transplants, NRM rate did not significantly differ (HR=1.3; 95% CI, 0.7–2.6; P=.4) between the two cohorts (Figure 2 A1-A2). These effects were independent of the use of ATG in the MUD/conventional cohort.

Overall survival: In univariate analysis, OS was comparable after Haplo/PTCy versus MUD/conventional transplantation with (HR=.8, 95% CI, 0.7–1.0, P =.08) or without (HR=1.0, 95% CI, 0.8–1.2, P = 0.9) ATG. Stratified analyses showed that factors that associated with OS were the same across the Haplo and MUD cohorts (Supplemental Figure 1B). In multivariate analysis (Table 2, Figure 2C), overall survival remained comparable after Haplo/PTCy versus MUD/conventional transplantation with (HR=1.05, 95% CI, 0.8–1.3, P = 0.7) or without ATG (HR=0.8, 95% CI 0.7–1.1, P = 0.1).

Chronic GvHD: Univariate analysis showed that, in patients with grade 2–4 aGvHD, cGvHD rate after Haplo/PTCy transplantation was lower (HR=.7, 95% CI, .6–.9, P = .009) compared with MUD/conventional transplantation without ATG, but equivalent (HR=1.2, 95% CI, .9–1.5, P = .2) compared with MUD/conventional transplantation with ATG. Stratified analyses showed that factors that associated with cGvHD were the same across the Haplo and MUD cohorts (Supplemental Figure 1C) except for conditioning regimen intensity. In the Haplo/PTCy cohort, the cumulative incidence of cGVHD developing in patients with grade 2–4 aGVHD was significantly higher (46% versus 31%, HR=1.6, 95% CI, 1.1–2.4, P =.02) after MAC versus RIC/NMA conditioning regimens. In contrast, in the MUD/conventional cohort, the incidence of cGVHD developing in patients with grade 2–4 aGvHD did not differ by conditioning intensity. This was true for MUD patients who received (cumulative incidence: 34% vs 31%, HR=1.0, 95% CI, .71.5, P = .8) or did not receive (cumulative incidence: 48% versus 49%, HR=.9, 95% CI, .8–1.1, P = .5) ATG. These effects persisted in multivariate analysis (Table 2). As a result, in recipients of MAC, cGVHD rate after Haplo/PTCy transplantation was similar (HR=.9, 95% CI, .7=1.3, P = .9) to that after MUD/conventional transplantation without ATG; and significantly higher (HR=1.6, 95% CI, 1.1–2.4, P = .02) than after MUD/conventional transplantation with ATG (Figure 2B1). In contrast, in recipients of RIC/NMA regimens, the cGVHD rate after Haplo/PTCy transplantation was similar (HR=.8, 95% CI, .5–1.2, P = .3) to the rate after

MUD/conventional transplantation with ATG, and lower (HR=.4, 95% CI, .3–.6, P < .001) than the rate after MUD/conventional transplantation without ATG (Figure 2B2).

Chronic GvHD cohort

The demographic, disease, transplant characteristics, and cGvHD characteristics of patients who developed cGvHD following receipt of Haplo/PTCy or MUD/conventional prophylaxis transplantation are described in Table 1B. The main differences in cGvHD characteristics between the Haplo/PTCy and MUD/conventional transplantation with or without ATG are described separately below.

Haplo/PTCy versus MUD/conventional with ATG transplantation

The spectrum of organ involvement did not differ significantly between the two groups, except for gastrointestinal tract involvement which was less common (21% vs 32%, P = .001) after Haplo/PTCy, irrespective of stem cell source. Genitourinary cGvHD involvement was more common after Haplo/PTCy transplantation with peripheral blood (9% vs 3%, P = .01), but not with bone marrow (3% vs 7%, P = .4). The proportion (24% vs. 27%, P = .4) of cGVHD involving >3 organs was not significantly different after Haplo/PTCy versus MUD/conventional transplantation with ATG. However, cGVHD in the Haplo/PTCy group was significantly less likely (10% vs 19%, P=.01) to involve two or more visceral (lung, liver, GI) organs. These trends were also observed in ≥60 year old patients (data not shown), except for a genitourinary cGvHD involvement which was comparable after Haplo/PTCy and MUD/conventional transplantation with ATG among the older subset of patients.

Haplo/PTCy versus MUD/conventional without ATG transplantation

Timing and type: The median time to diagnosis of cGvHD was earlier (6 vs 7 months, P = .001), and ***de novo*** cGvHD was less common (22% vs 32%, P = .01) after Haplo/PTCy transplantation.

Number of organ involved: The median number of cGVHD organs involved were 2 (1–7) and 4 (1–10) after Haplo/PTCy and MUD/conventional without ATG transplantation, respectively; and the proportion of cGvHD involving >3 organs was significantly lower (24% vs. 50%, P < .001) after Haplo/PTCy transplantation.

Type of organ involved: Gastrointestinal cGvHD involvement was less common after Haplo/PTCy (21% vs 32%, P = .001). Similarly, less common after Haplo/PTCy transplantation were involvement of the mouth (39% vs. 66%, P < .001), eyes (41% vs. 60%, P < .001), liver (29% vs. 42%, P <.001), lungs (18 vs 27%, P = .01), musculoskeletal (1 vs 11%, P < .001), or “other” organs (12% vs. 21%, P=.01). In addition, consistent with the comparison with MUD/conventional transplantation with ATG, cGVHD was significantly less likely (10% vs 27%, P < .001) to involve two or more visceral organs with Haplo/PTCy versus MUD/conventional transplantation without ATG. These trends were consistent in recipients of peripheral blood or bone marrow grafts, except for overall skin involvement which was less common (63% vs. 74%, P = .01) in the Haplo/PTCy versus MUD/conventional peripheral blood transplantation, but more common (78% vs. 62%,

P=.03) with bone marrow transplantation. The trends described above were also observed in ≥60 year old patients (data not shown).

Outcomes in patients with chronic GvHD.—Among surviving evaluable patients, the median follow-up after cGvHD diagnosis was 21 months (range, 0.23–56 months), 26 months (range, .23–58) and 27 months (range, 0.33–63 months) in the Haplo/PTCy, and MUD/conventional with and without ATG cohorts, respectively.

Non-relapse mortality: NRM rate was significantly lower in univariate analysis after Haplo/PTCy versus MUD/conventional transplantation with (HR=.5; 95% CI, .3–.9; P =.01) or without (HR=.5, 95% CI, .3–.8, P = .009) ATG. Stratified analyses showed that factors that associated with NRM were the same across the Haplo and MUD cohorts (Supplemental Figure 2A). NRM rate remained lower (HR=0.6; 95% CI, 0.3–0.9; P = .04) after Haplo/PTCy transplantation in multivariate analysis (Table 3, Figure 3A).

Overall survival: Overall survival did not differ in univariate analysis after Haplo/PTCy versus MUD/conventional transplantation with (HR=.9; 95% CI, .6–1.3; P =.6) or without (HR=.98, 95% CI, .7–1.3), P= .9) ATG. However, this effect was not consistent over time. Within the first 6 months after cGvHD diagnosis, OS was lower (HR=1.3; 95% CI, .9–2.0; P =.2) after Haplo/PTCy transplantation. After 6 months, OS tended to be higher (HR=0.7; 95% CI, .5–1.1; P =.2) after Haplo/PTCy. Stratified analyses showed that additional factors associated with OS were the same across the Haplo and MUD cohorts and that their effect did not vary over time (Supplemental Figure 2B). To facilitate the interpretation of the data, we present the results of the multivariate analysis separately for two time periods (Table 3). Consistent with the univariate analysis, multivariate analysis showed that within the first 6 months after cGvHD diagnosis, OS was significantly lower (HR = 1.6; 95% CI, 1.05–2.6; P =.03) after Haplo/PTCy transplantation (Figure 3B). After 6 months, OS was comparable (HR = 0.9; 95% CI, 0.6–1.4; P =.6) (Figure 3C) between the two cohorts. Consistent results were observed for the MUDI/conventional cohort with or without ATG. In patients aged ≥60 years who developed cGvHD, OS did it differ between the three cohorts (data not shown), nor did it differ over time.

DISCUSSION

In this study, we investigated how the clinical presentation and outcomes of GvHD differ after transplants with haploidentical donor with PTCy-based GvHD prophylaxis versus HLA-matched unrelated donor using conventional prophylaxis with or without ATG. Our data suggest that PTCy use may uniquely mitigate the presentation of GI GvHD. Compared with MUD/conventional transplantation, the use of Haplo/PTCy transplantation was associated with significantly lower prevalence of 1) stage 3–4 lower GI aGvHD and 2) cGvHD involving the GI tract. In addition, severe aGvHD was less common after Haplo/PTCy transplantation. These trends were consistent irrespective of the stem cell source and the use of ATG among recipients of MUD/conventional transplantation.

Our data shed light on the clinical presentation and outcome of GvHD after Haplo/PTCy versus MUD/conventional GvHD prophylaxis transplants; however, they are insufficient

to make inferences regarding the optimal donor/GvHD prophylaxis selection. Such recommendations would have to be based on studies including all recipients of stem cell transplantation, and not only the subset who developed GvHD.

Unlike the GI tract, the spectrum of all other acute or chronic GvHD organs did not significantly differ after Haplo/PTCy versus MUD/conventional transplantation with ATG in this patient population. This underscores the potential differential impact of PTCy on GI GvHD. To our knowledge, this is the first study to report a potential organ-specific effect of PTCy. Given the increasing use of PTCy and the increasingly recognized central role of the gastrointestinal tract in amplifying the severity and propagation of GvHD,[15–19] validation studies are warranted to confirm our observations. Results of retrospective studies comparing the use of ATG versus PTCy based prophylaxis have so far been conflicting [20–25]. This current study was focused on comparing organ manifestations in patients diagnosed with GvHD and did not address the question of the efficacy of PTCy versus ATG in preventing GvHD. However, our findings are consistent with those reported by Battipaglia et al[23] showing a lower incidence of grade 3–4 aGvHD and a trend towards lower extensive cGVHD with PTCy versus ATG in the 9/10 HLA-mismatched-unrelated donor transplantation. Similarly, PTCy was reported to be associated with lower incidence of severe aGvHD and cGvHD in a recently published meta-analysis by Gao et al.[26]

A multicenter phase II trial conducted through the Blood and Marrow Transplant Clinical Trials Network[27] also demonstrated that, in the setting of alloSCT from HLA-matched related or unrelated donors, PTCy was a more effective GvHD prophylaxis regimen than alternative agents that specifically target gut and liver GvHD[28] or that have general beneficial immunomodulatory effects[29]. Confirmation of the superiority of PTCy GvHD prophylaxis awaits the results of an ongoing randomized phase III study (BMT CTN 1703). Our data suggest that examination of the incidence of GI GvHD by prophylaxis regimen maybe warranted in future trials.

Our understanding of the mechanism of action of PTCy are still evolving.[30] In contrast to ATG which results in wide range T-cell depletion [20,31], PTCy is thought to target rapidly proliferating alloreactive T cells [32,33], and/or to facilitate the reconstitution of tolerogenic T cells[34]. Notably, among recipients of MUD/conventional transplantation, the use of ATG appears to attenuate GvHD involvement of most organs, but not that of the GI tract. Further elucidation of the immunologic mechanisms of action of PTCy, and specifically on GI GvHD, and the biomarkers [35]associated with these mechanisms may contribute to the optimization of available GvHD prophylaxis strategies and inform the development of more effective therapeutic approaches.

The reduced severity of acute and chronic GvHD translated into a lower NRM rate subsequent to GvHD in the Haplo/PTCy group. However, subsequent to grade 2–4 aGVHD, the reduction in NRM was limited to transplants that were *not* from a female donor into a male recipient. Subsequent to chronic GvHD, NRM was lower for the Haplo/PTCy group irrespective of donor and recipient sex. Several studies have generated conflicting results regarding the role of sex-mismatch in haploidentical transplantation [36,37 38–42]. Nevertheless, a male donor for a male recipient has consistently been recommended

in haploidentical donor selection algorithms [39,43,44]. Our findings indirectly support this recommendation, revealing a higher NRM rate after grade 2–4 aGvHD in male recipients of grafts from female donors. This effect was independent of the aGvHD maximal grade (data not shown), indicating inherently higher alloreactivity in female-to-male haploidentical transplants. The lower NRM rate in the Haplo/PTCy group did not translate into a higher OS in patients with acute or chronic GvHD. Relapse was a common cause of death in this subgroup, counter-balancing the lower NRM rate. There are no conclusive clinical data demonstrating higher relapse rate after PTCy-based GVHD prophylaxis. However, the use of PTCy has been shown to eliminate alloreactive T-cells and NK-cells early post-transplant [45]. We did not directly assess relapse risk in this study, primarily because it may not be independent of GvHD development and its treatment. Comprehensive evaluation of the relapse rate requires prospective assessment with clear and distinctive classification of the intensity of conditioning regimens. Such assessment was not within the scope of this study.

Our study has several limitations. First, in the context of a retrospective registry study, we compared two different donor/ GvHD prophylaxis platforms. This study design was dictated by the small number of HLA-matched transplants performed using PTCy-based GvHD prophylaxis at the time of conception of the study. As a result, it is impossible to determine whether our findings were attributable to the GvHD prophylaxis regimen itself or to the donor/GvHD prophylaxis platform. This limitation warrants further confirmatory evaluation in future studies of HLA-matched transplants receiving conventional versus PTCy-based GvHD prophylaxis. Second, we could not assess the organ-specific or overall severity of cGvHD because our study period predates the CIBMTR's adoption of the National Institutes of Health (NIH) Global Severity of cGvHD diagnostic and grading scale[46]. Standardized reporting of cGvHD manifestations using the NIH Global Severity criteria will be critical for a more comprehensive comparison of cGvHD characteristics and outcomes across various alloSCT platforms. Moreover, quality of life is increasingly being recognized as a clinically relevant outcome measure in patients with cGvHD , and could not be evaluated in our study. Solh et al [47] and Fatobene et al [48] found superior quality of life in patients with cGvHD who received PTCy-based GvHD prophylaxis with a significantly higher proportion of PTCy patients had stopped immunosuppressive therapy at two years. Despite these limitations, we believe that our study provides the first comprehensive assessment of GvHD for recipients of haploidentical transplantation treated with PTCy versus recipients of matched unrelated donors treated with conventional GVHD prophylaxis. Our findings could potentially inform the ongoing investigations into the mechanisms of action of PTCy in GvHD development and future studies aiming at optimizing GvHD prophylaxis regimens, with an ultimate goal of maximizing the benefit of allogeneic hematopoietic stem cell transplantation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Lower gastrointestinal tract *acute* GvHD is less severe after haploidentical transplantation with PTCy prophylaxis
- Lower gastrointestinal tract *chronic* GvHD is less common after haploidentical transplantation with PTCy prophylaxis
- Non-relapse mortality in patients with GvHD may be lower after haploidentical transplantation with PTCy prophylaxis

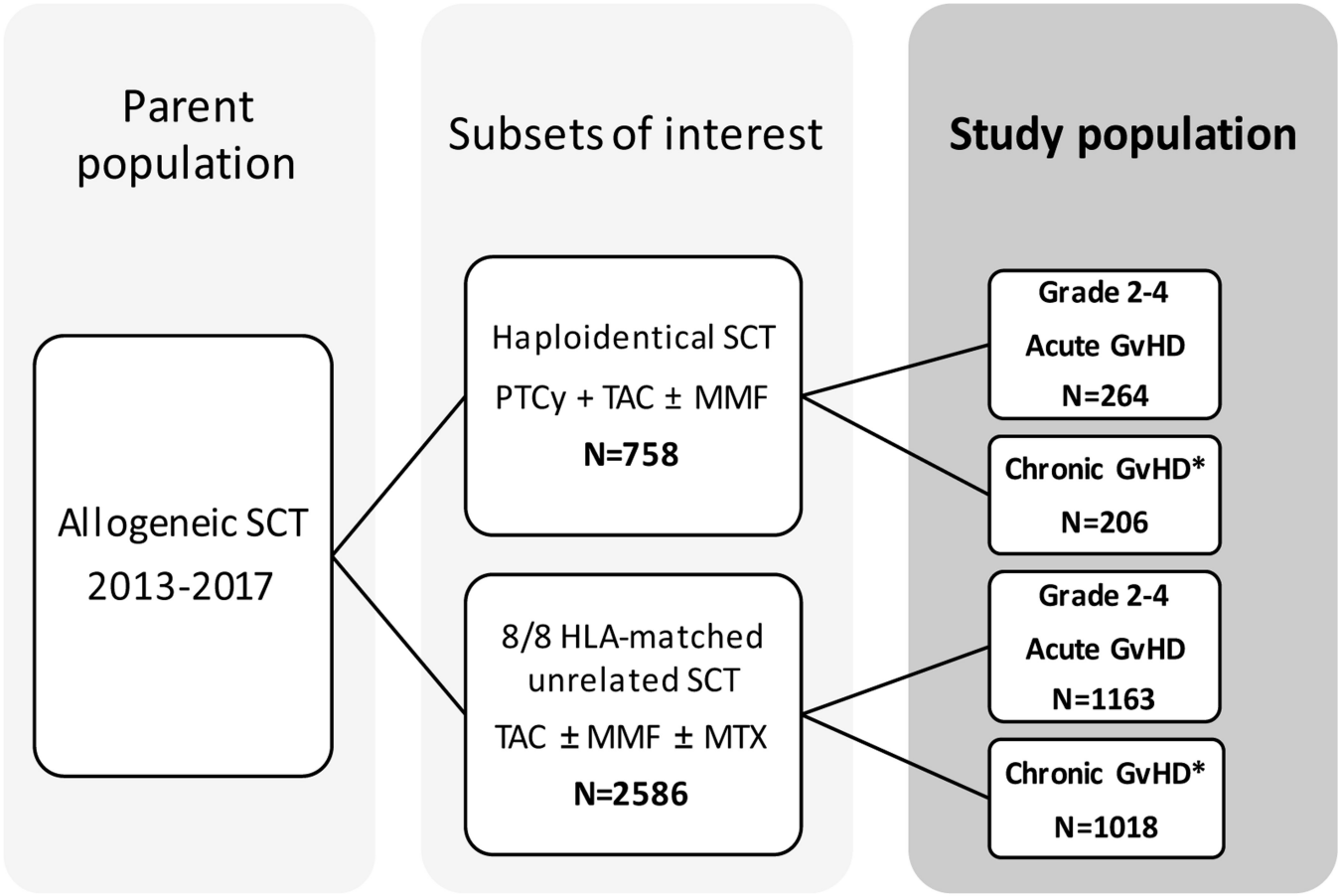


Figure 1. Patient population.

The study population consisted primarily of two cohorts: consecutive patients who developed 1) grade 2–4 acute GvHD and 2) those who developed *de novo*, progressive, or relapsing chronic GvHD after allogeneic stem cell transplantation from a haploidentical donor with post-transplant cyclophosphamide (PTCy) graft-versus-host disease prophylaxis or 8/8 HLA-matched unrelated donor with conventional GvHD prophylaxis performed between 2013–2017. Patients who developed grade 2–4 acute GvHD and chronic GvHD are included in both cohorts.

SCT, stem cell transplant; PTCy, post-transplant cyclophosphamide; TAC, tacrolimus; MMF, mycophenolate mofetil; HLA, human leukocyte antigen; MTX, methotrexate; GvHD, graft-versus-host disease

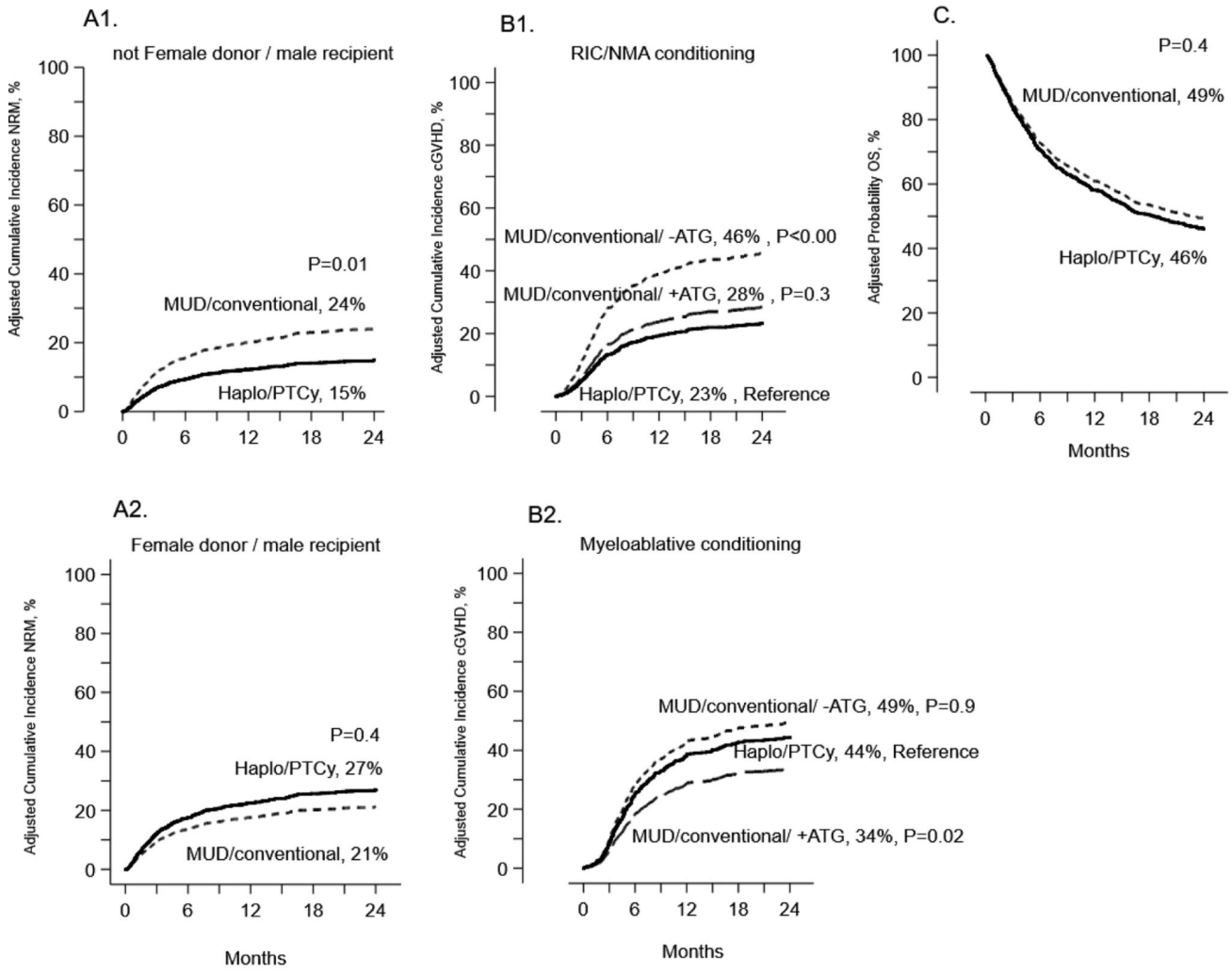
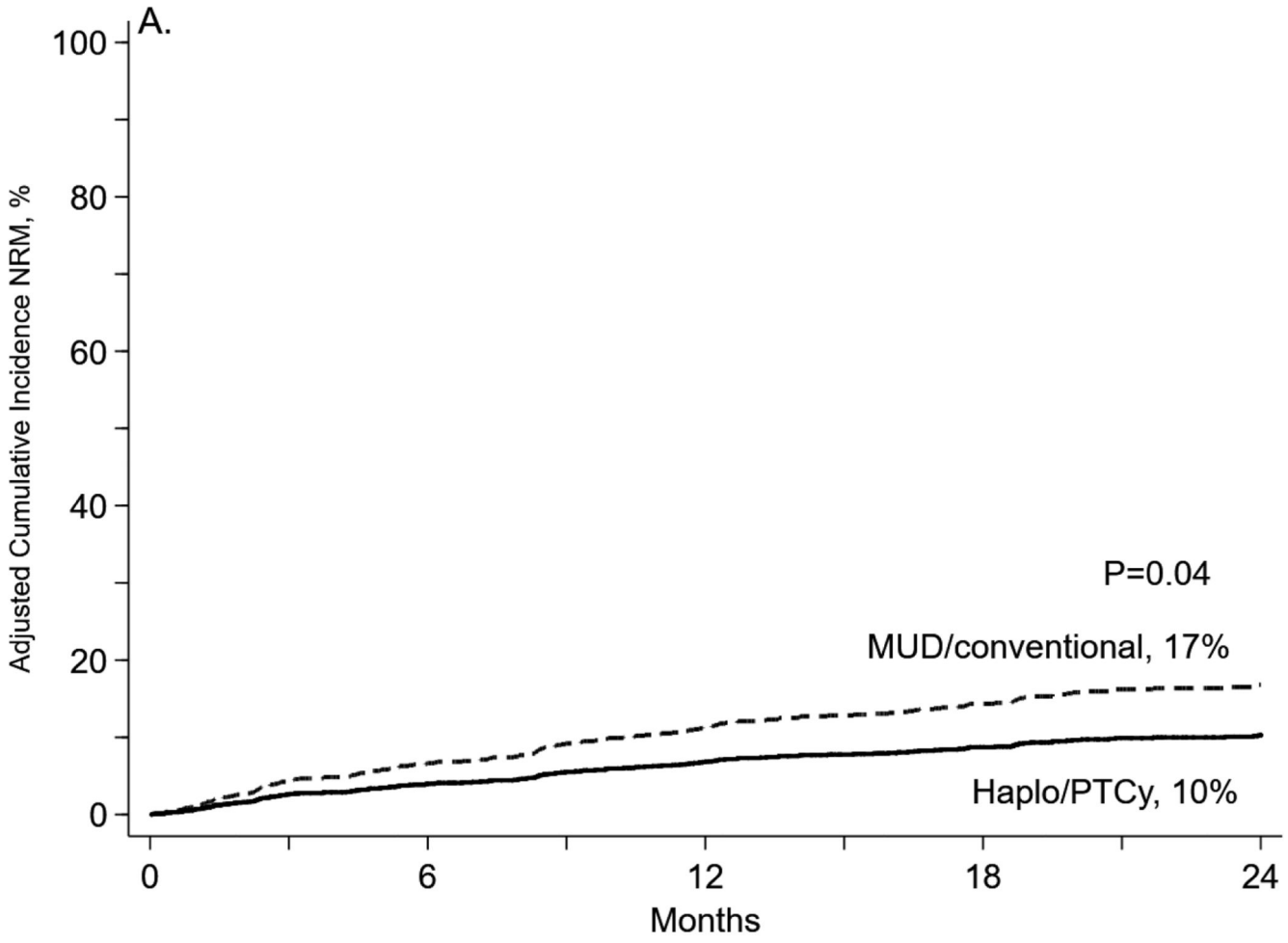


Figure 2. Outcomes in patients with grade 2–4 acute GvHD.

(A1) The cumulative incidence of non-relapse mortality by donor type in recipients of transplants that are not from a female donor to a male recipient by donor type, adjusted for grade 3–4 acute GvHD, recipient age ≥ 40 years, HCT-CI > 3, and seropositive recipient CMV status. (A2) The cumulative incidence of non-relapse mortality by donor type in recipients of transplants from a female donor to a male recipient by donor type, adjusted for grade 3–4 acute GVHD, recipient age ≥ 40 years, HCT-CI > 3, and seropositive recipient CMV status. (B1) The cumulative incidence of chronic GvHD by donor type in recipients of RIC/NMA conditioning, adjusted for grade 3–4 acute GvHD, high DRI, and KPS < 90. (B2) The cumulative incidence of chronic GvHD by donor type in recipients of myeloablative conditioning, adjusted for grade 3–4 acute GvHD, high DRI, and KPS < 90. (C) Actuarial OS by donor type, adjusted for grade 3–4 acute GvHD, high DRI, recipient age ≥ 40 years, HCT-CI > 3, and seropositive recipient CMV status.

MUD, matched unrelated donor; RIC, reduced intensity conditioning; NMA, non-myeloablative; haplo, haploidentical



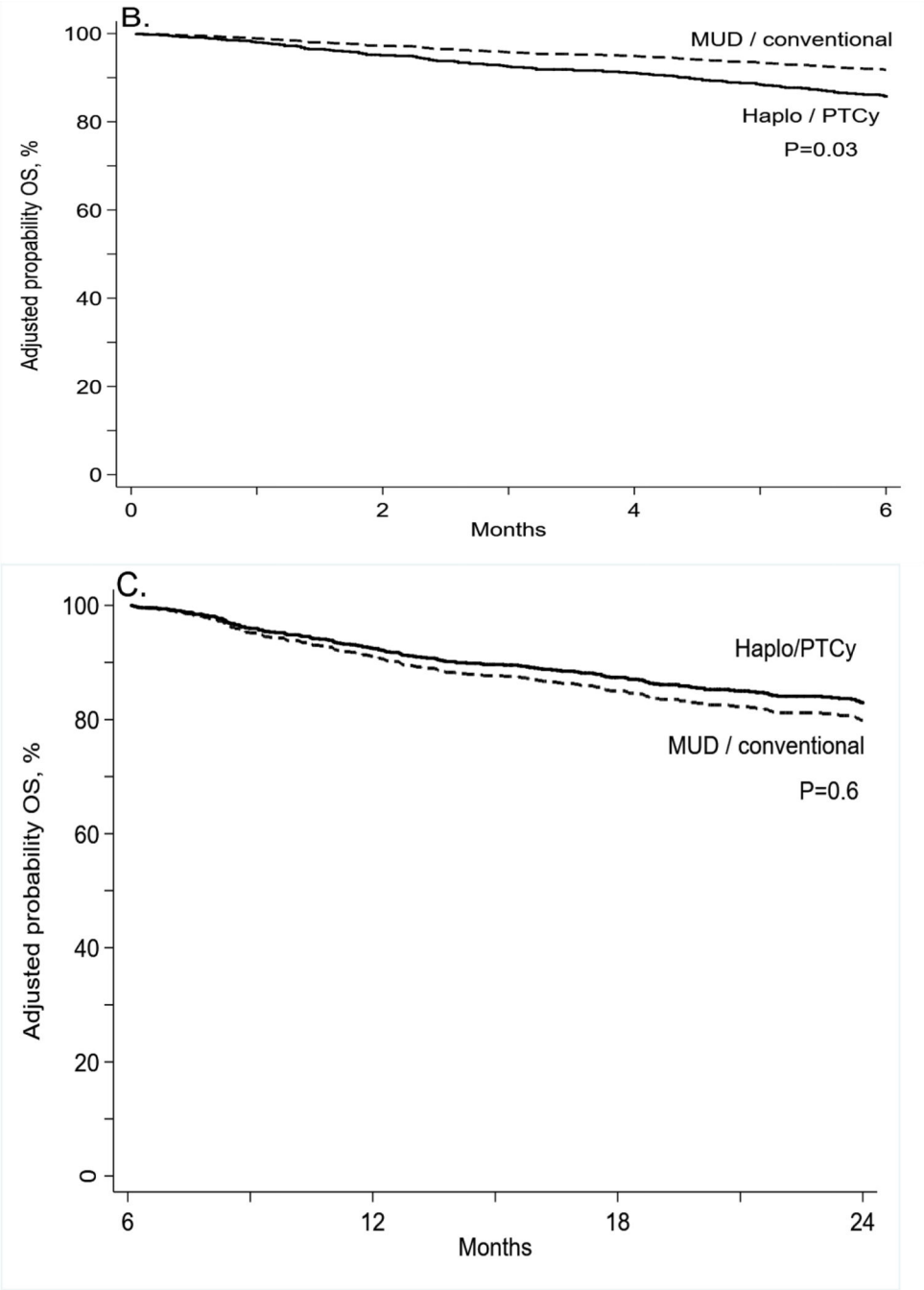


Figure 3. Outcomes in patients with chronic GvHD.

(A) The cumulative incidence of NRM by donor type, adjusted for recipient age ≥ 40 years, HCT-CI > 3, and transplants from CMV-seronegative donors into a CMV-seropositive recipients. (B) Actuarial OS within the first 6 months after chronic GvHD diagnosis by donor type, adjusted for recipient age ≥ 60 years, high or very high DRI, HCT-CI > 3, and transplants from CMV-seronegative donors into a CMV-seropositive recipients. (C) Actuarial OS 6 months after chronic GvHD diagnosis by donor type, adjusted for

recipient's age ≥ 60 years, high or very high DRI, HCT-CI > 3, and transplants from a CMV-seronegative donor into a CMV-seropositive recipient.

Table 1A.

Clinical characteristics of patients with grade 2–4 acute GvHD, by donor/prophylaxis template

Characteristic	Overall			MUD / conventional*			
	Haplo/PTCy (n = 264)	MUD/conventional (n = 1163)	*P value*	ATG (n=380)	No ATG (n=779)	*Haplo Vs MUD/ATG P value*	*Haplo Vs MUD/No ATG P value*
Recipient age, years			< .001			<.001	<.001
18–39	81 (31)	173 (15)		52 (14)	121 (15)		
40–59	91 (34)	364 (31)		118 (31)	244 (31)		
≥ 60	92 (35)	626 (54)		210 (55)	414 (53)		
HCT-CI score							
Median (range)	3 (0–10)	3 (0–13)	*.5*	3 (0–10)	3 (0–13)	*.5*	*.4*
[IQRT]	[1, 4]	[1, 4]		[1, 4]	[1, 4]		
Missing	5 (2)	32 (3)		8	24		
Donor age, years							
Median (range)	39 (9–71)	28 (18–61)	*< .001*	27 (18–61)	28 (18–61)	*< .001*	*< .001*
Donor-recipient sex							
Male/male	101 (38)	535 (46)		172 (45)	362 (46)		
Male/female	71 (27)	306 (26)		113 (30)	193 (25)		
Female/male	52 (20)	157 (13)	.01	47 (12)	109 (14)	.01	.03
Female/female	40 (15)	153 (13)		45 (12)	107 (14)		
Missing	0	12 (1)		3 (1)	8 (1)		
Disease			< .00			< .001	< .001
Acute myeloid leukemia	160 (61)	507 (44)		1 54 (40)	352 (45)		
Acute lymphoid leukemia	50 (19)	138 (12)		48 (13)	90 (11)		
Chronic myeloid leukemia	11 (4)	29 (2)		10 (3)	19 (2)		
Myelodysplastic syndrome	43 (16)	489 (42)		168 (44)	318 (41)		
Disease risk index			.003			.05	.001
Low	26 (10)	60 (5)		26 (7)	34 (4)		
Intermediate	128 (48)	536 (46)		166 (44)	368 (47)		
High	94 (36)	511 (44)		173 (45)	336 (43)		
Missing	16 (6)	56 (5)		15 (4)	41 (5)		
Graft type		v	< .001			< .001	< .001
Bone marrow	91 (35)	190 (16)		62 (16)	128 (16)		
Peripheral blood	173 (65)	973 (84)		318 (84)	651 (84)		
Conditioning intensity			< .001			< .001	< .001
Myeloablative/TBI	70 (27)	142 (12)		43 (11)	99 (13)		
Myeloablative/not TBI	57 (22)	432 (37)		133 (35)	297 (38)		
Non-myeloablative	135 (51)	585 (50)		204 (54)	379 (49)		
Median follow-up in survivors, months	24 (2.6–62)	34 (1–66)	*NA*	34 (4.5–66)	34 (.7–62)	*NA*	*NA*

Characteristic	Overall			MUD / conventional*			
	Haplo/PTCy (n = 264)	MUD/conventional (n = 1163)	*P value*	ATG (n=380)	No ATG (n=779)	*Haplo Vs MUD/ATG P value*	*Haplo Vs MUD/No ATG P value*
Maximum acute GvHD grade, n (%)							
2	187 (71)	699 (60)		240 (63)	459 (59)		
3 or 4	72 (28)	440 (39)	.001	132 (35)	304 (39)	.04	.001
Missing**	5 (2)	24 (2)		8 (2)	16 (2)		
Interval between transplant and GvHD							
Median (range), days	35 (5–218)	33 (7–374)	.006	34 (8–237)	32 (7–374)	.1	.001
> Day 100, n (%)	11 (4)	71 (6)	.2	18 (5)	56 (7)	.7	.08
Total number of organs							
including upper gastrointestinal, n (%)							
1	106 (40)	422 (36)		149 (39)	273 (35)		
2	108 (41)	439 (38)		149 (39)	287 (37)		
3	39 (15)	206 (18)		53 (14)	152 (19)		
4	5 (2)	52 (5)	*.03*	18 (5)	34 (4)	*.04*	*.04*
Missing	6 (2)	44 (4)		11 (3)	33 (4)		
> 2	44 (17)	258 (23)	*.04*	71 (19)	186 (25)	*.5*	*.01*
Total number of organs							
excluding							
upper gastrointestinal, n (%)							
0	29 (11)	117 (10)		45 (12)	72 (9)		
1	130 (49)	553 (47)		183 (48)	370 (47)		
2	88 (33)	364 (31)	0.06	118 (31)	242 (31)	.3	.03
3	11 (4)	85 (7)		23 (6)	62 (8)		
Missing	6 (2)	44 (4)		11 (3)	33 (4)		
Missing grade excluded	**n = 259**	**n = 1139**		**N=372**	**N=763**		
Skin stage, n (%)							
0	89 (34)	380 (33)	*.8*	129 (35)	251 (33)	*.9*	*.7*
1	36 (14)	157 (14)		67 (18)	89 (12)		
2	42 (16)	190 (17)		59 (16)	130 (17)		
3 or 4	92 (35)	412 (36)	*.8*	117 (31)	293 (38)	*.3*	*.4*
Liver stage, n (%)							
0	231 (89)	962 (84)	*.06*	318(85)	640 (84)		
1	11 (4)	49 (4)		14 (4)	35 (5)	*.2*	*.04*
2	7 (3)	49 (4)		15 (4)	34 (4)		
3 or 4	10 (4)	78 (7)	*.07*	24 (6)	54 (7)	*.1*	*.07*
Missing	0	1 (0.1)		1 (0)	0		
Upper gastrointestinal tract, n (%)							

Characteristic	Overall			MUD / conventional*			
	Haplo/PTCy (n = 264)	MUD/conventional (n = 1163)	*P value*	ATG (n=380)	No ATG (n=779)	*Haplo Vs MUD/ATG P value*	*Haplo Vs MUD/No ATG P value*
0	139 (54)	531 (47)	.04	179 (48)	349 (46)	.2	.03
1	120 (46)	608 (53)		193 (52)	414 (54)		
Lower gastrointestinal tract stage, n (%)							
0	116 (45)	509 (45)	0.9	176 (47)	333 (44)	.5	.9
1	79 (31)	244 (21)		78 (21)	166 (22)		
2	26 (10)	122 (11)		40 (11)	80 (10)		
3 or 4	37 (14)	245 (21)	.01	76 (20)	167 (22)	.05	.001
Missing	1 (0.4)	19 (2)		2 (0)	17 (2)		

*Excluded from this comparison are 4 patients in the MUD/conventional cohort who received campath during conditioning

**Diagnosis of grade 2–4 acute GvHD was confirmed; however, the exact maximum grade was unknown.

GVHD, graft-versus-host disease; PTCY, post-transplant cyclophosphamide; MUD, matched unrelated donor; N, number; TBI, total body irradiation

Table 1B.

Characteristics of the chronic GvHD cohort, by donor/prophylaxis template

	Overall			MUD / conventional		*Haplo vs MUD/ATG*	*Haplo vs MUD / no ATG*
Characteristic	**Haplo/PTCy (n = 206)**	**MUD/convention (n = 1018)**	***P* value**	**ATG (n=254)**	**No ATG (n=764**	***P value***	***P value***
Recipient age, years			*<.001*			*.001*	*<.001*
18–39	53 (26)	161 (16)		44 (17)	117 (15)		
40–59	82 (40)	305 (30)		78 (31)	227 (30)		
≥ 60	71 (34)	552 (54)		132 (52)	420 (55)		
HCT-CI score			*.03*			*.2*	*.03*
Median (range)	2 (0–9)	3 (0–13)		3 (0–10)	3 (0–13)		
Missing	2	29		7	22		
Donor age, years							
Median (range)	37 (9–71)	28 (18–60)	*<.001*	27 (19–53)	28 (18–60)	*<.001*	*<.001*
Missing	1	20		7	13		
Donor-recipient sex			*.08*			*.3*	*.06*
Male/male	73 (35)	450 (44)		109 (43)	341 (45)		
Male/female	57 (28)	270 (26)		66 (26)	204 (27)		
Female/male	38 (18)	158 (15)		45 (18)	113 (15)		
Female/female	38 (18)	135 (13)		33 (13)	103 (13)		
Missing	0	5(1)		1 (0)	4 (.5)		
Disease			*<.001*			*<.001*	*<.001*
Acute myeloid leukemia	120 (58)	470 (46)		112 (44)	358 (47)		
Acute lymphoid leukemia	48 (23)	127 (12)		39 (15)	88 (11)		
Chronic myeloid leukemia	8 (4)	19 (2)		2 (1)	17 (2)		
Myelodysplastic syndrome	30 (15)	402 (39)		101 (40)	301 (39)		
Disease risk index			*.003*			*.03*	*.02*
Low	18 (9)	52 (5)		14 (5)	38 (5)		
Intermediate	121 (59)	553 (54)		131 (52)	422 (55)		
High	59 (29)	383 (38)		101 (40)	282 (37)		
Missing	8 (4)	30 (3)		8 (3)	22 (3)		
Graft type			*<.001*			*<.001*	*<.001*
Bone marrow	63 (31)	144 (14)		29 (11)	115 (15)		
Peripheral blood	143 (69)	874 (86)		225 (89)	649 (85)		
Conditioning intensity			*<.001*			*<.001*	*<.001*
Myeloablative/TBI	47 (23)	113 (11)		29 (11)	84 (11)		
Myeloablative/not TBI	45 (22)	386 (38)		101 (40)	285 (37)		
Not myeloablative	114 (55)	518 (51)		124 (49)	394 (52)		
Missing	0	1 (0.1)		0	1(0)		
Median (range) follow-up, m	21 (0.2–56)	27 (.23–63)	*NA*	26 (.23–58)	27 (.33–63)	*NA*	*NA*

Characteristic	Overall			MUD / conventional		*Haplo vs MUD/ATG*	*Haplo vs MUD / no ATG*
	Haplo/PTCy (n = 206)	**MUD/convention (n = 1018)**	***P* value**	**ATG (n=254)**	**No ATG (n=764**	***P value***	***P value***
Lack of follow-up, n (%)	2 (1)	9 (1)		1 (0)	8 (1)		
Interval transplant to chronic GvHD diagnosis							
Median (range), months	6 (2–34)	7 (0.6–51)	*.007*	6 (2–51)	6.9 (0.6–39)	*.5*	*.001*
Prior acute GvHD grade, n (%)							
0	45 (22)	307 (30)		63 (25)	244 (32)		
1–4	155 (75)	702 (69)	*.02*	188 (74)	514 (67)	*.5*	*.01*
Missing	6 (3)	9 (1)		3 (1)	6 (1)		
Total number of organs involved, n (%)							
1	61 (30)	173 (17)		76 (30)	97 (13)		
2	41 (20)	198 (20)		58 (23)	140 (18)		
3	47 (23)	181 (18)		47 (18)	134 (17)		
4	25 (12)	182 (18)		38 (15)	144 (19)		
> 4	22 (11)	261 (26)		30 (12)	231 (30)		
Missing	10 (5)	23 (2)		5 (2)	18 (2)		
>3	47 (24)	443 (44)	*<.001*	68 (27)	375 (50)	*.4*	*<.001*
Missing organ data excluded Organ involved, n (%)	**n = 196**	**n = 995**		**n = 249**	**n = 746**		
Skin	133 (68)	691 (69)	*.7*	152 (61)	539 (72)	*.1*	*.2*
Mouth	77 (39)	600 (60)	*<.001*	107 (43)	493 (66)	*.4*	*<.001*
Eyes	80 (41)	566 (57)	*<.001*	116 (47)	450 (60)	*.2*	*<.001*
Liver	56 (29)	380 (38)	*.01*	65 (26)	315 (42)	*.6*	*<.001*
Gastrointestinal	42 (21)	311 (31)	*.006*	79 (32)	232 (31)	***.01***	*.01*
Lungs	35 (18)	249 (25)	.03	49 (20)	200 (27)	*.6*	*.01*
Genitourinary	14 (7)	76 (8)	.8	8 (3)	68 (9)	*.06*	*.4*
Musculoskeletal	3 (1)	91 (9)	*<.001*	8 (3)	83 (11)	*.2*	*<.001*
Hematologic	41 (21)	219 (22)	*.7*	47 (19)	172 (23)	*.6*	*.5*
Other	24 (12)	184 (18)	*.03*	30 (12)	154 (21)	*.9*	*.01*
Number of visceral organ involved [*], n (%)							
0	88 (45)	353 (35)		112 (45)	241 (32)		
1	88 (45)	395 (40)		90 (36)	305 (41)		
2	15 (8)	196 (20)		38 (15)	158 (21)		
3	5 (2)	51 (5)		9 (4)	42 (6)		
≥ 2 organs	20 (10)	247 (25)	*<.001*	47 (19)	200 (27)	*.01*	*<.001*

[*] visceral organs include: liver, lung, gastrointestinal tract

GVHD, graft-versus-host disease; PTCY, post-transplant cyclophosphamide; MUD, matched unrelated donor; N, number; TBI, total body irradiation

Table 2.

Multivariate analysis: risk of NRM, chronic GvHD, and overall mortality at 2-years in patients with grade 2–4 acute GvHD

Outcome	Overall Hazard ratio (95% CI)	≥ 60 years Hazard ratio (95% CI)
NRM *		
Not female to male transplant		
MUD/conventional prophylaxis	1.0	1.0
Haplo/PTCy-based prophylaxis	0.6 (0.4–0.9)	0.3 (0.1–0.7)
	P = .01	*P* = .003
Female to male transplant		
MUD/conventional prophylaxis	1.0	1.0
Haplo/PTCy-based prophylaxis	1.3 (0.7–2.6)	1.6 (0.6–4.2)
	P =.4	*P* = .3
Overall mortality †		
MUD/conventional prophylaxis	1.0	1.0
Haplo/PTCy-based prophylaxis	1.1 (0.9–1.3)	1.1 (0.8–1.6)
	P = .4	*P* = .4
Chronic GvHD ‡		
Not-myeloablative conditioning		
MUD/conventional prophylaxis - ATG	1.0	1.0
MUD/conventional prophylaxis + ATG	0.5 (0.3–0.6), *P* < .001	0.5 (0.4–0.7), *P* < .001
Haplo/PTCy-based prophylaxis	0.4 (0.3–0.6) , *P* <.001	0.4 (0.2–0.6), *P* < .001
Myeloablative conditioning		
MUD/conventional prophylaxis - ATG	1.0	1.0
MUD/conventional prophylaxis + ATG	0.6 (0.4–0.8), *P* = .001	0.7 (0.4–1.3), *P* = .3
HaploPTCy-based prophylaxis	0.9 (0.7–1.3),*P* = .9	1.3 (0.5–3.2), *P* = .5

CI, confidence interval; NRM, nonrelapse mortality; GvHD, graft-versus-host disease; PTCy, post-transplant cyclophosphamide; MUD, matched unrelated donor

* NRM rate, adjusted for acute GvHD grade, HCT-CI, recipient CMV serostatus, and recipient age (only for the overall group).‡†

† Overall mortality rate, adjusted for grade 3 or 4 acute GvHD, high-risk DRI, recipient age, recipient CMV serostatus, and HCT-CI.

‡ Chronic GVHD rate, adjusted for grade 3 or 4 acute GvHD, high or very high DRI, and KPS < 90 in the overall group and for grade 3 or 4 acute GVHD and stem cell source in the age ≥ 60 years group.

Haplo/PTCy vs MUD/conventional prophylaxis + ATG: in not-myeloablative: HR=.8 (.5–1.2), *P* = .3; in Myeloablative: HR=1.6 (1.1–2.4), *P* =.02

Table 3.

Multivariate analysis: risk of NRM and overall mortality at 2-years in patients with chronic GvHD

Outcome	Overall	≥ 60 years
NRM *		
MUD/conventional prophylaxis	1.0	1.0
Haplo/PTCy-based prophylaxis hazard ratio (95% CI)	.6 (0.3–0.9)	.6 (0.3–1.2)
P value	*P* = .04	*P* = .2
Overall mortality †		
MUD/conventional prophylaxis	N/A	1.0
Haplo/PTCy-based prophylaxis hazard ratio (95% CI)		1.3 (0.8–2)
P value		*P* = .2
Within 6 months‡ after chronic GvHD diagnosis		
MUD/conventional prophylaxis	1.0	N/A
Haplo/PTCy-based prophylaxis hazard ratio (95% CI)	1.6 (1.05–2.6)	
P value	*P* = .03	
Beyond 6 months after chronic GvHD diagnosis		
MUD/conventional prophylaxis	1.0	N/A
Haplo/PTCy-based prophylaxis hazard ratio (95% CI)	.9 (0.6–1.4)	
P value	*P* = .6	

CI, confidence interval; NRM, non-relapse mortality; GvHD, graft-versus-host disease; PTCy, post-transplant cyclophosphamide; MUD, matched unrelated donor

* NRM rate, adjusted for recipient age (≥ 40 years), HCT-CI (> vs ≤ 3), and donor/recipient CMV serostatus (- /+ vs all other combinations) in the overall group.

† Overall mortality rate, adjusted for recipient age (≥ 60 years), HCT-CI (> vs ≤ 3), donor/recipient CMV serostatus (−/+ vs all other combinations), and DRI (high/very high vs all other) in the overall group, and adjusted for HCT-CI (> vs ≤ 3) and donor/recipient CMV serostatus (−/+vs all other combinations) in the aged ≥ 60 years subset.

‡ The mortality rates differed over time. To account for this variation and facilitate the interpretation of the data, we presented the multivariate analysis results separately for outcomes before and ≥ 6 months since the diagnosis of chronic GvHD.