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# Number of HLA-Mismatched Eplets Is Not Associated with Major Outcomes in Haploidentical Transplantation with Post-Transplantation Cyclophosphamide: A Center for International Blood and Marrow Transplant Research Study

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SUPPLEMENTARY MATERIALS

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## Abstract

The number of haploidentical hematopoietic stem cell transplantations (haplo-HSCT) performed has increased substantially in recent years. Previous single-center studies using in silico algorithms to quantitively measure HLA disparity have shown an association of the number of HLA molecular mismatches with relapse protection and/or increased risk of acute graft-versus-host disease (GVHD) in haplo-HSCT. However, inconsistent results from small studies have made it difficult to understand the full clinical impact of molecular mismatch in haplo-HSCT. In this study, we investigated the potential of the HLA class I and II mismatched eplet (ME) score measured by HLA-Matchmaker, as well as ME load at a specific locus to predict outcomes in a registry-based cohort of haplo-HSCT recipients. We analyzed data from 1287 patients who underwent their first haplo-HSCT for acute lymphoblastic leukemia, acute myelogenous leukemia, or myelodysplastic syndrome between 2013 and 2017, as entered in the Center for International Blood and Marrow Transplant Research database. ME load at each HLA locus and total class I and II were scored using the HLA-Matchmaker module incorporated in HLA Fusion software v4.3, which identifies predicted eplets based on the crystalized HLA molecule models and identifies ME by comparing donor and recipient eplets. In the study cohort, ME scores derived from total HLA class I or class II loci or individual HLA loci were not associated with overall survival, disease-free survival, nonrelapse mortality, relapse, acute GVHD, or chronic GVHD ($P < .01$). An unexpected strong association was identified between total class II ME load in the GVH direction and slower neutrophil engraftment (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.75 to 0.91; $P < .0001$) and platelet engraftment (HR, 0.80; 95% CI, 0.72 to 0.88; $P < .0001$). This was likely attributable to ME load at the HLA-DRB1 locus, which was similarly associated with slower neutrophil engraftment (HR, 0.82; 95% CI, 0.73 to 0.92; $P = .001$) and slower platelet engraftment (HR, 0.76; 95% CI, 0.70 to 0.84; $P < .0001$). Additional analyses suggested that this effect is attributable to a match versus a mismatch in the graft-versus-host direction and not to ME load, as a dose effect was not identified. These findings contradict those of previous relatively small studies reporting an association between ME load, as quantified by HLA-Matchmaker, and haplo-HSCT outcomes. This study failed to demonstrate the predictive value of ME from HLA molecules for major clinical outcomes, and other molecular mismatch algorithms in haplo-HSCT settings should be tested.

**Keywords**

Haploidentical donors; Allogeneic transplantation; HLA mismatching

## INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the sole curative therapy available for many hematologic malignancies and nonmalignant disorders. The use of hematopoietic stem cells from a haploidentical donor has substantially expanded the availability of stem cell resources [1]. In the setting of haploidentical HSCT (haplo-HSCT), donor and recipient are mismatched in 1 HLA haplotype, usually resulting in bidirectional alloreactivity, causing a high incidence of graft rejection and hyperacute graft-versus-host disease (GVHD) in early practice [2]. Recent graft engineering and post-transplantation GVHD prophylaxis that preferentially manipulates alloreactive T cells has successfully prolonged graft survival and reduced the incidence of GVHD in haplo-HSCT recipients [3–5]. McCurdy et al. [6] found no difference in composite endpoints between HSCT from HLA-matched donor and haplo-HSCT with post-transplantation cyclophosphamide (PTCy) across different conditioning intensities and donor types. Moreover, compared with HSCT from an HLA-matched related donor, the haplo-HSCT could be associated with stronger antileukemia activity and a reduced risk of relapse, which might benefit patients with high-risk malignancies [7].

Compared with HSCT from a mismatched unrelated donor [8], HLA disparity assessed at the antigen level in haplo-HSCT appears to have no significant impact on transplantation outcomes [9,10]. Although no association was found between the cumulative number of mismatched HLA antigens and clinical outcomes, it was reported that an antigen mismatch at HLADRB1 was correlated with an increased risk of grade ≥II acute GVHD (aGVHD) with PTCy but not in antithymocyte globulin regimens [11]. This suggests that each mismatched HLA locus might not contribute to alloreactivity equally and aGVHD prophylaxis regulates the alloimmunity from HLA mismatches. Recently, the degree of HLA disparity was assessed at the molecular level by comparing the structural and functional differences between donor and recipient HLA molecules [12,13]. Several studies have suggested that the HLA disparity assessed at the molecular level, but not by the cumulative number of mismatched antigens, may be relevant to the clinical outcome of patients receiving haplo-HSCT [14–16]. The directionality of alloreactivity (graft-versus-host [GVH] or host-versus-graft [HVG]) and the mismatch at a specific allele could be better evaluated with in silico molecular mismatch algorithms [14].

Various algorithms of molecular mismatching to predict immunogenicity have been developed with different emphases, such as the number of mismatched amino acids or physiochemical properties of the amino acid substitution [17]. One of the best-studied computational prediction methods, HLA-Matchmaker focuses on structural similarity and compares eplets, the key structural component of epitopes, between the donor and recipient [18]. The mismatched eplets (ME) score has been successfully used to gauge the level of

disparity and the alloimmune response associated with certain clinical outcomes in the renal transplantation settings [19,20].

Although the ME score has been convincingly shown to be correlated with antibody-mediated rejection and de novo donor-specific anti-HLA antibody (DSA) development in solid organ transplant recipients [19,20], the predictive value of the ME for outcomes of HSCT has been investigated in only a few studies with limited numbers of patients. Moreover, the results from the various single-institution studies in haplo-HSCT are inconsistent. Rimando et al. [15] demonstrated that in peripheral blood haplo-HSCT recipients with higher levels of class II ME in the GVH direction was associated with a reduced risk of relapse [15], whereas another group found that ME derived from HLA-A in the HVG direction was associated with relapse protection in a cohort of transplantations using bone marrow grafts [14].

Given that haplo-HSCT is being increasingly performed in patients requiring transplantation, it is essential to understand the immunogenicity derived from alloantigens on the mismatched haplotype, and thus the present large registry-based study was conducted. In this study, we hypothesized that HLA molecular disparity quantified by ME score, either in aggregate or derived from a particular HLA locus, is associated with clinical outcomes of haplo-HSCT performed with PTCy-based GVHD prophylaxis.

## METHODS

### Patients and HSCT Characteristics

Data were obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR), a working group of transplantation centers worldwide. The study population comprised 1287 patients with hematologic malignancies who were age≥18 years and underwent first allogeneic HSCT from a haploidentical donor. The study was limited to patients undergoing haplo-HSCT for acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), or myelodysplastic syndrome (MDS) and reported to the CIBMTR between 2013 and 2017. All patients received PTCy-based GVHD prophylaxis.

All patients provided written informed consent for data submission and research participation in accordance with the Declaration of Helsinki. The Institutional Review Boards of the Medical College of Wisconsin and National Marrow Donor Program approved this study.

### HLA Typing and ME Analysis

Patients included in the study had donor and recipient HLA typing performed at the HLA-A, -B, -C, -DRB1, and -DQB1 loci at high resolution. The ME loads at each HLA locus and total class I and II were scored using the HLA-Matchmaker module incorporated in HLA Fusion v4.3, which identifies predicted eplets based on the crystalized HLA molecule models [18] and identifies ME by comparing donor and recipient eplets. The analyses were performed separately in both the GVH and HVG directions [14]. Eplet repertoires are listed in the HLA Epitope Registry (http://www.epitopes.net/downloads.html ). The class I ME score was the total ME load derived from HLA-A, -B, and -C loci, and the class II ME

score was the total ME load derived from HLA-DRB1 and -DQB1. An interlocus eplet was defined as a specific eplet found in ≥2 HLA loci. When identifying the ME, interlocus eplets mismatched in 1 locus but matched on a different locus were not included, to truly reflect molecular disparity.

### Statistical Analysis

The primary outcome was aGVHD, with 5 main testing variables, including ME-derived from HLA-A, -B, -C, total class I, and total class II loci. Secondary outcomes were overall survival (OS), disease-free survival (DFS), relapse, nonrelapse mortality (NRM), neutrophil and platelet engraftment, grade II-IV and III-IV aGVHD at day 100, and any chronic GVHD (cGVHD) at 1 year. The diagnosis and clinical grading of aGVHD were based on established criteria [21]. The event for OS was death from any cause, and relapse and DFS were defined as described previously [22]. Nonrelapse mortality (NRM) was defined as death without a previous relapse. Neutrophil engraftment was defined as the first date of an absolute neutrophil count $\geq 0.5 \times 10^9$/L for 3 consecutive days. The time to platelet engraftment was defined as the first day of a platelet count >20,000/$\mu$L without transfusion support for 7 consecutive days. cGVHD was graded based on conventional criteria as published by Sullivan et al. [23]. Ablative and nonmyeloablative HSCTs were defined according to the CIBMTR operational guidelines [24]. AML risk groups were defined according to the European Leukemia Net (ELN) guidelines published in 2010 [25], and MDS risk groups were defined according to the International Prognostic Scoring System [26].

Patient and HSCT characteristics were summarized using descriptive statistics. Categorical variables were reported as frequency and percentage; continuous variables, as median and range. The ME score also was analyzed in quartiles in exploratory analyses. The multivariable regression analysis was based on the Cox proportional hazards model. All the clinical variables were tested for affirmation of the proportional hazards assumption, and those violating the proportional hazards assumption were adjusted through stratification. The adjusted cumulative incidence probabilities were calculated using an SAS macro developed by Zhang and Zhang [27]. A stepwise backward model building procedure was used to select the adjusted covariates for each outcome, with a threshold of 0.05 for both entry and retention in the model. Each main ME variable was tested separately by forcing it into a model with the same set of adjusted covariates for each outcome. For the association of ME and clinical outcomes, a significance level of 0.01 was used to adjust for multiple testing. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

## RESULTS

### Patient and HSCT Characteristics

The median age of the study cohort was 55 years (range, 18 to 78 years). Clinical characteristics are summarized in Table 1. The pre-HSCT diagnosis was AML in 756 patients (59%), ALL in 273 (21%), and MDS in 258 (20%). Revised Disease Risk Index (DRI-R) data were missing in 124 patients (10%); 29% of the patients had a high DRI-R, and 3% had a very high DRI-R. Fiftythree percent of the patients had a Karnofsky

Performance Status of 90 to 100, and 53% had an HCT-CI score ≥3. Myeloablative conditioning was used in 43% of the patients. The median duration of follow-up in surviving patients was 29 months (range, 2 to 76 months). ME load was quantified on each locus in the HVG or GVH direction (Table 1). No correlation was identified between the number of ME in the HVG direction versus that in the GVH direction.

### Transplantation Outcomes

**OS, DFS, and TRM—**On univariable analysis, no association between the ME score (dichotomized at the median) and OS, DFS, or NRM reached the predetermined level of statistical significance ($P < .01$).

**Relapse, aGVHD, and cGVHD—**No significant associations were identified between the ME score (dichotomized at the median) and relapse, aGVHD, or cGVHD on univariable analysis. A non-statistically significant trend toward relapse protection was found with ME from HLA-DRB1 in the GVH direction (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.63 to 0.96; $P = .019$) (Supplementary Table S2). Further analysis using quartiles did not identify any significant dose-dependent association between 1-year, 2-year, or 3-year relapse and HLA-DRB1 ME in the GVH direction ($P = .030$) (Supplementary Table S1). In addition, a subset analysis for relapse was performed excluding AML patients who were either primary refractory or in relapse status and another 21 ALL patients (8%) who were not in remission at the time of transplantation. Similarly, a nonsignificant trend toward relapse protection was noted with ME from HLA-DRB1 in the GVH direction (HR, 0.77; $P = .017$). The selected risk factors associated with relapse and aGVHD II-IV are shown in Supplementary Tables S2 and S3.

**Engraftment—**The higher ME score from HLA class II in the GVH direction was associated with delayed neutrophil (HR, 0.82; 95% CI, 0.75 to 0.91; $P < .0001$) and platelet engraftment (HR, 0.80; 95% CI, 0.72 to 0.88; $P < .0001$) dichotomizing at the median, likely attributed to the ME derived from HLA-DRB1 in the GVH direction, which was independently correlated with slower neutrophil (HR, 0.82; 95% CI, 0.73 to 0.92; $P = .001$) and platelet engraftment (HR, 0.76; 95% CI, 0.70 to 0.84; $P < .0001$).

This association with neutrophil engraftment persisted ($P < .0001$) when the analysis was performed with class II GVH ME in quartiles (Figure 1A) and the multivariable analysis after adjusting for the other significant predictors of engraftment (Table 2). Similar associations were observed for platelet engraftment (Figure 1B) after adjusting for the other significant clinical predictors (Table 3). Similar to the association of ME in HLA-DRB1 in the GVH direction (Supplementary Figure S1), HLA class II GVH ME analyzed by quartiles suggested that the significant findings were driven mainly by the lowest quartile (0 to 7 ME, which includes matched pairs) versus the upper 3 quartiles (Tables 2 and 3), and no dose effect was noticed.

## DISCUSSION

The use of haplo-HSCTs continues to increase worldwide, with comparable clinical outcomes to HLA-matched transplants [1,4,5,28,29]. A recent comparative study from

the European Society for Blood and Marrow Transplantation (EBMT) showed that when using homogeneous GVHD prophylaxis with PTCy, haplo-HSCT is associated with an increased risk of aGVHD but is counterbalanced by a reduced risk of relapse compared with transplantations from a matched related donor or matched unrelated donor [30]. Moreover, in a similar study comparing outcomes between haploidentical and matched unrelated donor transplantations with PTCy GVHD prophylaxis, an elevated risk of aGVHD and inferior disease-free survival and OS were seen in haplo-HSCT when reduced-intensity conditioning regimens were used [31]. This suggests that donor-recipient HLA matching still could be clinically important in haplo-HSCT with PTCy GVHD prophylaxis. Understanding the risk or benefit associated with alloimmunity due to the mismatched HLA haplotype is essential for donor selection and risk stratification. This study investigated a molecular mismatching algorithm that goes beyond the classical way of counting the cumulative number of HLA antigens or allele mismatches to consider gradations of matching at each locus. In this cohort of patients receiving conditioning of varying intensity, we found that no associations between a higher number of ME, dichotomized at the median, and OS, DFS, NRM, relapse, acute GVHD, or chronic GVHD. The administration of PTCy-based prophylaxis, which exclusively manipulates alloreactive T cells and regulatory T cells [32,33], might largely mitigate the alloimmunity in response to HLA disparity.

Unexpectedly, a higher number of total HLA class II ME in the GVH direction, but not in the HVG direction, was significantly associated with slower neutrophil and platelet engraftment. Although the HLA-DRB1 ME in the GVH direction may be the key contributor to this effect, ME derived from HLADQB1 also contribute to the effect, with a similar trend associated with delayed neutrophil and platelet engraftment (HR, 0.90; $P = .039$ and HR, 0.90; $P = .078$, respectively). Theoretically, this result is difficult to explain, as this significant effect is observed only in the GVH direction, and we cannot exclude the possibility of a false-positive association considering the study's retrospective nature. A possible explanation could be the presence of HLA DSAs; however, this information is not currently available in the CIBMTR database. The reported prevalence of DSAs in haplo-HSCT ranges between 10% and 24%, likely due to pregnancy and transfusion history [34–37], and the presence of DSA has been associated with a significantly increased risk of graft failure and delayed engraftment [34–39]. Our cohort included haplo-HSCT procedures reported to the CIBMTR between 2013 and 2017 when detection and desensitization of DSA was not the routine practice. Higher numbers of ME are likely associated with a higher occurrence of DSA, which might be the key factor that could lead to the delayed engraftment observed. It is also noteworthy that in the quartile analysis, the statistical significance was driven by the lowest ME group versus the other 3 quartiles with higher numbers of ME, and a dose effect was not supported. Because the lowest ME group is composed mainly of the matched pairs, this further suggests that delayed engraftment is driven by the HLA-matched/mismatched status rather than the HLA class II ME score in the GVH direction.

The discordant results between the present study and previous similar studies may be related to heterogenicity in stem cell source, transplantation protocol, disease status, DSA, and ethnic cohorts in this multicenter study. Thus, the inconsistency does not completely disprove the predictive value of molecular mismatches in haplo-HSCT settings. A profound

understanding of alloimmunity derived from mismatched haplotype, optimization of in silico algorithms, and possibly application of these algorithms in a uniform cohort of patients are necessary for the potential future application. T cells recognize HLA alloantigens mainly through 2 considerably different pathways: direct and indirect. The former provides T cell recognition of intact allogeneic HLA molecules on the cell surface, leading to T cell activation and subsequent immune responses. During indirect allorecognition, the mismatched HLA molecules are processed into peptides and presented by shared HLA molecules to the T cells, which in turn are activated on recognition of foreign peptides [40]. Whereas HLAMatchmaker mainly considers surface positions on HLA molecules that are exposed to direct B cell recognition, T cell epitopes originating from polymorphisms on the nonexposed area of the molecules could be underestimated [15,41]. On the other hand, PIRCHE (Predicted Indirectly Recognizable HLA Epitopes) is another algorithm that focuses on the indirect recognition pathway and evaluates potential T cell epitopes by predicting the number of allogeneic HLA-derived peptides presented by the shared HLA molecules [42]. Although some alloreactive T cell clones specifically react to certain eplets identified by HLA-Matchmaker, and many polymorphic residues are engaged in both B and T cell epitopes [43–45], a comparison study of the location of immunogenic amino acids identified from both methods showed that a significant number of PIRCHE residues were not part of an eplet identified by HLAMatchmaker [46]. Lachmann et al. [47] reported that the PIRCHE score, independent of ME load, predicted the formation of de novo DSAs in patients who underwent kidney transplantation, suggesting that PIRCHE could assess the elicited alloreactivities from a different perspective. A future combinatorial algorithm considering the epitopes in different pathways could bring up an optimized matching program.

Interestingly, we found a tendency toward a lower risk of relapse associated with HLA-DRB1 ME in the GVH direction (HR, 0.78; $P = .019$), in agreement with a previous study showing an association between HLA-DRB1 antigen mismatching and a lower risk of relapse (HR, 0.65; $P = .04$) without a corresponding increase in acute GVHD [10]. In our study, we assumed a simple linear relationship between the ME score and alloreactivity, yet a recent study in kidney transplant recipients demonstrated that a molecular mismatching score has a natural logarithmic effect on antibody formation [48]. In other words, the additive impact of mismatching score on clinical alloreactivity is likely reduced once a certain threshold is reached. Further studies focusing on HLA-DRB1 molecular mismatches with optimized scale and cutoff are warranted.

In addition to the lack of DSA information and heterogeneity introduced by any multi-institutional study, our present study has several limitations. Data were obtained from the CIBMTR registry for patients who underwent transplantation between 2013 and 2017, to enable sufficient follow-up. Although this is the largest number of haplo-HSCTs in which the predictive value of molecular mismatch has been studied so far, the sample size still may be insufficient compared with other studies of HSCT from an unrelated donor, which might have limited the statistical power to detect subtle associations across various ME at different HLA loci. In addition, because the relevant typing data were not available, the impact derived from the HLA-DPB1 mismatch was not addressed in this study, although

this mismatch was previously shown to be associated with an anti-leukemia effect in haplo-HSCT [14,49].

In conclusion, with this registry analysis of patients with ALL, AML, or MDS, we could not reproduce the findings from earlier reports demonstrating that ME from a particular HLA locus or total HLA class I/II loci was associated with certain clinical outcomes in haplo-HSCT. Because this study failed to demonstrate the predictive value of ME from HLA molecules for clinical outcomes, other molecular mismatch algorithms in haplo-HSCT settings should be tested.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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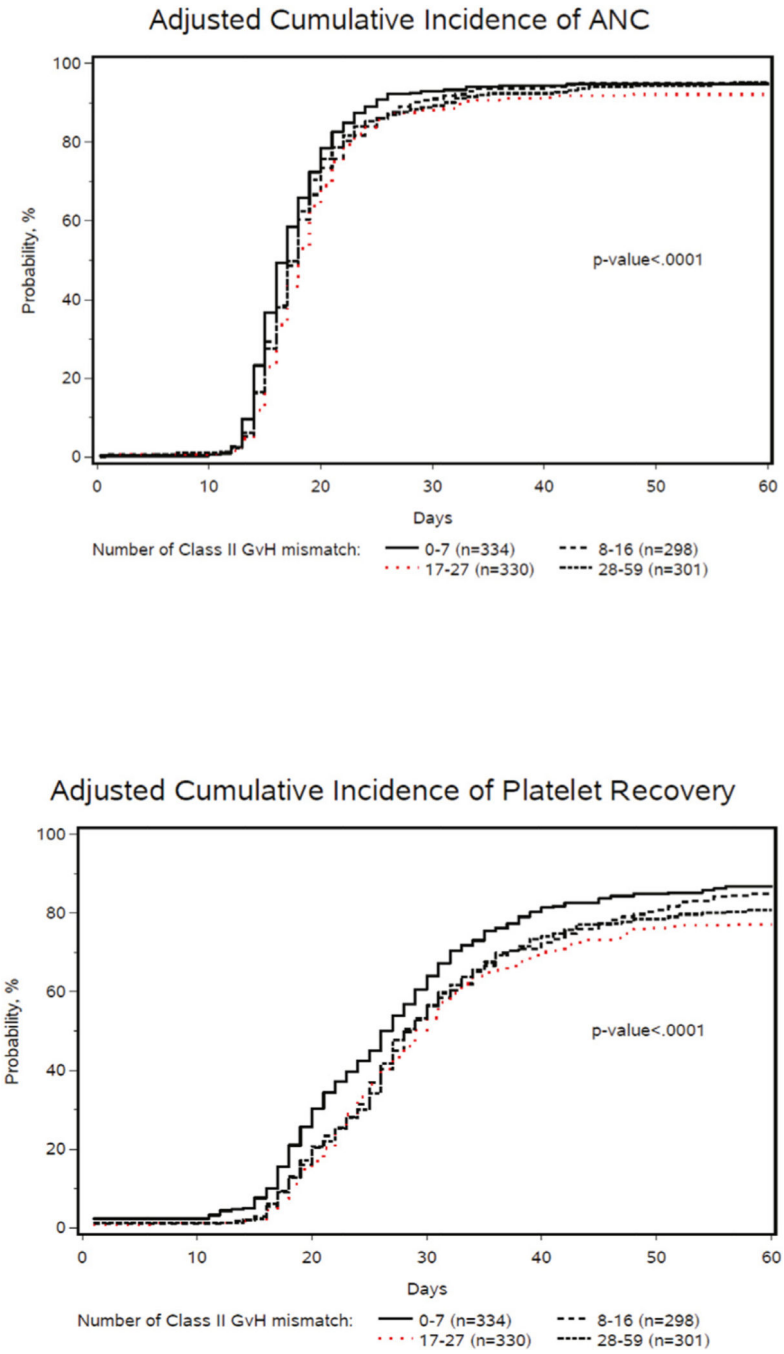


**Figure 1.**

Adjusted cumulative incidence of engraftment by class II mismatched eplets in the GVH direction. (A) Cumulative incidence of neutrophil engraftment by class II ME in the GVH direction in quartiles. (B) Cumulative incidence of platelet recovery by class II ME in the GVH direction in quartiles. HRs and P values were calculated in the univariable model using the lowest ME group (quartile 1) as a reference.

## Table 1

Patient/Donor Demographics and Transplantation Characteristics, 2013 to 2017

| Variable | Value | |
|---|---|---|
| Number of recipients | 1287 | |
| Number of centers | 97 | |
| Disease, n (%) | | |
| AML | 756 | (59) |
| ALL | 273 | (21) |
| MDS | 258 | (20) |
| AML disease stage, n (%) | | |
| Complete remission | 594 | (79) |
| Advanced: primary induction failure, relapse | 161 | (21) |
| Missing | 1 | (<1) |
| ALL disease stage, n (%) | | |
| Intermediate, CR1 | 170 | (62) |
| High, CR1 or CR2 | 74 | (27) |
| Very high, advanced: primary induction failure, relapse, nonresponse/progressive disease | 21 | (8) |
| Missing, CR unknown, CR3+, or untreated | 8 | (3) |
| MDS disease stage, n (%) | | |
| Early | 35 | (14) |
| Advanced | 217 | (84) |
| Missing | 6 | (2) |
| DRI-R, n (%) | | |
| Low | 52 | (4) |
| Intermediate | 692 | (54) |
| High | 376 | (29) |
| Very high | 43 | (3) |
| N/A: no category for patient characteristics | 40 | (3) |
| Missing disease status | 84 | (7) |
| Recipient age at transplantation, n (%) | | |
| 18–29 yr | 172 | (13) |
| 30–39 yr | 133 | (10) |
| 40–49 yr | 189 | (15) |
| 50–59 yr | 300 | (23) |
| 60+ yr | 493 | (38) |
| Recipient age at transplantation, yr, median (range) | 55 | (18–78) |
| Sex, n (%) | | |
| Male | 768 | (60) |
| Female | 519 | (40) |

| Variable | Value | |
|---|---|---|
| Karnofsky Performance Status, n (%) | | |
| 10–80 | 565 | (44) |
| 90–100 | 686 | (53) |
| Missing | 36 | (3) |
| HCT-CI, n (%) | | |
| 0 | 221 | (17) |
| 1 | 183 | (14) |
| 2 | 200 | (16) |
| 3+ | 683 | (53) |
| Race/ethnicity, n (%) | | |
| White, non-Hispanic | 756 | (59) |
| Black or African American, non-Hispanic | 209 | (16) |
| Asian, non-Hispanic | 76 | (6) |
| Native Hawaiian or other Pacific Islander, non-Hispanic | 4 | (<1) |
| American Indian or Alaska Native, non-Hispanic | 6 | (<1) |
| Hispanic | 170 | (13) |
| Missing | 66 | (5) |
| HLA-A GVH ME, n (%) | | |
| 0–2 | 348 | (27) |
| 3–8 | 345 | (27) |
| 9–16 | 283 | (22) |
| 17–42 | 311 | (24) |
| HLA-B GVH ME, n (%) | | |
| 0–2 | 331 | (26) |
| 3–4 | 350 | (27) |
| 5–10 | 290 | (23) |
| 11–26 | 316 | (25) |
| HLA-C GVH ME, n (%) | | |
| 0–0 | 336 | (26) |
| 1–4 | 365 | (28) |
| 5–7 | 357 | (28) |
| 8–13 | 229 | (18) |
| Class-I HLA GVH ME, n (%) | | |
| 0–11 | 355 | (28) |
| 12–19 | 307 | (24) |
| 20–29 | 313 | (24) |
| 30–77 | 312 | (24) |
| HLA-DRB1 GVH ME, n (%) | | |

| Variable | Value | |
|---|---|---|
| 0–2 | 350 | (27) |
| 3–8 | 312 | (24) |
| 9–19 | 303 | (24) |
| 20–47 | 322 | (25) |
| HLA-DQB1 GVH ME, n (%) | | |
| 0–0 | 324 | (25) |
| 1–6 | 328 | (25) |
| 7–10 | 359 | (28) |
| 11–21 | 276 | (21) |
| Class-II HLA GVH ME, n (%) | | |
| 0–7 | 341 | (26) |
| 8–16 | 306 | (24) |
| 17–27 | 336 | (26) |
| 28–59 | 304 | (24) |
| HLA-A HVG ME, n (%) | | |
| 0–1 | 324 | (25) |
| 2–8 | 360 | (28) |
| 9–18 | 291 | (23) |
| 19–42 | 312 | (24) |
| HLA-B HVG ME, n (%) | | |
| 0–3 | 310 | (24) |
| 4–5 | 304 | (24) |
| 6–12 | 329 | (26) |
| 13–26 | 344 | (27) |
| HLA-C HVG ME, n (%) | | |
| 0–1 | 405 | (31) |
| 2–4 | 252 | (20) |
| 5–7 | 349 | (27) |
| 8–12 | 281 | (22) |
| Class-I HLA HVG ME, n (%) | | |
| 0–12 | 347 | (27) |
| 13–21 | 321 | (25) |
| 22–34 | 302 | (23) |
| 35–76 | 317 | (25) |
| HLA-DRB1 HVG ME, n (%) | | |
| 0–2 | 358 | (28) |
| 3–8 | 285 | (22) |
| 9–21 | 335 | (26) |
| 22–58 | 309 | (24) |

| Variable | Value | |
|---|---|---|
| HLA-DQB1 HVG ME, n (%) | | |
| 0–0 | 338 | (26) |
| 1–7 | 380 | (30) |
| 8–10 | 290 | (23) |
| 11–21 | 279 | (22) |
| Class-II HLA HVG ME, n (%) | | |
| 0–7 | 328 | (26) |
| 8–17 | 339 | (26) |
| 18–29 | 308 | (24) |
| 30–67 | 312 | (24) |
| Graft type, n (%) | | |
| Bone marrow | 475 | (37) |
| PBSCs | 812 | (63) |
| Conditioning regimen intensity, n (%) | | |
| Myeloablative | 553 | (43) |
| Nonmyeloablative/reduced intensity | 734 | (57) |
| GVHD prophylaxis (PTCy § others) | | |
| PTCy + other(s) | 1222 | (95) |
| PTCy alone | 1 | (<1) |
| TAC + MMF § other(s) | 62 | (5) |
| TAC + MTX § other(s) (except MMF) | 1 | (<1) |
| TAC-based, adding PTCy | 1 | (<1) |
| Donor/recipient CMV serostatus, n (%) | | |
| +/+ | 542 | (42) |
| +/− | 103 | (8) |
| −/+ | 375 | (29) |
| −/− | 259 | (20) |
| Missing | 8 | (1) |
| Donor/recipient sex match, n (%) | | |
| Male/male | 473 | (37) |
| Male/female | 295 | (23) |
| Female/male | 295 | (23) |
| Female/female | 224 | (17) |
| Donor/recipient ABO match, n (%) | | |
| Matched | 396 | (31) |
| Minor mismatch | 106 | (8) |
| Major mismatch | 103 | (8) |
| Bidirectional | 18 | (1) |
| Not collected | 661 | (51) |

| Variable | Value | |
|---|---|---|
| Missing | 3 | (<1) |
| Donor age, n (%) | | |
| 0–9 yr | 3 | (<1) |
| 10–19 yr | 102 | (8) |
| 20–29 yr | 313 | (24) |
| 30–39 yr | 354 | (28) |
| 40–49 yr | 282 | (22) |
| 50+ yr | 233 | (18) |
| Donor age, yr, median (range) | 36 | (9–74) |
| Donor relationship to recipient, n (%) | | |
| Sibling | 290 | (23) |
| Parent | 88 | (7) |
| Child | 474 | (37) |
| Other relatives | 15 | (1) |
| Not collected | 417 | (32) |
| Missing | 3 | (<1) |
| Year of transplantation, n (%) | | |
| 2013 | 44 | (3) |
| 2014 | 175 | (14) |
| 2015 | 288 | (22) |
| 2016 | 385 | (30) |
| 2017 | 395 | (31) |
| Follow-up among survivors | | |
| No. evaluable | 795 | |
| Duration, mo, median (range) | 29 | (2–76) |

CR indicates complete remission; PBSCs, peripheral blood stem cells; TAC, tacrolimus; MMF, mycophenolate mofetil; MTX, methotrexate; CMV, cytomegalovirus.

*Only includes subjects with complete data for the presented variables and outcomes. Percentages may not add up to 100 because of rounding.

## Table 2

Multivariable Model for Neutrophil Engraftment with Class-II ME in the GVH Direction in Quartiles

| Factor | No. | Events | HR | 95% CI | *P* Value |
|---|---|---|---|---|---|
| Class-II ME in GVH direction | | | | | <.0001 |
| 0–7 | 334 | 321 | 1.00 | | |
| 8–16 | 298 | 288 | 0.81 | 0.71–0.92 | .0009 |
| 17–27 | 330 | 308 | 0.75 | 0.67–0.84 | <.0001 |
| 28–59 | 301 | 291 | 0.80 | 0.67–0.95 | .0118 |
| Disease stage | | | | | <.0001 |
| AML, CR | 590 | 573 | 1.00 | | |
| AML, advanced/ active | 160 | 150 | 0.83 | 0.71–0.96 | .0148 |
| ALL, intermediate | 169 | 164 | 1.08 | 0.91–1.27 | .3954 |
| ALL, high | 74 | 72 | 0.95 | 0.77–1.18 | .6634 |
| ALL, advanced | 21 | 21 | 0.92 | 0.71–1.18 | .4999 |
| MDS, early | 34 | 31 | 0.90 | 0.63–1.30 | .5804 |
| MDS, advanced | 215 | 197 | 0.70 | 0.60–0.81 | <.0001 |
| Graft type | | | | | <.0001 |
| Bone marrow | 470 | 448 | 1.00 | | |
| PBSCs | 793 | 760 | 1.46 | 1.24–1.71 | <.0001 |
| HCT-CI | | | | | .0011 |
| 0 | 216 | 215 | 1.00 | | |
| 1 | 177 | 170 | 0.87 | 0.70–1.07 | .1777 |
| 2 | 199 | 192 | 0.90 | 0.77–1.06 | .2243 |
| 3+ | 671 | 631 | 0.73 | 0.61–0.87 | .0006 |
| Year of transplantation | . | | | | .0002 |
| 2013–2014 | 215 | 205 | 1.00 | | |
| 2015–2016 | 658 | 624 | 1.05 | 0.85–1.29 | .6392 |
| 2017 | 390 | 379 | 1.31 | 1.10–1.57 | .0029 |

*Stratified by patient age. Includes only subjects with complete data for the presented variables and outcomes.

## Table 3

Multivariable Model for Platelet Recovery with Class-II ME in the GVH Direction in Quartiles

| Factor | No. | Events | HR | 95% CI | *P* Value |
|---|---|---|---|---|---|
| Class-II GVH ME | | | | | <.0001 |
| 0–7 | 334 | 307 | 1.00 | | |
| 8–16 | 299 | 264 | 0.77 | 0.67–0.89 | .0003 |
| 17–27 | 330 | 269 | 0.71 | 0.62–0.81 | <.0001 |
| 28–59 | 301 | 261 | 0.74 | 0.64–0.85 | <.0001 |
| Donor age | | | | | .0099 |
| 0–19 yr | 101 | 89 | 1.00 | | |
| 20–29 yr | 307 | 275 | 1.19 | 0.99–1.44 | .0630 |
| 30–39 yr | 349 | 289 | 1.07 | 0.88–1.30 | .5060 |
| 40–49 yr | 278 | 239 | 1.23 | 0.97–1.57 | .0868 |
| 50+ yr | 229 | 209 | 1.38 | 1.11–1.71 | .0032 |
| Disease stage | | | | | <.0001 |
| AML, CR | 591 | 529 | 1.00 | | |
| AML, advanced/ active | 160 | 130 | 0.79 | 0.67–0.93 | .0037 |
| ALL, intermediate | 169 | 158 | 1.10 | 0.94–1.28 | .2198 |
| ALL, high | 74 | 64 | 0.84 | 0.64–1.09 | .1900 |
| ALL, advanced | 21 | 17 | 0.60 | 0.36–1.00 | .0500 |
| MDS, early | 34 | 31 | 1.18 | 0.84–1.68 | .3434 |
| MDS, advanced | 215 | 172 | 0.68 | 0.58–0.79 | <.0001 |
| Ethnicity | | | | | <.0001 |
| White, non-Hispanic | 747 | 649 | 1.00 | | |
| Black or African American, non-Hispanic | 203 | 181 | 1.49 | 1.28–1.73 | <.0001 |
| Asian/Pacific Islander/American Indian | 84 | 71 | 0.92 | 0.69–1.23 | .5762 |
| Hispanic | 165 | 142 | 0.97 | 0.81–1.17 | .7417 |
| Missing | 65 | 58 | 1.23 | 0.93–1.62 | .1529 |
| Graft type | | | | | .0489 |
| Bone marrow | 470 | 403 | 1.00 | | |
| PBSCs | 794 | 698 | 1.29 | 1.00–1.65 | .0489 |
| HCT-CI | | | | | <.0001 |
| 0 | 216 | 203 | 1.00 | | |
| 1 | 176 | 159 | 0.90 | 0.72–1.13 | .3782 |
| 2 | 199 | 177 | 0.98 | 0.80–1.21 | .8721 |
| 3+ | 673 | 562 | 0.69 | 0.58–0.82 | <.0001 |
| Karnofsky Performance Status | | | | | .0402 |
| 10–80 | 554 | 469 | 1.00 | | |
| 90–10 | 675 | 605 | 1.16 | 1.02–1.32 | .0275 |
| Missing | 35 | 27 | 0.80 | 0.47–1.35 | .3993 |

| Factor | No. | Events | HR | 95% CI | *P* Value |
|---|---|---|---|---|---|
| Year of transplantation | | | | | .0724 |
| 2013–2014 | 215 | 183 | 1.00 | | |
| 2015–2016 | 659 | 562 | 1.05 | 0.86–1.28 | .6274 |
| 2017 | 390 | 356 | 1.22 | 1.01–1.49 | .0441 |

*Stratified by patient age. Only includes subjects with complete data for the presented variables and outcomes.