Cutaneous graft-versus-host disease incidence is similar in haploidentical and matched unrelated hematopoietic transplant recipients: A retrospective cohort study

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Background: Cutaneous graft-versus-host disease (GVHD) is common after hematopoietic cell transplants. Haploidentical transplants (Haplo) have historically higher rates of GVHD with overall outcomes improved with the use of posttransplant cyclophosphamide. Specific cutaneous outcomes have not been explored in haploidentical versus matched unrelated donor (MUD) transplants.

Objective: We sought to examine the incidence of GVHD in MUD and Haplo transplants.

Methods: This is a retrospective cohort study of patients' records that received MUD or Haplo transplants between 2010 and 2015 with determination of GVHD severity and features by one investigator.

Results: The Haplo cohort included more minorities (22.7% vs 6.8%; $P < .001$). The incidence of acute cutaneous GVHD was similar (Haplo 47.7% [95% confidence interval {CI} 37.0-58.6%] vs MUD 42.6% [95% CI 37.9-47.3%]; $P = .41$). Chronic GVHD was also similar (Haplo 17.1% [95% CI 9.9-26.6%] vs MUD 12.8% [95% CI 9.9-16.3%]; $P = .31$). The Haplo group had lower rates of sclerosis (13.3% [95% CI 1.7-4.05%] vs 50.9% [95% CI 37.3-64.4%]; $P = .0095$). Other secondary outcomes showed no difference.

Limitations: Severity of GVHD was determined retrospectively and not all patients were seen by a dermatologist.

Conclusions: No difference was observed between rates or severity of acute or chronic GVHD. Sclerosis was less common in the Haplo group. (J Am Acad Dermatol 2020;83:1654-8.)

Key words: bone marrow transplant; graft-versus-host disease; haploidentical transplant; stem cell transplant.

Graft-versus-host disease (GVHD) is a common complication of allogeneic hematopoietic transplantation and a leading cause of nonrelapse transplant mortality. Acute GVHD involves cutaneous, hepatic, and gastrointestinal manifestations, with cutaneous disease being the

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most common. Chronic GVHD has multiple manifestations including sclerosis.[1]

The traditional allogeneic transplant involves donors who are fully matched to their recipients at key loci of the major histocompatibility complex. Sibling-matched transplants remain the gold standard. Those without matched siblings can search for an unrelated donor through volunteer databases. There are major disparities in matched transplant availability to minorities, with >70% of whites compared with <20% of African Americans finding a full match in the National Match Registry Program.[2] In addition, searching for a fully matched donor through national registries can lead to critical delays.[3] Several investigators have looked into the viability of haploidentical (Haplo) donors as a solution to this problem and an alternative to a matched unrelated donor transplant.[4] In this model, a patient's parents or children are guaranteed to be eligible donors and any one sibling has a 50% chance of being haplo-matched in addition to the traditional 25% chance of being an identical match. Transplant mortality has historically been shown to incrementally increase with the degree of mismatch between donor and recipient.[5] Initial attempts at Haplo transplantation resulted in catastrophic graft versus host reactions with high mortality.[6] More recent advances in the use of posttransplant cyclophosphamide have led to GVHD-associated mortality outcomes comparable to fully matched transplantation.[7]

While GVHD is a multisystem disease, it does not affect all organs equally or at the same time. The pathophysiology is poorly understood and may differ between organ systems. The ideal in the GVHD community is organ-targeted therapy to provide specific treatments that are sparing of unwanted systemic consequences. For these reasons, studying organ-specific GVHD is worthwhile. We compared incidences of cutaneous GVHD in Haplo transplant patients treated with posttransplant cyclophosphamide to traditional allogeneic matched unrelated donor (MUD) transplants.

METHODS

We conducted a retrospective review to evaluate cutaneous GVHD outcomes in a large single-center patient population. The Washington University School of Medicine institutional review board approved this study. Patients were identified from the electronic health records at Barnes Jewish Hospital/Siteman Cancer Center. Eligible patients had received a peripheral blood transplant from a MUD or Haplo donor with a hematologic malignancy as the indication. The study period was March 1, 2010 to March 1, 2015. Because of the unclear effects of previous transplantation on GVHD in patients receiving subsequent transplantations, patients that had received >2 allogeneic transplants were excluded. If patients received 2 allogeneic transplants, data for the most recent transplant were analyzed. These exclusion criteria were determined before the analysis to avoid confounding by graft failure and to ensure that patients could only be included in the analysis once. Previous autologous transplants were allowed.

Our primary objectives were the incidence of acute and chronic cutaneous GVHD. Secondary endpoints included incidence of stage ≥2 acute cutaneous GVHD, late acute cutaneous GVHD, late acute cutaneous GVHD stage ≥2, cutaneous GVHD in overlap syndrome, consultation with dermatology, the number of skin biopsy specimens obtained, hospitalization for rash, and incidence of sclerosis caused by chronic GVHD.

Cutaneous GVHD was recorded based on the providers' documentation of clinical and physical findings. If the patient was referred to the dermatology department and the diagnosis differed from that of the primary transplant physician, the dermatology diagnosis was favored. Staging was performed by the investigator by estimating the percent body surface area of cutaneous involvement based on the descriptions in previous documentation. The Wallace rule of nines was used for estimation, where each body part is a multiple of 9%.[8] A palm size was equivalent to 1% body surface area, an upper extremity 9%, and a lower extremity 18%. The same investigator evaluated all charts. The recorded stage was determined as the maximum in the disease process. Acute GVHD staging was based on Przepiorka et al,[9] and chronic GVHD staging was based on the National Institutes of Health consensus criteria presented by Jagasia et al.[10]

Statistical analysis was performed using the Fisher exact test, the Jonckheere test for trend, and Kruskal–Wallis tests. GVHD is a time-related condition and because of a high risk of mortality in both groups, death is a competing risk for the development of GVHD. To account for this, Fine–Gray models were created to describe the cumulative incidence of classic acute, late acute, and classic chronic GVHD and to find confidence intervals. All analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC). Tests were 2-sided and alpha was 0.05 in all cases.

RESULTS

Six hundred thirty-seven eligible transplant events were reviewed. Eighty-three were excluded because

Table I. Baseline data and demographics

	Haplo (n = 88)	MUD (n = 444)	*P* value
Recipient age, y,* mean, median (range)	48.4, 53 (19-73)	51.2, 54 (18-74)	.18
Donor age, y,* mean, median (range)	40.8, 40.5 (15-70)	30.7, 27 (18-59)	<.001†
Sex mismatch, n (%)	45 (51.1)	183 (41.2)	.099
Female to male, n (%)	17 (19.3)	57 (12.8)	.13
Recipient race, n (%)			<.001†
White (including Hispanic)	68 (77.3)	414 (93.2)	
African American/Black	16 (18.2)	19 (4.28)	
Asian/Pacific Islander	4 (4.6)	4 (0.9)	
Other	0	7 (1.6)	
Pretransplant Karnofsky performance status,‡ n (%)			.07
<50	4 (4.5)	5 (1.1)	
60-90	76 (86.4)	400 (90.1)	
100	8 (9.1)	39 (8.78)	
Myeloablative conditioning, n (%) (n = 87 for Haplo)	26 (29.9)	252 (56.8)	<.001†
Median CD34 dose§ (range)	5.01 (1.74-14.24)	5.01 (1.00-16.71)	.31
Subsequent donor lymphocyte infusion, n (%)	24 (27.3)	65 (14.6)	.007†
AML patients—complete remission, n (%)	28/58 (48.3)	130/204 (63.7)	.047†
Skin biopsy, n (% [95% CI])	35 (39.8 [29.5-50.8])	130 (29.3 [25.1-33.8])	.059
Dermatology consult, n (% [95% CI])	35 (39.8 [29.5-50.8])	157 (35.4 [30.9-40.0])	.47
Hospitalized for rash, n (% [95% CI])	3 (3.4 [0.71-9.6])	34 (7.7 [5.3-10.5])	.18

Fisher exact test used in all cases with the following exceptions: *Jonckheere—Terpstra test, ‡Kruskal—Wallis test, and §Wilcoxon 2-sample test.

AML, Acute myeloid leukemia; *CI*, confidence interval; *GVHD*, graft-versus-host disease; *Haplo*, haploidentical; *MUD*, matched unrelated donor.

†$P < .05$.

the transplant source was not peripheral blood. One was excluded because of participation in an ongoing clinical trial for GVHD. Twenty-one patients had 1 previous allogeneic transplant, and for them data from the most recent transplant were recorded. No patients were excluded because of a history of ≥2 allogeneic transplants. These exclusions left 532 patients in the analysis: 88 Haplo donors and 444 MUDs. Baseline demographic characteristics of the 2 cohorts are shown in Table I. All patients who received a Haplo transplant received posttransplant cyclophosphamide (50 mg/kg) on days 3 and 4 after transplant and were T cell replete without $CD34^+$-selected primary grafts or any other ex vivo T cell depletion. Other GVHD prophylaxis was recorded but not directly compared because of marked differences in duration. Patients received a combination of tacrolimus, sirolimus, prednisone, mycophenolate mofetil, cyclophosphamide, or methotrexate for posttransplant GVHD prophylaxis. The median follow-up time was 11 months. One hundred fifty-eight patients died without any GVHD and 90 patients were alive at last follow-up without cutaneous GVHD.

Haplo donors were significantly older than MUDs (median 40.5 years [range 15-70 years] vs 27 years [range 18-59 years]; $P < .001$). The Haplo cohort had a larger nonwhite population compared with the MUD cohort (22.7% vs 6.8%; $P < .001$). More MUD recipients received myeloablative conditioning regimens compared with Haplo recipients (56.8% vs 29.9%; $P < .001$). There was no difference in sex mismatch between the 2 groups. The CD34 cell dose was similar between the 2 patient groups. The most common donor source for the Haplo cohort was a sibling (38 [43.2%]), followed by a child (35 [39.8%]) and a parent (14 [15.9%]). Acute myeloid leukemia was the most highly represented malignancy and transplant indication for both groups (Haplo 58 [65.9%], MUD 204 [45.9%]). Biopsy specimens were obtained in 39.8% of the Haplo cohort versus 29.3% of MUD recipients ($P = .059$). There was no difference in rate of dermatology consultation or hospitalization for rash.

Full details on GVHD outcomes are presented in Table II. The incidence of acute cutaneous GVHD in the Haplo cohort versus the MUD cohort were similar (47.7% [95% confidence interval {CI} 37.0-58.6%] vs 42.6% [95% CI 37.9-47.3%]; $P = .41$). Chronic GVHD was also similar between the Haplo and MUD groups (17.1% [95% CI 9.9-26.6%] vs 12.8% [95% CI 9.9-16.3%]; $P = .31$). The Haplo group had a lower rate of sclerosis as a proportion of patients with chronic GVHD (13.3% [95% CI 1.7-4.05] vs 50.9% [95% CI 37.3-64.4%]; $P = .0095$). Other cutaneous GVHD endpoints showed no difference.

Table II. Incidence of cutaneous graft-versus-host disease

	Haplo, n (% [95% CI])	MUD, n (% [95% CI])	*P* value
Classic acute cutaneous GVHD	42 (47.7 [37.0-58.6])	189 (42.6 [37.9-47.3])	.41
Classic acute cutaneous GVHD ≥ stage 2 (as a proportion of patients with acute GVHD)	32 (36.4 [26.4-47.3])	141 (31.8 [27.4-36.3])	.46
Late acute cutaneous GVHD	9 (10.2 [4.7-18.5])	35 (7.9 [5.6-10.8])	.52
Late acute cutaneous GVHD ≥ stage 2 (as proportion of patients with late acute GVHD)	8 (9.1 [4.0-17.1])	22 (5.0 [3.1-7.4])	.13
Classic chronic cutaneous GVHD	15 (17.1 [9.9-26.6])	57 (12.8 [9.9-16.3])	.31
Sclerosis in chronic GVHD (as a proportion of patients with chronic GVHD)	2/15 (13.3 [1.7-4.05])	29/57 (50.9 [37.3-64.4])	.0095*
Other systemic manifestations of GVHD (as proportion of patient with any GVHD)	50 (56.8 [45.8-67.3])	261 (58.8 [54.0-63.4])	.81

Data represent proportions of Fine—Gray models with death as a competing risk factor for GVHD development. The Fisher exact test was used in all cases.

CI, Confidence interval; *GVHD*, graft-versus-host disease; *Haplo*, haploidentical; *MUD*, matched unrelated donor.

*Statistically significant.

DISCUSSION

Our analysis includes several noteworthy findings. The data demonstrate similar incidences of acute and chronic cutaneous GVHD in the Haplo and MUD groups. This similarity remains despite a significantly higher number of Haplo transplants receiving myeloablative conditioning and subsequent donor lymphocyte infusion, which are risk factors for GVHD. Haplo transplants have historically high rates of GVHD because of histoincompatibility.[11] Posttransplant cyclophosphamide mitigates life-threatening hyperacute systemic GVHD in the immediate post-Haplo transplant period and leads to similar mortality outcomes to MUD transplants.[7,12] Specific cutaneous GVHD outcomes have not been as well studied. These results can further an organ-specific understanding of GVHD and potentially contribute to more effective counseling for patients anticipating a Haplo transplant.

Our data showed a higher incidence (50.9% [95% CI 37.3-64.4%] vs 13.3% [95% CI 1.7-4.05%]) of sclerotic findings among MUD patients who had chronic GVHD compared with Haplo recipients. Interestingly, no differences were seen between overall rates of chronic GVHD in the 2 groups. Our cohorts are large (n = 444 in the MUD group and n = 88 in the Haplo group) but remain limited by size in sclerosis (sclerotic GVHD = 2/15 in the Haplo group and n = 29/57 in the MUD group). The pathophysiology of sclerosis in chronic GVHD is poorly understood. Whereas acute GVHD is related to the activation of donor T cells and the release of proinflammatory cytokines, chronic GVHD, and presumably sclerosis as a part of chronic GVHD, results from alloreactivity as well as dysregulation of B and T cells.[13] There are also distinct risk factor profiles for acute and chronic GVHD.[14] Given the average follow-up time of 11 months it is possible that a higher proportion of Haplo recipients would have developed sclerosis at a similar rate to the MUD groups had they been observed for a longer period of time. It is also possible that this reflects a true difference and that posttransplant cyclophosphamide has longitudinal benefits in mitigating the risk of sclerotic GVHD. Additional studies are needed to examine the reproducibility of this finding, preferably in a prospective setting.

Secondary outcomes also did not differ between the 2 groups. Of note, our data supported the claim that Haplo transplants increase accessibility of the treatment to patients that previously would have had difficulty finding an appropriate match. Minority recipients were represented more in the Haplo cohort than the MUD cohort (22.7% vs 6.8%; $P < .001$). Dermatology consultation occurred for 39.8% and 35.4% of the Haplo and MUD cohorts, respectively. Advocating for a regular dermatology role in the care of transplant recipients is needed and appropriate.[15,16] These patients have multisystem diseases and cutaneous expertise could potentially minimize the overuse of steroids, inappropriate diagnosis of GVHD, or undertreatment. Additional studies are warranted to examine the benefits of a multidisciplinary approach to the care of these patients. There was a trend toward significance in the number of skin biopsy specimens obtained, with the Haplo cohort having an increased number of biopsy specimens obtained (39.8% [95% CI 29.5-50.8%] vs 29.3% [95% CI 25.3-33.8%]; $P = .059$). This may suggest that the referral threshold to dermatology was lower in the Haplo group than the MUD

because the actual incidence of cutaneous GVHD was not different.

Our study has several strengths, including the large sample size and the 5-year study period. There was consistency in the assessment of GVHD retrospectively because 1 investigator performed this task. However, ascertaining the presence and severity of cutaneous findings was restricted to what was previously documented in the medical record. Photographs were not available. A retrospective estimation of body surface area, although precise, may lead to error in accuracy. It is also feasible that rashes that presented posttransplant could have been considered GVHD by untrained practitioners. Conversely, more subtle findings in cutaneous GVHD could have been missed. Furthermore, to avoid confounding, only the most recent transplant data were included in patients with a history of 2 transplants. It is not known how the number of transplants affects GVHD outcomes, and this could have either omitted severe GVHD findings from previous transplants or allowed for overrepresentation of GVHD with subsequent transplants. However, the organ-specific focus of our study with such a large patient population is a valuable addition to the literature on cutaneous-specific GVHD. Future work will need to be done with prospective cutaneous GVHD trials and targeted therapies.

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