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Complement-Binding Donor-Specific Anti-HLA Antibodies and Risk of Primary Graft Failure in Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Detection of donor-specific anti-HLA antibodies (DSA) has been associated with graft rejection in all forms of transplantation. The mechanism by which DSA increase the risk of graft failure remains unclear. We hypothesized that complement-binding DSA are associated with engraftment failure in hematopoietic stem cell transplantation (HSCT) and analyzed 122 haploidentical transplant recipients tested prospectively for DSA. Retrospective analysis to detect C1q binding DSA (C1q+DSA) was performed on 22 allosensitized recipients. Twenty-two of 122 patients (18%) had DSA, 19 of which were women (86%). Seven patients with DSA (32%) rejected the graft. Median DSA level at transplant for patients who failed to engraft was 10,055 mean fluorescence intensity (MFI) versus 2065 MFI for those who engrafted ($P = .007$). Nine patients with DSA were C1q positive in the initial samples with median DSA levels of 15,279 MFI (range, 1554 to 28,615), compared with 7 C1q-negative patients with median DSA levels of 2471 MFI (range, 665 to 12,254) ($P = .016$). Of 9 patients who were C1q positive in the initial samples, 5 patients remained C1q positive at time of transplant (all with high DSA levels [median, 15,279; range, 6487 to 22,944]) and experienced engraftment failure, whereas 4 patients became C1q negative pretransplant and all engrafted the donor cells ($P = .008$). In conclusion, patients with high DSA levels (>5000 MFI) and complement-binding DSA antibodies (C1q positive) appear to be at much higher risk of primary graft failure. The presence of C1q+DSA should be assessed in allosensitized patients before HSCT. Reduction of C1q+DSA levels might prevent engraftment failure in HSCT.

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INTRODUCTION

Allosensitization is a common problem in both solid organ and hematopoietic stem cell transplantation (HSCT) [1,2]. Approximately 50% of all patients requiring a transplant could become allosensitized and develop anti-HLA antibodies, and up to 30% of patients might have donor-specific anti-HLA antibodies (DSA) that pose a threat to organ rejection or graft failure (GF) in HSCT [3,4]. Our group initially showed that DSA are associated with primary GF in HSCT with mismatched donors [5,6]. Although a clear association between DSA and GF in HSCT has been subsequently demonstrated [7-11], the mechanism by which DSA may cause GF in HSCT remains unclear.

Activation of the complement cascade has been shown in allosensitized recipients of solid organ transplantation and has been suspected in animal models of HSCT [12,13]. The classical pathway of the complement cascade is activated

when the antigen–antibody complex binds to C1q and initiates activation of other complement components, resulting in the formation of membrane attack complex, which in turn causes cell lysis with apoptosis and clearance of the targeted cells [14,15].

In HSCT, DSA that target donor HLA antigens present on the surface of hematopoietic progenitor cells, and antigen–antibody complexes that may bind to C1q, activate the complement cascade and cause destruction of the donor cells, resulting in allograft rejection. C1q assay was developed to detect C1q binding (complement binding or complement fixing DSA) in allosensitized recipients of solid organ transplants [16,17]; however, whether complement cascade activation represents a mechanism that mediates graft rejection in HSCT remains unclear. Here we hypothesized that complement-binding DSA might be associated with primary GF in HSCT and assessed the joint impact of DSA and C1q activation in a cohort of allosensitized recipients.

METHODS
Patients
One hundred twenty-two consecutive patients received HSCT at the University of Texas MD Anderson Cancer Center between September 2005 and September 2013, 21 (17%) with T cell depletion (CD34$^+$ selection) and 101 (83%) using a T cell–replete bone marrow graft and post-transplantation cyclophosphamide, tacrolimus, and mycophenolate for graft-versus-host disease prevention, as previously reported by us [18,19]. Patients were tested prospectively between 2008 and 2013, whereas a small number of patients (treated before 2008) were tested retrospectively for the presence of DSA in pretransplant specimens. Retrospective C1q assay was performed on banked serum samples in all patients with DSA.

DSA Testing
Pretransplant sera of all patients were tested prospectively for anti-HLA class I and class II antibodies using multianalyte bead assays performed on the Luminex platform (Luminex, Austin, TX), including LABScreen PRA, LABScreen mixed methods for screening. The binding level of donor-specific antibody was determined by the LABScreen single-antigen bead assay (One Lambda, part of Thermo Fisher Scientific, Canoga Park, CA) per manufacturer's instructions, and results were expressed as mean fluorescence intensity (MFI). Briefly, 5 μL of mixed beads, HLA class I and class II single-antigen beads, were added to 20 μL of sample serum and incubated for 30 minutes at room temperature in the dark with gentle shaking. After washing with wash buffer 3 times, 100 μL of goat anti-human IgG secondary antibody conjugated with R-phycoerythrin was added, and the samples were incubated in the dark for 30 minutes at room temperature. After washing 3 times, the samples were read on a Luminex-based LABScan 100 flow analyzer. Antibody specificity and binding level were analyzed and determined through HLA Visual or HLA Fusion software from the manufacturer.

C1q Assay
Complement-binding antibodies were detected retrospectively for patients with DSA using the C1q assay as reported by Chen et al. [16]. The complement component (C1q) bound by the antigen–antibody complex was detected with an R-phycoerythrin–labeled anti-C1q antibody. Fluorescence intensity was measured using a Luminex-based LABScan 100 flow analyzer. DSA specificity and binding level were determined by the C1qScreen assay per manufacturer's instructions (One Lambda). Briefly, 5 μL of human C1q and 5 μL of HLA class I and class II single-antigen beads were added to 5 μL of heat-inactivated sample serum and incubated for 20 minutes in the dark at room temperature, followed by adding 5 μL of R-phycoerythrin–labeled anti-C1q antibody and incubation for 20 minutes in the dark at room temperature. The samples were analyzed and the C1q binding specificity determined.

Treatment of Patients with DSA before Transplantation
Twelve patients with DSA (55%) received desensitization treatment before transplant with alternate day plasma exchange × 3 (1 to 1.5 × plasma volume), replaced with either fresh frozen plasma or with albumin, starting 1 week before admission for transplantation/beginning of conditioning chemotherapy, followed by 1 dose of 375 mg/m^2 rituximab (Rituxan) the next day after completion of plasma exchange, followed 1 day later by 1 dose of intravenous immunoglobulin (IVIG) 1 g/kg × 1 (PE/R/IVIG) [5]. In addition,

5 patients received a buffy coat infusion on day −1, prepared from the same haploidentical donor.

Buffy Coat Preparation
Bone marrow stem cell donors underwent 2 autologous phlebotomies within 30 days of the scheduled bone marrow harvest. On both occasions, 500 mL of whole blood was collected in citrate-phosphate-dextrose adenine collection bags. The buffy coat was prepared from the second phlebotomy performed 2 days before marrow stem cell infusion (day −2). The second autologous whole blood unit was separated by centrifugation within 8 hours of collection into packed RBCs and plasma containing the buffy coat layer. The plasma component then underwent a second centrifugation to separate the buffy coat. The final RBCs and buffy coat volume consisted of approximately 40 to 50 mL, which was then cross-matched, irradiated, and ready for infusion to the patient. All donors consented and were tested for infectious disease markers in accordance with the current American Association of Blood Banks and US Food and Drug Administration guidelines.

Statistical Methods
Summary statistics were computed for all patients and within specific subgroups. Categorical variables were summarized by frequencies and percentages and their associations assessed using either Fisher's exact test [20] or the Fisher-Freeman-Halton test [21]. Continuous variables were summarized by median and range (minimum, maximum) and their associations with categorical variables assessed using the Wilcoxon rank sum test [22]. GF was defined as the patient not engrafting, experiencing delayed engraftment beyond day 28 post-transplant, or neutrophil recovery with autologous reconstitution verified by chimerism. Associations between GF and patient covariates were assessed by fitting a Bayesian logistic regression model for the probability of GF as a function of numerical DSA value within each C1q status subgroup, type of pretransplant T cell depletion (T cell depleted versus T cell replete), age, gender, race, and diagnosis. A similar model, including only DSA value within each C1q status as covariates, was fit in the subgroup of 17 patients who received T cell depletion. In each fitted Bayesian model, the expression $Pr(\beta > 0 \mid Data)$ is the posterior probability that the coefficient of the associated variable is positive. Values either >.99 or <.01 may be interpreted as highly significant, values ranging from .95 to .99 or .01 to .05 may be interpreted as significant, and values ranging from .90 to .94 or .06 to .10 may be interpreted as moderately significant.

Overall survival (OS) was computed from date of HSCT to date of last known vital sign for those groups categorized at or before HSCT date. For GF status, which was assessed after the date of stem cell infusion, OS was determined using a landmark analysis where 1 month after HSCT was defined as the landmark time. Patients who did not experience engraftment within 1 month of HSCT were categorized as GF. Patients alive at the last follow-up date were administratively censored. Time to engraftment was computed from date of HSCT to date of engraftment or administratively censoring at either last follow-up date or date of delayed engraftment. The Kaplan-Meier method [23] was used to estimate unadjusted distributions of OS, and time to engraftment and the log-rank test [24] was used to assess differences between groups, where appropriate.

All statistical analyses were performed using SAS 9.3 for Windows (Copyright © 2011 by SAS Institute Inc., Cary, NC). All statistical tests used a significance level of 5%. No adjustments for multiple testing were made.

RESULTS
Baseline Characteristics of Transplant Recipients
Of 122 patients who received a haploidentical transplant and were tested for anti-HLA antibodies, 22 (18%) were found to have DSA in the initial samples. The median DSA level in the initial sample for all patients was 6040 MFI (range, 85 to 28,615), whereas the median DSA level at transplant was 4667 MFI (range, 614 to 22,944). Patient characteristics overall and by DSA status are summarized in Table 1. From the entire cohort of patients, 19 of 58 female patients (33%) were allosensitized versus 3 of 64 male patients (5%; P < .0001). Similarly, a much higher percentage of DSA-positive patients were women (86%) compared with those who were DSA negative (39%; P < .0001). In addition, women had higher DSA levels than men: median 7858 MFI versus 864 MFI, respectively (P = .021). No other significant differences were found between the DSA-positive and -negative groups except that a significantly higher percentage of patients with

DSA were diagnosed with acute myelogenous leukemia/myelodysplastic syndrome (76% versus 55%).

Impact of DSA and C1q Status on Engraftment

GF and DSA status were initially assessed for all patients (Table 1). Two patients died early and were not evaluated for GF. Overall, 11 of 120 assessable patients (9%) experienced GF. Consistent with what we previously reported [5], a significantly higher proportion of DSA-positive patients in this study experienced GF (7/22, 32%) compared with DSA-negative patients (4/98, 4%; $P < .001$). In patients who were allosensitized, all GF events occurred in those with DSA levels > 5000 MFI at transplant ($P = .004$, Table 2). The median DSA level at transplant for patients who engrafted versus those who rejected the graft was 2065 MFI versus 10,055 MFI, respectively ($P = .007$).

Time to engraftment was assessed by DSA status (Figure 1A) as well as by C1q (Figure 1B). The median time to engraftment for all patients was 18 days. A significant difference in time to engraftment was noted for DSA status ($P = .004$). Although the difference in median time to engraftment for DSA-positive patients compared with DSA-negative patients was very small (19 days versus 18 days), the percentage of patients experiencing engraftment was lower for DSA-positive patients (68%) compared with DSA-negative patients (96%). Within allosensitized patients, the median time to engraftment for those with DSA levels ≤ 5000 MFI was 16 days; however, for patients with DSA levels > 5000 MFI, the median time to engraftment was not reached because less than 50% of those patients engrafted.

Joint Impact of DSA and C1q Status on Engraftment for Patients with DSA

All patients with DSA and available serum were tested for the presence of C1q, both in the initial serum samples and after receiving treatment/before infusion of stem cells from

Table 1
Patient Characteristics and Outcomes Overall and by DSA Status

Measure	All (N = 122)	DSA		
		Yes (n = 22)	No (n = 100)	P^*
Gender, n (%)				
Male	64 (52)	3 (14)	61 (61)	<.0001
Female	58 (48)	19 (86)	39 (39)	
Age at transplant, yr				
Median	42.0	40.5	43.0	.64[†]
Range	18.0-67.0	20.0-63.0	18.0-67.0	
Race/ethnicity, n (%)				
White	52 (43)	8 (36)	44 (44)	.48[‡]
Black	29 (24)	8 (36)	21 (21)	
Hispanic	2 (2)	0	2 (2)	
Other	39 (32)	6 (27)	33 (33)	
Diagnosis, n (%)				
AML/MDS	71 (59)	16 (76)	55 (55)	.0211[‡]
ALL	14 (12)	1 (5)	13 (13)	
CLL/lymphoma	18 (15)	0	18 (18)	
CML/MPD	15 (12)	2 (10)	13 (13)	
Other	3 (2)	2 (10)	1 (1)	
Missing	1	1	0	
Transplant type, n (%)				
T cell depleted	21 (17)	5 (23)	16 (16)	.53
T cell replete	101 (83)	17 (77)	84 (84)	
C1q status at transplant, n (%) (DSA patients only)				
Positive	5 (24)	5 (24)	—	—
Negative	16 (76)	16 (76)	—	
Missing	1	1	—	
Treatment, n (%) (DSA patients only)				
None	10 (45)	10 (45)	—	—
Desensitization alone	7 (32)	7 (32)	—	
Desensitization + buffy coat	5 (23)	5 (23)	—	
Number of loci having antibodies (DSA patients only)				
1	12 (60)	12 (60)	—	—
>1	8 (40)	8 (40)	—	
Not assessable	2	2	—	
Outcomes				
GF, n (%)				
Yes	11 (9)	7 (32)	4 (4)	.0006
No	109 (91)	15 (68)	94 (96)	
Early death	2	0	2	
OS, mo				.14[§]
Median	14.1	8.9	16.0	
95% confidence interval	9.1-25.6	3.8-24.7	9.6-NE	

ALL/MDS indicates acute myelogenous leukemia/myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; CLL, chronic lymphoblastic leukemia; CML, chronic myelogenous leukemia; MPD, myeloproliferative disorder; NE, not estimated.

[*] Fisher's exact test.
[†] Wilcoxon rank sum test.
[‡] Fisher-Freeman-Halton test.
[§] Log-rank test.

Table 2
Associations between GF, C1q Status, and Treatment

Covariate	GF		Fisher's Exact Test *P*
	Yes (n = 7)	No (n = 15)	
C1q at transplant, n (%)			.0003
Positive	5 (100)	0	
Negative	1 (6)	15 (94)	
Nonassessable	1	0	
DSA levels at transplant, n (%)			.0039
>5000	7 (64)	4 (36)	
≤5000	0	11 (100)	
Treatment, n (%)			.14
None	3 (30)	7 (70)	
Desensitization alone	4 (57)	3 (43)	
Desensitization with buffy coat	0	5 (100)	

GF indicates graft failure; DSA, donor-specific anti-HLA antibodies.

the donor. Sixteen patients (73%) had serum available for testing in the initial samples, and 21 patients (95%) had serum available in the subsequent samples for C1q evaluation. At the time of initial testing, 9 of 16 patients (56%) were C1q-positive patients, with a median DSA level of 15,279 MFI (range, 1554 to 28,615), compared with 7 C1q-negative patients, who had a median DSA level of 2471 MFI (range, 664 to 12,254) ($P = .016$).

At the time of transplant, 5 of 9 patients who were positive at initial testing remained C1q positive. All 5 of these C1q-positive patients had DSA levels > 5000 MFI (median, 15,279; range, 6487 to 22,944), and all experienced GF. Conversely, all 4 patients who were initially C1q positive and became C1q negative at transplant experienced engraftment of donor cells. A significantly higher percentage of C1q-positive patients experienced GF compared with C1q-negative patients ($P < .001$, Table 2). The median time to engraftment for C1q-negative patients was 18 days; however, for C1q-positive patients the median time to engraftment was not reached because less than 50% of those patients engrafted.

As shown by Figure 3, the distributions of numerical DSA value in the C1q-positive and C1q-negative patients were very different, with on average much higher DSA values in the C1q-positive patients. Because of this strong association between DSA and C1q status, to assess effects of these variables and other patient covariates on the probability of GF, Prob(GF), a Bayesian logistic regression model was fit including terms for DSA within each C1q status subgroup, type of pretransplant T cell depletion (T cell depleted versus T cell replete with post-transplant cyclophosphamide), age, gender, race, and diagnosis. The fitted model, summarized in Table 3, shows that higher DSA was significantly associated with a larger Prob(GF) in C1q-positive patients, with $Pr(\beta > 0 \mid Data) = .95$, and was moderately significantly associated with a smaller Prob(GF) in C1q-negative patients. No other covariates had a significant effect on Prob(GF).

The joint effect of DSA and C1q status was assessed similarly in the subgroup of 17 DSA-positive patients who received T cell replete graft but without additional covariates included in the model because of the small subsample size. The fitted model, summarized in Table 4, shows that the significant association of higher DSA with a larger Prob(GF) in C1q-positive patients persisted in this subgroup, with $Pr(\beta > 0 \mid Data) = .98$. It thus appears that the deleterious effect of higher DSA in C1q-positive patients may be general and not dependent on type of graft-versus-host disease prophylaxis.
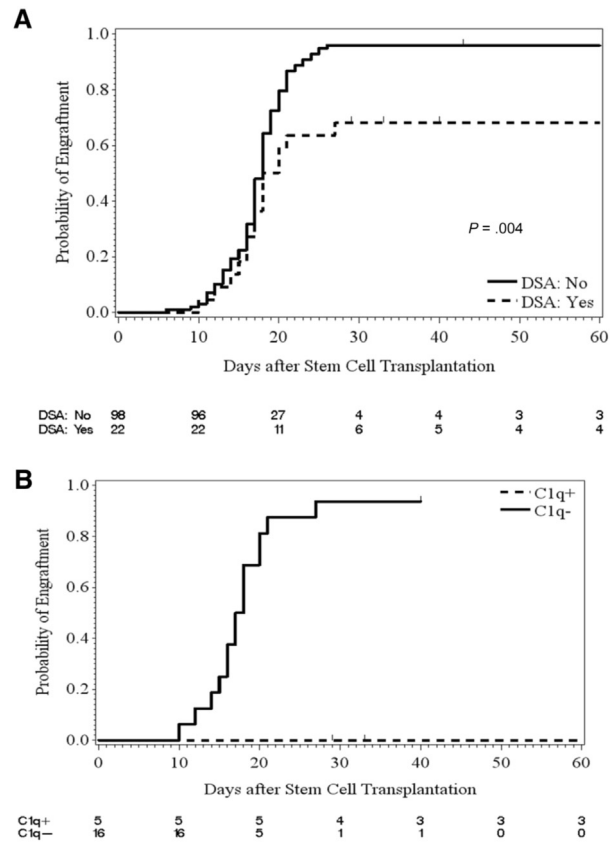

Figure 1. Probability of engraftment in patients by DSA status (A) and C1q status (B).

Treatment of Patients with DSA and Transplant Outcomes

We initially adopted a multimodality treatment strategy similar to that used in solid organ transplantation in an attempt to decrease antibody levels before the beginning of transplant conditioning chemotherapy and achieve engraftment in allosensitized recipients using the PE/R/IVIG regimen [5], as described in Methods. Because this treatment appeared to be only partially effective, we added infusion of an irradiated buffy coat prepared 24 to 48 hours in advance from a unit of donor peripheral blood and infused 1 day before the infusion of stem cells, hypothesizing that infusion of HLA antigens from the same donor would clear C1q+DSA and promote engraftment of donor cells.

Of the 22 patients with DSA, 10 (45%) received no desensitization treatment, whereas 12 patients (55%) received desensitization treatment with PE/R/IVIG alone (n = 7) or the same treatment plus the addition of buffy coat infused on day −1 (n = 5). In the untreated group, 2 of 6 C1q-positive patients remained C1q positive at transplant and experienced GF (1 patient had no serum left for testing, had high DSA levels of 11,283 MFI in the initial sample, and experienced GF), 5 of 7 patients in the desensitization alone group were C1q positive in initial samples, and 3 remained positive at transplant, and all experienced engraftment failure. In the buffy coat group, 2 of 5 patients were C1q positive, and both became negative before stem cell infusion and achieved engraftment of donor cells. In summary, all 5 patients who remain C1q positive after treatment/before transplant experienced engraftment failure, whereas all 4

patients who became C1q negative after treatment/before transplant engrafted the donor cells. Interestingly, we did not observe significant changes in antibody levels during treatment including with buffy coat before the stem cell infusion (data not shown). These results suggested that reduction to non−complement binding DSA should be the goal of treatment rather than clearing of the non−complement binding DSA, which appear to clear more slowly in the immediate post-transplant period and became undetectable in all patients within the first few weeks after transplant, similar to prior experience [25].

Assessment of OS

OS was assessed by DSA and C1q combined status (data not shown), GF status (using a landmark analysis, Figure 2), and by treatment group for patients with DSA (Supplemental Figure 1). The median OS 1 month post-transplant for patients who experienced GF was shorter compared with those who did not experience GF (5.3 months versus 17.1 months). Finally, median OS for DSA patients who did not receive treatment was 5.3 months compared with 8.9 months for DSA patients receiving desensitization alone and 13.4 months for patients receiving desensitization plus buffy coat.

DISCUSSION

We hypothesized that complement activation plays an important role in the development of GF in HSCT and investigated the role of C1q, the first component of the classical complement pathway, in a cohort of allosensitized HSCT recipients. Although demonstrated in a limited number of patients, a high association between complement binding DSA and engraftment was observed. Previous work by Chen et al. [16] showed no complete correlation between C1q binding antibodies and IgG MFI levels, indicating an effect associated with the ability of DSA to fix complement. These results also suggest a complement-dependent cytotoxicity rather than an antibody-dependent cell mediated cytotoxicity mechanism to primary GF in transplantation; however, potentiation by antibody-dependent cell mediated cytotoxicity cannot be excluded [13,26] and implies that at least a reduction of DSA to non−complement binding levels before transplant is of paramount importance in achieving engraftment in these highly allosensitized individuals.

As we have previously shown [6], a high-risk population is middle-aged multiparous women who become allosensitized through exposure to foreign HLA antigens during
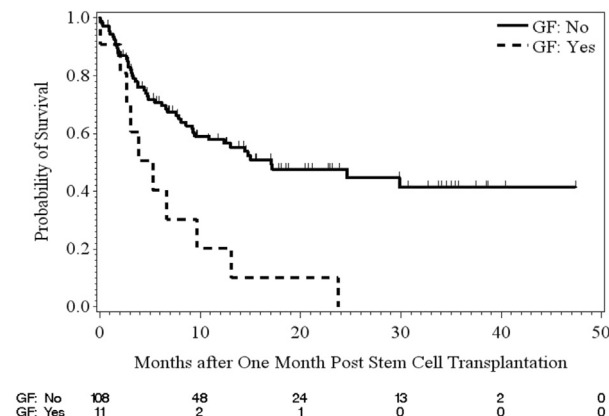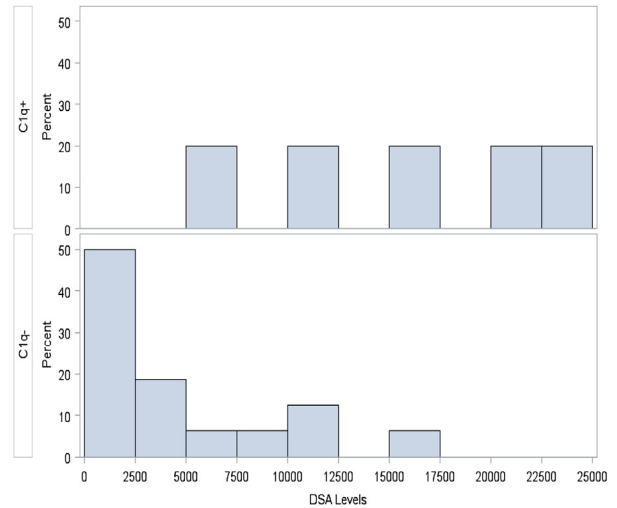

Figure 3. Histograms of DSA distributions within the C1q-positive (+) and C1q-negative (−) subgroups.

pregnancy. Updated results in this larger series of haploidentical transplant recipients confirmed those findings. A third of all female patients requiring a haploidentical transplant had DSA, and the great majority of allosensitized recipients were women (90%) with high MFI levels. Male recipients had much lower MFI levels, and none was C1q positive, suggesting a much lower risk population. Although GF can occur with lower MFI levels, it is evident now that female recipients are at much higher risk to become allosensitized, with pregnancy producing a much higher risk for allosensitization than transfusion of blood products.

This is the first study to examine the association between complement binding DSA and risk of primary GF in patients with HSCT. We observed significantly higher probability of GF in patients with higher DSA levels and C1q positivity (Table 3, Figure 4), and this effect also was seen in the subgroup of 17 T cell−replete haploidentical transplant patients. Our results indicate that presence of a positive C1q assay is associated with engraftment failure in patients with higher DSA and the goal of treatment should be clearing of the complement fixing antibodies before infusion of stem cells. A positive C1q assay was significantly associated with highly allosensitized patients (high DSA levels), suggesting that

Figure 2. Overall survival by GF status (landmark analysis).

Table 3
Fitted Bayesian Logistic Regression Model Assessing Covariate Effects on the Probability of GF in 21 DSA-Positive Patients for Whom C1Q Status Was Evaluated in which 6 Patients Suffered GF

Variable	Posterior Quantities			
	Mean of β	SD of β	95% Credible Interval	Pr(β > 0 | Data)
Intercept	−.408	1.906	−4.069 3.302	—
Log(DSA)*[DSA+/C1q+]	1.920	1.252	−.353 4.502	.95
log(DSA)*[DSA+/C1q−]	−1.373	1.005	−3.324 .557	.079
T cell depleted type vs. T cell replete type	−.539	1.704	−3.826 2.873	.382
Age at HSCT	.008	.075	−.132 .164	.564
Male vs. female	−.997	1.682	−4.306 2.315	.280
White vs. other	1.711	1.539	−1.351 4.661	.872
AML/MDS diagnosis vs. other	.755	1.585	−2.176 3.969	.679

SD indicates standard deviation.

Table 4
Fitted Bayesian Logistic Regression Model Assessing the Probability of GF in the Subgroup of 17 DSA-Positive Patients Who Received T Cell–Replete Grafts

Variable	Posterior Quantities			
	Mean of β	SD of β	95% Credible Interval	$Pr(\beta > 0 \mid Data)$
Intercept	−.293	1.829	−3.863 3.336	—
log(DSA)*DSA+/C1q+	1.845	1.170	−.240 4.212	.98
log(DSA)*DSA+/C1q−	−.737	.620	−1.956 .475	.113

activation of the complement pathway likely causes apoptosis of hematopoietic progenitor cells [27]. Although the number of patients with complement binding DSA was relatively small, the high risk of GF seen in patients who had high DSA levels and were C1q positive suggests that this is a very high-risk condition that should be avoided. Upfront testing of C1q in patients with DSA is necessary, as our data suggest that clearance of C1q is needed to obtain engraftment of donor cells. A 2-step cost-effective approach may be to screen for DSA patients with mismatched transplants and test for C1q patients who are allosensitized. Half of the patients with high DSA levels (>5000 MFI) tested negative for the C1q assay, and their risk for rejection was much lower. In fact, only 1 patient in this category rejected the graft (MFI of 6265.78). It remains unclear if complement pathway gets activated in these patients or not, and future studies should attempt to elucidate this aspect.

In contrast with reports from a different institution [28,29], our experience suggested that treatment with PE/R/IVIG is only partially effective in treating allosensitized recipients of HSCT, similar to the experience reported in solid organ transplantation [30,31]. A novel approach developed by our group has focused on blocking the DSA with HLA antigens from the donor using a buffy coat prepared from the donor cells (using HLA antigen of the donor). Peripheral blood mononuclear cells express both HLA class I and II on the cell surface and seem to be an ideal source for HLA antigens, as compared with RBCs or platelets, which may express only partially HLA antigens limited to mostly HLA class I [32]. In our experience, all patients with complement binding antibodies and high DSA levels (>5000 MFI) were broadly allosensitized against both HLA class I and class II antigens; thus, a blood product capable of reliably binding all antigens is needed.

Our results are in line with experience from solid organ transplantation [33]. Taken together, these data suggest that complement-mediated rejection plays a major role in antibody-mediated graft rejection and that the presence of C1q binding DSA should be tested routinely along with DSA levels before transplant. In addition, it appears that C1q negativity should be the goal of treatment, at least in C1q-positive patients, and high DSA levels may not clear right away from circulation. Infusion of donor HLA antigens in the form of a buffy coat is a promising approach for the treatment of C1q-positive patients and should be further explored in prospective clinical trials.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbmt.2015.05.001.
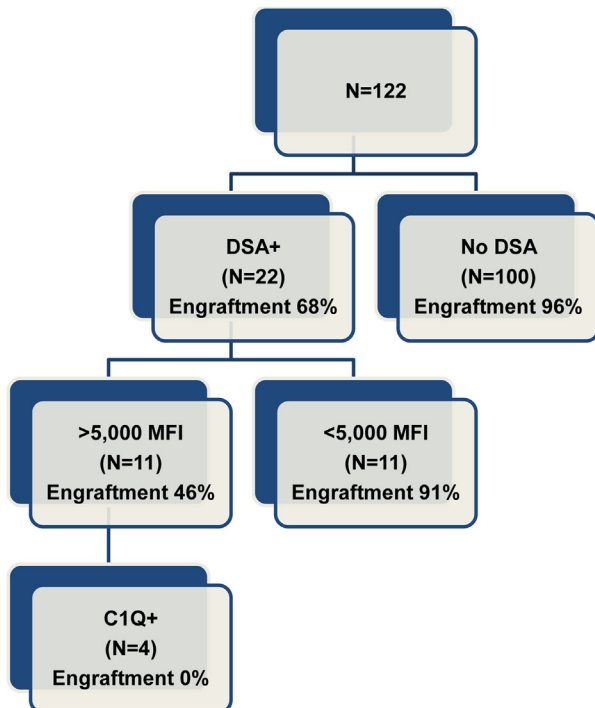

Figure 4. Diagram illustrating the decrease in rate of engraftment for all patients based on DSA and C1q status identified at the time of initial testing.

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