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Bortezomib and Immune Globulin Have Limited Effects on Donor-Specific HLA Antibodies in Haploidentical Cord Blood Stem Cell Transplantation: Detrimental Effect of Persistent Haploidentical Donor-Specific HLA Antibodies

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Donor-specific HLA antibodies (DSAs) have been associated with an increased risk of graft failure. To decrease DSA levels and reduce the risk of graft failure in haploidentical cord blood transplantation recipients, we studied the effect of bortezomib (BTZ) and i.v. immune globulin (IVIG) pretransplantation. Between 2012 and 2016, 14 patients with a DSA level >2000 mean fluorescence intensity (MFI) to 1 or more mismatched HLA alleles of haploidentical donors, cord blood donors, or both were treated with BTZ and IVIG. Fourteen patients received a median of 4 doses (range, 2 to 8 doses) of BTZ 1.3 mg/m^2 and a median total IVIG of 2 g/kg before transplantation. Only 2 of 14 patients attained a reduction in MFI to <2000 with this combination. After additional IVIG (n = 8), rituximab (n = 4), and/or plasmapheresis (n = 11), 12 of 14 patients were desensitized to a DSA level <2000 MFI at the time of engraftment. All obtained initial hematopoietic reconstitution, and no DSA rebound phenomenon was observed. Responders with DSA MFI <2000 to the haploidentical donor by transplantation engrafted at a rate comparable to that of historical controls, whereas engraftment in nonresponders took 3 times as long. BTZ and IVIG alone do not appear sufficient to rapidly induce DSA desensitization, and persistent DSAs to a haploidentical donor lead to delayed count recovery. Our data suggest that additional pretreatment with BTZ and IVIG in combination with the conditioning regimen may help abrogate the rebound phenomenon observed with plasmapheresis.

INTRODUCTION

Host-derived donor-specific HLA alloantibodies (DSAs) have been associated with increased risk of graft failure in hematopoietic stem cell transplantation (HSCT) from peripheral blood and marrow unrelated [1,2], single- and double-unit cord blood [3,4], and haploidentical [5] donors. However, owing to limitations of donor selection or significant host allosensitization, as is seen in heavily transfused or multiparous female recipients [2,6], DSAs may be unavoidable in some patients. In combined haploidentical cord blood (haplo-cord) transplantation [7], recipients may harbor DSAs to the haploidentical donor graft, umbilical cord blood (UCB) unit, or both. Importantly, the presence of DSAs in either graft also may affect engraftment [8]. In cases of DSAs to the haploidentical donor graft, UCB unit, or both, we have empirically used strategies to reduce DSA levels [9]. These include short-acting treatments, such as rituximab, plasmapheresis, and i.v. immune globulin (IVIG), in combination with a longer- acting approach to suppress antibody-producing plasma cells via proteasome inhibition. The use of proteasome inhibition was adapted from solid organ transplantation regimens [10] designed to decrease antibody-mediated graft rejection. Bortezomib (BTZ), a first-in-class proteasome inhibitor, has been shown to have direct proapoptotic effects on antibody-producing plasma cells and decreased IgG secretion in vitro [11,12].

In this study, we analyzed the efficacy of the combination of multiply-dosed BTZ and IVIG before haplo-cord HSCT on DSA levels. We also evaluated the effect of remaining DSAs against haploidentical donor grafts on engraftment, as well as the effect of residual DSAs against UCB units on cord chimerism on day +56.

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METHODS

We retrospectively reviewed the data of all patients who underwent haplo-cord HSCT on an Institutional Review Board-approved protocol between January 2012 and December 2016, in whom a DSA level >2000 mean fluorescence intensity (MFI) to 1 or more mismatched HLA alleles in the haploidentical graft, UCB unit, or both were identified and who were treated with BTZ and IVIG before transplantation. A total of 14 patients were identified. Serum samples of the recipients were tested for IgG antibodies against HLA class I and class II antigens by a solid-phase immunoassay (Luminex, Austin, Texas). All recipients undergoing haplo-cord HSCT during the same period (January 2012 to December 2016) without DSAs served as a control group matched for conditioning regimen and graft-versus-host disease (GVHD) prophylaxis.

Transplantation Specifics

UCB units for haplo-cord transplants were selected based on HLA typing and cell count. Grafts were matched for at least 5 of 8 HLA loci by high-resolution typing and contained a minimum cell count of 1.2 to 2×10^7 nucleated cells/kg of the recipient's body weight before freezing. During an initial dose deescalation trial, some grafts with as few as 0.5×10^7 nucleated cells/kg were used, but this was associated with delayed engraftment. Thus, a cutoff of 1.5×10^7 nucleated cells/kg was used for the vast majority of patients, including the patients studied here [8]. The haploidentical donor was a relative. Donors underwent stem cell mobilization using filgrastim for 4 consecutive days. Apheresis was started on day +5 and then continued daily with a target dose of 3 to 5×10^6 $CD34^+$ cells/recipient kg collected. After collection and before cryopreservation, haploidentical grafts were T cell depleted using the CliniMACS device (Miltenyi Biotec, Bergisch Gladbach, Germany). Haploidentical cells were infused on day 0, and UCB units were infused either later the same day or on the next day. Conditioning consisted of fludarabine, melphalan, and antithymocyte globulin as described previously [13]. Seven patients also underwent low-dose total body irradiation at 400 cGy. All patients received granulocyte colony-stimulating factor at 5 μg/kg/day starting on day +1 and continuing until neutrophil engraftment.

DSA Reductive Treatment

BTZ was given at the approved dosing schedule of 1.3 mg/m^2 on days 1, 4, 11, and 14 for one or two 21-day cycles. Patients also received IVIG at 1 to 2 g/kg per cycle. Patients not attaining a DSA MFI <2000 after this regimen went on to receive second-line treatment consisting of plasmapheresis (in most) with or without additional rituximab at 375 mg/m^2 and IVIG.

Response Assessment

MFI values were monitored weekly and on the day of stem cell infusion, as well as at neutrophil engraftment. An MFI of <2000 was considered a response. In patients with DSAs to more than 1 antigen (or stem cell source), we followed the highest number as the target metric.

Time to engraftment and chimerism at neutrophil recovery were compared between patients with and without persistent DSAs against the haploidentical donor at the time of stem cell infusion. These parameters were also compared with those of the control group.

Graft failure was defined as the return of recipient hematopoiesis as confirmed by chimerism analysis [14], and cord graft failure was defined as <5% umbilical cord blood chimerism in CD33 and CD3 at day +56 [15].

Statistical Considerations

Median time to neutrophil engraftment, median time to platelet engraftment, and median percent chimerism were compared between groups of interest (eg, responders versus nonresponders, total body irradiation [TBI] versus no TBI) using the nonparametric Wilcoxon rank-sum test. The correlation of DSA MFI with time to engraftment was calculated using the Pearson product moment method. The rate of UCB graft failure was compared between groups using the Fisher exact test. All *P* values are 2-sided, with statistical significance evaluated at an α level of .05. All analyses were performed with SPSS version 24.0 (IBM, Armonk, NY).

RESULTS

Patient Characteristics

Patient characteristics, as well as the HLA antigens corresponding to the DSAs and their MFIs in the respective patients, are shown in Table 1. Of the 14 patients, 7 had DSAs to the haploidentical donor only, 3 patients had DSAs to the UCB unit only, and 4 patients had DSAs to both the haploidentical donor and UCB unit.

The control group comprised 132 patients, including 69 males and 63 females. The median age of the control group was 58 years (range, 19 to 76 years). Diagnoses included acute myelogenous leukemia in 72 patients, acute lymphoblastic leukemia in 11, myelodysplastic syndrome in 16, non-Hodgkin lymphoma in 24, and other disorders in 8. Sixty-five patients (49.3%) were in complete remission, and 67 (50.7%) had progressive disease at the time of HSCT.

Response to Treatment Regimen

The patients were assigned to responder and nonresponder groups according to the DSA MFI (cutoff of 2000) at the time of stem cell infusion. The median MFI values at baseline, transplantation, and neutrophil engraftment, shown in Figure 1, demonstrate significantly lower median MFI values in the responder group at baseline (3217 versus 11,157; $P = .012$) and at the time of transplantation (1018 versus 4981; $P = .001$). At the time of neutrophil engraftment, all but 2 patients had a DSA MFI <2000, and median values were similar, at 551 for responders and 547 for nonresponders.

The 14 patients received a median of 4 doses (range, 2 to 8 doses) of BTZ 1.3 mg/m^2 and a median total IVIG dose of 2 g/kg divided over a median of 4 days (range, 1 to 8 days) pretransplantation. BTZ was initiated at a median of 47 days (range, 22 to 181 days) before stem cell infusion. The median time from initiation of treatment to stem cell infusion was similar in responders and nonresponders (43 days versus 50 days; *P*, not significant).

With BTZ and IVIG alone, the median MFI was reduced from 7756 (range, 2020 to 20,937) to 4630 (range, 1023 to 18,303), a 35% reduction, albeit not statistically significant ($P = .37$). Two patients (subjects 5 and 12) received rituximab (1 dose and 2 doses, respectively) along with the initial treatment. Only 2 patients (subjects 1 and 2; 14%) responded to the BTZ and IVIG regimen with a reduction to an MFI <2000. All others underwent additional treatments, as summarized in Table 1.

Subsequent to all combination therapies of BTZ and IVIG alone (n = 2), with additional plasmapheresis with or without rituximab and IVIG (n = 3), 5 of 14 patients (36%) were successfully desensitized to DSA levels with an MFI <2000 at the time of transplantation. All but 1 patient with a remaining DSA MFI >2000 at stem cell infusion received further plasmapheresis-based therapy, resulting in a total response in 12 of 14 patients (86%) at the time of neutrophil recovery. The dosing details and sequence of therapy are presented in Table 1. Data on DSA rebound after successful desensitization were available for 8 of the 9 patients who responded to plasmapheresis by the time of engraftment, and we found no resurgence of DSAs, with a median MFI of 257 (range, 0 to 1732) at a median of 5 weeks (range, 2 to 24 weeks) after the last apheresis procedure.

Engraftment

Because our previous data showed that early neutrophil engraftment is determined predominantly by the haploidentical donor [15], we focused our analysis of engraftment in 8 patients with DSAs against an haploidentical graft at an MFI >2000 at the time of stem cell infusion. The median time to neutrophil recovery was 30.5 days (range, 9 to 49 days) in those 8 patients. In contrast, the median time to engraftment in 5 patients with successful desensitization at the time of transplantation (n = 3) or who had DSA only against UCB (n = 2) was 11 days (range, 10 to 26 days) ($P = .065$), similar to the median time to neutrophil engraftment of 11 days in the control group of 132 patients without DSA (Table 2).

Table 1
Patient Demographic Data, DSA Targets, and Treatment Course and Engraftment

Patient	Age, yr	Sex	Diagnosis	Status	TBI	DSA Antigen(s)	MFI, Initial	Initial DSA 9Treatment	MFI, Interim	Secondary DSA Treatment Pre-HSCT	MFI, at HSCT	Secondary DSA Treatment Post-HSCT	MFI, at Engraftment	Engraftment, d median (range)	Chimerism Engraftment, Haploidentical Donor, %	Chimerism on Day +56, UCB, %
1	33	M	NHL	PD	N	C 0501-UCB	2020	BTZ × 3 IVIG 2 g/kg	1564		1018		78	60	37	N/A
2	41	M	ALL	CR1	Y	A 3201-haplo	6297	BTZ × 2 IVIG 2 g/kg	1023		810		266	11	86	100
3	48	F	AML	CR1	Y	B 5001-haplo	6698	BTZ × 8 IVIG 3 g/kg	4630	PP × 3 IVIG 1 g/kg	1572		982	10	100	100
4	45	F	MDS	CR1	N	DPB1 0201-UCB	2990	BTZ × 4 IVIG .5 g/kg	2278	PP × 2 IVIG .5 g/kg RTX × 4	404		551	26	36	0
5	52	F	AML	PD	Y	C 1502-haplo DPB1 0402-UCB	3217 2162	BTZ × 7 IVIG 2.5 g/kg RTX × 1	2993 1650	PP × 4	1047 361		608 352	12	35	100
6	22	F	AML	CR1	N	DRB1 0402- UCB	13,632	BTZ × 7 IVIG 2 g/kg	5914	IVIG 1 g/kg	4981	PP × 4	0	10	100	0
7	62	F	AML	CR1	Y	DRB1 0402-haplo A 2902-UCB	14,351 5566	BTZ × 5 IVIG 3 g/kg	18,303 11,523	PP × 3	10,351 4616	PP × 5 IVIG 2.5 g/kg	1646 400	27	0	100
8	68	F	AML	CR1	N	B 0801-haplo A 0301-haplo DRB1 1501-UCB	9916 598 9628	BTZ × 4 IVIG 1.5 g/kg	1912 7488 667	PP × 2 RTX × 1	1950 11,502 484	PP × 6 IVIG 2.5 g/kg	169 4422 70	35	0	100
9	65	F	AML	CR1	N	C 1502-haplo	3726	BTZ × 4 IVIG .5 g/kg	7221	IVIG .5 g/kg RTX × 1	2440	IVIG 1 g/kg	996	34	3	100
10	62	F	AML	CR2	Y	DRB1 0402-haplo	18,371	BTZ × 6 IVIG 2 g/kg	14,805	IVIG 2 g/kg	15,507	PP × 3	221	9	100	7
11	34	M	MDS	PD	N	A 0201-haplo	8421	BTZ × 4 IVIG .5 g/kg	6494	PP × 3	2283	PP × 4 IVIG 1 g/kg	547	49	2	0
12	54	F	ALL	CR1	Y	B 5701-haplo	4716	BTZ × 4 IVIG .5 g/kg RTX × 2	N/A	PP × 1	2227	PP × 10 IVIG 3 g/kg	13008	23	0	N/A
13	56	F	ALL	CR1	Y	B 3501-haplo	11,157	BTZ × 8 IVIG 2 g/kg	4506	PP × 3	3977		229	36	54	100
14	23	M	AML	CR1	N	DRB1 0901-haplo DRB1 0405-UCB	20,937 4014	BTZ × 8 IVIG 3.5 g/kg	11,625 444	PP × 2 IVIG 1 g/kg	6814 831	PP × 5 IVIG 1 g/kg	464 138	21	8	0

M indicates male; F, female; NHL, non-Hodgkin lymphoma; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; CR, complete remission; PD, persistent disease; haplo, haploidentical donor; TBI, total body irradiation; Y, yes; N, no; PP, plasmapheresis; RTX, rituximab.

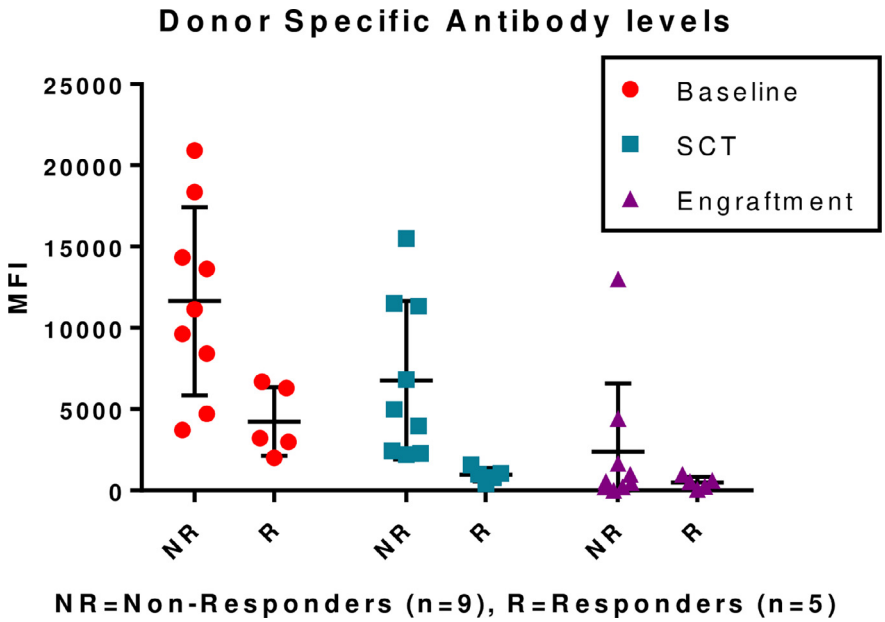

Figure 1. DSA MFI at baseline, at HSCT, and at engraftment in responders and nonresponders. The middle line represents the median MFI. The top and the bottom of the whiskers indicate the top quarter and bottom quarter percentiles, respectively.

.One patient (subject 1) was excluded from the analysis because he was found to have a post-transplantation parvovirus infection, which likely was responsible for his delayed engraftment at day +60. He recovered promptly after treatment with IVIG.

Chimerism studies for whole-blood or CD33 fractions were routinely performed at the time of neutrophil engraftment after UCB infusion. The contribution of the haploidentical donor targeted by DSAs to hematopoiesis was significantly lower in the group with persistent antibodies, compared with those with antibody clearance at the time of HSCT (2.5% versus 61.5%; P = .04). Haploidentical chimerism was comparable in the group without haploidentical DSAs at the time of HSCT and the control group (Table 2).

We also sought to correlate the DSA MFI against the haploidentical donor at the time of stem cell infusion with the time to neutrophil recovery and found no statistically significant correlation (r = -.06; 95% confidence interval, -.64 to .56; P = .86), likely due to low numbers and an outlier who attained neutrophil recovery at 9 days despite a high MFI of 15,507 at the time of stem cell infusion.

To avoid any confounding effect of TBI in the conditioning, we analyzed the association of TBI and engraftment in the 8 patients with haploidentical DSAs at the time of HSCT. Four of these patients had received TBI as part of their conditioning; however, we found no significant difference in median days to neutrophil engraftment between patients with TBI and those without TBI (25 days versus 34.5 days; P = .22).

DSAs Against UCB and Cord Engraftment

To evaluate the effect of DSAs against UCB units at the time of HSCT, we focused on UCB chimerism on day +56. For this analysis, a second patient (patient 12) had to be excluded, due to death from overwhelming toxoplasmosis before day +56, leaving 12 patients for this analysis. Of the 2 patients with UCB DSA >2000 MFI at the time of transplantation, 1 showed no UCB engraftment, with hematopoiesis derived entirely from the haploidentical graft, and the other had 100% UCB chimerism at day +56. Among the 10 patients who were either successfully desensitized (n = 4) or had DSAs only against haploidentical grafts (n = 6), the median cord chimerism at day +56 was 100% (range, 0 to 100%). This low number precluded a statistically meaningful comparison to the group without UCB DSAs at the time of transplantation. Cord chimerism data for individual patients are presented in Table 1.

DISCUSSION

We have previously reported that the infusion of third-party haploidentical stem cells in combination with a single UCB unit (haplo-cord transplantation) results in reliable rapid neutrophil engraftment and decreased rates of acute GVHD and chronic GVHD compared with double-UCB grafts [15,16].

Table 2
Engraftment and Chimerism with Haploidentical Directed DSAs at HSCT

Group	Neutrophil engraftment, d, median (range)	*P* Value	Platelet Engraftment, d, median (range)	*P* Value	Haploidentical Chimerism at Engraftment, %, median (range)	*P* Value
Control group (n = 132)	11 (9-62)		21 (10-169)		94 (0-100)	
DSA-negative (n = 5)	11 (10-26)	.95	31 (10-89)	.85	61.5 (35-100)	.35
DSA-positive (n = 8)	30.5 (9-49)	**.001**	61 (12-139)	**.044**	2.5 (0-100)	**.001**

DSA-negative indicates no DSA against haploidentical donor at HSCT; DSA-positive, DSA against haploidentical donor present at HSCT.

Given the evidence of the detrimental effect of DSAs on engraftment in single-UCB, double-UCB, and haploidentical HSCT [3–5], it is reasonable to assume a similar influence of DSAs on hematopoietic recovery after a haplo-cord transplantation. In our series, the rate of DSA reduction with BTZ/IVIG within the limited HSCT time frame is low, and most patients needed additional interventions. The postulated mechanism of decreasing antibody production via plasma cell depletion with proteasome inhibition [10] and shortening antibody half-life via blockade of the FcN receptor with IVIG [17] admittedly do not actively remove DSAs from the body, which may explain the persistence observed in this study. Thus, the time to response is dependent on the previous antibody level and its plasma half-life, where desensitization with BTZ and IVIG is unlikely to be an effective therapy for rapidly eliminating donor-specific HLA antibodies. This is corroborated by our finding of significantly higher antibody levels at baseline in patients with insufficient DSA clearance by the time of HSCT.

It is possible that a longer lead time to cell infusion would allow the DSA level to drop lower; however, this approach is unlikely to be practical, given the increased risk of progression or relapse of the underlying malignancy with time. Given that standard-dose BTZ and IVIG alone do not appear sufficient to rapidly induce DSA desensitization, higher doses and more frequent administration merit further study.

The majority of these patients also received plasmapheresis and/or rituximab near the time of cell infusion. Although plasmapheresis has shown efficacy in rapid reduction of IgM and IgG, its efficacy as a sole modality is hampered by a rebound phenomenon of de novo alloantibody synthesis [18]. Interestingly, there was no evidence of this effect with the use of BTZ and IVIG before plasmapheresis. Notably, although treatment with BTZ alone or in combination therapy does not guarantee a durable response, as reported in the solid organ transplant literature [19], we did not observe any DSA relapse after engraftment. This may be due in part to the conditioning regimen used in allogeneic transplantation, because desensitization has been observed with conditioning chemotherapy alone [20].

In a haplo-cord blood transplantation, the UCB unit, although more slowly engrafting, tends to establish dominance over time, whereas initial neutrophil recovery is derived mainly from the haploidentical graft [7]. Therefore, the persistence of DSAs against haploidentical grafts at HSCT may delay hematopoietic reconstitution by suppressing its contribution to early neutrophil recovery, and our results, although limited owing to our small sample size and thus not quite reaching statistical significance, are indicative of such a process. This is corroborated by the marked delay in neutrophil engraftment and, to a lesser extent, platelet engraftment in the group with haploidentical DSAs at the time of stem cell infusion compared with the control group, whereas while the engraftment data for the haplo-DSA responders and controls were identical. More evidence of the suppressive effect of persisting DSAs on haploidentical engraftment is provided by the pronounced difference in haploidentical chimerism at neutrophil recovery between the responders and nonresponders. Compared with controls, again there was no difference in haploidentical chimerism in the responders, but there was a significant difference in the nonresponders.

There were only 2 patients with elevated DSAs against UCB at the time of cell infusion, limiting our ability to draw conclusions regarding the effect of DSAs against UCB.

In summary, our engraftment and chimerism data provide evidence of the deleterious effect of DSAs against haploidentical grafts at the time of stem cell infusion. Therefore, without a rapidly effective therapy for DSAs, it is more prudent to deliberately avoid DSAs when considering HLA-mismatched donors. However, if all available stem cell sources are targeted by HLA antibodies, then our results justify a multimodality desensitization approach as described herein.

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REFERENCES

1. Spellman S, Bray R, Rosen-Bronson S, et al. The detection of donor-directed, HLA-specific alloantibodies in recipients of unrelated hematopoietic cell transplantation is predictive of graft failure. *Blood*. 2010;115:2704–2708.
2. Ciurea SO, Thall PF, Wang X, et al. Donor-specific anti-HLA Abs and graft failure in matched unrelated donor hematopoietic stem cell transplantation. *Blood*. 2011;118:5957–5964.
3. Takanashi M, Atsuta Y, Fujiwara K, et al. The impact of anti-HLA antibodies on unrelated cord blood transplantations. *Blood*. 2010;116:2839–2846.
4. Cutler C, Kim HT, Sun L, et al. Donor-specific anti-HLA antibodies predict outcome in double umbilical cord blood transplantation. *Blood*. 2011;118:6691–6697.
5. Yoshihara S, Maruya E, Taniguchi K, et al. Risk and prevention of graft failure in patients with preexisting donor-specific HLA antibodies undergoing unmanipulated haploidentical SCT. *Bone Marrow Transplant*. 2012;47:508–515.
6. Laundy GJ, Bradley BA, Rees BM, Younie M, Hows JM. Incidence and specificity of HLA antibodies in multitransfused patients with acquired aplastic anemia. *Transfusion*. 2004;44:814–825.
7. van Besien K, Childs R. Haploidentical cord transplantation: the best of both worlds. *Semin Hematol*53257–266.
8. van Besien K, Koshy N, Gergis U, et al. Haplo-cord transplant: HLA-matching determines graft dominance. *Leuk Lymphoma*. 2017;58:1512–1514.
9. Gergis U, Mayer S, Gordon B, et al. A strategy to reduce donor-specific HLA Abs before allogeneic transplantation. *Bone Marrow Transplant*. 2014;49:722–724.
10. Trivedi HL, Terasaki PI, Feroz A, et al. Abrogation of anti-HLA antibodies via proteasome inhibition. *Transplantation*. 2009;87:1555–1561.
11. Perry DK, Burns JM, Pollinger HS, et al. Proteasome inhibition causes apoptosis of normal human plasma cells preventing alloantibody production. Am J Transplant. 2009;9:201–209.
12. Nencioni A, Grünebach F, Patrone F, Ballestrero A, Brossart P. Proteasome inhibitors: antitumor effects and beyond. *Leukemia*. 2007;21:30–36.
13. Kwon M, Bautista G, Balsalobre P, et al. Haplo-cord transplantation using $CD34^+$ cells from a third-party donor to speed engraftment in high-risk patients with hematologic disorders. *Biol Blood Marrow Transplant*. 2014;20:2015–2022.
14. Tsai SB, Liu H, Shore T, et al. Frequency and risk factors associated with cord graft failure after transplant with single unit umbilical cord cells supplemented by haploidentical cells with reduced-intensity conditioning. *Biol Blood Marrow Transplant*. 2016;22:1065–1072.
15. Liu H, Rich ES, Godley L, et al. Reduced-intensity conditioning with combined haploidentical and cord blood transplantation results in rapid engraftment, low GVHD, and durable remissions. *Blood*. 2011;118:6438–6445.
16. van Besien K, Hari P, Zhang MJ, et al. Reduced-intensity haplo plus single cord transplant compared to double cord transplant: improved engraftment and graft-versus-host disease-free, relapse-free survival. *Haematologica*. 2016;101:634–643.
17. Hansen RJ, Balthasar JP. Intravenous immunoglobulin mediates an increase in anti-platelet antibody clearance via the FcRn receptor. *Thromb Haemost*. 2002;88:898–899.
18. Schroeder JO, Euler HH. Antibody rebound after plasmapheresis: experimental evidence and clinical consequences. *Prog Clin Biol Res*. 1990;337:415–417.
19. Everly MJ, Terasaki PI, Trivedi HL. Durability of antibody removal following proteasome inhibitor-based therapy. *Transplantation*. 2012;93:572–577.
20. Bartholomew A, Sher D, Sosler S, et al. Stem cell transplantation eliminates alloantibody in a highly sensitized patient. *Transplantation*. 2001;72:1653–1655.