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Bortezomib in Kidney Transplant Recipients with Antibody Mediated Rejection: Three Case Reports

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SUMMARY

Here, we report our experience on three patients with AMR who were treated with bortezomib after other therapeutic interventions had failed. Bortezomib was well tolerated by two of the three patients. The third patient developed worsening thrombocytopenia following the second dose. Despite a low adverse event profile, none of the three patients conclusively responded to the bortezomib treatment. As a result of the difference in our results from that of other centers we feel that a larger prospective study is needed to define appropriate guidelines for the use of bortezomib in cases of acute rejection.

INTRODUCTION

Antibodies specific to donor human leukocyte antigen (HLA), Class I and Class II molecules, have been associated with kidney allograft rejection for decades (1). Although formal proof is still lacking, these antibodies are presumed to actively participate in the allograft tissue destruction through complement mediated toxicity and other mechanisms (2). Current interventions to treat antibody mediated rejection (AMR) include the use of plasma exchange, intravenous gamma globulin (IVIG), anti-lymphocyte antibodies, rituximab and even splenectomy (3). These therapies have not proven to be fully effective and novel strategies are crucially needed. Remarkably, none of the current therapies directly targets the main antibody-producing plasma cells, which could explain their limited efficacy. The use of the proteasome inhibitor, bortezomib (Velcade, Millennium Pharmaceuticals, Cambridge, Massaschusetts), has recently been proposed as an effective way to deplete antibody-producing plasma cells and reduce donor specific antibodies (DSA) in patients with AMR (4–6). Proteasome inhibition induces a complex series of biochemical events that results in pleiotropic effects on multiple cell populations (6). It appears that plasma cells are particularly susceptible to the effect of bortezomib (7). We have also begun using bortezomib in advanced cases of rejection at Massaschusetts General Hospital. Here, we report our experience on three patients with AMR who were treated with this agent after other therapeutic interventions had failed.

CASE A

A 38 year old white male with history of medullary cystic kidney disease underwent a pre-emptive kidney transplant from a living unrelated donor. The HLA antigens of recipient and donor are as follows: recipient HLA: A30, 33; B14; Bw6; DR7, 13; DQ2, 7; DR52, 53; and donor HLA: A1, 2; B7, 8; DR15, 17; DQ2, 6; DR51, 53. Prior to transplantation, the complement-dependent cytotoxicity (CDC) cross-matches, both T and B cell, were negative. Peak panel reactive antibody (PRA) by ELISA screening was 9% Class I and 6% Class II, but reactivity did not appear to be HLA specific. The patient received induction therapy with Thymoglobulin (Genzyme, Cambridge, Massachusetts) and triple maintenance immunosuppression therapy with tacrolimus, mycophenolate mofetil, and prednisone. He had an uncomplicated post-operative course and reached a nadir serum creatinine of 1.5 mg/

dl. Despite a history of good compliance, he presented 40 months later with an increased serum creatinine of 2 mg/dl. ELISA screening showed 5% Class I with 6% Class II, and a weak antibody against donor's HLA-B8 antigen (Table 1). A kidney biopsy showed chronic active humoral rejection (CAHR) and C4d positive staining. The patient received rituximab (1 gm × 2 doses) and his creatinine remained stable at 2.3 mg/dl for the next 15 months with triple immunosuppression therapy. When his serum creatinine rose to 2.8 mg/dl, he underwent a second kidney biopsy, which showed CAHR and transplant glomerulopathy. No significant change in his donor specific antibody (DSA) level was detected at this time. As rescue therapy, the patient was then treated with 4 doses of bortezomib (1.3 mg/m^2), which he tolerated well. Despite this treatment, his creatinine continued to gradually rise to a peak of 3.3 mg/dl over the last 10 months while he was still receiving triple maintenance immunosuppression therapy.

CASE B

A 43 year old white female with a history of medullary sponge kidney and three previous pregnancies had been undergoing a desensitization protocol (plasma exchange × 3 with subsequent IVIG) in preparation for a kidney transplant from her one haplotype matched sister. The night before her scheduled living donor kidney transplant, she underwent an 8/8 antigen (A, B, DR, DQ) matched deceased donor kidney transplant. Prior to transplantation, the CDC (T and B cell) crossmatches were negative, and calculated PRA (CPRA, determined using UNOS CPRA calculator) by Luminex single antigen bead (SAB) screening (One Lambda, Inc, Los Angeles, California) was 73% Class I and 0% Class II. Post-transplantation, she received three units of packed red blood cells. The HLA antigens of recipient and donor are as follows: recipient HLA: A1, 3; B7, 8; Bw6; DR 15, 17; DQ2, 6; and donor HLA: A1, 3; B7, 8; Bw6, Cw7, DR15, 17; DQ2, 6; DR51, 52. The patient received induction therapy with Thymoglobulin, and then maintenance immunosuppression with tacrolimus, mycophenolate mofetil and prednisone. Her nadir creatinine was 1.3 mg/dl. However, 22 months post-transplant, the patient was found to have a creatinine of 2.7 mg/dl due to non-compliance. Luminex SAB testing showed the development of de novo HLA Class I and II specific antibodies, which were non-donor specific (Table 1). A kidney biopsy showed type II acute cellular rejection (ACR), with diffuse plasma cell-rich infiltrates, but without C4d deposition. The patient was treated with Thymoglobulin and OKT3 (Centocor Ortho Biotech Inc., Horsham, PA). Despite these treatments, her creatinine continued to rise to 4.1 mg/dl. A repeat kidney biopsy, eleven days later, showed resolving cellular rejection, although infiltrating plasma cells were still present. The patient subsequently underwent salvage radiation therapy directed to the allograft using high-energy photons (total 6Gy), together with bortezomib treatment (1.3 mg/m^2). Bortezomib treatment was stopped after 2 doses when she developed thrombocytopenia (platelet count of 45,000/μL). Over the 10 month period following this episode, her creatinine has improved to 2.2 mg/dl with triple maintenance immunosuppression.

CASE C

A 44 year old white male with a history of hemolytic uremic syndrome and three previously failed kidney transplants underwent a zero mismatch (A, B, DR, DQ) deceased donor kidney transplant. Prior to his fourth kidney transplant, his cPRA by Luminex SAB was 46% Class I and 0% Class II. The HLA antigens of recipient and donor are as follows: recipient HLA: A2, 68; B7, 60; Cw3, 7; DR 13, 15; DQ6; DR51, 52; and donor HLA: A2; B7, 60; Cw3, 7; DR13, 15; DQ5, 6; DR51, 52. Based on a blood sample obtained 14 days prior to his transplant, CDC and flow cytotoxic (T and B cell) crossmatches were negative. However, a blood sample collected 43 days earlier revealed a weakly positive B cell flow crossmatch. A decision was made to proceed with transplant. The patient received one dose of IVIG and

Thymoglobulin at the time of organ reperfusion. An intra-operative kidney biopsy was done one hour post-reperfusion which showed faint C4d deposition in the glomerular capillaries with infiltrating neutrophils. This was suggestive of hyperacute antibody mediated rejection. Post-transplant, patient underwent plasma exchange (×6), IVIG (×2), Thymoglobulin (1.5 mg/kg × 8 doses) and rituximab (1 gm × 1). Two subsequent kidney biopsies were performed within the first 12 days post-transplant, each showed acute tubular necrosis, negative C4d staining, and no signs of rejection (Table 1). He required hemodialysis until post-transplant day 13. A retrospective typing of the donor revealed a DP3 antigen; the patient had circulating DP3 reactive antibody at the time of transplant. The patient was maintained on triple therapy with tacrolimus, mycophenolate mofetil and prednisone. On post-transplant day 72, his creatinine fell to 3.5 mg/dl, but Luminex SAB assays noted that DP reactive antibodies were still present with a steady level of reactivity. On post-transplant day 79, a kidney biopsy showed CAHR with diffuse C4d staining. At this time, the patient received 4 doses of bortezomib (1.3 mg/m^2), which was well tolerated. Despite this treatment, his serum creatinine level continued to rise and on post-transplant day 200, he re-initiated hemodialysis.

DISCUSSION

There is increasing evidence that antibody mediated rejection is a major contributor to kidney allograft dysfunction (8). One of the characteristics of AMR is the presence of circulating antibodies (either DSA or non-DSA), which in itself is a predictor of poor graft survival (2). Current therapies for AMR appear to have limited efficacy, presumably because they are unable to sufficiently reduce DSA levels (3). Bortezomib, a novel agent specifically depleting antibody secreting plasma cells, has been introduced as an alternate therapy for antibody mediated rejection (4–6). The response rate following treatment with this agent, together with its effect on antibody levels, is still being investigated. We recently used bortezomib to treat two patients with AMR, and one patient with plasma cell-rich acute cellular rejection at our institution. All three patients had previously failed to respond to therapies conventionally used for AMR.

We report here the three cases together with lessons we learned from our experience. First, bortezomib was well tolerated by two of the three patients. The third patient developed worsening thrombocytopenia following the second dose. At this time, however, we cannot directly associate bortezomib to the severity of this adverse effect as the patient had previously received multiple consecutive myelosuppressive medications.

Second, none of the three patients conclusively responded to the bortezomib treatment. This appears inconsistent with previous studies reporting some beneficial effect of bortezomib treatment. One possible explanation for this discrepancy is that bortezomib was administered too late when most of the tissue damage was irreversible. Early treatment may prove more effective. It would be essential in future prospective studies to assess the degree of fibrosis and tissue damage by protocol kidney biopsies, prior to and after therapy to evaluate the effect of bortezomib.

Lastly, bortezomib treatment may be effective in other types of rejection such plasma cell-rich rejection in addition to antibody mediated rejection. Future studies should be designed to identify distinct subgroups of patients who would benefit more substantially from bortezomib.

Overall, our findings provide a cautionary note for the use of bortezomib in advanced cases of AMR. The lack of consistency between results obtained at various centers underscores

the need for larger prospective studies to define appropriate guidelines for the use of bortezomib in cases of acute rejection.

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Table 1

Patient Clinical History.

Patient	Days Post-tx	Creatinine (mg/dl)	CPRA		Circulating Antibodies	Kidney Biospy	Treatment
			Class I	Class II			
A	0	6.7	9%	6%			
	276	1.5					
	840	1.7					
	994	1.7					
	1203	2.0	5%	6%	DSA	CAHR, C4d+	Rituximab
	1679	2.8	4%	3%	DSA	CAHR, C4d+	Bortezomib
	1714	3.0					
	1886	3.2					
	1627	3.3					
B	0	4.9	73%	0%			PXE, IVIG
	330	1.3					
	504	1.2					
	608	1.7					
	665	3.0	96%	6%	Non-DSA	ACR, C4d−, plasma cells	Thymo / OKT3
	676	3.6				Resolving ACR, C4d−, plasma cells	Bortezomib / Radiation
	749	2.5					
	949	2.2					
C	0	9.2	46%	0%	DSA	?AAMR, C4d−	IVIG
	2	11.9					PXE, HD, Thymo
	4	13.9	23%	0%			PXE, HD, Thymo
	5	11.0				No rejection	PXE, HD, Thymo
	9	12.2	96%	0%	DSA		PXE, HD, Thymo, Rituximab
	11	12.0				No rejection	PXE, HD, Thymo
	18	10.2	85%	0%	DSA		Thymo
	37	5.5					
	58	3.4					

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Patient	Days Post-tx	Creatinine (mg/dl)	CPRA		Circulating Antibodies	Kidney Biospy	Treatment
			Class I	Class II			
	72	3.5	ND	0%	DSA	CAHR, C4d+	Bortezomib
	79	3.5					
	83	3.2					
	114	2.9					
	149	3.4					
	196	5.1					
	200	5.7					HD

Post-tx: post-transplant; CPRA: calculated panel reactive antigen; DSA: donor specific antibody; ND: not done; CAHR: chronic active humoral rejection; AAMR: acute antibody mediated rejection; ACR: acute cellular rejection; PXE: Plasma exchange; HD: hemodialysis; Thymo: Thymoglobulin

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