

EXPERIENCE WITH BORTEZOMIB IN ABO INCOMPATIBLE RENAL TRANSPLANTATION - A CASE SERIES

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ABSTRACT ABO-incompatible renal transplantation has gained widespread acceptance because of organ shortage. Acceptable Anti A and Anti B titres are achieved by various preconditioning regimens. Some patients have difficulty in achieving target titres due to refractory and rebound isoagglutinin titres. We share our experience with the use of Bortezomib in patients having moderately high baseline isoagglutinin titres who had difficulty in achieving target titres during the preconditioning treatment. The use of Bortezomib can reduce the number of plasma exchanges and their attendant complications.

KEYWORDS ABO-incompatible transplant, Bortezomib, Antibody titer

Introduction

ABO-incompatible renal transplantation involves the removal of preformed antibodies with various desensitization protocols. This involves usage of immunoadsorption chambers, Plasma exchange, Rituximab, Splenectomy etc. We share our experience in 4 patients where we used Bortezomib in addition to the regular protocol which consisted of Rituximab (200mg) 2 weeks prior to transplant followed by triple immunosuppressants and plasma exchange (SPECTRA OPTIA-Apheresis machine) on alternate days followed by 5gms Intravenous immunoglobulin after each session. The Anti A, Anti B titres was monitored every day. Bortezomib 2 mg, s.c, was administered after plasma exchanges in patients not dropping their titres despite two consecutive Plasma exchange (Refractory rebound titres). All patients were taken up for transplant after achieving target titres of IgG< 1:16 with Basiliximab induction.

Observations:

The following observations were made and summarized in table 1.

Patient 1

A 25 years old male, hypertensive with the unknown primary renal disease was transplanted with mother as the donor. His pre-transplant CDC, Flow crossmatch and DSA were negative. His baseline isoagglutinin titre (Anti A) was 1:128. He underwent a preconditioning regimen as per our unit protocol. His Anti A titre remained elevated despite two plasma exchanges and IVIg. He received two doses of Bortezomib with a one-week interval between two doses. His Anti A titre dropped to IgG 1:16 and transplantation was done. He is currently 15 months post-transplantation with a serum creatinine of 1.7 mg/dl. During the postoperative period, he was twice treated for upper respiratory tract infection. In the immediate postoperative period given elevated creatinine, he underwent a renal biopsy which showed no evidence of rejection. His kidney function improved with the reduction of tacrolimus dosage. The case summary is described in table 1.

Patient 2

A 31-year-old male, hypertensive with the interstitial renal disease was transplanted with mother as the donor. His pre-transplant CDC, Flow crossmatch and DSA were negative. His

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Table 1

	Patient 1	Patient 2	Patient 3	Patient 4
Donor Blood Group	A	AB	B	B
Recipient Blood group	O	A	A	O
Initial titre(IgG)	1:128	1:32	1:64	1:128
Final Titre(IgG)	1:16	1:2	1:4	1:16
Bortezomib dose number	2	1	1	1
Number of Plasma exchange	5	3	3	4
Months from transplant during the last follow up	15	15	14	6
Creatinine (mg/dl) at the last follow up	1.7	1.5	0.8	1.3
Complications	Upper respiratory tract infection	Nil	Recurrent Urinary tract infection, Nocardia	Urinary tract infection

Anti B titre was 1:32. His titre remained elevated despite two plasma exchanges and IvIg. He received one dose of Bortezomib. His Anti B titre dropped to 1:2 and transplantation was done. He is currently 15 months post-transplantation with a creatinine level of 1.5 mg/dl. He had acute febrile illness one year after transplantation with acute kidney injury (creatinine 2.1 mg/dl-which responded to fluids). The case summary is described in table 1.

Patient 3

A 45-year-old male, with reflux nephropathy and hypertension, underwent renal transplantation 18 years ago. The graft was lost due to recurrent pyelonephritis. He underwent second renal transplantation with the wife as the donor. His pre-transplant PRA, CDC, Flow crossmatch and DSA were negative. His Anti B titre at the baseline was 1:64. Despite preconditioning his anti B titre remained elevated at 1:32. He received one dose of Bortezomib, and his antibody titre dropped to 1:4 and transplantation was done. He is currently 14 months post-transplantation with serum creatinine 0.8mg/dl. He had recurrent urinary tract infection. He was also treated for Nocardia infection of the skin and subcutaneous tissue for which he is currently on long term antimicrobial therapy. The case summary is described in table 1.

Patient 4

A 58 years old male, with hypertension and diabetes mellitus with psoriasis with presumed diabetic nephropathy, was transplanted with the wife as the donor. His pre-transplant CDC, Flow crossmatch and DSA were negative. His baseline Anti B titre was IgG 1:128. His antibody titre remained elevated at 1:64 during the preconditioning. He received one dose of Bortezomib, and his antibody titre dropped to 1:16 and transplantation was done. During the immediate post-operative phase, he underwent ureter leak repair. During his subsequent follow up he had one episode of urinary tract infection. His serum creatinine was 1.3 mg/dl six months after transplantation. The case summary is described in table 1.

Discussion

There are a variety of preconditioning regimens for ABO-incompatible renal transplantation which includes splenectomy, plasma exchanges, specific anti body adsorption columns and rituximab to lower the antibodies to blood group antigens [1]. Rituximab with plasmapheresis remains the standard regimen in many centres [1,2]. Rituximab targets specifically mature B- cells which are a major source of antibody [2]. Many patients respond to the standard preconditioning protocol [2,3]. Some patients fail to achieve the target titre despite adequate preconditioning therapy [4].

For those not achieving target titres, plasma exchanges or adsorption column treatments are continued till the titres drop. This includes a large number of plasma exchanges with possible complications [9]. There have been reports of usage of Bortezomib in patients with refractory/rebound titres with variable outcomes [4,6]. In our study group, all patients had moderately high baseline titres, and these patients failed to decrease isoagglutinin titres despite two consecutive plasma exchanges and IvIg. In these patients, instead of further plasma exchanges, we used Bortezomib to target plasma cells [7].

Proteasomes are abundant multienzyme complexes that provide the main pathway for degradation of intracellular proteins and contribute to the maintenance of protein homeostasis and clearance of misfolded and/or unfolded and cytotoxic proteins [8]. Polyubiquitination is an essential event for proteins targeted for proteasomal degradation [8]. Proteins degraded by the proteasome include mediators of cell-cycle progression and apoptosis, such as the cyclins, caspases, B-cell lymphoma 2 (BCL2), and NF- κ B activation [8]. Proteasome inhibition can downregulate NF- κ B activity; decrease cell proliferation/differentiation; induce apoptosis via cell cycle arrest, endoplasmic reticulum stress and caspase induction due to the accumulation of unfolded or misfolded proteins; and downregulate antigen presentation, cell-cell interaction, and cell migration. Proteasome inhibition is more evident in cells with a high rate of protein synthesis and secretion, like plasma cells [7]. Since the plasma cells are another potential source of antibody production in this subset of patients for whom the mature B cells are already targeted with Rituximab, we targeted proteasomal inhibition through Bortezomib to decrease the antibody instead of the traditional method of

continuing plasma exchanges in such scenario.

We found that we were able to achieve satisfactory titres prior to transplant with the usage of Bortezomib in patients with moderately elevated isoagglutinin titres at the baseline. Among the four patients observed, we found no significant complications associated with Bortezomib. We also noticed that significant reduction in titres could be achieved with the use of Bortezomib. This also helps to avoid further plasma exchanges performed before the ABO-incompatible renal transplantations and avoiding its complications [9].

Conclusion

- In some patients with refractory/ rebound isoagglutinin titres, the additional use of Bortezomib was able to achieve the target titres.
- Bortezomib possibly also reduces the number of plasma exchanges and its attendant complications.

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Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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