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# Bortezomib Treatment in a Renal Transplant Patient with Combined Rejection and Myeloma - One Year of Follow Up

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## INTRODUCTION

Bortezomib is a proteasome inhibitor which became a cornerstone in the management of multiple myeloma and other haematological malignancies over the last decade [1]. Renal involvement in multiple myeloma carries poor prognosis. Treatment with bortezomib in combination with dexamethasone has been shown to be effective in reducing light chain production [2]. Therapeutic regimens based on proteasome inhibitors (PI) hold promise in managing resistant antibody-mediated acute rejection (AMR) [3]. We, hereby, present a case record of a renal transplant patient whose renal dysfunction due to renal involvement by multiple myeloma and acute rejection was managed successfully.

## CASE RECORD

A 50 years old lady had the end-stage renal disease due to presumed glomerulonephritis. She remained on haemodialysis from 2006 to 2011 before she received a renal transplant from a DCD (donation after cardiac death) donor. In 2010 she was diagnosed to have monoclonal gammopathy of undetermined significance (MGUS) after investigations including bone marrow biopsy. Baseline creatinine at the end of 2014 was 220-240 µmol/l and eGFR 19-21 ml/min. In 2015, gradual deterioration of the renal function was noticed and serum creatinine peaked up to a peak of 479 µmol/l and eGFR 8 ml/min. Renal allograft biopsy in February 2015 showed features of acute antibody-mediated rejection (AMR), i.e., positive C4d glomerular staining, glomerular basement membrane lamination and mild peritubular capillary lamination. The presence of intense staining for kappa light chains in tubular casts, vacuoles in proximal epithelium and the mild excess of plasma cells together with focal staining in the glomeruli indicated that kappa light chains were contributing to renal injury although this was not a disease-specific pattern. Paraprotein testing showed band 1 type: IgG kappa with a level of 12 g/l. Protein electrophoresis showed a compact band in gamma chains. Free light chain levels showed high IgG kappa with high kappa/lambda ratio. Haematology team diagnosed light chain myeloma after bone marrow biopsy.

The patient was treated with 4 cycles of bortezomib (Velcade® Millennium), thalidomide and dexamethasone in July 2015) that led to a partial response. She was continued on bortezomib for 8 cycles. She declined the option of high dose melphalan and autologous stem cell transplant because of the risk of renal failure.

The above-mentioned regimen stabilised her myeloma parameters with total protein around 7 g/l and kappa: lambda chain ratio of around 20. By the end of July 2016, serum creatinine plateaued at reading 317 mmol/l (eGFR 13 ml/min) (i.e., after 3 months of the last dose of Velcade® which was at the end of April 2016) **(Figures 1 and 2)**.

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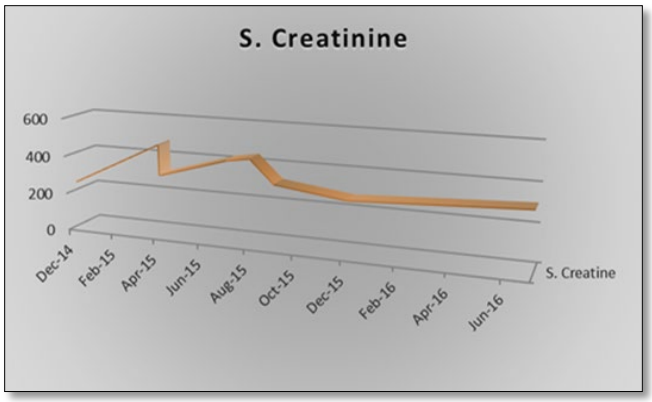


**Figure 1.** Serum creatinines follow up between December 2014 until June 2016.

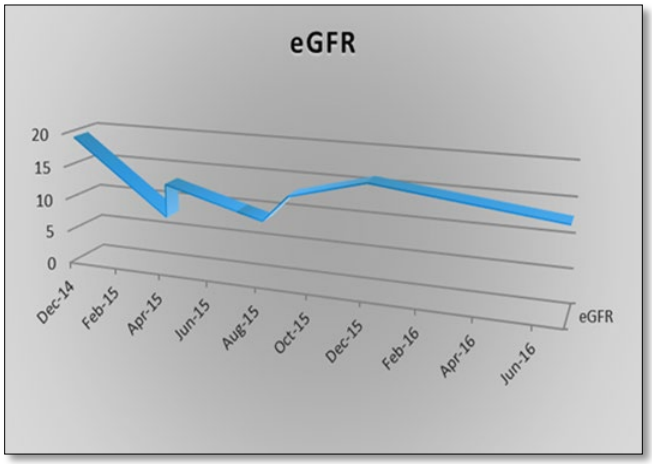


**Figure 2.** eGFR follow up between December 2014 until June 2016.

## DISCUSSION

Monoclonal gammopathy of undetermined significance (MGUS) affects 3% of people aged above 50 years and 5% of people above 70 years [4]. Criteria for diagnosing MGUS are monoclonal protein level less than 30 g/L, plasma cells less than 10% on bone marrow biopsy and lack of end-organ damage related to monoclonal proteins (anemia, hypercalcemia, renal impairment, lytic bone lesions or hyper viscosity). MGUS may progress to plasma cell myeloma at a rate of 1%/year in the general population [5]. MGUS is not a contraindication to solid organ transplantation. Exposure to long-term immunosuppression after renal transplantation carries a risk of developing malignancy as a well-known complication of immunosuppressive drugs. In our case, the patient's MGUS progressed to multiple myeloma about three years post renal transplantation. Goebel et al. [6] in 2015 published a retrospective study as they reviewed database of the patients in the California state inpatient, emergency, and ambulatory database in the period 2005-2011. This retrospective study included 24,358,669 patients, 22,062 of them had solid organ transplantation. Of the transplant patients, 72 had MGUS diagnosis before transplantation and 10 of them progressed to myeloma after transplantation. In the other group (transplant patients without MGUS, n=21,990), 37 patients documented to develop multiple myeloma post-transplantation. The risk of developing myeloma was 20-fold higher in patients with MGUS in comparison with patients without it, with a propensity score-adjusted risk ratio of 19.46 (95% CI=7.05, 53.73). Despite an increased risk for those patients with MGUS to get myeloma after a solid organ transplant, Goebel et al. [6] suggested that increased risk is not a good reason for excluding those patients from transplantation.

In another retrospective study, Safadi et al. [7] from Mayo clinic studied the cases that developed multiple myeloma after kidney transplantation between 2001-2012. Out of seven patients who developed multiple myeloma, four of them had previous MGUS diagnosis [7].

Bortezomib is a proteasome inhibitor which is used as first-line therapy for multiple myeloma. Its apoptotic effect is due to inhibition of the survival signals induced by nuclear factor kappa-B (NF-kB). Having a high rate of protein synthesis in differentiated plasma cells makes bortezomib highly effective against them [8].

Bortezomib has been shown to be effective in treating antibody-mediated rejection in several case reports. Yang et al. [9] in 2014 described six patients treated with bortezomib for acute AMR, 3 patients of them showed full recovery of graft function. In this index case, bortezomib was effective in improving the kidney function and stabilised her serum creatinine for over one year after three months of stopping renal function remained stable. This drug proved to be of dual benefit, i.e., in managing AMR as well as stabilizing myeloma as well. Cicora et al. [10] in 2013 described the effectiveness of bortezomib in managing AMR in renal transplant patients. Tzvetanov et al. [11] described the full and durable recovery of 3 patients with early AMR treated with this drug after failure of responding to plasmapheresis/intravenous immunoglobulin and splenectomy. This index case demonstrates the utility of bortezomib in managing late AMR led to a sustained response. The lack of complete resolution might be explained by co-presence of myeloma or poor reserves in allograft due to chronic changes. Bear in mind that a recent randomised trial by Eskandary et al. [12] in 2018 failed to show any effect of bortezomib in managing late AMR.

## CONCLUSION

Bortezomib can be used in managing multiple myeloma in renal transplant patients. It may be effective in managing AMR. Combined AMR and myeloma in a renal transplant patient deserve to be managed by bortezomib as the first line therapy, not as a drug in reserve for the second line; otherwise, it might be too late.

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