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Bortezomib therapy for nephrotic syndrome due to idiopathic membranous nephropathy

Choli Hartono,

The Rogosin Institute, 505 East 70th Street, Box 102, New York, NY 10021, USA. Division of Nephrology and Hypertension, Weill Cornell Medical College, New York, USA

Miriam Chung,

The Rogosin Institute, 505 East 70th Street, Box 102, New York, NY 10021, USA. Division of Nephrology and Hypertension, Weill Cornell Medical College, New York, USA

Sheng F. Kuo,

New York Hospital Queens, Flushing, New York, USA

Surya V. Seshan, and

Department of Pathology, Weill Cornell Medical College, New York, USA

Thangamani Muthukumar

The Rogosin Institute, 505 East 70th Street, Box 102, New York, NY 10021, USA. Division of Nephrology and Hypertension, Weill Cornell Medical College, New York, USA

Choli Hartono: chh2001@nyp.org

Abstract

Idiopathic membranous nephropathy is a common cause of nephrotic syndrome in adults. The nephrotic syndrome due to idiopathic membranous nephropathy is often resistant to glucocorticosteroids and requires an alkylating agent such as chlorambucil or cyclophosphamide to induce remission. Recent studies illustrate that antibodies against the autoantigen M-type phospholipase A2 receptor contribute to a vast majority but not all cases of idiopathic membranous nephropathy. Herein, we report a patient with nephrotic syndrome due to membranous nephropathy that was resistant to 6 months of therapy with ramipril and high-dose glucocorticosteroids but responded to a single cycle of bortezomib infusion.

Keywords

Bortezomib; Membranous nephropathy; Nephrotic syndrome; Proteasome inhibitor

Background

Idiopathic membranous nephropathy (MN) is a common underlying glomerular lesion for adults with the nephrotic syndrome [1]. Secondary MN may be due to solid organ malignancy, infections such as hepatitis B, various drugs, and autoimmune disease [1], but the majority of MN cases are idiopathic rather than secondary [1]. Spontaneous remission is not uncommon in adults with idiopathic MN and has been observed in up to 30 % of patients [1, 2]. Hence, for patients who have non nephrotic-range proteinuria and stable renal

function it is customary to keep them under observation without providing any immunosuppressive therapy. In contrast, patients presenting with >8 g of daily proteinuria and/or renal insufficiency have a 66–80 % chance of developing end-stage renal disease (ESRD) within 10 years [1, 3]. The probability of spontaneous remission is less likely when the daily proteinuria exceeds 10 g [1, 2]. According to the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines, immunosuppressive therapy should be considered in patients with nephrotic syndrome and persistent daily proteinuria exceeding 4 g despite a 6-month observation period with antiproteinuric treatment [4]. Patients with disabling symptoms (anarsarca, declining renal function, severe hypoalbuminemia) due to nephrotic syndrome also warrant therapy with immunosuppressive agents [4].

The pathogenesis of idiopathic MN remains unknown. However, recent studies have focused on the role of circulating autoantibodies of the non-complement-fixing immunoglobulin (Ig)G4 subclass against a podocyte surface antigen—M-type phospholipase A2 receptor (PLA2R)—in patients with idiopathic MN [5]. Circulating PLA2R antibodies could be detected in 70 % of patients with idiopathic MN [5]. Other autoantibodies of the IgG4 subclass with specificities against podocyte cytoplasmic antigens (aldose reductase, SOD2, and α -enolase) have also been demonstrated in patients with MN [6]. The source and origin of the autoantibodies are unknown and may be intrarenal or they may circulate freely. Lessons learned from recurrent disease after renal transplant suggest the latter.

Herein we report a patient who initially presented to her nephrologist with nephrotic syndrome and greater than 10 g of daily proteinuria. The renal biopsy was reported by an outside facility in error to be IgA nephropathy before she was referred to our investigator-initiated study (NCT01103778) of the proteasome inhibitor bortezomib in patients with severe IgA nephropathy. We were therefore able to observe without any prior knowledge of the disease the response of a patient with idiopathic MN (see Fig. 1a–c) and nephrotic syndrome to bortezomib.

Case report

A 58-year-old woman with nephrotic syndrome was screened for possible bortezomib therapy 6 months after a kidney biopsy reportedly revealed IgA nephropathy. Her nephrotic syndrome was resistant to 6 months of high-dose oral prednisone and ramipril (10 mg/day) (Fig. 2). The serum albumin was 1.3 g/dl 1 week prior to the kidney biopsy and remained below 1.9 g/dl from 1 month after the biopsy until screening (Fig. 2). Serum creatinine was 1.2 mg/dl 1 week prior to the kidney biopsy and remained below 0.8 mg/dl from 1 month after biopsy until it started rising to 0.97 mg/dl at screening (Fig. 2). At screening, the patient weighed 40 kg, was cushingoid and she was receiving 10 mg of oral prednisone and 10 mg of ramipril each day. Screening revealed a urine protein to creatinine (UP:C) ratio of 16.88 mg/mg, serum creatinine of 0.97 mg/dl, and serum albumin of 1.8 g/dl. Within 2 weeks of screening she received four doses of bortezomib (1.6 mg/dose) on days 1 (enrollment), 4, 8, and 11. Ramipril (10 mg/day) and prednisone (10 mg/day) were continued after enrollment (Fig. 2). The prednisone dose was reduced to 10 mg every other day for 3 months and stopped 4 months after enrollment. The patient received a constant dose of ramipril during the study period. Concurrent with an increase in serum albumin to 2.9 g/dl, the UP:C ratio decreased to 4.19 mg/mg after bortezomib infusion (Fig. 2). A timed 24-h urine sample confirmed the presence of 2.39 g of proteinuria 6 months after she received the single cycle of bortezomib, which was 1 year after the initial kidney biopsy. Thus, she remained proteinuric but no longer had nephrotic syndrome. At 9 months after enrollment, her initial kidney biopsy was verified as being idiopathic MN and not IgA nephropathy due to an error in reporting the IgA fluorescein isothiocyanate (see Fig. 1a–c). The timed 24-h urine sample revealed 0.55 g of proteinuria at 9 months and 0.36 g at 12

months after enrollment. The serum albumin concurrently improved to 3.8 g/dl at 9 months and remained stable 12 months after enrollment. We had observed that the serum creatinine was rising at screening and it peaked at 1.56 mg/dl before it improved 4 months after bortezomib treatment (Fig. 2). Neither abnormal complete blood counts, nor neuropathy—potential side effects of bortezomib—were observed during her 1-year follow-up visits.

Discussion

Severe idiopathic MN manifested by daily proteinuria >10 g with worsening renal function normally requires the use of the Ponticelli's regimen with an alkylating agent such as chlorambucil to induce remission [4, 7, 8]. Remarkably, our patient responded to four doses of intravenous bortezomib and we were able to rapidly taper the glucocorticosteroid thereafter. Bortezomib therapy in our patient resulted in remission of the nephrotic syndrome within 6 months without any adverse effects. Most importantly, the serum albumin and timed 24-h urine sample for proteinuria demonstrated that she remained in remission up to 1 year following bortezomib therapy (Fig. 2). Because of the retrospective nature of our case, we were unable to report the anti-PLA2R antibody or other autoantibody levels in our patient. However, the most critical aspect of our case is the clinical observation that a complete remission resulted within less than a year after the administration of bortezomib.

Although possible, it is unlikely that our patient had a spontaneous remission since she did not respond to 6 months of ramipril and high-dose glucocorticosteroid therapy prior to receiving bortezomib. Polanco et al. [2] showed in their retrospective study that complete remission occurred after diagnosis in only 7 of 51 patients (13.7 %) with baseline daily proteinuria >12 g over a period of 24.8 months. Unlike the cases in Polanco's study, our patient's remission occurred rapidly in the setting of glucocorticosteroid withdrawal and was sustained after bortezomib therapy.

Bortezomib, which is US Food and Drug Administration (FDA)-approved for treatment of multiple myeloma, inhibits the transcription factor nuclear factor kappa B (NF- κ B) and depletes ADAMTS13 antibodies in thrombotic thrombocytopenic purpura [9]. Extended bortezomib therapy has been reported to be associated with the resolution of de novo IgA nephropathy in a patient with multiple myeloma [10]. Anti-CD20 monoclonal antibody therapy (rituximab) has been reported to induce remission in idiopathic MN [11]. A mechanistic similarity in abrogating production of nephritogenic autoantibody exists between bortezomib and rituximab. However, bortezomib differs in having the capacity to deplete pathogenic professional antibody-producing cells or plasma cells whereas rituximab depletes only B cells [12].

In the study by Beck et al. [13] anti-PLA2R antibodies were measured serially from serum samples of 35 patients who were treated with rituximab for membranous nephropathy. Complete remission was reported at 12 months in only 2 of 35 patients. Of the 35 patients, anti-PLA2R antibodies could be detected in 25 patients (71 %) prior to rituximab treatment. Seventeen of the 25 patients (68 %) with pretreatment anti-PLA2R antibodies responded with decreasing or undetectable levels when serially monitored up to 12 months after rituximab therapy. Of the 17 patients, complete remission was achieved in 2, partial remission in 8, and no remission was seen in 7 patients at 12 months after rituximab therapy. Of note, six of the seven patients with no remission at 12 months had undetectable anti-PLA2R antibodies when compared to baseline. None of the ten patients with undetectable anti-PLA2R antibodies prior to rituximab treatment achieved complete remission at 12 months. Based on the experience of Beck et al. [13] we could only speculate that bortezomib induced remission in our patient within a year by abrogating pathogenic anti-PLA2R

autoantibodies. Compared to chlorambucil or cyclophosphamide, rituximab and bortezomib have a higher cost at our facility. The cost of 1 g of rituximab at our center is US \$12,000 whereas one cycle (4 vials of 3.5 cc) of bortezomib costs US \$8,000.

In conclusion, we were able to observe in a patient that the nephrotic syndrome due to idiopathic MN resolved after bortezomib therapy. Consistent with the rationale of rituximab intervention in idiopathic MN, we speculate that targeting professional antibody-producing cells may be useful to induce remission. We also speculate that inhibition of NF- κ B may be important in treating the nephrotic syndrome. The optimal treatment for idiopathic membranous nephropathy remains to be determined with new opportunities for targeted therapy. We recommend that a larger study be conducted to verify the efficacy and determine the mechanism of action of bortezomib in idiopathic MN.

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Fig. 1.

Membranous nephropathy. **a** Light microscopy of a glomerulus showed mild thickening of peripheral capillary walls without conspicuous spikes and intraglomerular proliferation (periodic acid-Schiff stain). **b** Immunofluorescence microscopy revealed coarsely granular immunoglobulin (Ig)G staining mainly along the capillary walls (IgG fluorescein isothiocyanate). **c** Electron microscopy image identified diffuse subepithelial electron dense deposits with early or no spikes and foot process effacement

Fig. 2.

Treatment course and laboratory results in the patient before and after initiation of bortezomib. A timed 24-h urine collection showed protein excretion of 6.5 g before kidney biopsy and 7.4 g at study screening. However, both collections were incomplete regarding the total creatinine amount, which was also measured. Repeat 24-h timed urine collections after the initiation of bortezomib treatment showed protein excretion of 13.9 g at 2 weeks, 2.4 g at 6 months, 0.55 g at 9 months and 0.36 g at 12 months