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Case Report

Use of Bortezomib in Heavy-Chain Deposition Disease: A Report of 3 Cases

Kinjal Patel, MD,[1] John J. Dillon, MD,[2] Nelson Leung, MD,[2,3] Andrew S. Bomback, MD,[4] Gerald B. Appel, MD,[4] Vivette D'Agati, MD,[5] and Pietro A. Canetta, MD[4]

Heavy-chain deposition disease (HCDD) is a rare complication of plasma cell dyscrasia in which monoclonal heavy chains deposit in glomerular and tubular basement membranes of the kidney. Clinical and pathologic features of HCDD have been well described in case reports and series, but evidence supporting specific therapies is sparse. Historically, the disease has had a poor prognosis, intensifying the need to clarify optimal treatments. We describe 3 cases of HCDD with biopsy-proven glomerular involvement, severe nephrotic syndrome, and decline in kidney function that were treated successfully with bortezomib, a proteasome inhibitor. None of these patients had multiple myeloma. In all cases, bortezomib-based therapy resulted in sustained resolution of nephrotic syndrome and improvement in kidney function. All 3 patients developed peripheral neuropathy; otherwise, treatment was well tolerated. To our knowledge, this is the first description of the clinical effectiveness of bortezomib against HCDD.

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Monoclonal immunoglobulin deposition disease (MIDD) in the kidney occurs in 3 forms: light chain deposition disease, heavy-chain deposition disease (HCDD), and combined light and heavy-chain deposition disease. All are characterized by non-amyloid deposition of monoclonal immunoglobulin fragments.[1,2] Presentation includes reduced kidney function and proteinuria, with light microscopy showing a nodular sclerosing glomerulopathy.[3-6] Immunofluorescence reveals glomerular and tubular basement membrane deposition of monoclonal chains, either heavy, light, or both.[5,6] HCDD is exceedingly rare, representing <0.1% of biopsy diagnoses at large academic referral centers.[7-9] The pathogenesis is distinct from multiple myeloma and involves deletion of the first constant heavy chain domain (CH1) within a plasma cell clone.[3,6]

The published literature on HCDD contains only isolated case reports and small series, with sparsely described therapies and generally poor outcomes.[3-6,10] Because the pathogenesis depends on pathologic protein secretion by an aberrant plasma cell clone, therapies targeting this process are a logical choice. Bortezomib is a proteasome inhibitor that has shown remarkable efficacy against relapsed or refractory multiple myeloma, inducing apoptosis in immunoglobulin-producing myeloma cells.[11] Although bortezomib has been used to treat light chain deposition disease, its use in HCDD has never been formally described. In this report, we present the clinical features and treatment courses of 3 patients with HCDD successfully treated with bortezomib.

CASE REPORTS

Case 1

A 75-year-old Hispanic man was referred to Columbia University Medical Center (CUMC) for nephrotic syndrome. He had been given the diagnosis of λ light chain monoclonal gammopathy of undetermined significance 8 years prior. Ten months before coming to CUMC, the patient abruptly developed nephrotic syndrome and uncontrolled hypertension despite treatment with amlodipine, hydrochlorothiazide, furosemide, and clonidine. He developed anemia, requiring multiple red blood cell transfusions despite use of erythropoiesis-stimulating agents. Hematologic studies are summarized in Table 1. He underwent gastrointestinal evaluation with esophagogastroduodenoscopy, colonoscopy, and capsule study, as well as computed tomography of the chest, abdomen, and pelvis to evaluate for occult malignancy, all of which revealed nothing of significance. A kidney biopsy performed elsewhere had shown nodular glomerulosclerosis but reportedly had negative immunofluorescence results. Because of the diagnostic uncertainty, a repeat kidney biopsy was performed at CUMC and definitively revealed HCDD (Fig 1).

The patient was started on treatment with bortezomib, 1.3 mg/m^2, intravenously twice weekly, with dexamethasone. The

From the [1]Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY; Divisions of [2]Nephrology and Hypertension and [3]Hematology, Mayo Clinic, Rochester, MN; and [4]Division of Nephrology and [5]Department of Cell Biology and Pathology, Columbia University College of Physicians and Surgeons, New York, NY.

Address correspondence to Pietro A. Canetta, MD, Columbia University College of Physicians and Surgeons, Division of Nephrology, 622 W 168th St, PH4-124, New York, NY 10032. E-mail: pac2004@columbia.edu

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Table 1. Hematologic and Nephrologic Parameters Obtained at Time of Diagnosis and Before/After Bortezomib-Based Treatment

Values at Diagnosis	Patient 1	Patient 2	Patient 3
Serum protein electrophoresis	Normal	Decreased total protein, albumin, and γ globulin; no monoclonal spike	Normal
Serum immunofixation electrophoresis	No monoclonal bands	No monoclonal bands	Small amount monoclonal κ in beta region
Urine protein electrophoresis	Monoclonal λ protein present	Normal	Normal
Urine immunofixation electrophoresis	Monoclonal λ Bence-Jones protein present	No monoclonal bands	Small monoclonal κ in alpha-2 fraction
Bone marrow biopsy	8% λ light chain restricted plasma cells	Normocellular marrow; no significant plasmacytosis; κ/λ staining not done	5% κ light chain restricted plasma cells
Complement studies			
Total complement (U/mL; reference range, 22-60)	Unavailable	22	Unavailable
C3 (mg/dL; reference range, 90-180)	81	49	69
C4 (mg/dL; reference range, 16-47)	38	Unavailable	27

Values Before/After Bortezomib Therapy	Patient 1		Patient 2		Patient 3	
	Before	After	Before	After	Before	After
Scr (mg/dL)	2.98	1.67	2.4	1.5	2.7	1.1
eGFR[a] (mL/min/1.73 m^2)	20	43	28	50	25	75
Urine protein excretion[b]	4.2 g/g	1.9 g/g	12 g/g	1.6 g/g	7200 mg/d	237 mg/d
Serum free κ/λ light chain ratio (reference range, 0.26-1.65)	0.09	0.14	70.6	12.0	3.4	1.1
Albumin (g/dL)	2.5	3.8	2.1	3.7	2.1	4.2
Hb (g/dL)	7.6	11.0	11.8	11.6	10.2	9.8

Abbreviations: eGFR, estimated glomerular filtration rate; Hb, hemoglobin; Scr, serum creatinine.
[a]eGFR calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.
[b]Urine protein excretion expressed as urine protein-creatinine ratio (g/g) for patients 1 and 2 and as 24-hour urine protein excretion (mg/24 h) for patient 3.

time course of his kidney indexes is shown in Fig 2A and Table 1. Within 2 months, nephrotic symptoms had improved markedly, hypertension became well controlled on only 2 medications, and transfusion-dependent anemia resolved with no erythropoiesis-stimulating agents needed. Nine months after starting bortezomib therapy, the patient developed neuropathy of the left hand and right foot. Bortezomib dosage was reduced to 1.3 mg/m^2 once weekly, with improvement. Seven months later, neuropathy recurred, and bortezomib dosage was decreased further to a regimen of 2 weeks on then 1 week off, with complete resolution of neuropathy. The patient is stable on this regimen, more than 2.5 years since initiating therapy.

Case 2

A 60-year-old white man first had presented with edema and hypertension 12 years earlier. Medical history was notable for only sleep apnea and hyperlipidemia. He initially was treated with pravastatin and diuretics. Urinalysis showed hematuria and proteinuria, and results of a urologic workup were unremarkable. A kidney biopsy performed 1 year after presentation was interpreted elsewhere as probable fibrillary glomerulopathy. He was referred to a hematologist for malignancy evaluation, but various tests, including complete blood cell count, peripheral smear, and bone marrow biopsy, produced normal results (Table 1).

The patient was referred to CUMC for further evaluation; test results for antineutrophil cytoplasmic antibodies and antinuclear antibodies were negative, and serum complement levels were normal. Review of his kidney biopsy revealed a nodular sclerosing glomerulopathy with membranoproliferative features, with immunofluorescence showing diffuse linear staining (3+) of immunoglobulin G (IgG) along glomerular and tubular basement membranes and vessel walls, but only trace κ and negative λ light chain staining, consistent with γ-type HCDD. Four of 29 glomeruli were globally sclerotic, and tubular atrophy and interstitial fibrosis involved ~15% of the sampled cortex.

Hypertension and hyperlipidemia were managed medically. Eight years after the biopsy, he developed worsening edema and hypertension. Laboratory tests showed increased proteinuria but stable serum creatinine levels (Fig 2B). He was given rituximab, 2 g, in divided doses 14 days apart. Nine months later, laboratory tests showed total peripheral B-cell depletion, and he experienced good clinical response. Eighteen months after receiving rituximab, his serum creatinine level increased again, and complement levels were now low (Table 1). He was given a second cycle of rituximab without response. Repeat kidney