Bortezomib in the Treatment of Acquired von Willebrand Disease Secondary to Monoclonal Gammopathy of Undetermined Significance

Kenneth Byrd, M.D.[1], Phu Truong, M.D.[1,2]
[1]University of Kansas School of Medicine-Wichita
Department of Internal Medicine
[2]Cancer Center of Kansas, Wichita, KS

Introduction

Acquired von Willebrand syndrome (AvWS) is a rare condition most commonly associated with the lymphoproliferative disorders, including monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, and Waldenström's macroglobulinemia.[1-3] It is a disorder of von Willebrand factor (vWF) concentration, structure, or function that is not inherited directly but is a consequence of another medical disorder.[4] There are multiple mechanisms leading to AvWS: autoimmune clearance or inhibition of vWF, increased shear-induced proteolysis of vWF, or increased binding of vWF to platelets or other cell surfaces.[2,3,4] Autoantibodies commonly are implicated in AvWS associated with MGUS.[1,4,5] Thus, these patients often do not respond to standard von Willebrand disease (vWD) therapy.[6] This case provided evidence that bortezomib may be an option for patients refractory to standard AvWS therapy in the setting of MGUS.

Case Report

A 67-year-old female without prior personal or family history of a bleeding diathesis originally presented with acute gastrointestinal bleeding. She subsequently had recurrent episodes of epistaxis and gastrointestinal bleeding requiring multiple blood transfusions. An extensive workup revealed the diagnosis of AvWS. She was not on blood thinners or any other medications known to cause AvWS. Her von Willebrand antigen at diagnosis was low at 3.1 units, von Willebrand ristocetin cofactor was 6, and factor VIII activity was 10.7%. A short time later, she also was diagnosed with MGUS.

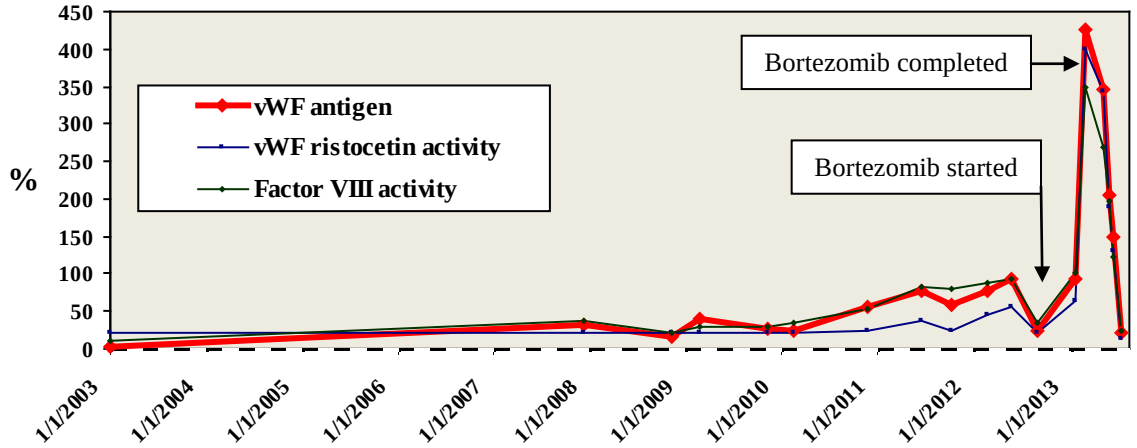
First line treatment with desmopressin was initiated, but the patient had severe nausea and her disease had very minimal response. She subsequently failed therapy with prednisone and vWF complex. Next, she was given four cycles of rituximab therapy with only minimal response. Even though the patient never had a confirmed vWF antibody, she was next treated empirically with intravenous immune-globulin (IVIG) monotherapy. She had good response to IVIG as evidenced by an increase in her vWF antigen, vWF ristocetin activity, and factor VIII activity.

Over the next nine years, the patient received IVIG infusions for two consecutive days every 2½ weeks. Her episodes of bleeding were decreased during this nine-year period, but she continued to have infrequent bleeding. She also had frequent headaches and nausea and another treatment strategy was explored.

Based on a published case report, bortezomib was added to the IVIG therapy.[7] Treatment included six cycles of bortezomib 2.5 mg on days one, four, eight, and 11 of a 21-day cycle.[7] Treatment with IVIG was continued during this four-month treatment period. During treatment, the patient had no

clinical bleeding and there was a remarkable increase in her vWF antigen, vWF activity, and factor VIII activity (Table 1). In addition, the MGUS monoclonal protein became undetectable. Once treatment with bortezomib and IVIG was stopped, remission was maintained for another two months, followed by relapse and an episode of gastrointestinal bleeding. The patient was not a candidate for additional bortezomib treatment due to drug-induced peripheral neuropathy. At that time, she resumed IVIG monotherapy which continued to be effective.

Table 1. Response of vWF antigen, vWF activity, and factor VIII activity during the 10-year treatment course of vWD.



Discussion

Similar to congenital vWD, the acquired syndrome can cause significant morbidity due to bleeding.[2] Unfortunately, standard vWD therapy is often ineffective for acquired von Willebrand syndrome.[5] These patients often do not respond to desmopressin or vWF replacement as there is frequently a circulating antibody that rapidly destroys the new circulating vWF.[5,6] Plasma antibodies to vWF are confirmed infrequently, but have been demonstrated by plasma mixing studies and functional assays.[4,6] In addition to antibodies, there is likely significant adsorption of the vWF to the increased circulating monoclonal cells. There is evidence of this occurring in multiple myeloma and it is possible that there is a similar mechanism involved in MGUS.[8]

Desmopressin produces at least short term improvement in only 32% of cases.[1] Factor replacement (vWF and FVIII) is also part of the standard vWD treatment, but has proven less effective in AvWS.[1,9] In patients who had a previous inadequate response to desmopressin and factor replacement, IVIG has some proven efficacy.[1,5,9] In one study, 33% of those who failed the first two therapies showed good response with IVIG.[1] Even if there is good clinical response, treatment with IVIG usually requires lifelong therapy that is both expensive and often difficult to tolerate. Other therapies such as plasmapheresis, antifibrinolytics, and rituximab have exhibited only marginal efficacy.[1,10,11]

In general, there appears to be minimal benefit to treating MGUS unless it

progresses to multiple myeloma.[12,13] However, there is insufficient evidence to guide the management of MGUS with other secondary complications, such as AvWS.[12] The standard approach to MGUS may be unsatisfactory when the patient has associated AvWS.

Bortezomib is a proteasome inhibitor commonly used in the treatment of multiple myeloma. It was shown in a prior case report to induce complete remission of both AvWS and MGUS.[7] Although the response was only short term in our case, bortezomib again appeared to have the potential to treat AvWS concurrent with MGUS effectively.

References

[1] Federici AB, Rand JH, Bucciarelli P, et al. Acquired von Willebrand syndrome: Data from an international registry. Thromb Haemost 2000; 84(2):345-349. PMID: 10959711.

[2] Veyradier A, Jenkins CS, Fressinaud E, Meyer D. Acquired von Willebrand syndrome: From pathophysiology to management. Thromb Haemost 2000; 84(2):175-182. PMID: 10959686.

[3] Tefferi A, Nichols WL. Acquired von Willebrand disease: Concise review of occurrence, diagnosis, pathogenesis, and treatment. Am J Med 1997; 103(6):536-540. PMID: 9428838.

[4] Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): Evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). Haemophilia 2008; 14(2): 171-232. PMID: 18315614.

[5] Federici AB, Stabile F, Castaman G, Canciani MT, Mannucci PM. Treatment of acquired von Willebrand syndrome in patients with monoclonal gammopathy of uncertain significance: Comparison of three different therapeutic approaches. Blood 1998; 92(8):2707-2711. PMID: 9763553.

[6] Mohri H, Motomura S, Kanamori H, et al. Clinical significance of inhibitors in acquired von Willebrand syndrome. Blood 1998; 91(10):3623-3629. PMID: 9572997.

[7] Ojeda-Uribe M, Caron C, Itzhar-Baikian N, Debliquis A. Bortezomib effectiveness in one patient with acquired von Willebrand syndrome associated to monoclonal gammopathy of undetermined significance. Am J Hematol 2010; 85(5):396. PMID: 20425807.

[8] Richard C, Cuadrado MA, Prieto M, et al. Acquired von Willebrand disease in multiple myeloma secondary to adsorption of von Willebrand factor by plasma cells. Am J Hematol 1990; 35(2):114-117. PMID: 2205095.

[9] Mohri H. Acquired von Willebrand syndrome: Features and management. Am J Hematol 2006; 81(8):616-623. PMID: 16823821.

[10] Kanakry JA, Gladstone DE. Maintaining hemostasis in acquired von Willebrand syndrome: A review of intravenous immunoglobulin and the importance of rituximab dose scheduling. Transfusion 2013; 53(8):1730-1735. PMID: 23252513.

[11] Tiede A, Rand JH, Budde U, Ganser A, Federici AB. How I treat the acquired von Willebrand syndrome. Blood 2011; 117 (25):6777-6785. PMID: 21540459.

[12] Kyle RA, Durie BG, Rajkumar SV, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia 2010; 24(6):1121-1127. PMID: 20410922.

[13] International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: A report

of the International Myeloma Working Group. Br J Haematol 2003; 121(5):749-757. PMID: 12780789.

Keywords: von Willebrand diseases, bortezomib, monoclonal gammopathy of undetermined significance