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BORTEZOMIB EFFECTIVENESS IN ONE PATIENT WITH ACQUIRED VON WILLEBRAND SYNDROME ASSOCIATED TO MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

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Running head: Successful Bortezomib in AVWS

Key words: AVWS, Bortezomib, Rituximab, MGUS
To the Editor,

Acquired von Willebrand Syndrome (AVWS) is a rare heterogeneous bleeding condition associated with several disorders, including monoclonal gammopathy of undetermined significance (MGUS) [1-3]. Successful therapy of the underlying disorder can lead to the improvement of AVWS [1].

Regarding the association of AVWS and MGUS, no long-term successful therapy has been reported. Indeed, most of these patients are not treated on a curative goal [1]. In a few single cases anti-CD20 targeted therapy (Rituximab) has shown no efficacy [4, 5]. We describe herein the case of a patient with AVWS accompanied by MGUS who was successfully treated with the proteosome inhibitor Bortezomib after failure of Rituximab. A 60-year-old man with poliomyelitis sequelae in one of his legs was referred to our hospital with a post-traumatic gluteal hematoma. The hypothesis of AVWS was based on the following findings: the patient had no personal and no family history of constitutional hemorrhagic disease; a prolonged activated partial thromboplastin time (aPTT): ratio 2.4 (PTTa, Stago, Asnieres, France); a severe decrease of VWF ristocetin cofactor activity (VWF:RCo) <1 % (VWF reagent, Siemens, Marburg, Germany); a low level of VWF antigen (VWF:Ag): 6 % (LIATEST, Stago) and FVIII: 6 % (plasma deficient FVIII reagent, Stago); a prolonged platelet occlusion time with collagen-epinephrine and collagen-ADP (240 and 275 seconds respectively) (PFA-100, Siemens, Marburg, Germany). An inhibitory activity was observed by in vitro functional assay (PTT-LA, Stago) with a measured Rosner index of 22. This inhibitory activity was considered as unspecific because no lupus anticoagulant (STACLOT DRVV, Stago) and no specific anti-FVIII inhibitor were detected; the lack of response to the desmopressin test; a high VWF-propeptide (VWFpp) (171%) (measured by fluorometry on Fluoroskan, Thermo, Waltham, USA; using the VWF reagent & propeptide assay, GTI diagnostics, Waukesha, USA) associated to a high VWFpp/VWF:Ag ratio (23.6), which was in favor of an increased clearance of mature VWF. In contrast, plasma distribution of VWF multimers assessed by 0.1% sodium dodecyl sulphate-1.5% agarose electrophoresis showed a normal profile and no specific anti-VWF auto-antibodies were detected by ELISA [6].
The diagnosis of MGUS was based on the lack of evidence of autoimmune/connective tissue disorders, multiple myeloma or other lymphoproliferative diseases: presence of a monoclonal IgG-kappa on serum immunofixation; normal serum immunoglobulin levels (g/L: IgG 9.2; IgA 1.3; IgM 0.6); normal serum creatinine, BUN and calcium values; negative antinuclear antibodies; no lymph-node enlargement on physical examination; no bone lytic lesions on skeleton X-ray; normality of CT-scan of the thorax, abdomen and pelvis; marrow smear examination showing 8 percent of morphologic and immunophenotypic normal plasma cells (CD38^pos^CD138^pos^CD20^neg^), but with a specific clonal IgH rearrangement (VH3-JH) detected by PCR. Bone marrow aspiration was performed only once an improvement of VWF-RCo (32%) was achieved after high-dose immunoglobulin intravenous infusion (HD-IVIG) (1g/kg of body weight (b.w.)/day during 2 days, followed by 0.5g/kg b.w. for 1 day. This improvement was transient lasting several days. Because of some efficacy observed in patients with acquired hemophilia A and other autoimmune disorders, we started anti-CD20 targeted therapy by weekly Rituximab at the dose of 375 mg/m². A peripheral blood deep B-cell depletion was rapidly achieved after the first Rituximab administration, but six cycles after we did not observe any improvement in AVWS. A new post-traumatic knee hematoma leads us to prescribe HD-VWF:VIIIIF concentrate (Wilstart, LFB, Cortaboeuf, France) without efficacy. Again, HD-IVIG induced a transient higher VWF:RCo activity, which allowed the evacuation of the hematoma. Afterwards, we started an every 21-day cycle 2nd-line therapy including Bortezomib 1.3 mg/m²/day plus dexamethasone 40 mg/day (both on days 1,4,8,11). After 3 cycles a dramatic improvement in all the parameters of AVWS was observed (Figure 1), including a normal value of VWFpp (116%) and VWFpp/VWF ratio (1.45). This time, the mutimeric distribution of VWF showed a slight excess (16%; normal 9%) of high-molecular-weight multimers (> 15 mers). Concerning MGUS a new marrow assessment (this time without any prophylactic therapy) showed 1% of normal plasma cells. The monoclonal IgG-kappa and the clonal IgH rearrangement were undetected (Figure 1). At this time serum free kappa and lambda chain concentrations were respectively of 6.1 mg/L (Normal values: 3.3-19.4 mg/L) and 2.4...
mg/L (Normal values: 5.7-26.3 mg/L) ; the k/λ ratio was 2.5 (Normal values: 0.26 –1.65). In total 6 cycles of bortezomib-dexamethasone were administered. Several weeks later, a new biological assessment confirmed the favorable results observed after the first three cycles. Serum free kappa and lambda chain concentrations were respectively of 8.1 mg/L and 6.9 mg/L ; the k/λ ratio was 1.17. The clinical and hematologic tolerance of this treatment was good, except a mild hypo-gammaglobulinemia (5 g/L). The follow-up is still short, but after 7 months the patient is still considered in remission of both AVWS and MGUS. Even if this favorable outcome after bortezomib would be interpreted with caution because it has been observed in this one case, it could represent an interesting therapeutic alternative in this clinical setting.
REFERENCES


FIGURES LEGENDS

Figure 1. ◆ VWF:RCo activity (%) following different therapies: HD-IVIG allowed a significant transient improvement; Rituximab (R) and HD-VWF/VIIIIF concentrate showed no effect; normal values were observed after 3 cycles of bortezomib-dexamethasone. Detectable and undetectable clonal IgH rearrangement (a) and serum monoclonal IgG-kappa (b) before (A, B) and after (A’, B’) 3 cycles of bortezomib-dexamethasone, respectively.