

Good Profile of Efficacy/Tolerance of Bortezomib or Idelalisib in Waldenström Macroglobulinemia Associated with Acquired Von Willebrand Syndrome

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Abstract: Acquired von Willebrand syndrome (AVWS) in the setting of Waldenström macroglobulinemia (WM) is a challenging condition. No real standard of care is recommended for these patients, although the therapeutic strategy should include a rapid approach to the emergency bleeding events and to the underlying malignant lymphoid disorder. We report here our experience treating three elderly patients with these concomitant hematologic entities. The use of a bortezomib-based chemotherapy regimen showed a good profile of tolerance and efficacy even in a long-term follow-up period. These patients were treated for several years before switching their therapy to idelalisib, a targeted oral therapy that inhibits phosphatidylinositol 3-kinase isoform-delta (PI3KD), which is part of the signaling pathway downstream B-cell receptor. This approach was well tolerated and efficacious, although some adverse effects were observed, particularly at hepatic levels, but were all reversible. The same profile of tolerance/efficacy was observed in one very old patient who received idelalisib as a first-line therapy. We think that bortezomib-based therapy could be considered in refractory patients with AVWS associated with WM.

Keywords: waldenström macroglobulinemia, acquired von Willebrand syndrome, bortezomib, idelalisib, proteasome inhibitors, von Willebrand factor

Background

At present, no real standard of care is available for patients with acquired von Willebrand syndrome (AVWS) in the setting of hematologic malignant disorders.¹ Waldenström macroglobulinemia (WM) is a lymphoproliferative disorder characterized by the production of serum monoclonal immunoglobulin M (IgM) and bone marrow infiltration by clonal lymphoplasmacytic cells, as well as eventual lymphoadenopathy or other organ involvement. Von Willebrand factor (VWF) is a glycoprotein produced by the vascular endothelium and megakaryocytes. VWF derives from the pro-VWF, a large 360-kDa molecule. Within the Golgi apparatus, pro-VWF is cleaved into mature VWF and a smaller molecule, the VWF propeptide (VWFpp). The VWF is stored as large multimers in endothelial Weibel-Palade bodies or in the alpha-granules of platelets. VWFpp is co-secreted from endothelial cells on an equimolar basis with VWF. VWFpp is cleared more rapidly than VWF, resulting in a distinct VWFpp/VWF antigen (VWF:Ag) ratio under steady-state conditions. Multiple pathogenic mechanisms are described in AVWS, including selective VWF adsorption on tumoral cells, increased VWF proteolysis, and anti-VWF autoantibodies—either immunoglobulin G (IgG) anti-VWF or a complex interaction between VWF and WM monoclonal

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immunoglobulin M (IgM).^{2,3} Nevertheless, some hemorrhagic signs and nasal bleeding also have been related to hyperviscosity syndrome.⁴

From the clinical point of view, AVWS associated with WM is a challenging condition, particularly when severe bleeding is observed at diagnosis. Emergency therapy is necessary as well as the rapid initiation of a treatment for the underlying condition although it is not always associated with a good and rapid response to the bleeding. Unfortunately, to date, there is no recommended “gold standard” emergency therapy to treat the bleeding in this setting. The use of intravenous high-dose immunoglobulins (HD-Ig) has demonstrated good, but not usually long-lasting, efficacy, as have high doses of recombinant VWF.¹ Rituximab (RTX) and/or corticosteroids that can be part of a first-line therapy of WM are rarely associated with good and rapid responses. Moreover, when a suspected hyperviscosity syndrome is suspected, the use of RTX can be associated with a flare syndrome.⁴

Based on our favorable experience with one patient with AVWS associated with an IgG-monoclonal gammopathy of undetermined significance (MGUS) that was refractory to RTX and who responded successfully to a bortezomib (BZ)-based therapy,⁵ in this study we similarly treated two other patients with WM who presented a concomitant severe AVWS (Table 1). These cases were refractory to several cycles of the chemo-immunotherapy regimen R-CVP21 (RTX 375 mg/m²/day × 1 day; Cyclophosphamide 750 mg/m²/day

× 1 day; Vincristine 1.4 mg/m²/day × 1 day, and methylprednisolone 60 mg/m²/day × 5 days). A third patient who also had WM and AVWS received idelalisib as first-line therapy.

Population

All the three patients in the study had given their written informed consent to have the case details and any accompanying images published and with approval from the institutional pluridisciplinary clinical and ethics committee to publish the case details (RCP-Hématologie, Secteur Sanitaire IV, Region Alsace, France). They were all men; their ages were 70 (UP1), 90 (UP2), and 79 (UP3) years. At diagnosis of WM, they presented AVWS with severe bleeding signs (refractory epistaxis and spontaneous ecchymosis associated with severe anemia in two cases and less severe in one case). Fundoscopic examination was performed in two of three patients with high serum levels of IgM without evidence of hyperviscosity syndrome. The diagnosis of AVWS associated with WM was made based on clinical and biological criteria (Tables 1 and 2). The primary biological parameters were the following:

WM

(a) monoclonal gammopathy IgM-kappa (+); (b) respective serum IgM levels UP1/UP2/UP3 83/72/39 g/L; (c) all presented the common somatic variant in WM, L265P of the MYD88 gene; and (d) in one of the cases (UP1), we found the other somatic variation S338 CXCR4 WHIM-like.

Table 1 Laboratory Parameters at Diagnosis of Waldenström Macroglobulinemia

UPN	Age at Diagnosis (Years)	Monoclonal Gammopathy	Serum Immunoglobulin Values (g/L)	Bone Marrow Cytology and Immunophenotyping in Favor of WM	Mutation L265P of MYD88	CXCR4 Mutation	Marrow Cytogenetics
UP1	90	IgM kappa	IgM: 83.4	Yes	Positive	Positive	Normal
			IgG: 4.50			S338 CXCR4 WHIM like	
			IgA: 0.82				
UP2	70	IgM kappa	IgM: 72	Yes	Positive	Negative	Normal
			IgG: 5.3				
			IgA: 0.2				
UP3	79	IgM kappa	IgM: 39	Yes	Positive	Negative	Normal
			IgA: 0.18				
			IgG: 4.4				
MEAN	77.5		IgM 62				

Table 2 Laboratory Parameters at Diagnosis of AVWS Concomitant with Waldenström Macroglobulinemia

UPN	aPTT	Platelet occlusion time	FVIII:C	VWF:Ag	VWF:RCo	Concentration VWFpp (%)	Ratio VWFpp/VWFAg	Assessment Multimers VWF	anti-VWF antibodies	
	N < 1.2 T	collagen-ADP & collagen-epinephrine				(55–148)	(> 2.8 group 0 & > 2.4 other group = increased VWF clearance)			
		(seconds)	(%)	(%)	(%) activity					
		ADP N 49–108	N 50–150	(O 42–140)	N O 40–125					
		Epinephrine N 66–150		(No O 66–176)	Non O 49–163					ABO group
UP1	Prolonged	Prolonged	57	26	39	78	High 2.8	Yes	Neg	O+
UP2	Prolonged	>300/>300	21	28	27	78	High 3.4	Yes	Neg	A+
UP3	Prolonged 1.55	>300/>300	44	37	41	91	High 3.5	Normal pattern	Pos (un-interpretable)	O+
MEAN	all	>2N/>2N	43	28	32.2			All normal		

AVWS: (e) all presented a prolonged aPTT > normal control; (f) FVW:RCo (%) UP1/UP2/UP3 39/27/41; (g) FVW:Ag (%) UP1/UP2/UP3 26/28/37; (h) FVIII:C (%) UP21/UP2/UP3 21/57/44; (i) TOP-epinephrine and ADP > N; (j) the anti-FVW antibodies were (-) in all cases; (k) the concentration of VWFpp was measured in all the cases UP1/UP2/UP2 78/78/91%, respectively (l) all presented an elevated ratio VWFpp/VWF:Ag UP1/UP2/UP3 2.8/3.4/3.5. This increased VWFpp/VWF:Ag ratio is in favor of an increased clearance of VWF. Under steady-state conditions, VWFpp is cleared more rapidly than VWF, resulting in a distinct VWFpp/VWF antigen (VWF:Ag) ratio, so an increased consumption of VWF can be associated with a more elevated VWFpp/VWF:Ag ratio. The assessment of VWF multimers was performed in all patients showing a normal pattern in one of them (UP3). In the two other the presence of high levels of monoclonal IgM altered the interpretation of the test according to the laboratory report.

Treatment

A) BZ-based chemotherapy was given to two RCVp21-refractory patients (UP1, UP2). Each VMP (BZ + melphalan + prednisone)-like cycle duration was 35 days and included BZ 1.3 mg/m² in a weekly intravenous administration (in the last years by the subcutaneous route) for 4 weeks plus oral melphalan 8 mg/m²/day × 4 days and oral methylprednisolone

60 mg/m²/day × 4 days. During the maintenance period, the cycles were given every 90 days; B) the third male patient (UP3) received idelalisib [a B-cell receptor (BCR) signaling inhibitor via inhibition of the PI3K] as first-line therapy because of his older age and his refusal of chemotherapy in the hospital setting.^{6–8}

Response Assessment

UP1 had refractory R-CVPx4, achievement of a very good partial response (VGPR) after VMP, and received 25 cycles of VMP over 4 years that was followed by the administration of idelalisib 200 mg/j. UP2 was refractory to R-CVPx4, with achievement of VGPR after VMP; this patient also received 17 cycles of VMP that was followed by idelalisib 200 mg/d as maintenance therapy; all the parameters of hemostasis were normalized. UP3 received idelalisib 200 mg/j as first-line therapy; we observed a reversible liver toxicity (grade 1–2), and the patient achieved a VGPR.

All the patients reported here presented a very good response to WM, showing a rapid improvement in coagulation parameters related to AVWS (Table 3).

The baseline biological characteristics of these patients at diagnosis were compared to those observed while receiving long-term BZ-based therapy or idelalisib (Table 3).

Table 3 Laboratory Parameters During Treatment with Bortezomib-Based Therapy in Patients UPI (41 Months in Duration) and UP2 (36 Months in Duration) and After Switching to Idelalisib Treatment (in UPI from 44th[#] Month, i.e., 3 Months After Stopping Bortezomib-Based Therapy and in UP2 from the 37th Month*, i.e., 1 Month After Stopping Bortezomib-Based Therapy). UP3 Received Only Idelalisib, and the Follow-Up Corresponds Only to the Outcome Under This Therapy

		Months After Chemotherapy									
VWFAG (%)	0	1	6	12	24	36	37*	44 [#]	53	60	76**
UPI	26			120	67	173		224	207	134	208
UP2	19	21	65	57	39	42	60	100	STOP ^{&}		
UP3	37	62	52	64	101						
VWFRCo (%)	0	1	6	12	24	36	37	44	53	60	72
UPI	39			117	61	110		134	150	114	150
UP2	27		73	65	36	48	47	79	STOP		
UP3	41	55	52	64	90						
VIII F (%)	0	1	6	12	24	36	37	44	53	60	72
UPI	57			133	100	142		192	179	141	241
UP2	21	29	94	43	59	71		82	STOP		
UP3	44	52	61	78	87						
IGM g/L	0	1	6	12	24	36	37	44	53	60	72
UPI	83			44	37	13		12	10	7.3	3.9
UP2	75	63	24	23	54	50	42	50	STOP		
UP3	39	25	17	12	11.7						
aPTT N< 1.2 sec	0	1	6	12	24	36	37	44	53	60	75
UPI	1.44			N	N	N		N	N	N	N
UP2	1.57	1.51	N	N	1.4	1.28	1.25	1.23			
UP3	1.55	1.35	1.28	1.27	1.2						

Notes: [&]Date of idelalisib stop in UPI. ^{**}UP2 has a very long follow-up (>6 years) and is still on therapy.

Long-term therapy over 3 years with the VMP regimen has shown a very good safety profile and a persistently good clinical response to the AVWS associated with WM. In particular, no peripheral neuropathy was observed.

This efficacy was maintained when BZ was switched from the intravenous to the subcutaneous route. Later, both patients were switched to idelalisib (a newer targeted oral therapy).⁶⁻⁸ Ibrutinib was not chosen because of the reported drug-related bleeding risk, in particular when it is given combined with platelet anti-aggregants.⁹ One of the patients (UPI) is doing well with idelalisib, whereas the other one (UP2) discontinued this therapy because of severe hepatic and mucocutaneous toxicity. This patient showed a rapid relapse of AVWS and progression of WM 2 months after stopping idelalisib.

Discussion

Diagnosis of AVWS in the setting of hematological malignancies as WM is a rare and very challenging situation where an accurate clinical suspicion needs to be supported by a well-recommended laboratory workup that must

include a VWF analysis.^{1,10-12} The ISTH (International Society of Haemostasis and Thrombosis) and others have provided recommendations for a laboratory workup algorithm where the screening tests should be followed by specific tests of VWF. It is important to perform laboratory workup based on this algorithm in order to detect AVWS that can be underdiagnosed in several hematological settings as well as to do a differential diagnosis of AVWS with inherited VWD.^{12,13} The therapeutic strategy of AVWS should include a rapid approach to emergency bleeding events and to the underlying malignant lymphoid disorder. Following this diagnostic algorithm helped us to confirm the diagnosis of AVWS in this series of patients with severe WM. All these three patients had no history of family history or recurrent bleeding. Laboratory characteristics showed in all cases a prolonged aPTT and platelet occlusion times as well as low concentrations of VWF:Ag, VWF:RCO and FVIII:C (Table 2). Moreover, in all of them an elevated VWFpp/VWF:Ag ratio was observed. Regarding therapeutic agents that can be administered in this setting previous favorable experiences with BZ

prompted us to pursue its use in other AVWS patients associated with lymphoid malignancies as in this series of three patients with severe WM.⁵ BZ is a potent, reversible, and specific inhibitor of the proteasome. Proteasome inhibition has the potential to arrest the cell cycle and induce apoptosis in cancer cells through the disruption of a large number of growth regulatory pathways.¹⁴

The efficacy of BZ in WM has been assessed in several clinical trials, most of them in association with RTX. The combination of BZ, dexamethasone, and RTX was given to 23 untreated patients, with administration of intravenous BZ at 1.3 mg/m², dexamethasone at 40 mg twice per week on days 1, 4, 8, and 11, and RTX 375 mg/m² on day 11 for four cycles as induction treatment and four more cycles at 3 months as maintenance treatment.^{4,15} The overall response rate (ORR) and major response rate (RR) were 96% and 83%, respectively, with a median time in target range (TTR) of 1.4 months. Sixty percent of patients discontinued treatment after four cycles because of treatment-related peripheral neuropathy. BZ once per week was also investigated: 26 patients received intravenous BZ at 1.6 mg/m² on days 1, 8, and 15 during six cycles in a 28-day cycle and RTX at 375 mg/m² at each cycle during four cycles.¹⁶ The ORR was 88%, with a 65% major RR. The 1-year event-free survival (EFS) was 79%. The neurologic complications were limited, and no grade 3/4 treatment-related peripheral neuropathy was reported. Grade 3/4 neutropenia was observed in 12% of patients. Among patients previously treated with this regimen, the ORR was 81%, with a 51% major RR and a median progression-free survival (PFS) of 15.6 months. Sixteen percent of patients developed grade 3 neutropenia, and 5% of patients had grade 3 neuropathy.¹⁶

The BZ-based regimen given to our patients did not include RTX. Despite this, it was associated with a rapid TTR against AVWS and to significant control of WM over the years.

Moreover, we consider that BZ was the main therapeutic agent because when melphalan was not given, a good and persistent response was always observed. Two of these patients stopped a BZ-related regimen because of shared medical and patient choice not related to efficacy and/or tolerance issues.

Idelalisib is a potent inhibitor of the phosphatidylinositol 3-kinase isoform-delta (PI3Kd) that plays a role in B-cell development and signal transduction of downstream BCR and other cytokine or integrin receptors.⁶ The PI3Kd signaling pathways are hyperactivated in B-cell lymphoid malignancies.⁷ Idelalisib was the drug of choice because of related bleeding episodes in patients with

B-lymphoproliferative disorders receiving ibrutinib.⁹ However, idelalisib has not been exempted from significant adverse effects, in particular hepatic and infectious effects.^{17,18} The use of idelalisib was recently reported in one patient with WM and hemorrhagic syndrome (not related to AVWS), implying a contraindication to the use of ibrutinib.¹⁹ Severe hepatic toxicity was observed in one of the patients we treated (UP2); the toxicity persisted after reducing the dose posology, but it was finally reversed. The therapy of this patient was discontinued after 8 months. In the patient (UP3) who received first-line therapy with idelalisib, a moderate degree of hepatic toxicity was observed that was reversed after decreasing doses. This patient has a follow-up of almost 2 years, and he is doing well without modification of the dose of idelalisib in the last year. Only one patient (UP1) did not present any significant hepatic toxicity, and he is doing well receiving idelalisib for more than 3 years. At present, ibrutinib is approved for its use in monotherapy or associated with RTX in patients with WM, and there is no formal contraindication when an AVWS is observed.^{20,21} A maintenance therapy with this drug could be designed after a first-line BZ-based therapy once biological parameters related to AVWS had been resolved. A recent trial has shown a long-term efficacy of this drug in previously treated WM patients, although some variants of the mutational status MYD88/CXCR4 have an impact on the response.²² Interestingly, it has been reported that the negative impact of CXCR4 mutation can be overcome by BZ.²³ This finding is consistent with the good response observed in the patient (UP1) who presented a CXCR4 mutation (Table 1). Regarding idelalisib, very few reports have been published in the last years, explained in part by a less favorable toxicity profile compared with ibrutinib.¹⁸

Conclusions

The use of BZ and/or idelalisib in patients with WM and severe AVWS has shown a good profile of efficacy and tolerance. The use of another inhibitor of the BCR signaling pathway (ibrutinib) is an alternative, but potential alterations of platelet function have to be considered.

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Willebrand Disease”. Тромбоз, гемостаз и реология [Thrombosis, Hemostasis and Rheologia]. 2016;67 (S3):10-10 (abstract). <https://elibrary.ru/item.asp?id=26902644>; b)-Oral presentation at the XXXIX Annual Meeting of the Chilean Society of Internal Medicine (24–27 October 2018), Santiago de Chile, Chile. Mario Ojeda-Urbe, Valérie Rimelen, Cathérine Marzullo. “Good profile of efficacy/safety of bortezomib and targeted therapies against BCR signaling in acquired von Willebrand Disease associated to IgG or IgM monoclonal gammopathies” (<http://www.smschile.cl/new/congreso-chileno-medicina-interna-2/>).

Disclosure

The authors report no conflicts of interest in this work.

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