Letter to the Editor

Bortezomib: Potential Key Role in the Treatment of Multiple Myeloma-Related Acquired Hemophilia A

Gil de Paiva Brás, MD[1] Ricardo Jorge Sancio Moreira Pinto, MD[1]
Maria Manuela Marques Cardoso Carvalho, MD[2] Susana Patrícia Beleza Nobre Fernandes, MD[2]
Joaquim José Aguiar Andrade, MD[1] José Eduardo Torres Eckenroth Guimarães, PhD[1]

[1] Serviço de Hematologia Clínica, Centro Hospitalar de São João, Porto, Portugal
[2] Serviço de Imunohemoterapia, Centro Hospitalar de São João, Porto, Portugal

Address for correspondence Gil de Paiva Brás, MD, Department of Clinical Hematology, Serviço de Hematologia Clínica, Centro Hospitalar de São João, Porto, Portugal (e-mail: gpaivabras@gmail.com).

Semin Thromb Hemost 2017;43:109–112.

As previously reviewed in this journal, acquired hemophilia A (AHA) is a rare autoimmune disorder due to autoantibodies against factor VIII (FVIII).[1–3] The autoantibodies against FVIII, commonly described as polyclonal and of immunoglobulin G (IgG) class, may inhibit the interaction of FVIII with FIXa, phospholipids, and von Willebrand factor.[1] This interaction typically results in isolated prolongation of activated partial thromboplastin time (aPTT), limited correction in mixing studies with normal plasma, low levels of FVIII, and detection of a FVIII inhibitor.[2] In 50 to 60% of cases, AHA is apparently idiopathic. The remaining cases are related to solid tumors, lymphoproliferative diseases, autoimmune disorders, viral infections, drug exposure, and pregnancy.[3,4] The association between multiple myeloma (MM) and AHA is extremely rare. In a meta-analysis, from 30 patients with AHA and hemato-oncological diseases, only 4 had MM.[5]

This report describes a case of MM-related AHA responsive to proteasome inhibitor (PI)-based therapy. To our knowledge, this is the second published clinical report showing the efficacy of PIs in the treatment of AHA[6] and the first such report in a case of MM-related AHA.

A male patient, 87 years old, was diagnosed with smoldering MM (sMM) IgG/kappa in February 2011: myeloma protein (M component) of 25 g/L, immunofixation positive for IgG/kappa gammopathy, and plasmocytes accounting for 11% of nuclear cells in bone marrow smear. Some 13 months later, in April 2012, he developed anemia (hemoglobin [(Hb]: 8.9 g/dL) and progressed to symptomatic MM, Stage II-A in Durie-Salmon Staging System and Stage II in International Staging System. He was initially treated with seven cycles of melphalan, prednisone, and thalidomide (MPT), achieving a minimal response with a reduction of 41% on the M component, from 22.2 to 13.2 g/dL.

After 16 months with thalidomide maintenance therapy without progression, in July 2014, he appeared with cutaneous ecchymoses and hematomas, a tumefaction in the abdominal wall and an increase in diameter of the right thigh. The ultrasonography revealed two large hematomas: one (12 × 9 × 3.5 cm) in the left rectus abdominal muscle and another (19 × 12 × 11 cm) in the right thigh. The Hb decreased to 8.0 g/dL and an isolated prolonged aPTT of 73.6 seconds (normal: 24–36 seconds) was observed, with limited correction with 1:1 mixture (40 seconds) with normal plasma (28 seconds). An incubated mix test was not performed. The FVIII activity was 1.4 U/dL and FVIII inhibitor titer was determined to be 18.4 Bethesda Units (BU). Lupus anticoagulant and autoimmunity markers were negative. AHA was diagnosed and combined therapy with activated prothrombin complex concentrate (FEIBA) 50 IU/kg each for 8 hours (3,500 IU, three times/day) and cyclophosphamide 50 mg/day plus dexamethasone 20 mg/week was started. After 2 weeks, both hematomas and Hb became stable and the administration of FEIBA was suspended. After 1 month of immunosuppression, the aPTT lowered to 44.6 seconds, FVIII activity increased to 13U/dL, and FVIII inhibitor titer dropped to 8 BU (►**Table 1**).

In October 2014, after 2 months of immunosuppression, the patient developed cellulitis on the right thigh. The ultrasonography revealed persistence of hematoma in the right thigh (14 × 6 cm) and Hb dropped to 7.9 g/dL. The aPTT (41

published online December 19, 2016

Issue Theme Editorial Compilation III; Guest Editors: Emmanuel J. Favaloro, PhD, FFSc (RCPA), and Giuseppe Lippi, MD.

DOI http://dx.doi.org/10.1055/s-0036-1597648.
ISSN 0094-6176.

Table 1 Summary of complementary diagnostic exams during the diagnosis of AHA and during treatment of AHA with cyclophosphamide + prednisone and bortezomib + dexamethasone

	Reference range	AHA presentation	Cy + Pred 1 mo	Cy + Pred 2 mo	1st VD	4th VD	AHA relapse	1st VD at relapse	6th VD at relapse
Time	NA	July 2014	August 2014	September 2014	November 2014	March 2015	September 2015	October 2015	March 2016
Hemoglobin (g/dL)	13.0–18.0	**8.0**	**8.8**	**7.9**	**9.5**	**9.5**	**9.4**	**10.1**	**9.9**
Creatinine (μmol/L)	59–103	**149**	101	**126**	**111**	**119**	**112**	**145**	**129**
IgG (mg/dL)	600–1,500	**1,780**	–	**1,640**	1,380	1,440	**1,960**	–	1,450
K light chains (mg/dL)	200–440	**512**	–	**457**	369	407	**595**	–	**453**
aPTT (s)	24.2–36.4	**73.6**	**50.5**	**44.6**	36.0	33.7	**64.1**	**43.5**	**36.7**
FVIII activity (U/dL)	70.0–150.0	**1.4**	**2.5**	**13**	90	–	**6**	**51**	**36**
FVIII inhibitor titer (Bethesda Units)	0	**18.4**	**35**	**8**	0	–	**3.6**	–	**0.8**
AHA treatment	NA	Cyclophosphamide + prednisone			Bortezomib + dexamethasone		Bortezomib + dexamethasone (retreatment)		

Abbreviations: AHA, acquired hemophilia A; aPTT, activated partial thromboplastin time; Cy + Pred, cyclophosphamide + prednisone; IgG, immunoglobulin G; MM, multiple myeloma; MPT, melphalan + prednisone + thalidomide; sMM, smoldering multiple myeloma; VD, bortezomib + dexamethasone.
Note: Abnormal test results are shown in bold.

seconds) did not increase in comparison with the previous recorded value. As there was no significant increase in M component and no signs of hemolysis, the hemoglobin level was considered an effect of infection and re-bleed into the hematoma site. After 8 days of FEIBA administration, it was decided to switch from cyclophosphamide + prednisone to PI-based therapy. A dose of bortezomib 1.3 mg/m^2, weekly, by intravenous route, to avoid the risk of subcutaneous administration, in association with dexamethasone 40 mg, days 1 to 4 (all cycles) and days 9 to 12 (cycles 1 and 2), was administered in 3-week cycle (VD protocol). At the end of the first cycle, aPTT normalized to 36 seconds, FVIII increased to 90 U/dL, and no FVIII inhibitor was detected. The dose of bortezomib was reduced to 1.0 mg/m^2 in the second cycle due to thrombocytopenia. A total of four cycles of VD were completed. At the end, the aPTT was 33.7 seconds (►**Table 1**).

The patient had a further 7 months of survival with no events, until September 2015, when he appeared with new cutaneous ecchymoses and epistaxis. aPTT increased to 64.1 seconds, FVIII activity dropped to 6 U/dL, and a FVIII inhibitor was again detected, this time at a level of 3.6 BU. There was a slight increase in M component, but no progression to symptomatic MM. The VD protocol, with full-dose of Bortezomib, was again started. After 2 weeks of treatment, aPTT decreased to 49.9 seconds and FVIII activity increased to 22 U/dL. In March 2016, the patient completed the sixth VD cycle and aPTT decreased to 36.7 seconds, FVIII activity increased to 36 U/dL, and FVIII inhibitor dropped to 0.8 BU (►**Table 1**).

It has been accepted that polyclonal antibodies of IgG class with affinity to FVIII are the origin of the majority of AHA cases.[1–4] Decaux et al reported a patient with sMM IgA/kappa, who presented with AHA and demonstrated that the IgA myeloma protein was acting as FVIII inhibitor.[7] This report was the first evidence for a monoclonal source of FVIII inhibitor in cases of MM-related AHA.

Cyclophosphamide is an alkylating agent whose cytotoxic effect on B and T lymphocytes is dose dependent: at low doses (1–2 mg/kg/day) cyclophosphamide has cytotoxic effect on B cell, preserving T-helper (Th) cell function and decreasing the number of regulatory T cells[8]; at high doses, cyclophosphamide induces profound depletion of all lymphocyte populations.[9] A FVIII inhibitor derived from the myeloma clone is a possible explanation for the unsatisfactory response to cyclophosphamide in our patient. A low dose of cyclophosphamide might be sufficient to induce B cell cytotoxicity, but does not have a strong activity against the monoclonal plasma cell pool, namely, the long-lived plasma cells (LLPC). The LLPC constitute a pool of bone marrow plasma cells that survive for extended periods of time and persistently secrete immunoglobulins without antigen stimulation.[10] In MM, the interaction between clonal plasma cells and the microenvironment contributes to the survival of the neoplastic clone, which behaves as a pool of LLPC.[11] Cyclophosphamide is able to block B cell and proliferation of plasma blasts, inhibiting the supply of fully differentiated plasma cells, but does not affect the pool of LLPC in bone marrow, especially those in quiescent stage.[12]

The chimeric monoclonal anti-CD20 antibody, rituximab, has been used as second-line therapy for AHA.[13] Rituximab causes depletion of CD20+ B lymphocytes. The expression of CD20 begins at the pre-B cell stage and is lost prior to

differentiation into immunoglobulin-secreting plasma cells.[14] With B cell depletion and consequently the interruption of the generation of plasma blasts, rituximab reduces the production of autoantibodies, but does not affect the preexisting myeloma clone. This was the theoretical reason that led us not to choose rituximab as a second-line option in our patient.

The evidence that FVIII inhibitor can be produced by a myeloma clone led us to treat our patient with PI-based therapy. A dramatic response was observed after the first VD cycle: aPTT normalized, FVIII activity raised to 90 U/dL, and no FVIII inhibitor was detected (0 BU). Bortezomib has direct cytotoxic effects in abnormal plasma cells, besides the direct effects on cellular and humoral immune response: reduces the proliferation of activated B cells, impairs B cells to initiate antibody-mediated responses, modulates T cell response with decrease of CD4-activated T cell populations, and inhibits nuclear factor-kappa B (NF-Kb) with reduction of Th1 cytokines.[15] In terms of cytotoxicity to abnormal plasma cells, the axis proteasome/NF-Kb inhibition is the major player. MM cells depend on NF-Kb to promote transcription of cytokine growth factor interleukin-6 to induce angiogenesis through vascular endothelial growth factor and also to permit adherence to stromal tissue in bone marrow, through the cell adhesion molecule VCAM-1. So, the block of NF-Kb pathway results in potent antitumor activity against MM cell lines.[16,17] This is crucial for the efficacy of bortezomib in MM-related AHA: it not only impairs the FVIII inhibitor secretion but also has a direct cytotoxic effect in FVIII inhibitor producing myeloma clone. Bortezomib has been studied as a promising therapeutic option in autoimmune diseases mediated by autoantibodies production, such as systemic lupus erythematosus and myasthenia gravis,[18–20] as well as in antibody-mediated renal allograft rejection.[21,22] Given the fact that AHA could represent an autoimmune disease mediated by production of autoantibodies against FVIII domains, bortezomib's direct cytotoxic effect on B cells and plasma cells and its ability to block antibodies production may be a rationale to consider the potential role of PIs in other types of AHA not related to MM.[6]

The limitation of bortezomib in MM-related AHA is the same observed in the treatment of MM: it is not able to eradicate the quiescent and chemoresistant clone that recapitulates the initial tumor burden at relapse.[23] This will explain the AHA relapse observed in our patient that occurred concurrently with a slight increase in M component. To prolong the hemophilia-free survival period, considering that small amounts of M component are sufficient to AHA relapse, we decided to go up to six cycles of VD, at a higher cumulative dose of bortezomib than initially, to reach a deeper response.

In summary, AHA is a rare autoimmune disorder due to autoantibodies against FVIII. The majority of AHA cases are idiopathic. Apart from being described in hemato-oncological diseases, mostly in lymphoproliferative diseases, the association between MM and AHA is extremely rare. This report describes an AHA developing in MM under maintenance therapy with thalidomide. In this particular case, cyclophosphamide proved to be insufficient to control FVIII inhibitors of MM origin and a dramatic decline in FVIII inhibitor was observed after administration of PI-based therapy. This report shows that PIs might be an efficacious approach in cases of MM-related AHA.

In conclusion, AHA management is a therapeutic challenge. When a concurrent plasma cell dyscrasia is present, the neoplastic clone might be responsible for the inhibitor production. The therapeutic approach with immunosuppression based on cyclophosphamide and corticosteroids might not be sufficient to control inhibitor production. Bortezomib is an option that not only has effects on cellular and humoral immunity but also decreases the myeloma clone responsible for the inhibitor.

References

1 Webert KE. Acquired hemophilia A. Semin Thromb Hemost 2012; 38(7):735–741
2 Tiede A, Werwitzke S, Scharf RE. Laboratory diagnosis of acquired hemophilia A: limitations, consequences, and challenges. Semin Thromb Hemost 2014;40(7):803–811
3 Coppola A, Favaloro EJ, Tufano A, Di Minno MN, Cerbone AM, Franchini M. Acquired inhibitors of coagulation factors: part I-acquired hemophilia A. Semin Thromb Hemost 2012;38(5): 433–446
4 Franchini M, Mannucci PM. Acquired haemophilia A: a 2013 update. Thromb Haemost 2013;110(6):1114–1120
5 Franchini M, Targher G, Manzato F, Lippi G. Acquired factor VIII inhibitors in oncohematology: a systematic review. Crit Rev Oncol Hematol 2008;66(3):194–199
6 McFadyen JD, Tran H, Kaplan ZS. Factor VIII inhibitor eradication with bortezomib in acquired haemophilia A. Br J Haematol 2016; doi: 10.1111/bjh.14185
7 Decaux O, Benoit G, Millet A, et al. Acquired hemophilia associated with smoldering myeloma: demonstration that the monoclonal gammopathy acts as the factor VIII inhibitor. In: 51st American Society of Hematology Annual Meeting and Exposition; Dec 5–8, 2009; New Orleans, United States. Abstract 1307
8 Bracci L, Schiavoni G, Sistigu A, Belardelli F. Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer. Cell Death Differ 2014;21(1):15–25
9 Mackall CL, Fleisher TA, Brown MR, et al. Lymphocyte depletion during treatment with intensive chemotherapy for cancer. Blood 1994;84(7):2221–2228
10 Winter O, Dame C, Jundt F, Hiepe F. Pathogenic long-lived plasma cells and their survival niches in autoimmunity, malignancy, and allergy. J Immunol 2012;189(11):5105–5111
11 Bianchi G, Munshi NC. Pathogenesis beyond the cancer clone(s) in multiple myeloma. Blood 2015;125(20):3049–3058
12 Hiepe F, Dörner T, Hauser AE, Hoyer BF, Mei H, Radbruch A. Long-lived autoreactive plasma cells drive persistent autoimmune inflammation. Nat Rev Rheumatol 2011;7(3):170–178
13 Collins P, Baudo F, Knoebl P, et al; EACH2 registry collaborators. Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). Blood 2012; 120(1):47–55
14 Dierickx D, Delannoy A, Saja K, Verhoef G, Provan D. Anti-CD20 monoclonal antibodies and their use in adult autoimmune hematological disorders. Am J Hematol 2011;86(3):278–291
15 Pellom ST Jr, Dudimah DF, Thounaojam MC, Sayers TJ, Shanker A. Modulatory effects of bortezomib on host immune cell functions. Immunotherapy 2015;7(9):1011–1022

16 Adams J. Proteasome inhibition in cancer: development of PS-341. Semin Oncol 2001;28(6):613–619
17 Berenson JR, Ma HM, Vescio R. The role of nuclear factor-kappaB in the biology and treatment of multiple myeloma. Semin Oncol 2001;28(6):626–633
18 Neubert K, Meister S, Moser K, et al. The proteasome inhibitor bortezomib depletes plasma cells and protects mice with lupus-like disease from nephritis. Nat Med 2008;14(7): 748–755
19 Alexander T, Sarfert R, Klotsche J, et al. The proteasome inhibitor bortezomib depletes plasma cells and ameliorates clinical manifestations of refractory systemic lupus erythematosus. Ann Rheum Dis 2015;74(7):1474–1478
20 Gomez AM, Vrolix K, Martínez-Martínez P, et al. Proteasome inhibition with bortezomib depletes plasma cells and autoantibodies in experimental autoimmune myasthenia gravis. J Immunol 2011;186(4):2503–2513
21 Everly MJ, Everly JJ, Susskind B, et al. Bortezomib provides effective therapy for antibody- and cell-mediated acute rejection. Transplantation 2008;86(12):1754–1761
22 Walsh RC, Everly JJ, Brailey P, et al. Proteasome inhibitor-based primary therapy for antibody-mediated renal allograft rejection. Transplantation 2010;89(3):277–284
23 San Miguel J. Multiple myeloma: a model for scientific and clinical progress. Hematology (Am Soc Hematol Educ Program) 2014; 2014(1):1–7