Annals of Hematology & Oncology

Open Access

Austin Publishing Group

Case Presentation

Dual Mechanism of Severe Bleeding Diathesis in a Patient with CLL: Acquired Von Willebrand Syndrome and Ibrutinib - Mediated Platelets Dysfunction

Bürki S* and Novak U
Department of Medical Oncology, Bern University Hospital, Switzerland

***Corresponding author:** Bürki S, Department of Medical Oncology, Bern University Hospital, Bern, Switzerland

Received: February 16, 2020; **Accepted:** March 10, 2020; **Published:** March 17, 2020

Abstract

We here report an informative case of severe bleeding diathesis in a patient with Chronic Lymphocytic Leukaemia (CLL), due to Acquired Von Willebrand Syndrome (AVWS) and impaired platelets aggregation under the treatment with Ibrutinib.

Keywords: CLL; Acquired von Willebrand syndrome; Ibrutinib; Bleeding

Introduction

The diagnosis of Acquired Von Willebrand Syndrome (AVWS) might be challenging because of the broad spectrum of its clinical and laboratory features. The AVWS is a rare bleeding disorder caused by a structural or functional defect in von Willebrand Factor (vWF) that can be associated with autoimmune conditions, neoplasia, lymphoproliferative, myeloproliferative and cardiovascular disorders [1,2]. A variety of pathogenic mechanisms have been described, and include the formation of antibodies to the von Willebrand Factor (vWF) (antibodies to vWF are shown *in vitro* in only a minority of the cases), its absorption from the surfaces of transformed cells or platelets and its mechanical destruction under the shear-stress [3].

The bleeding history is usually characterized by spontaneous mucocutaneous and/or gastrointestinal haemorrhage, occurring in patients without a family history of bleeding disorders [4]. The diagnosis is based on the detection of low of a plasma concentration or impaired activity of vWF [5].

Bruton Tyrosine Kinase (BTK) functions downstream of multiple surface receptors in hematopoietic cells. Its constant activation *via* B-cell antigen receptor signalling in various B-cell malignancies leads to downstream activation of essential cell survival pathways such as NF-B and MAPK [6,7]. Reversible inhibition of BTK by Ibrutinib disrupts proliferation, differentiation and migration of normal and malignant B-cells, rendering it an effective therapeutic agent in B-cells neoplasms [8-10].

BTK activation *via* several platelet transmembrane receptors, including the platelet collagen receptor glycoprotein VI is required for a normal platelet activation. BTK blockage by Ibrutinib also leads to an impaired platelets aggregation, and can cause a severe hemorrhagic diathesis, including subdural hematomas and gastrointestinal bleedings [6,11-15]. Additionally, *in vitro* and *in vivo* studies show that Ibrutinib can affect platelet adhesion to the vWF *via* inhibition of the GPIb-receptor signaling [16,17].

We here describe the case of patient with Chronic Lymphocytic Leukaemia (CLL) that presented with both, a severe persistent hemorrhagic diathesis due to the combination of an AVWS as well as an impaired platelets function under the treatment with Ibrutinib.

Case Description

65-year old male patient with a past medical history of arterial hypertension and a Deep Vein Thrombosis (DVT) on the left low extremity presented in October 2012 with constitutional symptoms, generalized lymphadenopathy and lymphocytic leucocytosis.

Immunophenotyping of peripheral blood lymphocytes by flow cytometry and immunohistochemistry on a bone marrow biopsy reveal a typical B-CLL phenotype: CD5+, CD23+, CD20weak, and FMC7 and Cyclin D1 negativity. Investigations revealed a Binet B and Rai I. Neither cytogenetic nor molecular (mutation TP53) analysis is available as this was not routinely performed at the time in the external hospital.

The patient received six cycles of Rituximab/Bendamustin as a first line treatment, and achieved a good partial remission. Seven months later, he presented with new and significant B-symptoms. Richter's transformation to Diffuse Large B-Cell Lymphoma (DLBCL) was excluded by a repeated lymph node biopsy. R-CHOP to treat this early progression lead to a minor response only. Treatment intensification was initiated with O-DHAP. Unfortunately, autologous stem cell collection with Navelbine failed.

Response after this treatment lasted only a couple of weeks, and the patient again presented with progressive disease with generalized lymphadenopathy and anemia (Hb 90-110g/l, thrombocytes 150-200G/l). A treatment therapy with Ibrutinib was started. This resulted in a partial remission, as confirmed by CT-scan two months after treatment initiation. A dose reduction to 140 mg/day was needed due to grade 3 diarrhoea.

Furthermore, recurrent muco-cutaneous bleedings, rated by 9 points according to the ISTH-Bleeding-score standardized questionnaire occurred. The platelet number was normal at that time. The coagulation tests revealed the only mild aPTT (activated Partial Thromboplastin Time) prolongation (44sec). Further investigation showed normal values of Fibrinogen, Factor II, V, VII, IX, XI and XII. However, both the vWF and VIII-factor activities were reduced to 35% and 44%, respectively, in this patient with of 0 (Rh+) blood group.

Citation: Bürki S and Novak U. Dual Mechanism of Severe Bleeding Diathesis in a Patient with CLL: Acquired Von Willebrand Syndrome and Ibrutinib - Mediated Platelets Dysfunction. Ann Hematol Oncol. 2020; 7(3): 1290.

Table 1: Results of hemostasis test during the treatment in the CLL patients.

		vWF ACT%	vWF AG%	FV111%
During Ibrutinib	13 Months	35	44	49
	14 Months	16	25	18
	1 h after 3000 E Haemate	72	185	87
	5 h after Haemate	18	93	77
	24 h after Haemate	11	55	92
After Ibrutinib		16	25	18
During Idealisib		19	35	39

The advanced platelet function analysis showed prolonged closure time with both collagen and epinephrine. The platelet aggregation test revealed an impaired platelet aggregation in response to collagen and a Ristocetin test revealed a biphasic platelet activation curve. The normal platelet aggregation could be restored in presence of ADP and arachidonic acid. Altogether, the findings were consistent with the diagnosis of an AVWS.

He experienced a severe epistaxis in August 2015. Emergency embolization of the A. maxillaris bilateralis was needed. Imaging revealed an epipharyngeal mass as a possible source of the bleeding, a biopsy showed an infiltration by the small lymphocytic lymphoma. Radiation therapy with 20Gy was given to the nasopharyngeal cavity.

Due to progressive disease, Ibrutinib was stopped in August 2015. The bleeding tendency, however, persisted, and therapy with the PIK3A inhibitor Idealisib was initiated.

Repetitive hemostasis tests showed a progressive decline of the von Willebrand factor and factor VIII:C. The clearance test of vWF clearly shows a higher activity of 72% after the Haemate substitution (Table 1).

Two months after the initiation of Idelalisib therapy, the patient presented a severe mucositis. He also developed a significant and further deterioration of his performance status. A CT-scan confirmed a further disease progression, and the patient died shortly after.

Discussion

This patient's history is informative as it includes a multifactorial aetiology of persistent severe bleeding diathesis and illustrates a possible therapeutic dilemma when treating such patients.

The AVWS was of origin of the disease-related hemostatic failure in this patient. The main supposed mechanism in CLL is a destruction of vWF by autoantibodies that are secreted by malignant B-lymphocytes [2]. The treatment approach here is based on the malignant clone eradication. Since CLL in our case was primary resistant, the hemorrhagic diathesis due to the vWF exhaustion correlated positively with the disease progression.

The second mechanism that played an important role in the bleeding persistence in our case was the qualitative (thrombopenia) and quantitative (impaired aggregation) platelet function perturbation.

The defective platelet aggregation was a manifestation of AVWS, and a consequence of inhibition of platelets signal transduction by Ibrutinib. Since the BTK-inhibitor can influence the platelet activation *via* blockage of vWF/GPIb-IX-V signalling, the platelet aggregation assay was not specific enough to distinguishing AVWS-from Ibrutinib-mediated platelets function perturbation.

The PIK3A-inhibitor Idealisib could apparently ameliorate platelet function in patients with CLL, as it was shown by platelet aggregation essay [18].

In our case, we did not observe any improvement in the bleeding syndrome after Idealisib introduction. We believe that it could be explained by concomitant progressive AVWS, which levelled all possible positive effects of Idealisib on platelet aggregation. Moreover, and with regard to the bleeding problems, Idealisib was probably introduced too late, already in setting of a highly resistant disease associated with severe secondary thrombopenia. An earlier switch from Ibrutinib to Idealisib could probably have been a better strategy, at least for bleeding symptoms improvement.

Concerning the possible approach to the underlying progressive AVWS, Intravenous Immune Globulins (IVIG) could also have been an option as previously shown, especially in the cases with anti-vWF autoantibodies. The IVIG association with AVW concentrates may be even more beneficial [19].

We believe that the thorough work-up of a case like ours could help to better understand the aetiology and the management of a bleeding diathesis in patients with lymphoproliferative disease under Ibrutinib, and thus, help to better define possible therapeutic strategies.

Acknowlegments

We thank Julia Engels and Michael Nagler for valuable comments. We also thank the Department of Hematology and Center of Laboratory Medicine (ZLM) for the lab analyses.

Authorship Contributions

SB analyzed data and wrote the paper; UN contributed vital material, had the idea, designed research, analyzed data, and wrote parts of the paper.

References

1. Curnow JL, Pasalic EJ, Favaloro. Treatment of von Willebrand Disease. Semin Thromb Hemost. 2016; 42: 133-146.
2. Federici AB. Acquired von Willebrand syndrome: data from an international registry. Thromb Haemost. 2000; 84: 345-349.
3. Tiede A. How I treat the acquired von Willebrand syndrome. Blood. 2011; 117: 6777-6785.
4. Mohri H. Acquired von Willebrand syndrome: features and management. Am J Hematol, 2006; 81: 616-623.
5. Mital A. Acquired von Willebrand Syndrome. Adv Clin Exp Med. 2016; 25: 1337-1344.
6. Burger JA. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med. 2015; 373: 2425-2437.
7. Khan WN. Defective B cell development and function in Btk-deficient mice. Immunity. 1995; 3: 283-299.
8. Wang ML. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013; 369: 507-516.
9. Byrd JC. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013. 369: 32-42.

10. Cinar M. Bruton tyrosine kinase is commonly overexpressed in mantle cell lymphoma and its attenuation by Ibrutinib induces apoptosis. Leuk Res. 2013; 37: 1271-1277.

11. Hallek M. The HELIOS trial protocol: a phase III study of ibrutinib in combination with bendamustine and rituximab in relapsed/refractory chronic lymphocytic leukemia. Future Oncol. 2015; 11: 51-59.

12. de Weerdt. Incidence and management of toxicity associated with ibrutinib and idelalisib: a practical approach. Haematologica. 2017; 102: 1629-1639.

13. Byrd JC. Ibrutinib *versus* ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014; 371: 213-223.

14. Shatzel JJ. Ibrutinib-associated bleeding: pathogenesis, management and risk reduction strategies. J Thromb Haemost. 2017; 15: 835-847.

15. Aguilar C. Ibrutinib-related bleeding: pathogenesis, clinical implications and management. Blood Coagul Fibrinolysis. 2018; 29: 481-487.

16. Levade M. Ibrutinib treatment affects collagen and von Willebrand factor-dependent platelet functions. Blood. 2014; 124: 3991-3995.

17. Liu J. Bruton tyrosine kinase is essential for botrocetin/vWF-induced signaling and GPIb-dependent thrombus formation *in vivo*. Blood. 2006; 108: 2596-2603.

18. Reda G. Idelalisib rapidly improves platelet function tests in patients with chronic lymphocytic leukemia. Br J Haematol, 2018; 183: 825-828.

19. Mohri H. Clinical significance of inhibitors in acquired von Willebrand syndrome. Blood. 1998; 91: 3623-3629.