Ribociclib Causing Transient Glanzmann Thrombasthenia-like Picture: A Report of 4 Cases

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Clinical Practice Points

- Breast cancer is the most common cancer in females.
- Cyclin-dependent kinase 4 and 6 inhibitors are new therapeutic agents being used in hormone-positive breast cancer.
- Ribociclib is used in hormone-positive, epidermal growth factor receptor 2-negative breast cancers. Many adverse events have been reported with the use of this agent. However, platelet dysfunction has never been reported.
- We report 4 cases of Glanzmann thrombasthenia-like picture following the use of ribociclib.
- Physicians should be alerted to look for the development of Glanzmann thrombasthenia in patients who receive ribociclib and develop bleeding symptoms with normal platelet counts.

Clinical Breast Cancer, Vol. 19, No. 5, e593-5 © 2019 Elsevier Inc. All rights reserved.
Keywords: Acquired platelet dysfunction, Breast cancer, CD4 and CD6 inhibitors, Cyclin-dependent kinase 4 and 6

Introduction

Breast cancer is the most frequent cancer in females as well as the most common cause of cancer death in females.[1] Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors are a new class of drugs that are indicated in hormone receptor-positive (HR^+) and normal expression of human epidermal growth factor receptor 2 (HER2-negative [$HER2^-$]) breast cancer with a positive impact on response and survival.[2] Three of these compounds are approved in the United States, Europe, and many other countries: palbociclib, ribociclib, and abemaciclib.[3]

Adverse events with these compounds include neutropenia (including grades 3 and 4), infection, fatigue, nausea, anemia, thrombocytopenia, alopecia, rash, constipation, vomiting, and stomatitis.[4]

In a recent review, serious adverse events from any cause were found in 19% of patients.[5] Although thrombocytopenia is well-documented, platelet dysfunction has not been reported previously.

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Submitted: Apr 13, 2019; Revised: May 18, 2019; Accepted: Jun 4, 2019; Epub: Jun 24, 2019

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Congenital Glanzmann thrombasthenia (GT) is an autosomal recessive disorder of integrin. It is a lifelong disorder that leads to mucocutaneous bleeding and bleeding caused by minimal trauma. The platelets in GT fail to aggregate in response to physiologic agonists such as adenosine diphosphate (ADP), collagen, thromboxane A2, and epinephrine. GT is caused by quantitative or qualitative deficiencies of $\alpha IIb\beta 3$, an integrin coded by the ITGA2B and ITGB3 genes. This glycoprotein serves as a receptor that binds to fibrinogen and other adhesive proteins, thus joining platelets together in the aggregate.[6]

In this article, we report 4 cases of breast cancer that received ribociclib and developed, while on treatment, platelet dysfunction consistent with GT.

Material and Methods

A group of post-menopausal female patients with HR^+, $HER2^-$ metastatic breast cancer, who failed more than 1 line of therapy, including aromatase inhibitors, were compassionately given ribociclib 600 mg orally daily for the first 3 weeks of a 4-week cycle.

All patients consented to the use of the drug. An informed consent consistent with the Helsinki declaration was signed by each patient. Institutional review board approval was obtained to report these cases.

The patients were followed and monitored as per the recommended protocol of the drug. The monitoring included platelet count but did not include platelet function.

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https://doi.org/10.1016/j.clbc.2019.06.002

Table 1 Patient Details

Patient[a]	Patient Characteristics	Symptoms (C, D)	Baseline PLT × 103 μL and BT/min	Baseline Agg Test (C, D)	Tests After Starting the Medication: BT/min and Agg (C, D)	Time for Agg Testing and BT to Normalize After Stopping the Medication
Patient 1	50-year-old, postmenopausal, stage IV post hormonal failure. Failed rescue chemotherapy	Epistaxis (C1, D7)	PLT: 160 BT: 6	Not done	Agg: Abnormal[b] BT: > 12 (C1, D7)	3 wk
Patient 2	53-year-old, postmenopausal, stage IV post hormonal failure. Failed rescue chemotherapy	Asymptomatic	PLT: 282 BT: 6.2	Normal (C1, D1)	Agg: Abnormal BT: > 10 (C1, D21)	2 wk
Patient 3	50-year-old, postmenopausal, primary refractory failed multiple line of neoadjuvant chemotherapy and progressed to stage IV	Epistaxis and gum bleeding (C2, D21)	PLT: 160 BT: 6	Normal (C2, D1)	Agg: Abnormal BT: > 10 (C2, D21)	1 wk
Patient 4	54-year-old, postmenopausal, stage IV hormonal therapy failure. Failed second-line chemotherapy	Easy bruising (C1, D7)	PLT: 219 BT: 5	Normal (C1, D1)	Agg: Abnormal BT: > 10 (C1, D7)	3 wk

Abbreviations: Agg = aggregation; BT = bleeding time; C = cycle; D = day; PLT = platelet count.
[a]All the patients had flow cytometry of platelets done when aggregation test was abnormal and showed normal CD41 and CD61 results.
[b]Abnormal defined as platelets fail to aggregate with adenosine diphosphate and collagen, but may show low aggregation with ristocetin.

Platelet aggregation was done using electric impedance instrument (multiplate analyzer, Roche Diagnostics International Ltd, Rotkreuz, Switzerland). The following agonists were used: ADP, collagen, and ristocetin, as per the recommendation of the manufacturer. Acquired Glanzmann thrombasthenia (AGT) was defined as the failure of platelets to aggregate with ADP and collagen but may show low aggregation with ristocetin.

All patients had flow cytometry of platelets using BD FACSCanto II cell analyzer (BD, Franklin Lakes, NJ) and data were analyzed with BD FACSDiva software (BD). Gating on the platelets with their characteristic side scatter/forward scatter distribution or their positivity to CD42 was employed. Monoclonal antibodies for CD 41 (PE), CD42b (Percp-cyc5.5), and CD61 (FITC) were selected based on the platelet aggregation pattern, which was consistent with the GT pattern. All monoclonal antibodies were supplied by BD. Bleeding time was done using template bleeding time. None of the tested patients had thrombocytopenia or any other abnormality in the coagulation screen tests.

Patient Details

A total of 6 patients received ribociclib; 2 patients were completely asymptomatic with normal aggregation testing at the end of the first cycle (C1D21). Four patients had aggregation testing results consistent with AGT. Because the development of AGT is not a known side effect of ribociclib, no baseline aggregation testing was done for patient 1. On C1D7, she developed epistaxis, which prompted us to further investigate the cause. Platelet aggregation testing was done and was found to be abnormal with prolonged bleeding time.

After patient 1, the subsequent patients receiving ribociclib had baseline platelet aggregation testing. Patient 2 had normal platelet aggregation testing before initiating ribociclib. During the course of her treatment, she did not have any bleeding symptoms, although platelet aggregation testing at the end of the first cycle (C1D21) was abnormal. Given the fact that she was asymptomatic, she started her second cycle following a 1-week rest as per medication protocol. Platelet aggregation was retested on C2D14 and was abnormal, but because she was asymptomatic, she was allowed to finish the second cycle. At the end of the rest week, she still had an abnormal platelet aggregation test. She was given an extra rest week, and the platelet aggregation was retested, which came back as normal.

Patient 3 had a normal baseline platelet aggregation test. On C2D21, she developed epistaxis and gum bleeding with an abnormal platelet aggregation test. After the rest week, she started her third cycle. At the end of the third cycle (C3D21), she developed gum bleeding and epistaxis. She was retested following the 1-week rest and was found to have a normal platelet aggregation pattern.

Patient 4 also had normal baseline platelet aggregation pattern. She developed easy bruising on day 7 (C1D7) and had an abnormal platelet aggregation test. Given her mild symptoms, the decision to continue the cycle was made. She still had easy bruising at the end of the cycle and still had an abnormal platelet aggregation test (C1D21). At the end of the rest week, she still had abnormal platelet aggregation testing. Starting cycle 2 was postponed for another week. She had a platelet aggregation test done at the end of the second rest week, which still showed an abnormal aggregation pattern. Platelet aggregation testing was normal at the end of the

third rest week (3 rest weeks in total). She was re-challenged with ribociclib after the third rest week, but developed easy bruising again at day 14 (C2D14) with an abnormal platelet aggregation test; the decision to stop ribociclib was made.

Tests for coagulation screen using prothrombin time/international normalized ratio, partial thromboplastin time, and thrombin time were done and were normal. All patients had a normal platelet count during the treatment and follow-up periods.

The only concomitant medication all these patients were receiving was letrozole 2.5 mg daily. They were not taking any antiplatelet or herbal medications. Table 1 shows the details of patients and their findings.

Discussion

The CDK4/6 inhibitors are a new class of drugs for HR^+, $HER2^-$ breast cancer that seem to have a positive impact on tumor response and survival.[2] They are gaining widespread use in most countries. Three of these compounds have been approved by the United States Food and Drug Administration and European Medicines Agency. They include palbociclib, ribociclib, and amebaciclib.

Although their adverse events have been well-described in clinical trials, discontinuation of these drugs is not common because of these adverse events.[5] Post-marketing surveillance and monitoring are needed to capture the full spectrum of adverse events.

AGT is known to occur in lymphoproliferative disorders, chronic myeloid leukemia,[7,8] and multiple myeloma.[9] There have been no cases of AGT reported with the treatment of breast cancer. In a recent systematic review and meta-analysis of the hematologic toxicity of CDK4/6, there was no report of AGT with this new class of drugs.[10] These seem to be the first cases of AGT related to ribociclib therapy.

CD41/CD61, a member of family integrin receptors, is mainly expressed by platelets and megakaryocytes. The resting form of the CD41/CD61 complex is involved in platelet activation and aggregation by binding to fibrinogen. An absence or dysfunction of CD41/CD61 on the platelet surface results in GT, which can be inherited or acquired.

It is of interest that CD41/CD61 on the surface of the platelets were normal by flow cytometry, indicating that the effect of the drug did not cause reduction of these surface antigens on platelets, but rather a dysfunction of it or probably a block in the activating pathways of the receptor.

Because other CDK4/6 inhibitors are not listed on our formulary, we were not able to address this issue with patients treated with other CDK4/6, and we cannot confirm if it is a class effect or not.

It was reassuring that patients with AGT had minimal or no symptoms at all. However, the bleeding tendency may manifest in a patient requiring an emergency surgery while on ribociclib, and therefore, careful monitoring is warranted because they may need platelet transfusion despite the normal platelet count or may need other agents such as recombinant factor VII-a or tranexamic acid. Additional work is needed to clarify the mechanism of AGT in patients receiving ribociclib.

Conclusion

This report should alert prescribers of ribociclib to this adverse event, and they should actively look for it in patients with bleeding symptoms with normal platelet count or in patients planned for surgery while on ribociclib.

Acknowledgment

The authors wish to thank Novartis Jordan for providing ribociclib on a free companionate basis to the patients, and would like to thank Dr Nuhad Ibrahim from MD Anderson Cancer Center, Houston, TX, for his feedback and guidance.

Disclosure

The authors have stated that they have no conflicts of interest.

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