

Tyrosine Kinase Inhibitor–Associated Platelet Dysfunction: Does This Need to Have a Significant Clinical Impact?

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The management of chronic myeloid leukemia (CML) entirely changed after the emergence of tyrosine kinase inhibitors (TKIs). In the era of TKIs, the 10-year overall survival now exceeds 80%, and the prevalence of patients receiving long-term TKI therapy has substantially increased. In addition to the efficacy, CML caring physicians now mainly focus on the management of the TKI-associated long-term nonhematologic toxicities, generally so-called the “off-target” effects of these drugs.

Second-generation TKIs—dasatinib, nilotinib, and bosutinib—are more potent than imatinib and these drugs also have different off-target multikinase inhibitory effects than imatinib. These adverse events (AEs) may or may not have an impact on the health-related quality of life (HRQoL), especially depending on the grades of these toxicities. The nonhematologic AEs may occur anytime during the follow-up, and sometimes they can have a negative clinical impact.

TKIs are known to be associated with defective platelet function.^{1,2} Dasatinib, a potent inhibitor of *BCR-ABL1* and SRC family kinases (SFK), is known to cause aberrant platelet function and can induce bleeding, independent of thrombocytopenia.² But many patients with a clinically significant bleeding have low platelet counts and advanced disease phases (eg, blast crisis) that usually require higher daily dasatinib doses.^{2,3} Platelet function abnormalities have been described to a lesser extent with imatinib and bosutinib, but these laboratory tests generally appear not to be affected by nilotinib because of the different spectrum and intensity of inhibition of off-target signaling pathways by the individual TKIs.^{1,4} Also, the third-generation TKI, ponatinib, is known to cause atherothrombotic events; on the other hand, it may also impair platelet functions.^{1,5}

In this issue of the Journal, Sener and colleagues⁶ investigated the possible effects of TKI therapy on platelet functions and other hemostatic parameters in 68 patients with CML in chronic phase (CML-CP) receiving different TKIs. The authors divided their patient cohort into 3 according to the TKI

consumed (eg, imatinib [n = 47], dasatinib [n = 15], and nilotinib [n = 6]), and there were no cases with bosutinib nor ponatinib.

For all patients, the platelet counts were $>100 \times 10^9/L$, and only 1.5% of the patients had minimal prolongation in prothrombin time, and 3% of them had minimally prolonged activated partial thromboplastin time. Similar to what was observed in the previous studies performed among patients with CML receiving various TKIs, in this study,⁶ impaired platelet functions detected by light transmission aggregometry were observed in 29.8%, 40%, and 50% of the patients in imatinib, dasatinib, and nilotinib groups, respectively.

The mechanism of this effect is not fully understood, and Quintás-Cardama and coworkers² analyzed the impact of TKI therapy on platelet functions via the stimulation of platelet aggregation with adenosine diphosphate, arachidonic acid, epinephrine, collagen, and ristocetin, together with using the platelet function analyzer (PFA-100) in 75 patients with CML-CP. The authors observed that most of the patients receiving dasatinib (23/27, 85%) had platelet dysfunction. Also, they found that 4 (15%) of the 26 patients receiving bosutinib and 10 (66%) of the 15 patients receiving imatinib had impaired platelet function test. On the other hand, they also revealed that all patients treated with nilotinib (n = 7) had normal platelet functions in vitro.

There are other studies reporting TKI—mainly dasatinib-induced platelet dysfunction and the possible underlying mechanisms of this sometimes clinically relevant situation.^{3,7,8} Dasatinib may alter platelet aggregation by inhibiting key

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kinases such as SFKs, LYN, and FYN that might play a role in the platelet homeostasis.² On the other hand, bosutinib, which is a multikinase inhibitor similar to dasatinib, was detected to cause platelet dysfunction in the study of Quintás-Cardama et al,² but no clinically significant bleeding events were reported with bosutinib.

Sener et al⁶ and Quintás-Cardama et al² revealed that impaired platelet functions were observed in 29.8% (14/47) and 66% (10/15) of the cases receiving imatinib, respectively. However, in other studies, imatinib was found not to cause platelet dysfunction.^{1,4} Similarly, nilotinib was generally not associated with platelet dysfunction *in vitro*,¹⁻⁴ although Sener and colleagues⁶ found half of their cases using nilotinib had impaired platelet function tests; however, the number of patients receiving nilotinib in their cohort was very limited. Furthermore, there are some studies reporting that ponatinib might have an impact on platelet functions, and these reports reveal that ponatinib may inhibit platelet activation, spreading, granule secretion, and aggregation, likely through broad-spectrum inhibition of platelet tyrosine kinase signaling.^{1,5} These findings are interesting, because as observed in clinical trials, ponatinib may cause atherothrombotic events, although it may also impair platelet functions. So, most probably, there is more to be done in the field of ponatinib-associated thrombotic complications in the future.

Sener and colleagues⁶ also tried to objectively quantify the bleeding diathesis in their cohort using a standardized questionnaire. According to this bleeding questionnaire (the International Society on Thrombosis and Haemostasis/Scientific and Standardization Committee [ISTH/SSC] Bleeding Assessment Tool), 22% (n = 15) of 68 patients had bleeding symptoms. However, all of these bleeding events were minor, including epistaxis, cutaneous bleeding, minor wound bleeding, bleeding after tooth extraction, and menorrhagia. Approximately one-fourth of the cases receiving imatinib and 20% of patients with dasatinib had bleeding symptoms, whereas no patients had bleeding in the nilotinib group. And when compared to cases who had platelet dysfunction, they found no correlation between presence of any bleeding or total bleeding score and plasma secretion defect or any aggregation abnormality. However, Quintás-Cardama et al³ revealed that bleeding episodes were observed in 23% of patients with CML treated with dasatinib. This complication was more frequent among those patients with advanced disease who were receiving higher doses of dasatinib and affected the gastrointestinal tract in 81% of the cases, and they emphasized that especially thrombocytopenia and disease status of CML were associated with an increased risk of bleeding. All patients in the cohort of Sener et al⁶ were CML-CP, without any cases with significant thrombocytopenia, and no bleeding in the gastrointestinal tract was observed.

Gastrointestinal tract bleeding is a relatively common treatment-emergent AE in patients receiving dasatinib. Although all patients on dasatinib therapy have a faulty collagen-induced platelet aggregation, only a fraction of them develop clinically significant bleeding complications, with the

remaining majority of cases being asymptomatic.⁸ In the study of Brave et al,⁹ the authors focused on the bleeding tendency of patients receiving dasatinib. Minor bleeding was mostly due to platelet dysfunction plus thrombocytopenia. On the other hand, major bleeding was mainly observed in cases having 2 or more predisposing factors including thrombocytopenia, advanced disease phase, impaired platelet functions, impaired coagulation, and so on.⁹ In addition to these predisposing factors, gastrointestinal tract bleeding can also be seen under dasatinib due to hemorrhagic colitis.¹⁰

Dasatinib is also known to disrupt the barrier function of the vascular endothelium.^{7,8} This transient increase in vascular leakage, enhanced by decreased coated platelet generation—even at low (ie, therapeutic) plasma levels of dasatinib—and impaired platelet aggregation might all contribute to bleeding diathesis.⁸ Furthermore, dasatinib has been thought to affect bleeding time and also has an impact on thrombopoiesis, promoting megakaryocyte differentiation within the bone marrow but impairing the ability of megakaryocytes to migrate and form into platelets.^{4,11}

In conclusion, according to the present study by Sener et al⁶ and some others, TKIs may cause platelet dysfunction mainly *in vitro*, which do not necessarily translate into significant clinical outcomes. Especially, dasatinib was shown to have some negative effects on platelet functions, which sometimes may lead to significant bleeding affecting the HRQoL, mainly in the setting of thrombocytopenia and in cases with advanced disease phases. In general, it is not recommended to test for platelet functions prior to or during TKI therapy routinely in CML cases; however, one should always keep in mind that, if a patient with CML under TKI therapy has bleeding diathesis, TKI could be the underlying cause. Thus, in patients with CML having a clinically significant bleeding tendency under TKI treatment, short-term interruption of the therapy could be necessary and beneficial, especially before major surgical procedures.

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