The clinical impact of ponatinib on the risk of bleeding in patients with chronic myeloid leukemia

We have read with interest the early release paper by Neelakantan *et al.* regarding platelet dysfunction associated with ponatinib in patients with chronic myeloid leukemia (CML) resistant to multiple tyrosine kinase inhibitors (TKI) therapy.[1] The authors have shown a prolonged closure time with PFA 100 (a sensitive measure for primary hemostasis)[2] in 5 patients with CML resistant to TKI who had been receiving ponatinib for at least two weeks without interruption. Although none of these patients developed clinical bleeding during the study period, the authors concluded that ponatinib may inhibit platelet function, suggesting that physicians should be vigilant when patients with ponatinib are facing any hemostatic challenges.[1]

To define the clinical implication of this finding on the risk of bleeding among CML patients receiving ponatinib, we reviewed the medical records of 80 patients diagnosed with chronic phase CML (CML-CP) according to previously described criteria and treated with ponatinib on clinical trials conducted at The University of Texas, MD Anderson Cancer Center between August 25th 2008 and December 21st 2012. All patients signed informed consent to participate in the trials in accordance with the Declaration of Helsinki, and all protocols were approved by the institutional review board.

The median number of prior therapies for patients included in this analysis was 3 (range 0-6). Six patients had a prior history of bleeding (2 menorrhagia, 2 gastrointestinal bleeding, one subdural hematoma, and one retinal hemorrhage). The median platelet count at the start of ponatinib therapy was 256x10^9/L (range 21-1447x10^9/L). Seven (9%) patients were receiving anticoagulation therapy while on ponatinib for atrial fibrillation (n=3), portal vein thrombosis, pulmonary embolism, lower extremity deep vein thrombosis, or stroke (one each). Four of them were treated with enoxaparin (2 of them additionally received aspirin 81 mg daily), one dabigatran, one warfarin, and one rivaroxaban. Twenty-five (31%) patients were receiving antiplatelet therapy while on ponatinib (19 aspirin alone, 5 aspirin and clopidogrel, one aspirin and plasugrel).

A total of 9 (11%) patients experienced bleeding events. Three patients had vaginal bleeding, one occurred while ponatinib was on hold for grade 3 thrombocytopenia (platelets recovering to 55 x10^9/L at the time of bleeding), one had grade 1 vaginal bleeding associated with a high grade squamous cervical intraepithelial lesion (CIN 3), and one experienced grade 1 menorrhagia with negative workup while simultaneously taking aspirin and rivaroxaban. Two patients had hematochezia: one had a single episode of self-limited hematochezia (grade 1) associated with prolonged constipation, and one had multiple grade 1 rectal bleeding episodes with bowel movements before and after an uncomplicated hemorrhoidectomy due to a thrombosed hemorrhoid while also receiving aspirin. One patient presented with a minor (grade 1) self-limited bleed in the site of a shave biopsy and curettage for a dermatological lesion (squamous cell carcinoma) while platelet count was 75x10^9/L. He also had a minor bleeding complication after a dental extraction (platelet count 62x10^9/L); this patient was concomitantly receiving warfarin. One patient had one episode of epistaxis (grade 1) that was self-limited and required no interventions. One patient experienced 2 episodes of hematuria related to urinary tract infection while ponatinib was on hold due to thrombocytopenia. One patient had a hematoma in the gluteal area and lower extremity after a fall in the setting of thrombocytopenia (platelets 55x10^9/L) and concomitant use of aspirin. None of these episodes were considered related to ponatinib or required interruption or dose adjustment of ponatinib. Seventeen patients had a combined total of 23 surgical procedures performed during treatment with ponatinib; only 2 procedures had a bleeding complication in the same patient, as described above.

The mechanism of platelet dysfunction reported to occur with ponatinib is currently unknown. It has been suggested that inhibition of several kinases such as SFK, LYN, and FYN, that play an important role in early platelet activation, may be responsible for the effect of ponatinib on platelet function.[1,4,5] In our experience, a small minority of patients who received ponatinib experienced clinical bleeding and in none of these cases did the bleeding appear to be directly related to ponatinib. Furthermore, most patients with prior history of bleeding or who are receiving anticoagulation and/or antiplatelet therapies did not experience any bleeding episodes while treated with ponatinib. These findings suggest that ponatinib may be safely used even on patients with history of bleeding or receiving antiplatelet /anticoagulation therapies. Attention should be given to other precipitating factors for bleeding such as low platelet count or concomitant use of anticoagulants or antithrombotic agents while patients are receiving ponatinib.

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References

1. Neelakantan P, Marin D, Laffan M, Goldman J, Apperley J, Milojkovic D. Platelet dysfunction associated with ponatinib, a new pan BCR-ABL inhibitor with efficacy for chronic myeloid leukemia resistant to multiple tyrosine kinase inhibitor therapy. Haematologica. 2012;97(9):1444.
2. Favaloro EJ. Clinical utility of the PFA-100. Semin Thromb Hemost. 2008;34(8):709-33.
3. O'Hare T, Shakespeare WC, Zhu X, Eide CA, Rivera VM, Wang F, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell. 2009;16(5):401-12.
4. Ezumi Y, Shindoh K, Tsuji M, Takayama H. Physical and functional association of the Src family kinases Fyn and Lyn with the collagen receptor glycoprotein VI-Fc receptor gamma chain complex on human platelets. J Exp Med. 1998;188(2):267-76.
5. Quek LS, Pasquet JM, Hers I, Cornall R, Knight G, Barnes M, et al. Fyn and Lyn phosphorylate the Fc receptor gamma chain downstream of glycoprotein VI in murine platelets, and Lyn regulates a novel feedback pathway. Blood. 2000;96(13):4246-53.