Dasatinib and Dysfunction of Platelets

Kamal Kant Sahu¹ · Uday Yanamandra¹ · Vikrant Bhar¹ · Deba Prasad Dhibar¹ ·
Subhash Chander Varma¹ · Pankaj Malhotra¹

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Dear Editor,

In the post imatinib era, the newly developed 2nd generation tyrosine kinase inhibitors (TKI's) have revolutionized the treatment of chronic myeloid leukaemia (CML). In 2006, FDA approved dasatinib for chronic myeloid leukaemia (CML) and Ph +ve acute lymphoblastic leukaemia (ALL). Since then, it holds a key place in the therapeutic armamentarium for CML. There are few recent reports of dasatinib induced “platelet dysfunction” [1, 2]. Aim of this report is to sensitise haematologists regarding this rare but clinically significant adverse-effect secondary to dasatinib.

In 2005, a 40-year-old male was diagnosed as CML-CP (Sokal—high risk group) and was started on imatinib 400 mg OD. He did well and achieved complete cytogenetic response at eleven months of starting therapy. He was subsequently followed at regular intervals with good drug compliance and tolerability. In April 2015, he had disease progression while on therapy with loss of major molecular response. As per National Comprehensive Cancer Network (NCCN) recommendations, kinase domain mutation analysis was done which showed F359V (Phenylalanine to Valine) mutation in the imatinib binding domain of ABL1 tyrosine kinase. As per in vitro sensitivity, dasatinib was found to be the most sensitive TKI with lowest IC 50 of 1.49 as compared to 2.86 and 5.16 for imatinib and nilotinib, respectively (measurement of relative resistance). Hence, he was started on dasatinib 100 mg OD. After 3 weeks, patient developed subcutaneous ecchymosis over

his upper and lower limbs. There was no history of passage of maroon colored stool, dull headache, gum bleeding, blurring of vision or haemoptysis. For these complaints, patient visited nearest healthcare centre to avail first aid and symptomatic care. After tele-consulting with us, general physician stopped dasatinib temporarily and gave supportive care.

Two weeks later, he visited our centre for definitive therapy. His coagulogram and hemogram were normal with the platelet count of $170 \times 10^9/L$. Patient had no other comorbidities requiring use of other drugs like ecosprin, clopidogrel, warfarin or NSAIDS in recent past. Hence possibility of bleeding secondary to thrombocytopenia, NSAID abuse, anticoagulants or antiplatelets were ruled out. Other causes of ecchymosis due to capillary bleeding such as acquired or inherited connective tissue/collagen vascular disorders (acquired like Vitamin C deficiency, inherited like Ehlers Danlos syndrome, autoimmune like Rheumatoid arthritis) were also considered. Analysis for these disorders was done by asking disease specific present, personal and family history. We did a detailed systemic examination focussing especially on ocular, loco-motor, skeletal and cardiovascular system. Clinical diagnosis of “dasatinib related platelet dysfunction” was suspected after ruling out the above mentioned causes of subcutaneous ecchymosis. As the patient had already stopped dasatinib, representative ideal blood sample could not be retrieved from the patient and hence platelet function assay couldn't be done in index case. In view of significant temporal correlation between dasatinib withdrawal and resolution of ecchymosis patches, we considered him to be a case of “dasatinib related platelet dysfunction”. Subsequently, he was started on nilotinib 300 mg BD. Thereafter, he did not develop fresh bleeding episodes from any part of the body confirming our diagnostic assumption. At

✉ Pankaj Malhotra
hematpgi@gmail.com

¹ Department of Clinical Haematology, Internal Medicine,
Postgraduate Institute of Medical Education and Research,
Chandigarh 160012, India

present, he is tolerating nilotinib well and is planned to undergo repeat RQ-PCR (IS) for BCR-ABL1 transcripts after 3 months. This case clearly suggests that a high index of suspicion is required to diagnose such cases and early interruption of dasatinib is rewarding before the patient develops life threatening bleeding episodes.

Confirmation of platelet dysfunction is done by PFA-100 assay and light transmission aggregometry. An important aspect while conducting platelet function tests is that, as per International Society Of Thrombosis And Haemostasis (ISTH) guidelines, analysis of platelet rich plasma (PRP) with a platelet count of $<150 \times 10^9/L$ and $>450 \times 10^9/L$ is though possible but the results should be interpreted with great caution using appropriate internal control [3]. In general, 140 mg OD dose of dasatinib has a better usual side effect profile (e.g. pleural effusion) than 70 mg BD [4]. However, with reference to platelet dysfunction, Quintás-Cardama et al. did not find any significant difference amongst different dose schedule of dasatinib [5].

Dasatinib is a CYP3A4 substrate, thereby meaning that the enzyme inhibitors like ketoconazole, clarithromycin, indinavir, metformin and voriconazole etc. can increase the dasatinib blood levels and hence the toxicity [6]. Interestingly, we tend to overlook the dietary habits of patient while prescribing dasatinib. Grapefruit juice and fish oil can increase plasma concentrations of dasatinib and are hence recommended to be avoided [7, 8]. Factors like age and gender have not been shown to significantly affect the pharmacokinetics of dasatinib. However, there are anecdotal reports where older, frail patients who were unable to tolerate usual recommended dose of dasatinib have achieved a good response with minimal doses [9].

In most cases, gastrointestinal tract is the common site of bleeding [2]. The exact cause of site predilection is yet unknown, but CD8+ve lymphocytic colitis secondary to dasatinib may be one of the explanations [10]. It is imperative to stress upon the fact that symptoms like vague headache and passage of dark colored stools may go unattended unless they are specifically asked from patients by the treating haematologists. Ignorance, illiteracy and distant medical facilities like in our case are still the major reasons for delayed presentation, thereby preventing a timely diagnosis. These facts make the role of treating haematologists in the current era of second generation TKIs even more challenging than previous.

Unlike imatinib for which we have almost more than a decade of experience, dasatinib and other 2nd generation

TKIs are relatively newer in clinical practice. Although they have expanded horizons of treatment, but are still unpredictable as far as side-effects are concerned. We conclude with a remark that for the better understanding of side-effect profile and pharmacokinetics of these newer drugs, we suggest reporting of such side effects is extremely important and should be promoted.

Compliance with Ethical Standards

This article does not contain any studies with human participants or animals performed by any of the authors.

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