Thrombosis & Haemostasis: Research

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Austin Publishing Group

Case Presentation

Major Gastrointestinal Bleeding with Severe Platelet Dysfunction in Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia Patient Treated with Imatinib

Crestani S[1]*, Michieli M[1], Ciancia R[1], Steffan A[2], Turetta M[2] and Cozzi MR[2]

[1]Oncoematologia Trapianti Emopoietici e Terapie Cellulari, Centro di Riferimento Oncologico (CRO) IRCCS, Italy

[2]Immunopatologia e Biomarcatori Oncologici, Centro di Riferimento Oncologico (CRO) IRCCS, Italy

***Corresponding author:** Crestani S, Oncoematologia Trapianti Emopoietici e Terapie Cellulari, Centro di Riferimento Oncologico (CRO) IRCCS, via Gallini 2, 33081 Aviano, Italia

Received: December 01, 2020; **Accepted:** December 18, 2020; **Published:** December 25, 2020

Abstract

Impairment of platelet function is reported among *off-target* effects of Tyrosine Kinase Inhibitors (TKIs) treatment with a marked inter-individual variation in vitro. Particularly, only minor bleeding was observed in a small percentage of Imatinib treated patients and with no correlation between bleeding and in vitro platelet dysfunction. This case report refers to a 69-year-old Ph+ALL patient in complete haematological response who developed hemorrhagic diathesis with a major gastrointestinal bleeding during imatinib treatment. We discuss clinical presentation, possible causes of bleeding disorder and treatment. Our report demonstrates the putative association between imatinib and development of reversible platelet dysfunction associated with major bleeding.

Keywords: Acute lymphoblastic leukemia; Philadelphia chromosome; Tyrosine kinase inhibitors; Imatinib; Acquired platelet dysfunction; Bleeding disorders

Abbreviations

ALL: Acute Lymphoblastic Leukemia; Ph: Philadelphia Chromosome; CML: Chronic Myeloid Leukemia; TKIs: Tyrosine Kinase Inhibitors; LTA: Light Transmission Aggregometry; SFK: Src Family Kinase

Introduction

Acute Lymphoblastic Leukaemia (ALL) is a rare disease in adults with an estimated annual incidence of about 1 per 100.000 in Europe [1]. Up to 25% of adult ALL carry chromosomal translocation t(9;22)(q34;q11.2), also called Philadelphia chromosome, and resulting in BCR-ABL fusion protein with a constitutive tyrosine kinase activity. The incidence of t(9;22) rises with age, exceeds 50% in patients over 50 years old [2] and becomes the most frequent cytogenetic abnormality in adult patients with ALL.

Prior to the advent of Tyrosine Kinase Inhibitors (TKIs), adult patients with Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia (Ph^+ALL) had a very poor prognosis: although there was high Complete Response (CR) rate (60-90%), the long term Overall Survival (OS) was 10% to 19%, improved by allogenic Hematopoietic Stem Cell Transplantation (HSCT) to approximately 30% [3,4]. However, intensive chemotherapy and allogenic HSCT are often not feasible options for patients over 55-60 years old, and the determination of treatment needs to consider co-morbidities and fitness.

With the introduction of TKIs the outcome of patients has improved dramatically, with CR rates ranging from 72% to 96% and 2-year OS around 40%. For elderly Ph^+ALL patients (>60 years old), who had the poorest outcome, monotherapy with TKIs (plus steroid) was explored with a CR in almost all patients with no deaths in induction [5,6] and some patients still alive after ten years [7].

The most we know about TKIs' side effects comes from experience with Chronic Myeloid Leukemia (CML): TKIs therapy is well tolerated, especially with imatinib whose most common adverse events are myelo suppression, diarrhoea and peripheral edema.

TKIs are also known to be associated with defective platelet function: impaired platelet aggregation were observed in 29.8% of CML patients in imatinib treatment group [8] but no correlation was found between presence of any bleeding or total bleeding scores and platelet dysfunction. The minor bleeding observed was correlated with primary haemostatic failure such as epixtasis, bruising and minor wound bleeding, despite improvement in platelet counts and no defects in coagulation parameters (prothrombin time, activated partial thromboplastin time). Certain authors assume that the mechanism responsible for these side effects is related to the Src Family Kinases (SFKs) inhibition by TKIs that affect platelet signalling required for spreading, aggregation and other functional responses [9]. Platelet membrane Glycoprotein VI (GP6) in particular, is an important receptor for thrombus formation, and is constitutively associated with SFKs and its downstream effectors as enzymes and cytoskeletal proteins that coordinate platelet activation. GP6 locus is highly polymorphic and the two common alleles of GP6 in normal subjects (*a* and *b*) may have from 5 to 10 fold different level of receptor expression. Clinical studies indicate that patients with low GP6 expression could be more susceptible to bleeding than thrombotic events, whereas enhanced GP6 surface expression has been associated with myocardial infarction and acute coronary syndrome [10].

We report here a case of a Ph^+ALL patient treated with imatinib and developing severe hemorrhagic diathesis, in absence of thrombocytopenia, due to severe acquired platelet dysfunction associated with lower platelet GP6 surface density.

Citation: Crestani S, Michieli M, Ciancia R, Steffan A, Turetta M and Cozzi MR. Major Gastrointestinal Bleeding with Severe Platelet Dysfunction in Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia Patient Treated with Imatinib. Thromb Haemost Res. 2020; 4(4): 1051.

Case Presentation

A 69-year-old man was admitted to our Institution with a new diagnosis of Ph+ALL. His past history was remarkable for panhypopituitary insufficiency and diabetes insipidus due to previous pituitary tumor surgery. In Figure 1A we summarise the timeline of the case including therapeutic interventions, useful clinical information and events that occurred during follow-up.

Day 0: on admission to the emergency department, the patient had dispnea due to pulmonary edema, fever higher than 39°C and was rapidly transferred to intensive care (non invasive ventilation for respiratory failure and amine support). A complete blood count revealed Haemoglobin (Hb) level of 8.9 g/dL and severe thrombocytopenia with a platelet count of 13×10^3/μL. Lymphoid blasts were about 10% of total leukocyte count (WBC: 8.2×10^3/μL) and t(9;22) BCR- ABL p190 was detected in nested RT-PCR. Induction treatment with imatinib was started at the escalation dose of 600mg/day, associated with steroids.

Day 35: The patient slowly improved his condition; platelet count exceed $>100\times10^3$/μL, no defects in coagulation parameters had been identified, BCR-ABL p190 was undetectable but cutaneous bleedings still persisted with extensive hematomas.

Day 55: Since coagulation parameters, including prothrombin time, activated partial thromboplastin time, fibrinogen and von Willebrand Factor were in normal range, we evaluated primary haemostasis by platelet functional studies according to the classical Born method (LTA). Platelet aggregation and release reaction were tested in association with platelet expression profile of CD41 (integrin alpha chain IIb, GPIIb), CD42a (glycoprotein IX, GPIX), CD61 (glycoprotein IIIa, GPIIIa), CD49b (integrin alpha2 chain) and GP6 (Glycoprotein VI) by flow cytometry. LTA studies revealed marked response impairment to collagen (about 50% of maximal amplitude MA compared to control) and ablated release reaction with all agonists used (Figure 1B). Expression of main platelet membrane receptors was not significantly different between patient and control group except for reduction of GP6 expression (Figure 1C). Packed red blood cell units were administered for severe anemia.

Day 66: Patient presented severe gastrointestinal bleeding which required massive blood transfusions and surgical hemostasis. Imatinib was stopped for 14 days.

Day 80: No platelets functional abnormalities were identified (Figure 1B) and imatinib was resumed with a dose adjusted to 400 mg/die.

Day 100: Despite imatinib reduction, cutaneous bleedings still persisted with low Hb levels. Platelet aggregation and release reaction were tested again, reduced maximal amplitude compared to control (about 20%) and release reaction at the lower limits of normal range were found (Figure 1B).

Day 110: Considering treatment-related toxicity imatinib was stopped.

Day 124: No platelet functional abnormalities were identified (Figure 1B) and a third-generation TKIs (ponatinib) was administered.

At all times, the expression of main platelet membrane receptors

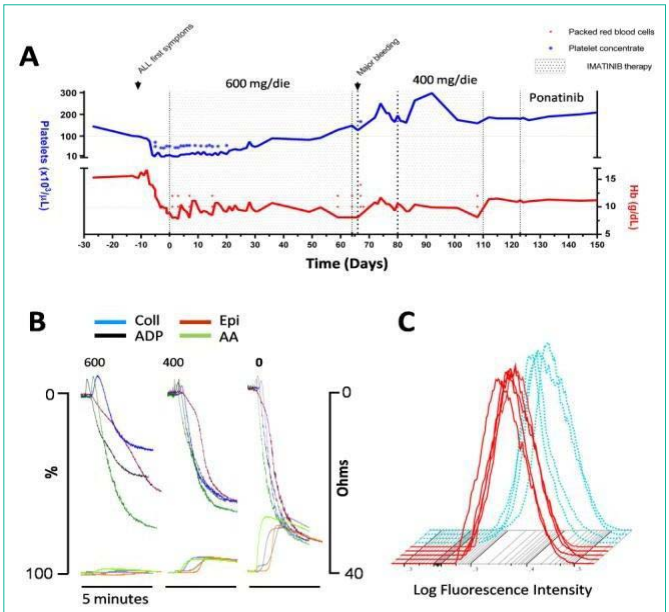

Figure 1: (A) timeline including therapeutic interventions and useful clinical information during follow-up; **(B)** results of Light Transmission Aggregometry (LTA) in patient on-imatinib (600 and 400mg/die) and post-imatinib therapy (0 mg/die). Aggregations in Platelet Rich Plasma were performed with platelet count comprised between 150 and 300 $x10^9$/L like in controls. Collagen (2 microg/ml), ADP (4 microM), Epinephrine (5 microM) and Arachidonic Acid (1mM) were used as agonists; **(C)** flow cytofluorimetric analysis of patient platelets labeled with PE mouse Anti-Human platelet GP6 (red line), compared to different healthy blood donors (dotted blue line). The fluorescence histograms were derived from 10.000 gated events with the forward and side scatter characteristics of single intact platelets.

was not significantly different between patient and control group except for GP6, whose MFIs values were 3.2 ± 0.91 and 5.3 ± 0.57 (p=0.0033), respectively (Figure 1C).

After a 10-month follow-up no evidence of bleeding or impaired platelet function are observed and complete hematological response persists.

Discussion

Bleeding complications during long-term TKIs treatment in CML patients are known and related to impaired primary haemostasis. Defective i*n vitro* platelet aggregation and gastrointestinal bleeding in dasatinib and ponatinib treated patients have been previously reported: the incidence of bleedings ranging from 8% to 40% during dasatinib therapy but only a small number of patients has grade 3 bleeding (6.5%) and no grade 4 or 5 bleeding was observed [11-13].

Considering the prevalence of minor bleeding diathesis, testing platelet function during TKIs therapy is not recommended.

Within the second and third generation TKIs, it has been reported that patients do not have the same response or the same "off-target" effects on haemostasis. Recently, authors have proposed a sensitivity map as a tool to assist in the selection of the right TKIs choice for patients with history of bleeding rather than atherothrombotic disease [14].

As far as we are aware, we report here, for the first time, a case of severe platelet dysfunction with cutaneous and gastrointestinal grade

4 bleeding in an elderly Ph+ALL patient treated with imatinib without thrombocytopenia, hypofibrinogenemia or coagulopathy.

Patient platelet function during imatinib treatment was evaluated using the more sensitive method, i.e. Light Transmission Aggregometry (LTA): it revealed reduced response and secretion defect with all agonists tested. Moreover, platelets showed a low density of GP6 receptor expression compared with 6 different healthy blood donors in control groups.

Previous studies described natural polymorphisms linked to GP6 density on platelet surface which also have reduced responses to fibrinogen binding, α-granule release and aggregation. The patients who have this platelet haplotype, with GP6 expression range 2- to 10-fold lower, are classified as hypo-responder platelets patients but those platelets are still able to ensure hemostatic functions due to compensatory mechanisms.

Moreover, clinical studies indicate that bleeding manifestations in patients with a genetic GP6 deficiency are heterogeneous and range from zero to severe [15]. The authors assume that these patients may have no bleeding symptoms and bleeding, when it occurs, could be due to the association of GPVI deficiency and another disorder.

We surmise that our patient, with significant lower GP6 expression, has hypo-responder platelets and the association of imatinib therapy results in a profound inhibition in platelet signalling with dysfunctional thrombus formation and high bleeding phenotype.

In conclusion, anti-platelet effects of imatinib should be taken into account and carefully evaluated at the beginning of bleeding symptoms.

Acknowledgment

This work was supported by the Italian Ministry of Health (RicercaCorrente) [no grant number provided].

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