DOI: 10.7860/JCDR/2022/52524.16434

Case Report

Oncology Section

Dasatinib causing Intracerebral Bleeding in a Patient with Chronic Myeloid Leukaemia

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ABSTRACT

Dasatinib is a potent inhibitor of BCR-ABL (break point cluster-Abelson) kinase, Src family of kinases, C-kit, and Platelet Derived Growth Factor Receptor beta (PDGFR-beta), and used in the treatment of Chronic Myeloid Leukaemia (CML), Ph-positive acute lymphoblastic leukaemia, and Acute Myeloid Leukaemia (AML). The most common side effects of dasatinib are myelosuppression, gastrointestinal disturbance, fluid retention, cutaneous eruption, and bleeding diathesis. This report is about a recently diagnosed, 45-year-old female with CML, BCR-ABL positive. After six-month therapy with imatinib, the patient developed resistance to imatinib. The treatment was changed to dasatinib 70 mg, once a day. Three months after starting the therapy, the patient showed a cytological response. While receiving dasatinib, she complained of headaches, nausea, and vomiting. Her complete blood count was within the normal limit. Coagulogram was within the normal limit. Non Contrast Computerised Tomography (NCCT) of the head showed intracerebral bleed in the right frontal area of the brain. The patient was then treated with mannitol and put on artificial ventilation. She succumbed on day fourth of the Intensive Care Unit (ICU). Dasatinib has been associated with impaired platelet aggregation, and can show fatal bleeding manifestations.

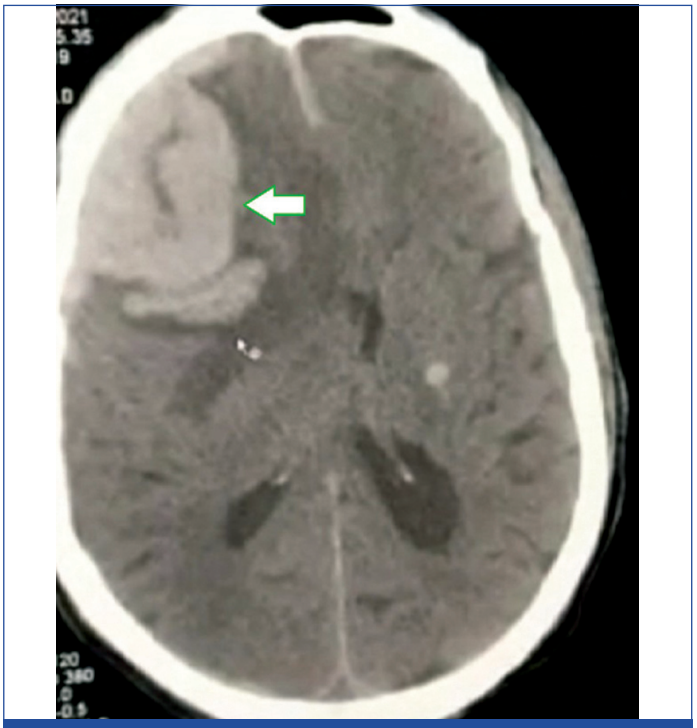
Keywords: Frontal brain, Nausea, Vomiting

CASE REPORT

A 45-year-old female patient was diagnosed with CML BCR-ABL positive, in 2020. Initially, she was treated with imatinib 400 mg, once a day. The patient had incomplete cytological response in the first three months. Six months after therapy, she developed resistance to imatinib. The drug was changed to dasatinib 70 mg, once a day. Three months after dasatinib therapy the patient was in complete cytological response, and Cerebrospinal Fluid (CSF) was negative for blast cells.

Four months into the dasatinib treatment, she was admitted with headache, nausea, and vomiting. On evaluation, the patient revealed, Haemoglobin (Hb) of 9.8 gm%, Total Leukocyte Count (TLC): 6000/m^3, platelet: 80×10^9/L, Prothrombin Time (PT) 12 seconds, International Normalised Ratio (INR) 1.12, Activated Partial Thromboplastin Clotting Time (APTT) 39 seconds, and fibrinogen level of 363 mg/dL. There was no significant history of any trauma to the patient and a history of taking anticoagulant medication.

The NCCT of the head showed intracranial bleed in the right frontal area with midline shift [Table/Fig-1]. Glasgow coma scale was 8/15. The patient was given single donor platelet apheresis, and mannitol, and was put on artificial ventilation in ICU. Dasatinib was stopped. On the day 4th, the patient succumbed due to cardiac arrest. On Narajano drug adverse reaction dasatinib scored 8/10. Thus, the most likely cause of intracranial bleed in this patient was dasatinib. In the present case, platelet aggregation study was not done.



[Table/Fig-1]: Non contrast computerised tomography of head showed intracranial bleed in right frontal area with midline shift (green arrow).

DISCUSSION

Dasatinib is a potent second-generation, broad-spectrum adenosine triphosphate competitive inhibitor of oncogenic kinase including BCR/ABL, Src, C-kit, PDGFR, and ephrin [1]. Due to its deeper and faster response approved for the treatment of all phases of CML, and Ph+ acute lymphoblastic leukaemia and resistance to, or intolerance of, prior therapy, including imatinib [1,2]. The dasatinib has an acceptable toxicity profile, and common side-effects are myelosuppression, peripheral oedema, skin rashes, pleural effusion, and gastrointestinal haemorrhage [3]. Bleeding manifestations have been reported in 4-40% of the patients using dasatinib [3]. The common bleeding sites are gastrointestinal, genitourinary, soft tissue haematoma, and central nervous system bleeding [4]. Dasatinib-related bleeding manifestations are common in the gastrointestinal tract but central nervous system bleeding is rare. The development of a subdural haematoma has been previously reported only in four patients [4-6]. In the present case bleeding was intracerebral. The most common cause of intracerebral bleeding is a vascular malformation, hypertension, trauma, coagulopathy, thrombocytopenia, and leptomeningeal invasion by leukaemic cells. In the present case, the patient did not had any history of head trauma, and the brain imaging study did not show any evidence of vascular aneurysms. In present case, CSF cytology and previous gadolinium-enhanced Magnetic Resonance Imaging (MRI) were negative. Other important predisposing factors to intracerebral bleed are thrombocytopenia and coagulopathy, both of which were not present in index patient. There was no underlying hypertension in index case.

Dasatinib is an inhibitor of BCR-ABL, Src family kinase, c-KIT, PDGFR-b, and ephrin receptor tyrosine kinases [1]. There are very few studies regarding mechanisms leading to bleeding manifestation in dasatinib therapy.

The proposed mechanisms of dasatinib causing platelet dysfunction are:

- Being a broad-spectrum inhibitor of kinases (including BCR-ABL, Src family, c-KIT, PDGFR-b, and ephrin receptor), it inhibits platelet aggregation [7].
- Dasatinib causes impaired platelet activation there is a reduced epinephrine-induced and arachidonic acid-induced platelet aggregation as well as impaired platelet activation by thrombin or adenosine diphosphate [3].
- Dasatinib causes inhibition of platelet signalling and functions initiated by collagen or Fcg RIIA cross-linking, which require Src family kinase phosphorylation of immunoreceptor tyrosine-based activation motifs [8].
- Dasatinib causes impaired platelet aggregation by inhibiting key kinases SFKs, LYN, and FYN which are required for early platelet activation by glycoprotein VI, upstream of SYK, PLC gama2, and integrin alfa2b1 [9,10].
- The study involving PDGFR null mice showed defective angiogenesis and capillary wall development. There was a microaneurysm and haemorrhage formation in mice [11].
- Post-dasatinib therapy, there is clonal expansion of Large Granular Lymphocyte (LGL). There is a close association between the clonal expansion of large granular lymphocytes and bleeding manifestation in patients receiving dasatinib [12] Clonal LGL can cause bleeding manifestation in such patients.
- Bleeding risk with dasatinib increase when the platelet count is less than 30×10^9/L, and in advanced disease (accelerated and blast phase of CML, advanced leukaemia). [Table/Fig-2] summarises similar published literature on different sites of bleeding and treatment received [4-6,13-23]. The gastrointestinal site is the most common site of bleeding compared to the central nervous system. To date, 11 cases of gastrointestinal bleeding with dasatinib therapy have been reported [13-23]. All 11 cases responded well to steroids, after with holding dasatinib, with cessation of the bleeding.

The prognosis in patients manifesting with gastrointestinal bleeding is good, and all the 11 cases survived after treatment [12-23]. As far as, central nervous bleeding is concerned, there are published reports of patients who survived with supportive care [4-6]. Yhim HY et al., reported a 58-year-old woman with acute lymphoblastic leukaemia Ph+, who developed relapse after post stem cell transplant with additional chromosomal abnormalities +13, and was started on dasatinib therapy [4]. One week after therapy patient started developing a headache, which increased over the next four weeks. A computerised tomography scan of the head

Author name, reference	Medical condition	Location of bleeding	Haematological parameters	Proposed mechanism of bleeding	Treatment given	Outcome
Yhim HY et al., [4]	ALL	Bilateral subdural haematoma	Platelet: 40×10^9/l Coagulogram normal	Thrombocytopenia	Platelet support and count maintained >20000/m^3	Survived
Erkut M et al., [13]	CML	Liver	Hb: 10.9 g/dL, Platelet: 470×10^9/l Coagulogram normal	Acute colitis, CMV hepatitis	Levofloxacin, gangciclovir.	Survived
Shimokaze T et al., [14]	ALL	Gastrointestinal	Hb 6.3 gm/dL Platelet: 322 021510^9/l Coagulogram: Normal	Colitis due to CD3 lymphocyte infiltration of lamina propria	Tab prednisolone 2 mg/kg	Survived
Ishida Y et al., [15]	ALL	Gastrointestinal	Platelet: $>30\times10^9$/l Coagulogram normal	Colitis due to lymphocytic infiltration of the mucous membrane, gastrointestinal GVHD	Tab prednisolone 2 mg /kg	Survived
Ono Y et al., [16]	CML	Gastrointestinal	Platelet: 21×10^9/l Coagulogram normal	Colonic ulcers.	Dasatinib stopped and bleeding ceased. After 12 days colitis became normal	Survived
Chen J et al., [17]	CML	Gastrointestinal	WBC 0.6 6×10^9/L; Hb 5.6 g/L; PLT: 10×10^9/L Coagulogram normal	Colitis due to lymphocytic infiltration of the colonic mucosa and platelet dysfunction.	Thymosin 100 mg Tab methylprednisolone 80 mg	Survived
Sunami Y et al., [18]	CML	Gastrointestinal	Platelet: 43×10^9/ l Coagulogram normal	Haemorrhagic colitis due to lymphocytic infiltration of the colonic mucosa and platelet dysfunction.	Dasatinib stopped and bleeding ceased.	Survived
Patodi N et al., [19]	CML	Gastrointestinal	Platelet: 110×10^9/l Coagulogram normal	Acute colitis.	High dose methylprednisolone, mesalamine	Survived
Sartor C et al., [20]	ALL	Gastrointestinal	Platelet: 17×10^9/l Coagulogram normal	Haemorrhagic colitis	Dasatinib was replaced by nilotinib. The patient died during treatment.	Survived
Kmira Z et al., [21]	CML	Gastrointestinal	Platelet: 185×10^9/l Coagulogram normal	Colitis due to CD3 lymphocyte infiltration of lamina propria	Dasatinib withheld treatment with broad-spectrum antibiotics. Colitis resolved after 10 days.	Survived
Chisti MM et al., [22]	CML blast crisis with ALL	Gastrointestinal	Platelet: 90×10^9/l Coagulogram normal	Colitis due to lymphocyte infiltration of lamina propria	Tab prednisolone 2 mg/kg×3 weeks.	Survived
Saito M et al., [23]	CML	Gastrointestinal	Platelet: 150×10^9/l Coagulogram normal	Colitis due to CD8 lymphocyte infiltration	Dasatinib was withheld and colitis improved.	Survived
Ureshino H et al., [5]	ALL	Bilateral subdural haematoma	In both patients platelet counts and coagulogram were normal	Bleeding likely due to platelet dysfunctions	The first patient was treated with trephination and the second patient was treated symptomatically. Dasatinib was withheld in both patients.	Both survived
Mustafa Ali MK et al., [6]	ALL	Subdural haematoma	Platelet: 230×10^9/ Coagulogram normal	Platelet dysfunction due to Dasatinib	Mannitol and left subdural evacuation with two burr hole surgery.	Survived
The present case	CML	Right frontal intracerebral bleed	Platelet: 80×10^9/ Coagulogram normal	Platelet dysfunction due to Dasatinib	Dasatinib withheld and artificial ventilation, mannitol. The patient died on the fourth day of ICU care.	Succumbed

[Table/Fig-2]: Compilation of cases published in the literature related to the bleeding manifestations after Dasatinib therapy [4-6,13-23].
ALL: Acute lymphoblastic leukaemia; GI: Gastrointestinal; CML: Chronic myelogenous leukaemia; CMV: Cytomegalovirus

revealed bilateral subdural haematoma. Dasatinib was withheld for a while.Trepanation of left parietal bone done after two days of subdural haematoma with platelet support. The patient then clinically improved. Ureshino H et al., reported patients who were Ph+ Acute Lymphoblastic Leukaemia (ALL) [5]. The first patient was a 77-year-old female who was on steroid and dasatinib therapy and developed bilateral subdural haematoma three months after therapy. She presented with headache, gait abnormality, and urinary incontinence. Dasatinib was stopped and emergency trephination was done. The patient clinically improved. The second patient was a 75-year-old Ph+ female who was on steroid and dasatinib therapy. Two months after therapy she developed malaise and loss of appetite, computerised tomography head was done and showed left-sided subdural haematoma. The patient was managed with conservative treatment and the haematoma resolved. Mustafa Ali MK et al., reported a 29-year-old Ph+ ALL female who was on Hyper CVAD/methotrexate, cytarabine chemotherapy [6]. While on dasatinib therapy in the last four hyper CVAD cycles she complained of severe headaches. Computerised tomography of the brain showed a left subdural haematoma. Dasatinib was stopped and the patient underwent burr hole surgery to evacuate the subdural haematoma. The patient clinically improved [6]. In the index case, prognosis was poor because the patient had an intracerebral bleed and delayed presentation to the hospital.

The duration of developing bleeding manifestation after dasatinib therapy ranges from 10 days to 16 weeks [4,5,12-23]. Clinical signs during cranial bleeding include headaches, gait abnormality, and clouding consciousness. The prognosis depends on early diagnosis and treatment of the condition.

In the present case, the patient succumbed to death. There is no clear guideline regarding reinstituting dasatinib in a patient who had life-threatening intracranial bleeding. Thus, further research is required for the safety of reinstating dasatinib therapy in patients who had symptomatic bleeding.

CONCLUSION(S)

Intracerebral bleeding is a very rare and serious complication of dasatinib therapy. The physician should be aware of such kind of complications while treating a case of CML and Ph-positive ALL with dasatinib.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Sep 22, 2021
- Manual Googling: Apr 28, 2022
- iThenticate Software: May 19, 2022 (13%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Sep 21, 2021**
Date of Peer Review: **Nov 17, 2021**
Date of Acceptance: **May 02, 2022**
Date of Publishing: **Jun 01, 2022**