CASE REPORT

Dasatinib-induced haemorrhagic colitis in chronic myeloid leukaemia (CML) in blast crisis

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SUMMARY

We report a rare case of haemorrhagic colitis attributed to dasatinib therapy in a 47-year-old African-American woman who was diagnosed with extramedullary T-lymphoblastic transformation of chronic myeloid leukaemia. The patient received intensive chemotherapy and dasatinib 100 mg/day. After achieving complete cytogenetic and major molecular response after 9 months of therapy, she developed bloody diarrhoea and pancytopenia. Colonoscopy showed inflammation of the descending colon and histopathology revealed patchy increase in intraepithelial lymphocytes. Dasatinib was stopped with prompt resolution of diarrhoea. The current literature suggests that there is an association in a subset of patients on dasatinib between clonal T-cell lymphocytosis in the peripheral blood and developing colitis and pleural effusions. These patients had a good response to dasatinib as did our patient. Our patient illustrates a unique disease presentation along with a rare drug adverse event.

BACKGROUND

Dasatinib has recently been approved as a first-line dual tyrosine kinase inhibitor used for chronic myeloid leukaemia (CML) and also for second-line therapy particularly when there is resistance or intolerance to imatinib therapy. Although gastrointestinal (GI) bleeding has been widely reported with dasatinib therapy for CML, haemorrhagic colitis is a much rarer event.¹ Here we describe the previous reports of haemorrhagic colitis associated with dasatinib therapy and some of the mechanisms which may be important.

Dasatinib is approved for the treatment of chronic, accelerated and blast crisis of CML and Philadelphia-positive acute lymphoblastic leukaemia (ALL).² It potentially inhibits BCR-ABL, SRC kinases, c-KIT, EPHA2 and platelet-derived growth factor receptor.¹ A daily 100 mg dose in chronic phase CML has been shown to induce cytogenetic and major molecular response more rapidly and more frequently than imatinib, lowers the incidence of disease progression and prolongs progression-free survival.³ Despite its efficacy and that it is generally well tolerated, dasatinib has a range of reported side effects, mostly moderate and manageable including myelosuppression, GI symptoms such as diarrhoea and vomiting, constitutional symptoms such as anorexia and oedema.⁴ Although GI bleeding has been reported commonly in the literature, haemorrhagic colitis is rare. We present this case report of this drug-related rare adverse effect of

haemorrhagic colitis which seems to be dose dependent.

CASE PRESENTATION

A 47-year-old female patient diagnosed in December 2010 with Philadelphia chromosome positive-CML blast crisis with ALL was treated with hyper CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) chemotherapy and prophylactic intrathecal methotrexate chemotherapy. By August 2011, the patient had achieved partial cytogenetic response with 0.9 log reduction in BCR-ABL mRNA transcript level by the reverse transcription (RT-PCR) method, which was initially 95% at the time of diagnosis. She declined allogeneic bone marrow transplant. In September 2011, she was started on dasatinib therapy at a daily dose of 100 mg. Within 1 month, she developed several well-documented side effects to dasatinib including pancytopenia, skin rash and neuropathy. The dasatinib dose was reduced to 70 mg/day. A month later, she developed intermittent episodes of diarrhoea with haematochezia. She was admitted to the hospital for possible infectious colitis with tender abdomen, tachycardia, mild fever and blood pressure 100/60 mm Hg. CT scan of the abdomen did not reveal any abnormality. Stool studies investigating enteric pathogenic organisms including *Clostridium difficile* PCR were negative. Blood counts had dropped significantly during hyper CVAD chemotherapy but had recovered prior to initiation of dasatinib therapy. Her haemoglobin (Hb) was 11.2 g/dL, platelets 157 000/μL, borderline increased lactate dehydrogenase and lactic acid but normal amylase and lipase. Prothrombin time (PT), international normalised ratio (INR) and activated partial thromboplastin time (aPTT) were within the reference range. Bone marrow biopsy showed complete cytogenetic response with no evidence of Philadelphia chromosome positivity. Four months later, she was hospitalised for bloody diarrhoea. Colonoscopy showed congested, erythematous and granular mucosa from the rectum to the transverse colon (figure 1). Biopsies showed increased intraepithelial lymphocytes with no evidence of active colitis, dysplasia or malignancy likely to be reactive lymphoid infiltrates (figure 2). Extensive studies including immunohistochemical stains, T-cell and B-cell gene derangement studies and also the fluorescence in situ hybridisation studies for BCR-ABL fusion transcript were all negative for a neoplastic process. Dasatinib was continued at 70 mg/day. Seven months later,

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To cite: Chisti MM, Khachani A, Brahmanday GR, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-200610

Figure 1 Colonoscopic appearance of congested, erythematous and granular mucosa from the rectum to the transverse colon.

Figure 3 Mucosal biopsy of the colon. Increased lymphoplasmacytic inflammation of the lamina propria and focal areas with increased intraepithelial lymphocytes.

she was admitted for worsening of diarrhoea, abdominal cramps and dehydration and anaemia Hb 6.5 g/dL). Platelet count was 90 000/ μ L. Repeat colonoscopy showed a patchy area of mildly congested, erythematous, granular and vascular patterned with decreased mucosa found from the rectum to the transverse colon (figure 3). Histopathology was similar to the prior biopsy in January 2012 and showed colonic mucosa with crypt architectural changes, increased lymphoplasmacytic inflammation of the lamina propria and focal areas with increased intraepithelial lymphocytes. There was neither local leukaemic involvement, nor was there any evidence of inflammatory bowel disease. Cytomegalovirus (CMV) stain was negative. She was diagnosed with haemorrhagic colitis secondary to dasatinib. Dasatinib was discontinued for 2 weeks when she experienced resolution of diarrhoea and it was then restarted at a lower dose of 50 mg/day. Three days later, diarrhoea recurred. Nilotinib was declined due to the presence of a prolonged QTc duration. Dasatinib was discontinued and steroids were started (subsequently tapered off over 3 weeks) which led to resolution of symptoms. RT-PCR assay of BCR-ABL increased from International Standard value of 0 to 0.49 in 4 weeks. Cytogenetics revealed 1 of 200 cells

(<1%) positive for the Philadelphia chromosome. After much consideration, dasatinib was restarted at 20 mg/day, which has been well tolerated, with RT-PCR trending down. Currently she is in major molecular remission (0.015%), with mild anaemia (Hb 11.2 g/dL), platelet count 145/ μ L, within the reference range liver and kidney function values and no GI or systemic adverse effects.

DIFFERENTIAL DIAGNOSIS

- ▶ Infectious colitis: varied infectious disease panel like CMV, *Clostridium difficile*, parasite studies, bacterial antigens, etc were negative in our case.
- ▶ Inflammatory bowel disease: neither the biopsy corresponds to inflammatory bowel disease nor the patient had any similar history.
- ▶ Ischaemic colitis: the biopsy did not show any signs of ischaemic changes or areas of necrosis.
- ▶ Bleeding diathesis: her PT, INR and aPTT were within the reference range and there was no history of bleeding diathesis.
- ▶ Vascular malformations: no vascular malformations were found on the CT scan of the abdomen or colonoscopy in the patient.

OUTCOME AND FOLLOW-UP

Currently, she continues to be in major molecular remission on a low dose of dasatinib. The overall response has been 2 years and 8 months and she has been progression free for 20 months now, since starting this low dose, which emphasises that even low dose of dasatinib is effective and the adverse effect of haemorrhagic colitis encountered was dose dependent.

DISCUSSION

CML results from a genetic translocation involving chromosomes 9 and 22 resulting in the formation of the Philadelphia chromosome. The resulting oncogenic fusion gene BCR-ABL encodes for tyrosine kinase believed to be pathognomonic in CML development. Dasatinib is a first-line tyrosine kinase inhibitor approved for the treatment of chronic, accelerated and blast crisis of CML and Philadelphia-positive ALL.² It has the advantage of being effective at inhibiting several tyrosine kinases and is active against almost all BCR-ABL mutations, conferring resistance to imatinib.² Haemorrhagic colitis is a rare bleeding complication of dasatinib therapy.⁴⁻⁷ During a 6-month median of the treatment, the majority of patients experience adverse events. The most

Figure 2 Repeat colonoscopy showed a patchy area of mildly congested, erythematous, granular and vascular patterned with decreased mucosa found from the rectum to the transverse colon.

frequent non-haematological side effects experienced are GI. Diarrhoea is seen in 36% of cases treated in the myeloid blast phase.⁸ Dasatinib therapy has been associated with bleeding episodes in 23% of patients with CML and 35% in the blast phase.⁸ In the blast phase, dasatinib can cause GI bleed in 12% of cases.⁸ Bleeding occurs in the GI tract in 81% of the cases and 85% of these are located in the lower GI tract when the patient is in the blast phase.⁸ When lymphocytosis occurs during dasatinib treatment, there is an association with developing colitis.^{9–11} In one study, 18 of 22 patients developed colitis along with clonal development of T-cells.¹⁰ In the Quintas-Cardama *et al*'s⁸ study, 41% of patients with lower GI bleeds had lymphocytosis. These patients did not have evidence of lymphocytosis but developed haemorrhagic colitis. Dasatinib-induced colitis has also been associated with CMV enterocolitis.⁶ CMV staining was negative in the biopsy of our patient. Thrombocytopenia, advanced-phase CML and increased length of dasatinib therapy are all associated with an increased risk of bleeding on dasatinib.⁸ In this case, mild thrombocytopenia was present (90 000/ μ L—grade 1 as per Common Terminology Criteria for Adverse Events (CTCAE) classification). It is unclear whether dasatinib caused bleeding by interfering with platelet function which has been previously postulated. Onset of first episode of bleeding does not correlate with dosing and there is a decreased incidence of bleeding with decreased dose. In the Quintas-Cardama *et al*'s⁸ study, recurrence of bleeding was observed in 37% of cases on restarting therapy, and in 22% of cases termination of dasatinib was deemed necessary. In our case, GI symptoms resolved after discontinuation of therapy but recurred when dasatinib was resumed. When dasatinib therapy fails, Nilotinib is licensed as a second-line tyrosine kinase inhibitor.^{4 12 13} Nilotinib induces QTc prolongation which precluded use in our patient who had evidence of prolonged QTc. Dasatinib dose was restarted at the lowest possible

dose until she became asymptomatic. Follow-up molecular and cytogenetic studies are crucial to assess whether the patients can be maintained on low-dose dasatinib which will be key in predicting long-term disease and progression-free survival.

Haemorrhagic colitis is a rare complication of treatment with dasatinib which can respond well to discontinuation of dasatinib therapy.⁶ Cautious introduction at a lowered dose is possible with reduction in GI symptoms, which implicates a dose-related effect. Treating physicians need to be aware of this presentation and undertake appropriate investigation and exclusion of common causes before considering this differential diagnosis. Our case demonstrates effective management, by lowering dasatinib dose which leaves the patient with greater therapeutic option and survival potential.

Acknowledgements The authors would like to acknowledge the William Beaumont Hospital.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- Haemorrhagic colitis is a rare complication but responds well to the discontinuation of therapy.
- It seems to be a reversible adverse effect with no long-term sequelae.
- Haemorrhagic colitis seems to be a dose-dependent adverse effect. Dasatinib can be restarted at a lower dose which causes reduction in gastrointestinal symptoms.
- After adjusting the dose accordingly, continuous monitoring of molecular and cytogenetic studies is essential to monitor the ongoing effectiveness of therapy.
- Switching to alternative tyrosine kinase inhibitor therapy should be carefully considered on a case-by-case basis. We recommend this should be performed in cases where there is recurrence of any adverse side effects or evidence of disease progression on lower tolerated dose as per current guidelines.

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