Journal of Taibah University Medical Sciences (2015) 10(3), 365–368

Taibah University

Journal of Taibah University Medical Sciences

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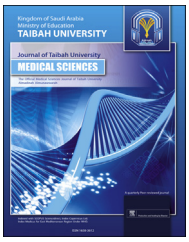

Case Report

Drug-induced immune thrombocytopenia associated with use of tyrosine kinase inhibitor imatinib

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Received 19 August 2014; revised 11 December 2014; accepted 9 January 2015; Available online 26 February 2015

الملخص

تستخدم مثبطات التيروزين كيناز على نطاق واسع لعلاج مختلف أنواع السرطانات، منذ بدء العمل بها في أواخر التسعينات من القرن الماضي. والآثار الجانبية للإيماتينيب، أحد مثبطات التيروزين كيناز، موثقة جيدا في الأدبيات وتشمل الإجهاد، والطفح الجلدي، وكبت النخاع العظمي، واختلال إنزيمات الكبد. كتبت تقارير عدة عن الآثار الجانبية النادرة من المشرفين على المسوحات التي أجريت في مرحلة ما بعد التسويق، مثل الدكاك القلبي ومتلازمة ستيفن جونسون. في هذا التقرير، نعرض لحالة نادرة لنقص الصفائح الدموية المناعي المرتبطة بالإيماتينيب أدت إلى نزف حاد داخل البطن. مع توضيح موجز لحالات مماثلة من نقص الصفائح الدموية المناعي سببتها مثبطات التيروزين كيناز.

الكلمات المفتاحية: نقص الصفائح الدموية؛ مثبطات التيروزين كيناز؛ الإماتينيب؛ كبت النخاع العظمي؛ نقص الصفائح الدموية الناتج عن العقاقير

Abstract

Since their introduction in the late 1990s, tyrosine kinase Inhibitors (TKIs) have been widely used for the treatment of various cancers. The side effects of the TKI imatinib are well-documented in the literature and include fatigue, skin rash, myelosuppression, and derangement of liver enzymes. Rare side effects have been observed in the postmarketing surveillance and include cardiac tamponade and Steven Johnson Syndrome. In the present report, we present a rare case of imatinib-associated immune thrombocytopenia leading to severe intra-abdominal bleeding. A brief account of similar cases of TKI drug-induced immune thrombocytopenia (DIT) is also described.

Keywords: Drug-induced immune thrombocytopenia; Imatinib; Myelosuppression; Thrombocytopenia; Tyrosine kinase inhibitor

Introduction

Tyrosine kinase inhibitors (TKIs) have played an indispensable role in the treatment of various haematological and solid organ malignancies. The blocking pathological tyrosine kinase activity results in the arrest of oncogenic pathway that drives the growth of cancer cells. The first TKI that was introduced was imatinib mesylate, which has been used in treatment of various diseases, including chronic myeloid leukaemia (CML), Ph+ acute lymphoblastic leukaemia (ALL), and gastrointestinal stromal tumours (GIST). These agents are not free from adverse effects. Side effects, such as myelosuppression (or hypo-/amegakaryocytic thrombocytopenia), have been noted to affect up to 45% of imatinib recipients[1] and have also been described for other TKIs such as sunitinib.[2,3] Clinical trials have shed light on the common

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Peer review under responsibility of Taibah University.

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 http://dx.doi.org/10.1016/j.jtumed.2015.01.005

side effects associated with TKIs; however, rarer side effects, such as autoimmune phenomena, have only become apparent in postmarketing reports (e.g., cardiac tamponade). We present a rare complication of the use of imatinib that caused drug-induced immune thrombocytopenia (DIT) in a patient with a gastrointestinal stromal tumour (GIST) and a summary of similar cases.

Case

A 72-year-old female patient was started on imatinib 400 mg PO daily for an advanced gastrointestinal stromal tumour (GIST) with liver metastasis. Her medical history was unremarkable for any autoimmune, HIV, hepatitis B or C infection or any bleeding disorders. She denied any alcohol use and any history of recreational drug use. Her baseline complete blood count (CBC) revealed the following: white blood cell count (WBC), 6.91×10^9/L (normal 4–11); haemoglobin (Hb), 128 g/L (normal 120–160); and platelets, 226×10^9/L (normal 150–400). Less than four weeks later after beginning imatinib, she sought medical attention after developing a generalized petechial rash and right upper quadrant (RUQ) pain. On her arrival to the emergency room, her CBC revealed severe thrombocytopenia (platelets 10×10^9/L), a WBC count of 3.74×10^9/L and anaemia (Hb 107 g/L).

Investigations

The possible causes of the acute onset of thrombocytopenia were investigated. Disseminated intravascular coagulation (DIC) and thrombotic microangiopathy (TMA) were unlikely and were excluded based on a normal coagulation profile, a peripheral blood smear examination that revealed no evidence of schistocytes and normal lactate dehydrogenase (LDH) levels. She was not exposed to heparin prior to admission, and thus it was unlikely that she had developed heparin-induced thrombocytopenia (HIT).

Her next CBC revealed a Hb level of 76 g/L, a WBC of 2.76×10^9/L and a platelet count of 2×10^9/L. Additionally, her reticulocyte count (103.4×10^9/L) and immature reticulocyte fraction (33.9%) were both elevated. Due to a strong suspicion of possible intra-abdominal bleeding, she underwent a contrast CT scan of her abdomen, which confirmed intraperitoneal bleeding from the superior intra-renal artery. This finding explained her new onset RUQ pain and the drop in haemoglobin.

Treatment

The patient underwent a successful embolization of the culprit vessel to stop the bleeding. After excluding common causes of acute onset of thrombocytopenia, imatinib-associated immune thrombocytopenia was suspected because this drug had recently been initiated prior to her presentation; thus, imatinib was immediately stopped. Due to the seriousness of the thrombocytopenia (platelet count of 2×10^9/L with severe bleeding), treatments of prednisone 1 mg/kg PO once daily, intravenous immunoglobulin (IVIG) 2 g/kg over two days, and supportive transfusion with packed red blood cells and platelets with evidence of refractoriness to platelet transfusions were simultaneously initiated. Additionally, the patient also received a single 2-mg dose of vincristine. Following the cessation of imatinib and the introduction of these immunomodulation measures, her platelet count exhibited an initial recovery within eight days to 31×10^9/L and ultimately reached 138×10^9/L at the time

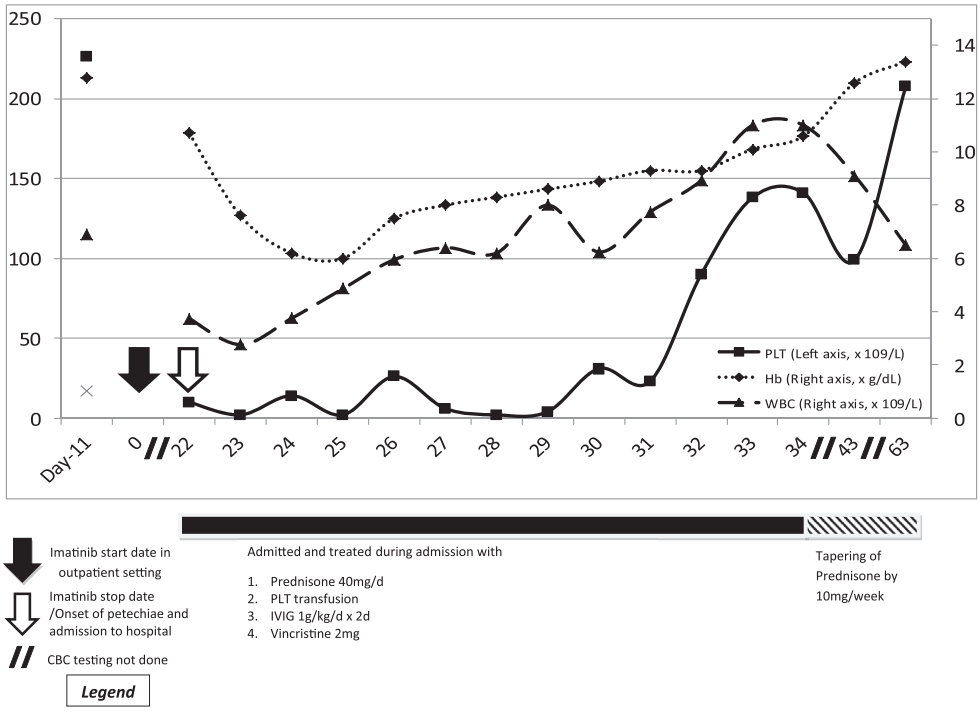

Figure 1: Temporal profile of association between tyrosine kinase inhibitor use, blood counts, and treatments.