Introduction

Gastrointestinal stromal tumours (GISTs) are rare neoplasms of the gastrointestinal (GI) tract that are mesenchymal in origin and have an incidence of approximately 1.2/100,000 per year in all countries. GISTs account for less than 1% of primary GI neoplasms, span throughout the intestinal tract and are characterised by the presence of an activating mutation in either KIT gene or platelet-derived growth factor receptor alpha (PDGFRα) which are the main oncogenic drivers. Tyrosine kinase inhibitors (TKIs) form the backbone of current targeted therapy as they can block these receptors. The introduction of TKIs resulted in significant improvement in survival of patients with GIST even in advanced disease conditions. A 43-year-old adult male who is a known case of gastrointestinal stromal tumour of the stomach, on adjuvant therapy with imatinib, presented with a history of gross haematuria of several episodes as well as persistent microhaematuria and was evaluated for the same. He was investigated for all possible causes, but all were negative. The patient was advised to withhold imatinib. Haematuria resolved 1 month after stopping imatinib. Then it was rechallenged. He had recurrence of symptoms, so it was discontinued. In view of the temporal relation of haematuria and administration of imatinib, a diagnosis of imatinib-induced haematuria was made.

Case history

A 43-year-old adult male underwent surgery for a GIST in the fundus of the stomach 2 years ago and was on adjuvant imatinib, 400 mg/day. After 12 months of treatment with imatinib, he presented with a history of haematuria, sometimes severe, several episodes not associated with any fever, pain, cough or weight loss. In between, microhaematuria persisted. The patient did not have any significant co-morbid illness. He was not on any non-steroidal anti-inflammatory or antiplatelet drugs. Routine blood tests, serum creatinine, peripheral smear and coagulation profile (prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, bleeding time) were all normal. A computed tomography (CT) scan abdomen was done, and it was found to be normal.

Urine routine showed 30–40/RBC/HPF (red blood cells per high-power field) cells, 1–3/HPF pus cells and few epithelial cells. Urine for cytology and culture

Abstract

Gastrointestinal stromal tumours are rare neoplasms of the gastrointestinal tract that are mesenchymal in origin. The introduction of tyrosine kinase inhibitors resulted in significant improvement in survival of patients with gastrointestinal stromal tumour even in advanced disease conditions. A 43-year-old adult male who is a known case of gastrointestinal stromal tumour of the stomach, on adjuvant therapy with imatinib, presented with a history of gross haematuria of several episodes as well as persistent microhaematuria and was evaluated for the same. He was investigated for all possible causes, but all were negative. The patient was advised to withhold imatinib. Haematuria resolved 1 month after stopping imatinib. Then it was rechallenged. He had recurrence of symptoms, so it was discontinued. In view of the temporal relation of haematuria and administration of imatinib, a diagnosis of imatinib-induced haematuria was made.

Keywords

Gastrointestinal stromal tumour, imatinib, haematuria, tyrosine kinase inhibitors

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Imatinib-induced haematuria necessitating drug discontinuation

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Mechanism of bleeding is not yet clear. Such patients developed side effects in any cancer patients also get inhibited. The side effects of imatinib may be influenced by the germline genetic polymorphisms of drug targets, namely, c-KIT and PDGFRA/B. The pharmacokinetics of imatinib may indirectly regulate toxicity. The uptake/efflux of imatinib could be influenced by the mutation of SLC22A1, SLC22A5 and ABCB1 genes. This can lead to alteration in the concentration of imatinib intracellularly and hence results in toxic variability in patients.

On imatinib therapy, the majority of the side effects observed in patients are mild and well-tolerated. The common haematological side effects are anaemia (70%–80%), neutropenia (45–50%) and thrombocytopenia (18%).

Non-haematological toxicities include peri-orbital oedema (70%–80%), diarrhoea (45–50%) and fatigue (50%). Other side effects (20–40%) reported include nausea, muscle cramps, leg oedema, anorexia and rashes.

Bleeding manifestations such as haematuria, conjunctival haemorrhage, blood in the stool, epistaxis, post-procedural haemorrhage, bruising and contusion were observed in 22% of patients with GIST treated with imatinib 400 mg/day. GI and subconjunctival haemorrhage are more common, and usually, it is mild to moderate and improves with drug holiday. Haemorrhage of all grades occurs in about 30% of patients on imatinib, but only in 2%, it is grades 3–4. Mechanism of bleeding is not yet clear. Such patients often have normal platelet counts and normal coagulation studies but may have impaired platelet aggregation. This is possibly related to the on-target or related off-target tyrosine kinase inhibition in megakaryocytes and platelets.

Imatinib mesylate is a TKI that inhibits the BCR-ABL, c-Kit and PDGFR tyrosine kinases. Imatinib is mainly used in the treatment of chronic myeloid leukaemia (CML) and GISTs. In addition to cancer cells, the tyrosine kinase enzymes of non-cancer cells also get inhibited. The side effects of imatinib may be influenced by the germline genetic polymorphisms of drug targets, namely, c-KIT and PDGFRA/B. The pharmacokinetics of imatinib may indirectly regulate toxicity. The uptake/efflux of imatinib could be influenced by the mutation of SLC22A1, SLC22A5 and ABCB1 genes. This can lead to alteration in the concentration of imatinib intracellularly and hence results in toxic variability in patients.

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Impaired or decreased platelet aggregation was seen in 29.8%, and release defect was observed in 26% of patients with CML on imatinib. There was no relationship between bleeding and the impairment of platelet function.

Renal manifestations like acute kidney injury (AKI), haematuria, proteinuria, hypophosphataemia and Fanconi syndrome have also been reported with imatinib; however, it is very rare. Acute renal injury has been reported in a few instances previously and may occur after 1 week to 3 months of treatment. In one case of biopsy-confirmed acute tubular injury (ATI) while on imatinib, renal function improved when the dose of imatinib was reduced by 50%. The mechanism for imatinib-induced AKI is not fully understood. An increase in susceptibility to both ATI and chronic kidney disease (CKD) due to TKIs may be due to the interference with the PDGFR-mediated tubular repair mechanisms. Age and co-morbidities like diabetes, hypertension or coronary artery disease are known risk factors for renal injury. A total of 12% of those patients developed chronic renal failure. Long-term TKI treatment results in renal dysfunction, and in many cases, it may be irreversible even after treatment discontinuation. Imatinib-induced haematuria observed in our case is a rare type of adverse drug reaction possibly related to cystitis in this case. His coagulation profile and calculated glomerular filtration rate (GFR) was normal.

Discussion

Imatinib mesylate is a TKI that inhibits the BCR-ABL, c-Kit and PDGFR tyrosine kinases. Imatinib is mainly used in the treatment of chronic myeloid leukaemia (CML) and GISTs. In addition to cancer cells, the tyrosine kinase enzymes of non-cancer cells also get inhibited. The side effects of imatinib may be influenced by the germline genetic polymorphisms of drug targets, namely, c-KIT and PDGFRA/B. The pharmacokinetics of imatinib may indirectly regulate toxicity. The uptake/efflux of imatinib could be influenced by the mutation of SLC22A1, SLC22A5 and ABCB1 genes. This can lead to alteration in the concentration of imatinib intracellularly and hence results in toxic variability in patients.

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Conclusion

With the increasing use of imatinib for various cancers, it is crucial to understand its various adverse effects. Majority of patients develop a tolerance for side effects on continued use of the drug. Even though haematuria associated with imatinib is rare, both physician and caregiver have to be vigilant regarding its occurrence. Hence, ideal patient counselling regarding the occurrence of these common side effects and adequate individualised patient monitoring during treatment is of utmost significance.

Patients on long-term imatinib treatment should be monitored for renal toxicity (especially to look for proximal tubule dysfunction and hypophosphataemia).

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