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Rare Case Presentation of Imatinib Induced Hepatotoxicity

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Abstract

Imatinib, a tyrosine kinase inhibitor, is a life-saving treatment for Chronic myeloid leukemia (CML) and several other malignancies. Imatinib induced hyperbilirubinemia and hepatic toxicity is seldom reported among all side effects. not a widely known fact. We present a case of a 25 year old male patient who developed hyperbilirubinemia while on imatinib for treatment of CML. On further genetic testing for polymorphism, the patient is homozygous for UGT1A1*28 polymorphism. Due to persistent hyperbilirubinemia while on 400 mg, dose was reduced to 300 mg daily. The patient's hyperbilirubinemia was manageable with a minimal decrement of 25% from the initial dose of imatinib. If handled in a timely fashion by a physician, it helps to control hyperbilirubinemia while the patient receives a reduced dosage of imatinib for life long treatment of CML.

Keywords: chronic myeloid leukemia, CML, imatinib, hyperbilirubinemia, Gilbert, UGT 1 A1 polymorphism, hepatotoxicity

Introduction

Imatinib, a tyrosine kinase inhibitor (TKI), is a cornerstone in the treatment of chronic myeloid leukemia (CML) and other malignancies [1]. TKIs work by binding at the TK active sites, close to the ATP binding sites of the BCR/ABL gene. Thus inhibiting enzyme semi-competitively, leading to inhibition of multiple downstream pathways such as Ras/MAPK pathway, PI/PI3K/AKT/Bcl-2 pathway, and JAK/STAT pathway, leading to cell proliferation, cell survival, and apoptosis prevention[2]. Imatinib is metabolized in the liver mainly by CYP3A4, with other CYP enzymes and the primary route of elimination is in bile and feces. It is advisable to avoid concomitant use of drugs, herbal products acting on CYP3A4 as an inducer or inhibitor

while the patient is taking imatinib. Among all adverse effects of imatinib, hepatotoxicity in the form of hyperbilirubinemia, hepatitis, and focal necrosis is seldom reported [3,4].

Case Presentation

A 25-year-old Asian male presented with a recent diagnosis of CML. Bone marrow biopsy and FISH analysis confirmed the presence of the Philadelphia chromosome, which is consistent with chronic phase CML. The patient started on Imatinib 400 mg daily for four weeks. Since then the patient has asymptomatic hyperbilirubinemia on blood tests. The patient was referred to a gastroenterologist for further evaluation.

Baseline liver function tests (LFTs) were within normal limits. The patient's blood count and liver function test were monitored weekly for the initial 4 weeks, followed by once in 2 weeks and later once in four weeks. After 4 weeks, unconjugated hyperbilirubinemia (1.9 mg/dL) was noted without transaminitis or other cholestatic changes. Bilirubin continued to rise, peaking at 3.8 mg/dL at 24 weeks. The patient remained asymptomatic with no evidence of hemolysis, autoimmune disease, or viral hepatitis. A liver ultrasound was unremarkable. The patient had a BMI of 21, lifetime non-smoker, non alcoholic, no history of drug abuse or over-the-counter/herbal medications. Screen for hepatitis panel and HIV was unremarkable.

Due to the persistent hyperbilirubinemia, genetic testing was performed, revealing homozygosity for the UGT1A1*28 allele which led to diagnosis of Gilbert syndrome. Imatinib was temporarily withheld for a week, and bilirubin decreased to 2.9 mg/dL. Upon reintroduction at a reduced dose of 300 mg daily, bilirubin stabilized between 1.7–1.9 mg/dL, and the patient continued to achieve hematologic and cytogenetic remission. We followed patient for 2 years.

Table1 shows trends of liver function tests after starting a patient on Imatinib therapy. Lab work includes AST, ALT, alkaline phosphatase and total bilirubin including direct and indirect (Image1).

Discussion

Gilbert's syndrome (GS) is an autosomal recessive hereditary disorder of bilirubin glucuronidation. Clinically present with mild, chronic unconjugated (indirect) hyperbilirubinemia in the absence of hepatic injury or overt hemolysis [5]. GS is due to reduced expression of uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) enzyme, which results in unconjugated hyperbilirubinemia. This enzyme is also responsible for detoxifying other drugs in the liver [6], e.g., irinotecan which is metabolized by UGT1A1. We present a case necessitating a therapeutic dose modification while managing imatinib therapy in a patient with previously undiagnosed Gilbert's Syndrome.

Gilbert's syndrome is present in approximately 3–10% of the population and is usually clinically silent [7]. It arises from decreased bilirubin glucuronidation due to UGT1A1 promoter polymorphisms, most commonly the TA7 repeat (*28 allele) [8]. Drugs metabolized by UGT1A1, such as irinotecan and, in rare instances, imatinib, may precipitate exaggerated hyperbilirubinemia in affected individuals [9,10]. During imatinib treatment, impaired bilirubin conjugation in GS can unmask hepatotoxicity [11]. This case aligns with reports indicating UGT1A1 polymorphism involvement in TKI-associated hyperbilirubinemia. While routine UGT1A1 screening is not standard practice, selective

testing may be warranted in patients with unexplained hyperbilirubinemia during TKI therapy.

In our case, dose reduction allowed us to continue treatment with imatinib with similar efficacy and without significant elevation in bilirubin. However, we followed the prescribing information (PI) as follows, although no formal guidelines exist [11]:

- Withhold if bilirubin >3x upper limit of normal (ULN) or ALT/AST >5x ULN;
- Resume after bilirubin <1.5x ULN and ALT/AST <2.5x ULN at a reduced dose (i.e. 400 mg to 300 mg; 600 mg to 400 mg; 800 mg to 600 mg); and
- Withhold if severe hepatotoxicity; once resolved, reduce dose by 25%.

The precise mechanism by which imatinib induces hyperbilirubinemia in GS patients is not fully understood, but it is hypothesized to interfere with UGT1A1 enzyme activity or inhibit bilirubin uptake by hepatocytes [12].

Conclusion

This case presentation illustrates clinically relevant but rare adverse effects of imatinib, unconjugated hyperbilirubinemia, induction of Gilbert syndrome while on imatinib therapy. Physicians should be aware of this potential association, and should consider monitoring bilirubin levels while patient on imatinib treatment. If unexplained rise in total bilirubin while on imatinib, patients should be screened for UGT1A1 polymorphism. After recognition of genetic factors, imatinib dosage should be adjusted based on hyperbilirubinemia. Dosage reduction can start from 25% reduction from previous dosage for Imatinib rather than switching to another drug. If incidence of imatinib induced Gilbert's syndrome tends to rise continuously, then it may prompt FDA to make it compulsory, to test for UGT1A1 polymorphism before starting imatinib, similar to nilotinib.

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Legend Figure and Table

Figure 1: Trend in bilirubin while on imatinib therapy

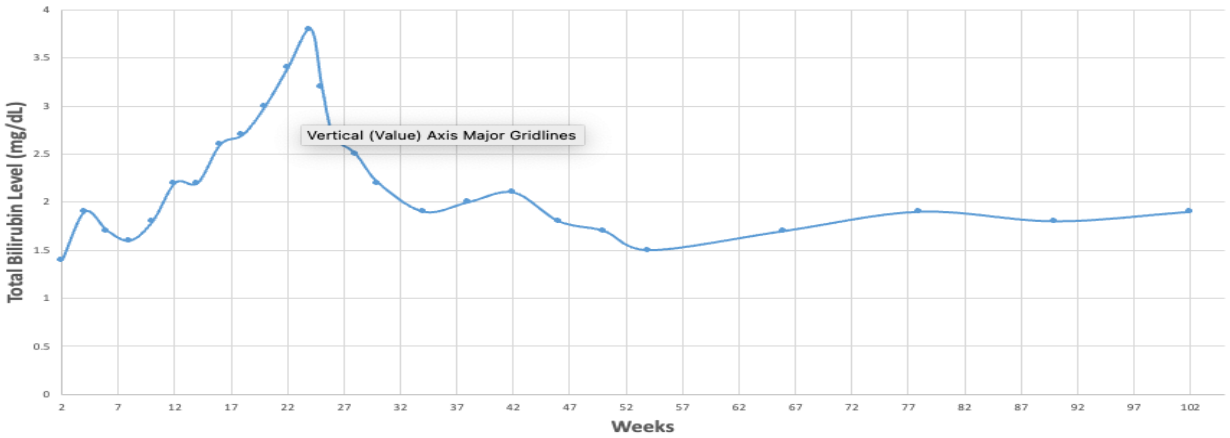

Table 1: Liver function profile while on imatinib therapy

Date	AST	ALT	ALK	Direct Bilirubin	Indirect Bilirubin	Total Bilirubin	Comment
12/19/2022	24	30	85	0.5	0.6	1.1	Baseline LFT
01/05/2023	42	49	102	0.5	0.7	1.2	First week after starting imatinib 400 mg po daily
01/12/2023	48	57	118	0.6	0.8	1.4	
01/20/2023	52	58	132	0.5	1.1	1.6	
01/28/2023	44	48	147	0.7	1.2	1.9	Fourth week after starting imatinib
02/11/2023	32	40	126	0.6	1.1	1.7	
02/25/2023	25	38	114	0.5	1.1	1.6	
03/11/2023	37	46	110	0.7	1.1	1.8	
03/26/2023	42	46	119	0.8	1.4	2.2	Bilirubin started rising at 12 th week
04/08/2023	43	51	102	0.9	1.3	2.2	
04/22/2023	38	46	114	0.7	1.9	2.6	
05/06/2023	41	48	108	0.8	1.9	2.7	
05/20/2023	22	28	119	0.6	2.4	3	Continuously rising bilirubin levels at 20 th week
06/03/2023	30	36	102	0.8	2.6	3.4	
06/18/2023	28	32	110	0.7	3.1	3.8	Imatinib held at 24 th week
06/25/2023	32	38	92	0.8	2.4	3.2	Level started dropping, while imatinib on hold
07/02/2023	22	26	90	0.7	2	2.7	Diagnosed with GS syndrome, resumed imatinib 300 mg PO daily
07/16/2023	23	28	79	0.6	1.9	2.5	
07/30/2023	32	34	84	0.8	1.4	2.2	Continue imatinib 300 mg daily
08/27/2023	28	35	73	0.7	1.2	2.2	Gradually dropped 34 week
09/24/2023	30	38	70	0.7	1.3	2	
10/22/2023	22	26	72	0.7	1.4	2.1	
11/20/2023	28	36	75	0.8	1	1.8	
12/18/2023	26	32	68	0.6	1.1	1.7	
01/24/2023	24	28	65	0.5	1	1.5	At 54-week bilirubin level stable
04/05/2024	26	30	66	0.6	1.1	1.7	
06/27/2024	30	28	69	0.7	1.2	1.9	At 78 week
09/18/2024	34	36	72	0.7	1.1	1.8	
12/05/2024	28	30	68	0.8	1.1	1.9	At 102 week