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CASE REPORT

Imatinib-induced fatal acute liver failure

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Abstract

Imatinib mesylate is a drug that has been approved for treatment of chronic myeloid leukemia (CML) in blast crisis, accelerated or chronic phase, and also for advanced gastrointestinal stromal tumors. Severe hepatic toxicity and three deaths from hepatic failure have been reported. We report the case of a 51-year-old woman who was admitted to our institution with severe acute hepatitis. She was diagnosed with CML and began treatment with imatinib mesylate at a dose of 400 mg/d. Five months after beginning treatment, she developed severe hepatitis associated with coagulopathy, and was admitted to our institution. She had been consuming acetaminophen 500-1000 mg/d after the onset of symptoms. She had a progressive increase in bilirubin level and a marked decrease of clotting factor Ⅴ. Five days after admission, grade Ⅱ encephalopathy developed and she was referred for liver transplantation. Her clinical condition progressively deteriorated, and 48 h after being referred for transplantation she suffered a cardiac arrest and died. This report adds concern about the possibility of imatinib-mesylate-induced hepatotoxicity and liver failure, particularly in the case of concomitant use with acetaminophen. Liver function tests should be carefully monitored during treatment and, with the appearance of any elevation of liver function tests, treatment should be discontinued.

Key words: Imatinib mesylate; Hepatotoxicity; Acute liver failure; Liver transplantation

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INTRODUCTION

Imatinib mesylate (Gleevec; Novartis, East Hanover, NJ, USA) is a drug that targets *bcr-abl* tyrosine kinase, an enzyme that is regarded as the cause of Philadelphia-chromosome-positive chronic myelogenous leukemia (CML). It induces a much higher rate of complete cytogenetic remission (CCR), with improved tolerability and better progression-free survival compared to other therapies. It has been approved for treatment of CML in blast crisis, accelerated or chronic phase[1,2], and also for advanced gastrointestinal stromal tumors[3].

Severe hepatic toxicity has been reported in clinical trials. This includes grade 3 (5-20 times ULN) or 4 (> 20 times ULN) transaminase elevation in 1%-5.1% of patients, and grade 3 (3-10 times ULN) or 4 (> 10 times ULN) bilirubin elevation in 0.4%-3.5% of patients. Hepatotoxicity is usually resolved with imatinib dose reduction or interruption. Yet, permanent imatinib discontinuation for hepatic toxicity has been required in 0.5% of patients[4-6]. Three deaths from hepatic failure have been reported: two during treatment for CML (one in a phase 2 clinical trial[4,5] and the other during regular treatment[7]) and one during treatment for polycythemia vera[8]. We report another case of fatal acute hepatic failure in a patient receiving imatinib for CML.

CASE REPORT

A 51-year-old woman was admitted to our institution with severe acute hepatitis. She was diagnosed with CML 7 mo before admission. She was initially treated with hydroxyurea for 1 mo and then began treatment with imatinib mesylate at a dose of 400 mg/d. Five months after starting treatment, she developed asthenia. Laboratory tests showed elevated aminotransferases with normal bilirubin (Table 1). Treatment with imatinib was discontinued. Liver function tests worsened and she developed jaundice (Table 1). Fourteen days after imatinib was discontinued she was admitted to our institution with severe hepatitis associated with coagulopathy (prothrombin time 30% and clotting factor V level 19%) (Table 1). On admission she was jaundiced, had no signs of chronic liver disease and no evidence of encephalopathy. Abdominal ultrasound showed a reduced-size, homogeneous liver. The spleen was normal, and there were no signs of biliary

Table 1 Laboratory values

Date	AST	ALT	ALP	TB	DB	WBC	Neu	PT (%)
29/12/5	70	55	197	0.5	0.14	247	148.2	
21/2/6	9	13	330	0.3	0.08	5.78	4.769	
10/5/6	38	49	204	0.47	0.1			
31/5/6	1060	1493	288	0.68	0.2			
14/6/6	2224	3185	648	8.43	5.45			
16/6/6	2595	3028	668	12.19	7.65			30
21/6/6	1887	1941	831	25.4	19.81	9.86	7.701	13
22/6/6	1626	1757	756	26	20.28	9.47	7.59	11
23/6/6	1495	1752	793	27	20.79	10	7.36	9
24/6/6	1467	1767	800	26.8	21.44	14.4	11.16	9
25/6/6	1359	1553	789	32	23.36	17	12.75	6
26/6/6	1212	1121	774	36	26.64	22.2	17.1	6
27/6/6	1024	900	686	24.7	9.5	86.8	39.9	N-M[1]
28/6/6	1269	561	362	11.5	4.8	42	33.6	N-M[1]

TB: Total bilirubin, $n < 12$ mg/L; DB: direct bilirubin, $n < 3$ mg/L; AST: Aspartate aminotransferase, $n < 40$ IU/L; ALT: Alanine aminotransferase, $n < 35$ IU/L; ALP: Alkaline phosphatase, $n < 240$ IU/L; GGT: Gamma-glutamyltransferase, $n < 32$ IU/L; WBC: White blood cells, $n = 4000$-10000 cells/mm^3; Neu: Neutrophils, $n = 2000$-6500 cells/mm^3; PT: Prothrombin time, $n = 70\%$-100%; [1]N-M: Non-measurable due to extremely prolonged prothrombin time.

obstruction. Portal and suprahepatic veins were patent, with adequate blood flow. Minimal ascitic fluid was observed.

The patient had no known risk factors for viral or alcoholic liver disease. She had not recently used any dietary products or herbal remedies. She had been consuming acetaminophen 500-1000 mg/d after the onset of symptoms. Screening was negative for viral (HAV, HBV, HCV, CMV, EBV, HSV I and Ⅱ) and autoimmune hepatitis (ANA, ASMA, ANCA, LKM1 negative). Urinary copper level was normal, and she had a mild iron overload.

Concerning her CML, status detection of t (9; 22) BCR ABL (p 210) was performed by RT-PCR. It tested positive in peripheral blood and in the bone marrow. During the following days, the patient had a progressive increase of bilirubin level and a marked decrease of clotting factor V (Table 1). Five days after admission, grade Ⅱ encephalopathy developed. Prothrombin time was 6% and clotting factor V level was 10%, with a bilirubin level of 360 mg/L. She was referred for liver transplantation.

On arrival at the transplantation unit, the patient was admitted to the intensive care unit. Encephalopathy progressed to grade Ⅲ. During the following 24 h, she developed multiorgan failure with hypotension, low urinary output, respiratory distress and metabolic acidosis. Vasopressors were required, and high dose steroids (60 mg/d per nasogastric tube) and broad-spectrum antibiotics were started empirically. She was intubated and mechanical ventilation was initiated. Blood, urinary and ascites cultures were negative. Neutrophil count in peritoneal fluid was < 250/mm^3. No evidence of major bleeding was observed. Her clinical condition progressively deteriorated, and 48 h after admission she suffered a cardiac arrest that was unresponsive to resuscitation, and died.

DISCUSSION

Imatinib mesylate is a selective tyrosine kinase inhibitor that is used in CML, Philadelphia-positive acute lymphoblastic leukemia, and also gastrointestinal stromal tumors. Grade 3 or 4 transaminase elevation has been reported in up to 5.1% of patients in phase 2 and 3 clinical trials[4-6]. There have been three reported cases of fatal acute liver failure. In a phase 2 clinical trial, one death was suspected to be related to treatment in a patient taking 600 mg/d. The patient had received a bone marrow transplant and had been concomitantly taking 3000-3500 mg/d acetaminophen 1 mo before starting treatment. The patient died 12 d after beginning treatment[5]. A 46-year-old woman with CML developed abnormal liver function tests and subsequent acute liver failure after 18 mo of treatment with 400 mg/d. She received a liver transplant but later died due to sepsis. The explanted liver had histological features of severe hepatic necrosis[7]. In the third case, a 61-year-old woman with polycythemia rubra vera in spent phase/myelofibrosis received treatment with 400 mg/d 7 wk. She died 6 d after admission, secondary to extensive hepatic necrosis. Post-mortem histology revealed microthrombi within the vasculature of the liver, lungs and spleen. The authors postulated that the mechanism of hepatic necrosis was due to an exacerbation of the underlying prothrombotic tendency of polycythemia vera, which is not present in CML[8].

There are other references to liver toxicity with imatinib, yet all of them resolved after discontinuation of treatment. Data about liver histology varies between reports of focal necrosis with lymphocytic infiltration[9,10]; from marked periportal necrosis with mixed lymphocyte, neutrophil and plasmocyte infiltration[13]; to massive hepatic necrosis[11] or cytolytic acute hepatitis[12]. The time between beginning treatment and development of liver toxicity varies from 11 d to 49 wk[9-12]. In one study, treatment was reinitiated twice after normalization of laboratory tests. In both cases of re-challenge, including one with 2.5% of the current therapeutic dosage, liver toxicity reappeared[13]. See Table 2 for a comparison of previously reported cases of serious (fatal and non-fatal) drug-induced liver damage following treatment with imatinib mesylate (adapted from the report of Cross *et al*[7]).

Data about management of imatinib liver toxicity are scarce. Ferrero *et al* have reported that corticosteroids at low to intermediate dosage can reverse imatinib-induced hepatotoxicity. The use of prednisone (25-37 mg/d) or methylprednisolone (40 mg/d) resulted in the normalization of aminotransferase levels in 2-4 wk in all five patients treated. Imatinib therapy was then resumed at increasing dosage while corticosteroids were gradually tapered, without reappearance of liver toxicity[14].

Novartis, the manufacturer of imatinib, recommends in the package insert of Gleevec that liver function tests (transaminases, bilirubin, alkaline phosphatase and prothrombin time) should be monitored before initiation of treatment and then monthly, or as clinically indicated. If elevation in bilirubin is > 3 × the institutional upper limit of normal (IULN) or if liver transaminase is > 5 × IULN, then Gleevec should be withheld until bilirubin levels have returned to < 1.5× IULN and transaminase has returned to < 2.5 × IULN. Deininger *et al* have recommended obtaining liver function tests before

Table 2 Summary of previously reported cases of serious (fatal and non-fatal) drug-induced liver damage following treatment with imatinib mesylate

Reference	Diagnosis	Time to hepatic dysfunction	Liver histology	Outcome of liver enzymes
Ohyashiki *et al* (2002)	CML	12 d	Focal necrosis of hepatocytes	Resolution after stopping drug
Lin *et al* (2003)	Polycythemia vera	7 wk	Hepatic necrosis	Patient died fatal acute hepatic necrosis
James *et al* (2003)	CML	49 wk	Acute severe cytolytic hepatitis. With necrosis and mild cholestasis	Resolution after stopping drug
	CML	22 wk	Acute cytolytic hepatitis with spotty and some piecemeal necrosis	Resolution after stopping drug
Kikuchi *et al* (2004)	CML	36 wk	Hepatic necrosis	Resolution after stopping drug
Ayoub *et al* (2005)	CML	2 yr	Portal and lobular inflammation. Bridging and multifocal lobular necrosis	Resolution after stopping drug
Cross *et al* (2007)	CML	77 wk	Severe necrosis with multilobular confluent cell dropout and reticulin collapse, multinodular regeneration	Patient died 10 d after liver transplantation
Ridruejo *et al* (2007)	CML	22 wk	Not available	Patient died fatal acute hepatic necrosis

treatment is started, every other week during the first month of therapy, and at least monthly thereafter[15].

Acetaminophen is widely known as a cause of acute liver failure[16] and has been implicated as a significant co-factor in the pathogenesis of acute liver failure in patients with acute hepatitis B and in those taking antitubercular therapy[17]. Even though there is some controversy regarding the safety of acetaminophen in patients treated with imatinib, Deininger *et al* have recommended that patients be advised to use it with caution[15].

Acute liver failure is a rare condition that requires prompt evaluation for liver transplantation[18]. Pretransplant evaluation is required to exclude contraindications, such as malignancy[18,19]. Acute liver failure in patients with potentially treatable or curable cancer, such as hematological malignancy, is extremely unusual. The role of liver transplantation in these cases is unknown. The decision must be individualized to each patient, and discussed between the liver transplant and oncology teams.

The present case report confirms the possibility of imatinib-mesylate-induced liver failure, particularly in the case of concomitant use with acetaminophen. Liver function tests should be carefully monitored during treatment, and with the appearance of any elevation, treatment should be discontinued. Corticosteroids might be an option for treatment in selected cases.

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