Imatinib mesylate-related fatal acute hepatic failure in a patient with chronic myeloid leukaemia and chronic hepatitis B infection

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ABSTRACT

Imatinib mesylate (Gleevec™) is widely-used in the treatment of chronic myeloid leukaemia (CML) and gastrointestinal stromal tumour. Up to four percent of patients treated with imatinib may develop hepatotoxicity, which usually resolves with discontinuation of the drug. We report a 45-year-old Chinese man with CML and chronic hepatitis B virus infection, on imatinib treatment, presenting with herpetic rash and acute liver failure. This case illustrates the diagnostic challenges in the management of such a patient, as well as the need for greater vigilance in the monitoring of liver function tests for patients treated with imatinib. A short review on imatinib-related hepatotoxicity is also presented.

Keywords: hepatitis B virus infection, hepatic failure, imatinib mesylate (Gleevec™), myeloid leukaemia, reactivation of HBV replication

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INTRODUCTION

Imatinib mesylate (Gleevec™) is a potent, specific, tyrosine-kinase inhibitor, which has revolutionised the treatment of chronic myeloid leukaemia (CML) and gastrointestinal stromal tumour.[1] It is hailed as a prime example of drugs that are able to kill cancer cells without damage to healthy cells via the principle of molecular targeting, with specific competitive inhibition of BCR-ABL tyrosine kinase. While hepatotoxicity has been observed in 1%–4% of CML patients treated with imatinib, liver dysfunction resolves either with dosage reduction or discontinuation of imatinib.[2] To date, there has only been one imatinib-related liver failure and death in a CML patient, but chronic acetaminophen ingestion may have played a contributory role.[3] We report a CML patient with chronic hepatitis B virus (HBV) infection, presenting with herpetic rash and fatal hepatic failure, to highlight the diagnostic challenges in the management of such a patient, as well as the potential severe hepatotoxic complication arising from imatinib treatment.

CASE REPORT

The patient was a 45-year-old Chinese man, with CML and chronic HBV infection. Pre treatment, his liver function test was essentially normal and he was HBe-antigen negative with a low grade viraemia of HBV DNA level 3.09×10^5 copies/ml. Imatinib was initiated at a daily dose of 400 mg, and subsequently increased to 600 mg daily after three weeks of treatment, because of poor haematological response. Liver function tests performed in the first three months of treatment were normal. Five months after starting imatinib, the patient presented with jaundice, fever and lethargy for four days. Upon admission, he was alert and haemodynamically stable with only significant findings of fever, periorbital oedema, jaundice and herpes simplex virus (HSV) vesicular rash over the perioral region. Imatinib was discontinued immediately and a detailed drug history revealed no other concurrent contributory hepatotoxic drugs.

Admission investigations showed acute hepatitis with a deranged coagulation profile and thrombocytopenia (Table I). Ultrasonography revealed a normal-sized liver, spleen and biliary tree with a small amount of ascites. Antiliver failure therapy consisting of lactulose, parenteral vitamin K, proton pump inhibitor for bleeding prophylaxis, and prophylactic antibiotics were promptly instituted. Lamivudine and acyclovir treatment were commenced for possible HBV reactivation flare and HSV hepatitis, respectively, within 48 hours of admission. On day three of admission, the patient developed grade II hepatic encephalopathy and his liver biochemistry continued to worsen (Table I). Septic work-up consisting of blood and urine cultures were negative. Serological tests for hepatitis A, hepatitis C, hepatitis D, hepatitis E, cytomegalovirus, Epstein-Barr Virus, leptospira and HSV were also negative. HBV core IgM was negative, but the HBV DNA level had increased to $> 100 \times 10^6$ copies/ml. An urgent transjugular liver biopsy revealed multi-acinar hepatocellular necrosis with mild portal chronic inflammation. Immunohistochemical stains for HBV surface and core antigens, HSV-1 and HSV-2, were negative. Molecular adsorbents recirculating system (MARS®) therapy was instituted on day five of admission,

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Table I. Baseline and trend of laboratory results.

Laboratory results	Normal range	Pre-imatinib treatment	Day one admission	Day three admission	Day five admission (pre-MARS)	Day seven admission (post-MARS)
Albumin (g/L)	37–51	43	37	32	33	31
Total bilirubin (μmol/L)	3–24	11	183	267	346	268
ALT (U/L)	7–36	34	4,193	3,752	2,108	942
AST (U/L)	15–33	41	4,264	3,371	1,161	403
ALP (U/L)	32–103	102	151	144	156	108
White cell count ($\times 10^9$/L)	4.0–10.0	315.0	4.2	7.2	5.6	3.5
Haemoglobin (g/dL)	14.0–18.0	10.5	14.2	12.4	12.0	7.0
Platelet ($\times 10^9$/L)	140–440	277	64	39	83	60
Prothrombin time (s)	10.7–13.4	12.9	25.9	32.0	50.4	39.9
APTT (s)	27.6–39.6	33.3	45.6	52.5	52.9	50.9
Creatinine (μmol/L)	44–141	93	82	105	67	98
Ammonia (μmol/L)	-	-	-	-	67	76

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase

in view of progressive liver failure, and continued for two cycles. However, the patient's clinical condition continued to deteriorate and he developed bleeding at vascular access sites, finally succumbing to the disease on day eight of admission.

DISCUSSION

To our knowledge, this is the first imatinib-related death reported in a CML patient with chronic HBV infection. Our case illustrates the diagnostic challenges in determining the cause of fulminant hepatic failure. The three most likely differential diagnosis of severe hepatitis in this clinical setting would include hepatitis B reactivation flare, HSV hepatitis, as well as imatinib-related hepatotoxicity. Clinical management involved immediate cessation of the suspected culprit drug, as well as avoidance of all potentially hepatotoxic agents. Prompt antiviral treatment for potentially treatable causes, such as HSV and HBV infections, was clinically appropriate, even if a drug cause for hepatitis and liver failure was initially considered.[4]

HSV hepatitis, although a rare cause for fulminant hepatic failure, was suspected in our patient, given the presence of HSV labialis rash. However, our case presented with marked jaundice, which is unusual for HSV hepatitis, as up to 90% of HSV-affected patients remain anicteric despite extreme elevation of transaminases.[5] The definitive diagnosis of HSV hepatitis is based on liver biopsy demonstrating parenchymal necrosis and characteristic viral inclusions;[6] positive HSV immunohistochemical stains would further increase diagnostic sensitivity. Therefore, it was unlikely that the patient had HSV hepatitis, due to the presence of jaundice and absence of histological proof. Varicella-zoster virus (VZV) infection has been described in patients with CML and gastrointestinal stromal tumour, and treated with imatinib mesylate.[7,8] In these reports, patient presented with classical dermatomal distribution of varicella rash and responded well to antiviral agents. None of these patients were reported to have visceral involvement or hepatitis related to varicella infection. VZV hepatitis with acute liver failure has been described in the context of immunocompromised patients secondary to transplantation, corticosteroids and AIDS. These patients typically present with cutaneous varicella lesions, acute abdominal pain or back pain, and fever.[9] Given the limited perioral rash in our patient, we did not suspect VZV infection. Furthermore, although VZV immunohistochemistry would have been helpful in the differential diagnosis, it was deemed unnecessary due to the absence of viral inclusion bodies.

Reactivation of HBV replication is a well-recognised complication of patients who have chronic HBV infection, and are being treated with cytotoxic or immunosuppressive therapy.[10] The frequency of hepatitis caused by reactivation of HBV in hepatitis B carrier patients undergoing chemotherapy has been reported to vary from 14%–72%.[11] Ikeda et al recently reported a case of fatal HBV reactivation flare in a CML patient treated with imatinib, demonstrating histological evidence of sub-massive liver necrosis and focal inflammatory infiltrates.[12] Supporting their diagnosis of HBV reactivation was the development of severe hepatitis occurring only after imatinib had been discontinued for more than two weeks.

Table II. Summary of reports on clinical features and histological pattern of imatinib-related liver toxicity.

Reports	Case one[17]	Case two[18]	Case three[18]	Case four [19]	Case five[20]	Present case
Age (years)	56	58	35	22	40	45
Gender	F	F	F	F	F	M
Time to onset of hepatic dysfunction from use of imatinib (estimated in weeks)	< 2	49	22	104	22	20
Bilirubin (μmol/L)	Normal	84	Normal	177	46	183
AST (U/L)	220	3,230	487	1,796	406	4,264
ALT (IU/L)	342	2,430	159	1,225	559	4,193
Concomitant medications	Unknown	Roxithromycin	None	Alcohol Paracetamol < 4 g over 2 days	None	None
Time of liver biopsy after stopping imatinib (estimated in days)	17	13	90	17	42	3
Main histological features	Focal necrosis of hepatocytes and mild infiltration of lymphocytes	Acute and severe cytolytic hepatitis with mild cholestasis	Acute cytolytic hepatitis with spotty and piecemeal necrosis	Marked portal tract chronic inflammation with many eosinophils. Prominent interface hepatitis with bridging necrosis. Multifocal parenchymal collapse	Severe centrilobular hepatic necrosis	Multiacinar hepatic necrosis
Outcome of liver toxicity	Survived	Survived	Survived	Survived	Survived	Died

AST: aspartate aminotransferase; ALT: alanine aminotransferase

This is consistent with other reports of liver function derangement occurring most severely after withdrawal of chemotherapy, when immunocompetence is restored and infected hepatocytes are rapidly destroyed.[13] Our patient had received imatinib treatment up to the point of presentation with liver failure, and does not typically fit the clinical picture of a hepatitis flare from HBV reactivation. According to Ikeda et al, the mechanism for reactivation of HBV with imatinib treatment is unclear, and the risk for HBV flare cannot be established on the basis of one case report. Furthermore, while there have been reports of immunosuppression related to imatinib therapy,[14,15] preclinical data suggests that there is no increased risk of acquiring viral infections,[16] and currently, imatinib is not regarded by clinicians to be an immunosuppressive agent.

Severe elevations of transaminases or bilirubin were observed in 1%–4% of patients on imatinib treatment during phase two studies. To date, there has only been five reported cases of imatinib-related liver toxicity with histological studies performed, and the clinical profile and histological findings of these cases are presented in Table II. The onset of hepatic dysfunction from the use of imatinib in these case reports ranged from < 2 weeks to 104 weeks, with a variable degree of liver enzyme elevation. Unlike our reported case, all of them were female patients,

with three out of five cases complicated by jaundice. All survived the imatinib-related liver toxicity event. Liver biopsies revealed variable degrees of hepatocyte necrosis and lymphocytic infiltration, and these histological findings were noted to closely resemble that of an acute viral hepatitis.[17] One report suggested that the diffuse pattern of inflammation without lymphoid follicles was helpful in distinguishing imatinib-related hepatotoxicity from other viral hepatitis,[18] but other authors did not report similar observations.

The onset of hepatic dysfunction from the use of imatinib can range from two weeks to two years, with a median time of 100 days. As such, regular and continual monitoring of liver function tests while on treatment is necessary. The recommended frequency of liver function test monitoring is monthly, or as otherwise clinically indicated.[21] Extra caution is necessary with co-administration of CYP3A4 inhibitors (e.g. ketoconazole, erythromycin) as these may increase imatinib levels and the risk of hepatotoxicity, since imatinib is metabolised primarily by the CYP3A4 isozyme.

Although liver dysfunction is known to reverse with the discontinuation of imatinib, the clinical course in our patient was unfortunately fatal. At this point, the mechanism of imatinib-related hepatotoxicity is not understood, but it is likely to represent an idiosyncratic reaction in susceptible individuals. Whether chronic HBV infection predisposes individuals to a more severe form of imatinib-induced liver injury, and poorer clinical outcome, is not clear at this stage. This case highlights the diagnostic challenges in a CML patient with concomitant chronic HBV infection, on imatinib treatment presenting with acute liver failure and herpetic rash, as well as the need for greater vigilance and regular liver function monitoring for imatinib-related hepatoxicity.

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