Late-onset Imatinib-induced Liver Failure Treated with Dasatinib for Two Years Resulted in Long-term Undetectable Response

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Abstract

A 21-year-old man who was diagnosed with chronic-phase CML and treated with imatinib (400 mg/day) during September 2004 achieved a complete molecular response within 14 months. His liver function remained normal during this period. The results of liver function tests after four years of treatment showed AST, 547 IU/L; ALT, 1124 IU/L, and viral hepatitis and autoimmune hepatitis were undetectable. Drug toxicity was suspected and imatinib was immediately discontinued. A liver biopsy showed hemorrhagic necrosis and hemosiderin deposition around the central vein indicating a diagnosis of imatinib-induced liver failure. Aminotransferases normalized within three months after imatinib withdrawal. Seven months after imatinib discontinuation, bcr-abl transcripts were detected twice during the next four months. Thus, dasatinib (100 mg) was administered, which resulted in an undetectable molecular response within two months.

The patient decided to stop taking dasatinib two years after achieving the undetectable molecular response and he has remained in this condition for four years since. Patients with liver damage require follow-up. To confirm the benefit of changing medication from imatinib or other drugs to dasatinib will require more information from accumulated cases.

Keywords: Tyrosine kinase inhibitors; Chronic phase; Imatinib therapy

Introduction

Tyrosine kinase inhibitors (TKI) have revolutionized the treatment of Philadelphia chromosome-positive chronic myelogenous leukemia (CML). They are approved for the treatment for patients with newly diagnosed CML in blast crisis, accelerated, or chronic phase [1].

Imatinib is a BCR-ABL selective TKI that occupies the ATP-binding sites of several TK molecules including ABL, cKIT, and platelet-derived growth factor receptor. Although generally well-tolerated, imatinib can cause severe hepatotoxicity in 1% to 5% of treated patients, usually within the first few months of treatment [2]. Treatment withdrawal often resolves this type of hepatotoxicity although severe and fatal liver failure has been reported [3]. However, liver failure in a patient who has been treated for over a year has rarely described [4].

On the other hand, the second-generation TKI, dasatinib, rarely causes hepatotoxicity. We describe a 21-year-old male with CML who achieved a complete molecular response with dasatinib after imatinib therapy had caused liver dysfunction. The molecular response has remained undetectable at almost four years after stopping dasatinib. The present findings suggest that not only short-term but long-term imatinib treatment might confer a risk of liver failure with necrosis.

Case Presentation

A 17-year-old man was diagnosed with chronic-phase CML during August 2004. Initial peripheral blood tests showed hemoglobin, 13.4 g/dL; white blood cells, 5.3x10^7/μL; and platelets, 15.7x10^9/μL. Abdominal CT revealed splenomegaly. The patient was classified as being at low risk based on a Sokal score of 0.43 and started on a standard dose of imatinib (400 mg/day) during September 2004. Real-time quantitative transcription-polymerase chain reaction (RQ-PCR) according to methods having an international conversion factor (CF) did not reveal bcr-abl transcripts [5]. Thus, he achieved a complete molecular response after 14 months of imatinib therapy (Figure 1). Liver function indicators at the time of diagnosis were within normal limits. He did not consume drugs or large amounts of alcohol.

**Figure 1**: Clinical course and transition of bcr-abl transcripts in present patient <50, bcr-abl transcripts undetectable by RQ-PCR [5].
Liver function tests after four years of treatment (November 2008) showed aspartate aminotransferase (AST), 446 IU/L; alanine aminotransferase (ALT), 784 IU/L. Imatinib treatment was discontinued, but liver function indicators worsened and he was admitted to our hospital with elevated aminotransferases (AST, 547 IU/L; ALT, 1124 IU/L). Alkaline phosphatase (ALP), bilirubin, albumin, and PT remained within normal limits. Viral hepatitis and autoimmune hepatitis were undetectable. A liver biopsy showed hemorrhagic necrosis and hemosiderin deposition around the central vein (Figure 2). Aminotransferase values were normalized at three months after imatinib withdrawal. Seven months after imatinib discontinuation, bcr-abl transcripts again became detectable during the next four months. Dasatinib (100 mg) was started and a complete molecular response (CMR) was soon achieved with no adverse effects. After two years of sustained CMR, the patient elected to stop the dasatinib therapy. The bcr-abl transcripts have remained undetectable for almost four years after dasatinib was discontinued.

Imatinib mesylate is a selective BCR-ABL tyrosine kinase inhibitor that is used to treat CML, Philadelphia chromosome-positive acute lymphoblastic leukemia, and gastrointestinal stromal tumors [1]. Imatinib induces hepatotoxicity in up to 5% of patients, but it usually resolves after the imatinib is withdrawn, although severe and fatal liver failure with liver necrosis has been reported [2,4]. Amino-transferase values became normalized in our patient at three months after imatinib withdrawal.

Several reports have described imatinib-induced histopathology and hepatocellular necrosis is by far the most frequent feature [2,4]. A liver biopsy from our patient showed hemorrhagic necrosis and hemosiderin deposition around the central vein, which support reported histo-pathological findings.

Although severe hepatotoxicity associated with TKI is not uncommon, little is known about its histological features. Much of the available information relates to imatinib-induced hepatotoxicity, since it has been clinically applied for a longer period. Reports suggest that hepatocellular necrosis is by far the most frequent form of TKI-induced liver injury. Cross et al. summarizes the key reports describing the liver histology of patients with TKI-induced hepatotoxicity that we were able to extract from the literature [6]. The time-to-onset of increased amino-transferases for most patients is within 2–8 weeks of starting therapy. The median time to the development of increased transaminases is 100 days. However, a few reports have described transaminase elevation 12, 14, and 24 months after starting imatinib treatment. We did not find any common features between the present patient and other patients with liver failure. Our patient did not consume alcohol, drugs such as acetaminophen, or any other drugs or herbal medicines [2] and no common predisposing risk factors were apparent. To the best of our knowledge, this is the first report to describe imatinib-induced hepatotoxicity occurring after four years of treatment. Because imatinib-induced hepatotoxicity can occur at any time during therapy, liver function should be carefully monitored, and treatment should be immediately discontinued if liver enzyme values start to increase.

Whether TKI therapy can be stopped for optimal responders has not reached consensus. The European Leukemia Net (ELN) guidelines do not recommend discontinuing TKI therapy. However, some clinical trials have found that a complete molecular response is maintained in 40% to 60% of patients with CML who stop TKI therapy [7].

The pathogenic mechanisms of imatinib-induced hepatotoxicity are unknown. Imatinib is metabolized by cytochrome P450 enzymes such as CYP3A4. Although dasatinib is also metabolized by CYP3A4, its chemical structure differs from that of imatinib. The liver damage in the present patient developed during long-term, not short-term imatinib treatment. Thus, the risk of liver damage via an immune response to dasatinib is lower than to imatinib. Furthermore, imatinib at a dose of 400 mg/day was stopped after the patient had remained in molecular remission for four years, but the disease recurred within seven months. Thus, we treated the patient with dasatinib, which is a TKI with a different structure, and a complete molecular response was rapidly achieved again [8]. The disease was controlled without side effects or a detectable molecular response for two years. The patient decided to stop dasatinib after 24 months, and the molecular response has remained undetectable for almost four years. Patients with liver damage require follow-up. To confirm the benefit of changing medication from imatinib or other drugs to dasatinib will require more information from accumulated cases.

Figure 2: Liver histology: Liver biopsy shows hemorrhagic necrosis (A) and hemosiderin deposition around central vein (B).
References


