Novel treatment (new drug/intervention; established drug/procedure in new situation)

Recurrent imatinib-induced hepatotoxicity in a chronic myeloid leukaemia patient successfully managed with prednisone

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Summary

Imatinib, the frontline tyrosine kinase inhibitor (TKI), has revolutionised the management of chronic myeloid leukaemia (CML). Severe hepatotoxicity, although uncommon, can occur with this drug. This tends to subside with dose reduction or cessation, but can recur with reintroduction of the drug. Recurrent severe hepatotoxicity mandates permanent discontinuation of imatinib. This can cause difficulties in the management of CML, more so if the patient cannot afford or get access to alternate therapy. Furthermore, alternate therapy, for example, second-line TKIs, can impose a huge economic burden on a healthcare system. Here, the authors report the case of 20-year-old CML patient who developed recurrent hepatotoxicity with the use of imatinib. Introduction of corticosteroids enabled successful reintroduction of imatinib therapy.

BACKGROUND

Imatinib, the frontline tyrosine kinase inhibitor (TKI), has revolutionised the management of chronic myeloid leukaemia (CML). One study showed an overall survival rate of 89% at 60 months among newly diagnosed CML patients in the chronic phase who received imatinib as initial therapy.¹ Although imatinib is well tolerated, severe hepatotoxicity has been noted with its use. Liver and kidney toxicity is also seen with many other bioactive drugs (eg, interferon) used in the management of CML.²⁻³ Imatinib-induced hepatotoxicity can require permanent discontinuation of imatinib therapy.⁴ In resource-poor settings where patients may not be able to afford or access alternate therapy, inability to use imatinib can cause serious problem in the management of CML. Here, we describe a case of recurrent imatinib-induced hepatotoxicity in a young CML patient, where use of oral prednisone allowed successful reintroduction of imatinib.

CASE PRESENTATION

A 20-year-old woman presented to the emergency department complaining of nausea and vomiting of 2 days' duration. She had recently been diagnosed with CML in the chronic phase and initially started on hydroxyurea 6 weeks previously while waiting for her health insurance to take effect. Subsequently, the therapy had been changed to oral imatinib 400 mg daily 2 weeks previously. She denied any other medical or surgical history. She denied smoking, drinking alcohol or use of illicit drugs.

On physical exam, she had a pulse of 97 beats/min, blood pressure of 128/64 mm Hg, respiratory rate of 18/min and temperature of 36.9 °C. On abdominal examination, she had mild tenderness in the right hypochondrium, a palpable liver and splenomegaly 4 cm below the left costal margin in the mid-clavicular line. The rest of the physical examination was unremarkable.

INVESTIGATIONS

Laboratory studies included: white blood cell 13 400/μl with 55.0% granulocytes, haemoglobin 11.9 g/dl and platelet count 522 000/μl. She had alanine aminotransferase of 2364 IU/l, aspartate aminotransferase of 1406 IU/l, alkaline phosphatase of 97 IU/l, total bilirubin of 1.0 mg/dl, total protein of 5.8 g/dl, albumin of 3.3 g/dl, sodium of 128 mmol/l, potassium of 3.3 mmol/l, chloride of 94 mmol/l, bicarbonate of 25 mmol/l and calcium of 8.1 mg/dl. The glucose, lactate, amylase, lipase, uric acid, renal function test, coagulation profile and acetaminophen and salicylate levels were all within normal limits. Viral hepatitis profile was negative. Ultrasound of the liver was remarkable only for hepatomegaly with a homogeneous liver measuring 20 cm.

TREATMENT

The patient was started on normal saline infusion, oral potassium and intravenous metoclopramide. As there was a possibility of imatinib-induced hepatitis, it was decided to discontinue imatinib. This led to rapid resolution of clinical symptoms and the patient was discharged home on day 3 of hospitalisation.

OUTCOME AND FOLLOW-UP

On outpatient follow-up, the patient's liver function tests continued to improve and normalised over 3 weeks (table 1). She was restarted on oral imatinib 200 mg daily. However, 1 week later she was again noted to have increased transaminases. Her imatinib was again discontinued with subsequent normalisation of liver function tests within 2 weeks. Because of the terms of the patient's health insurance and economic issues, it was not possible to start her on second-line TKIs. At this point, therefore, she was started on oral prednisone 25 mg daily and rechallenged with oral imatinib 200 mg daily. This time, the patient tolerated imatinib well without any liver dysfunction. The

Table 1 Trends in liver function tests

Tests	7 Weeks before initiation of imatinib	During imatinib therapy	3 Weeks after discontinuation of imatinib	1 Week after reintroduction of imatinib	2 Weeks after discontinuation of imatinib	8 Weeks after concurrent imatinib and steroid use
Bilirubin (mg/dl)	0.8	1.0	1.1	2.5	0.8	0.5
Alkaline phosphatase (IU/l)	52	97	83	131	80	66
AST (IU/l)	20	1406	68	332	43	29
ALT (IU/l)	14	2364	95	654	83	30

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

dose of imatinib was subsequently escalated to 400 mg daily and prednisone was gradually tapered over 8 weeks.

Three months after receiving oral imatinib 400 mg daily, the patient attained complete haematological response and major cytogenetic response. Furthermore, she continues to tolerate imatinib without any side effects.

DISCUSSION

Imatinib therapy is associated with mild liver dysfunction in up to 10% of patients, which often normalises despite continued imatinib use.⁴ Grade 3 or 4 hepatotoxicity occurs in less than 5% of patients.^{1–5} Severe hepatotoxicity usually resolves with imatinib dose reduction or interruption⁵; however, it can recur with reintroduction of imatinib.^{6–9} This recurrent hepatotoxicity has been noted to be the second most common reason for permanent discontinuation of imatinib therapy,⁴ thus causing difficulties in the management of CML.

Imatinib-induced hepatotoxicity tends to occur during the first few months of therapy^{4–10} with a median delay of 22 weeks (range 1.7–104 weeks) after drug initiation among reported cases.¹¹ Liver function tests, on the other hand, return to normal within about 7 weeks (range 2–20 weeks) of discontinuation of imatinib. Histopathological examination of biopsied liver samples reveals necrotic hepatitis associated with a non-specific inflammatory infiltrate in the majority of patients, while interface hepatitis and bridging necrosis can be seen in some cases.¹¹ The mechanism of the hepatotoxicity is currently unclear, although on liver biopsy it appears to be drug-induced hypersensitivity.^{4–10} However, an immuno-allergic mechanism may play a role in some patients.¹¹

When imatinib is used, it is recommended that liver function tests are monitored at baseline and regularly thereafter, for example, every few weeks for the first month and every month or 3 monthly thereafter. In case of hepatotoxicity, any hepatic toxins, particularly alcohol and acetaminophen, should be avoided.^{4–10–11} A thorough hepatic evaluation is recommended for grade 2 hepatotoxicity or higher.⁴ While imatinib can still be continued under close monitoring in the event of grade 1/2 hepatotoxicity, therapy must be interrupted if grade 3/4 hepatotoxicity ensues.^{4–10} It can be resumed at the same¹⁰ or reduced⁴ dose when liver function tests decrease to grade 1 or less. If it has been restarted at a reduced dose, the dose can be escalated if hepatotoxicity does not recur within 6–12 weeks.⁴ In cases of recurrent grade 3/4 hepatotoxicity, it is recommended that imatinib therapy is permanently discontinued.^{4–10}

In resource-poor settings where patients may not be able to afford or access alternate therapy, the inability to use imatinib can cause serious problems in the management of

CML. Furthermore, use of an alternate therapy, for example, second-line TKIs, can impose a huge economic burden on the health system. This is especially relevant in light of imatinib going off patent in 2015, which will dramatically reduce its cost.¹²

In this patient, it was possible to safely restart imatinib with concomitant use of oral prednisone. The introduction of corticosteroids into the patient's regimen has been previously shown in a few case reports to enable use of imatinib in patients who develop recurrent hepatotoxicity, even at reduced doses.^{6–9–13–14} Steroids used in these case reports included oral prednisone 25 mg daily tapered over 5–8 months,⁶ prednisone 30 mg daily tapered over 5 months,⁹ prednisone 20 mg daily (duration not mentioned)¹³ and prednisone 25 mg twice daily (duration not mentioned).¹⁴ The usefulness of corticosteroids may be based on their ability to suppress the inflammatory response in the liver as a part of drug-hypersensitivity or an immuno-allergic reaction.

Learning points

- ▶ Imatinib can cause severe hepatotoxicity.
- ▶ Imatinib-induced hepatotoxicity is reversible with discontinuation of the drug but tends to recur with subsequent use.
- ▶ Recurrent grade 3/4 hepatotoxicity can necessitate permanent discontinuation of the drug.
- ▶ In such conditions, use of corticosteroids can enable successful reintroduction of the drug.

Competing interests None.

Patient consent Obtained.

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