Corticosteroids can reverse severe imatinib-induced hepatotoxicity

Background. **Imatinib can induce severe hepatotoxicity,in 1-5% of CML patients, many of whom need permanent imatinib discontinuation. Design and *Results:* We report 5 CML patients who developed grade 3-4 hepatotoxicity after 2-8 months in imatinib. Different aetiologies of liver damage were ruled out and toxicity recurred in 2 patients with further attempts at low dose imatinib. In all patients prednisone or methylprednisolone at 25-40 mg/day resolved hepatotoxicity in 3-8 weeks and allowed imatinib to be resumed at full doses. Corticosteroid were tapered off in 3-5 months without hepatotoxicity recurrence. *Conclusions*. Corticosteroid may avoid discontinuation for hepatotoxicity of the most effective anti-CML therapy.**

Tyrosine- kinase inhibitor imatinib (STI571) has become the first line therapy for most patients with chronic myelogenous leukemia (CML)[1,2] gastro-intestinal stromal tumors (GIST)[3] and other rare neoplasms (dermatofibrosarcoma protuberans, myeloproliferative disorders with 5;12 chromosomal translocation, hypereosinophilic syndromes) with genetic abnormalities involving PDGF receptors.[4,5] In combination with cytotoxic drugs it has acquired an important role in the treatment of BCR/ABL positive acute lymphoblastic leukemia [6, 7] and evidenced some activity in relapsed malignant gliomas.[8] In spite of a generally good tolerance, imatinib can induce severe hepatotoxicity in 2-5% of treated patients.[1, 9, 10] While generally reversible after imatinib discontinuation, this adverse effect often recurs with drug reintroduction and many patients are prevented from the use of a very effective drug.[1, 9-11, 13]

Here we describe 5 CML patients displaying imatinib-induced hepatotoxicity that completely resolved after the introduction of corticosteroids for a few months, thus allowing imatinib resumption and achievement of complete hematological and cytogenetic responses (CCR).

Patients and results

All patients displayed normal values of liver enzymes and functions at the beginning of imatinib therapy. The first patient evidenced markers of previous hepatitis B (HbsAg negative, HBV-DNA negative, anti-HbsAg positive, anti-HBc positive); no liver disease was found in the others. All markers of active viral hepatitis were negative at the time of aminotransferase increment.

Case 1. Fifty year old male with chronic phase CML. He began imatinib therapy in October 2000 for cytogenetic resistance to interferon + cytarabine. Two months later AST and ALT values increased, in spite of prompt drug discontinuation, up to 10 × (350 U/l) and 30 × (1080 U/l), respectively, the upper normal limits (UNL). Bilirubin, ALP, albumin, PT, fibrinogen remained unchanged, whereas anti-thrombin III dropped to 42% of the normal level. No HBV reactivation was detected. Anti-mitochondria and anti-smooth muscle antibodies were absent. Liver biopsy documented areas of necrosis, fibrous scars and peri-portal inflammatory infiltrate. Aminotransferases and anti-thrombin III normalised in 2 months after drug withdrawal; however, 2 further attempts at low dose imatinib were again followed by aminotransferase increments. Meanwhile, CML hematological relapse occurred. In July 2001 imatinib therapy was further attempted, starting from 300 mg/day, in association to prednisone 25 mg/day for 5 months: hepatotoxicity did not recur and imatinib dose could be escalated to 400 mg/day. A CCR was achieved, while prednisone was tapered and discontinued after 5 more months. The patient is still on imatinib therapy, in CCR, without hepatotoxicity recurrence.

Case 2. Sixty-six old woman with chronic phase CML. She began imatinib treatment (400 mg daily) in November 2000 for cytogenetic resistance to interferon. After 8 months of therapy aminotransferase values increased up to 406 (AST) and 421 (ALT) U/l (13 x UNL), without evidence of cholostasis or liver failure. Anti-mitochondria and anti-smooth muscle antibodies were absent. Imatinib was discontinued, without aminotransferase improvement for 2 months. Prednisone was then given at 50 mg/day for 4 weeks (September 2001) with resolution of hepatotoxicity, then tapered off in 2 more weeks. A further attempt at lower dose imatinib (200 mg daily) was again followed by hepatotoxicity, that regressed after prednisone resumption at 25 mg/ day. Prednisone at 25 and then 12.5 mg daily for 6 months allowed imatinib to be reintroduced at 300 mg daily without hepatotoxicity. CCR was obtained but the patient died of undifferentiated thyroid cancer in June 2004.

Case 3. Seventy-nine old woman. She started imatinib (300 mg/day) in April 2002 for CML in chronic phase, after 6 months in hydroxyurea treatment. In September 2002 imatinib was increased to 400 mg daily but, 4 weeks later, while partial cytogenetic response had been achieved, AST and ALT levels progressively increased in spite of drug discontinuation up to 946 and 2243 U/l (31 and 60 × UNL, respectively). Cholostasis markers and hepatic synthesis were not affected. Anti-mitochondria and anti-smooth muscle antibodies were absent. Methylprednisolone was given (40 mg daily) and aminotransferase values completely subsided in 3 months, while CML hematological relapse occurred. Imatinib therapy was then resumed (200 and then 300 mg daily), together with prednisone 25 mg/ day, without hepatotoxicity recurrence. Prednisone was tapered (5-10 mg daily) and then discontinued after 8 months, while imatinib dose was increased to 400 mg daily, with optimal tolerance and CCR achievement. The patient is still taking imatinib in continuous CCR.

Case 4. Seventy-eight old male with accelerated phase CML. He started imatinib treatment at 300-600 mg daily in May 2001. Six months later, while in hematological remission, AST and ALT levels increased up to 117 and 183 U/l (4 × and 6 ×, respectively, UNL) and GGT to 150 U/l. Imatinib was temporary stopped and prednisone given (25 mg daily), to achieve hepatotoxicity resolution. Imatinib could be resumed 3 weeks later at 300 and then 600 mg daily, while prednisone was reduced to 12.5 mg daily and maintained at that level because of concomitant chronic bronchopneumopathy. Cytogenetic response was not obtained and the patient died of blastic phase in May 2003.

Case 5. Sixty old woman. Chronic phase CML was diagnosed in June 2004 and imatinib started at 400 mg daily. In January 2005, while in CCR, AST and ALT values increased up to 190 and 360 U/l, (6 × and 10 × UNL, respectively), without other liver abnormalities. Imatinib was stopped but one week later aminotransferase values were unchanged. Prednisone (25 and then 37 mg/day) was given and hepatotoxicity resolved in 4 weeks. CML relapse occurred and imatinib has been resumed in March 2005 (300 and then 400 mg/day), while maintaining

prednisone 25 and then 12.5 mg/day until May 2005. From June 2005 imatinib dose was increased up to 800 mg/day because of acquired CML resistance. Hepatotoxicicity did not recur but only a partial hematological response was achieved, due to an acquired BCR/ABL mutation. A complete hematological and minor cytogenetic response has been then achieved by December 2005, after addition of continuous low dose ARA-C (10 mg/day) to imatinib 800 mg /day without signs of liver toxicity.

Table1 summarises main clinical data of the 5 patients.

Discussion

Liver toxicity developed in our patients after 2-8 (median 6) months of imatinib therapy. Aminotransferase increase was very pronounced (grade 4 toxicity according to W.H.O.) in 2 patients, moderate (grade 3) in 3, although, differently from other reports (11-13), bilirubin remained in the normal range. Patient 1 probably had the most severe liver damage, with reduction of AT III and istological findings of hepatic necrosis, fibrosis and inflammatory infiltrate. However, re-activation of previous hepatitis B could be ruled out.

The role of imatinib in liver damage was evidenced in patients 1 and 2 by the recurrence of aminotransferase increment every time the drug was resumed before corticosteroid addition and, in all patients, by the absence of different liver damage aetiologies.

Pathogenic mechanisms of imatinib-induced hepatotoxicity are unknown; however, istopathology findings from patient 1 and the response to corticosteroids suggested an inflammatory reaction. Some recent reports of imatinib-induced toxicity also pointed out similar- hepatitis features: aminotransferase increment[11-13] and istological evidence of focal necrosis and inflammatory infiltrate.

While liver damage seems to be reversible after imatinib discontinuation, 2 cases of fatal hepatic failure were reported: the first was a CML patient taking imatinib and paracetamol, this suggesting a synergism in drug toxicity[14]; the last was a patient treated for polycythemia vera.[15] In that case, pathological examination revealed different features: massive necrosis and diffuse microthrombi in liver, spleen and lung vessels.

Four of our 5 and 3 of the 5 described patients[11, 12, 15] were > 60 year old when hepatotoxicity developed; however, imatinib hepatotoxicity was not found to be more frequent in large casistics of old patients.[16,17]

In our patients hepatotoxicity promptly regressed after the addition of prednisone or methyl-prednisolone. This allowed imatinib prosecution and CCR achievement in 3 chronic phase patients. Moreover, corticosteroids were discontinued after a few months without hepatotoxicity recurrence in spite of increased imatinib dosage in 2 patients up to 600 and 800 mg/day, respectively.

Therefore, corticosteroids look as a promising approach in imatinib- induced hepatotoxicity to avoid the permanent discontinuation of a very effective anti- neoplastic drug.

Authors' contribution to the study: EMP and his co-workers PP and MF first started prednisone therapy in patient 1 in Monza and collected part of his clinical data. DF, CD and EC continued patient 1 follow up in Torino, started corticosteroid therapy in patients 3 and 5 and collected their data. DF also wrote the manuscript. MB supervised clinical care and reviewed the manuscript. GRC and her co-workers CF and GM independently started prednisone therapy in patients 2 and 4 in Orbassano and collected their clinical data. GRC also reviewed the manuscript.

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Table 1. Patients' main clinical features.

	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	
Age	50	66	79	78	60	
previous hepatic disease	Hepatitis B	No	No	No	No	
diagnosis °	CML CP	CML CP	CML CP	CML AP	CML CP	
daily imatinib dose (mg)	400	400	400	600/400*	400-800	
weeks from imatinib star	t7	32	25	25	28	
peak AST value (U/l)	350	406	946	117	190	
peak ALT value (U/l)	1080	412	2243		183	360
other liver abnormalities	AT III 42%	No	No	GGT 150 U/l	No	
weeks to normal AST/ALT	7	12	12	3	6	
liver toxicity recurrence	without steroid **	Yes	Yes	ND	ND ND	
liver toxicity recurrence with steroid	No	No	No	No	No	

**Dose reduced for hematological toxicity before the occurrence of liver toxicity.; °CP: chronic phase; AP: accelerated phase.; ** Hepatotoxicity recurrence at 2nd –3rd attempt to imatinib therapy before corticosteroid addition.*

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