Short Communication

Imatinib administration in two patients with liver metastases from GIST and severe jaundice

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Imatinib is the only effective and approved systemic therapy for the treatment of patients with advanced gastrointestinal stromal tumours (GISTs). Although metastases from GISTs most commonly involve the liver, yielding hyperbilirubinaemia, very few data on imatinib administration in subjects with jaundice are available. We provide evidence that imatinib tolerability was not adversely affected by jaundice in two patients with advanced GIST.

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We report on two patients who received a full-dose administration of Imatinib for extended periods of time despite severe jaundice.

RESULTS

Case 1

The first patient was a 67-year-old male treated with imatinib 800 mg (400 mg b.i.d.) p.o. for synchronous omental and liver metastases from gastric GIST. More than 10 liver metastases were observed at the time of diagnosis, with the longest diameter up to 50 mm. The patient had no relevant hepatobiliary medical record; red cell transfusions were given for WHO G4 anaemia (5.1 g dl−1) before starting imatinib administration. The first three treatment weeks were uneventful; then imatinib administration was discontinued because of G2 rash and oedema. During the next 2 weeks after treatment discontinuation, the patient suffered from a G3 elevation of transaminases and increase in both alkaline phosphatase and serum bilirubin (4.1 mg dl−1, conjugated 3.8 mg dl−1). A liver ultrasound and an abdominal CT scan showed a tumour stabilisation, without remarkable anatomic changes, such as biliary duct compression; HAV, HBV and HCV markers were negative. The pathogenesis of the cholestasis remained unclear, even if a drug-related hepatotoxicity or a toxicity related to the previous red-cell transfusions were hypothesised. The cholestasis worsened, with alkaline phosphatase up to 4118 IU l−1 and serum bilirubin up to 12.2 mg dl−1 (refer to the graphic). At 6 weeks after treatment discontinuation, despite a persistent jaundice (total serum bilirubin 10.8 mg dl−1, conjugated 8.1 mg dl−1) and without evidence of disease progression, the treatment with imatinib was resumed at the reduced dose of 400 mg p.o. day−1; dexamethasone 8 mg daily was also initiated.

After 6 weeks of imatinib treatment, jaundice resolved: in this period of time, only G2 oedema occurred, not requiring treatment discontinuation nor dose reduction. Stable disease and subsequent
Imatinib in patients with severe jaundice

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Clinical summary

Figure 1 Clinical summary

disease progression were confirmed by CT scan 2 and 5 months after treatment restarting, respectively (refer to the graphic).

Case 2

The second patient was a 42-year-old female treated with imatinib 400 mg p.o. day \(^{-1}\) for synchronous liver metastases (more than 10, up to 120 mm of the longest diameter) from a retroperitoneal GIST refractory to ifosfamide plus doxorubicin chemotherapy. The patient had no relevant hepatobiliary medical record. The first 10 weeks of treatment were uneventful; then treatment was discontinued because of G3 elevation of transaminases and G2 increase in alkaline phosphatase, followed, a few days later, by a conjugated hyperbilirubinaemia (6.4 mg dl \(^{-1}\)) and disease progression in the liver (more than 30% according to RECIST criteria), without relevant anatomic changes, such as biliary duct compression. At 20 days after treatment discontinuation, serum bilirubin increased up to 11.2 mg dl \(^{-1}\) and a liver ultrasound and CT scan showed disease progression (more than 20% of the longest diameter in most liver metastases) with no biliary duct compression. According to this observation, a disease-progression-related cholestasis was hypothesised. According to an informed patient’s preference, administration of imatinib 400 mg p.o. day \(^{-1}\) was resumed and delivered in combination with dexamethasone 8 mg daily for 11 weeks, despite a persistent jaundice (serum bilirubin decreased to 3.0 mg dl \(^{-1}\) after 3 weeks, then increased up to 9.0 mg dl \(^{-1}\)). During this period of treatment, no G2-4 imatinib-related toxicity was observed, and treatment was delivered without interruptions or dose reductions.

Afterwards (week 25), because of the worsening jaundice (serum bilirubin 9 mg dl \(^{-1}\)) and disease progression were confirmed by CT scan 2 and 5 months after treatment restarting, respectively (refer to the graphic).

DISCUSSION

With this report, we provide evidence that imatinib tolerability was not adversely affected by jaundice, in two patients with advanced GIST, despite full-dose administration of the drug for extended periods of time. This information should be considered with caution, since only two patients were examined and the lack of pharmacokinetic analysis and liver tissue analyses did not provide a clear interpretation of these data. Theoretically, elimination of imatinib is expected to be impaired to some degree in patients with hepatobiliary dysfunction, and a pharmacokinetic study of imatinib in patients with hepatic impairment is currently underway.

Imatinib has a very high rate of clinical benefit in patients with c-KIT-positive GIST and, in the absence of other systemic treatment options, it is the only chance of cure in this subset of patients. According to this limited experience and until more information is available, Glivec administration in patients with advanced GIST and jaundice should be cautiously considered.

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