Anti-Cancer Drugs 2002, **13,** pp. 847–849

Case report

Imatinib mesylate therapy in patients with gastrointestinal stromal tumors and impaired liver function

Sebastian Bauer,[1] Volker Hagen,[2] Hermann J Pielken,[2] Peter Bojko,[1] Siegfried Seeber[1] and Jochen Schütte[1]

[1]Innere Klinik und Poliklinik (Tumorforschung), Universitätsklinikum Essen, Westdeutsches Tumorzentrum, 45122 Essen, Germany. [2]St-Johannes-Hospital, Medizinische Klinik II, 44137 Dortmund, Germany.

Hepatic and peritoneal metastases are the most frequent metastatic lesions in patients with gastrointestinal stromal tumors (GIST), and may result in intra- or extrahepatic cholestasis and altered drug metabolism. While the tyrosine kinase inhibitor imatinib, which has been recently shown to represent the treatment of choice for GIST, is primarily metabolized by the liver, data on the pharmacokinetics and the tolerability of imatinib in patients with increased cholestasis parameters are not yet available. We here report on two patients who received imatinib in the presence of increased bilirubin and/or cholestasis parameters. With a follow-up duration of 3–4 months, we observed no toxicities outside of well-known side effects including some degree of myelosuppression and fluid retention. This report may aid in the decision of imatinib being given under close surveillance to this kind of patients. [© 2002 Lippincott Williams & Wilkins.]

Key words: Cholestasis, gastrointestinal stromal tumors (GIST), imatinib, liver function.

Introduction

Imatinib mesylate (STI571) has been recently found to be a highly active drug for the treatment of patients with chronic myeloid leukemia and c-KIT$^+$ gastrointestinal stromal tumors (GIST).[1–4] It is predominantly metabolized by the liver, resulting in the exclusion of patients with impaired liver function from clinical trials and a current paucity of information about its tolerability in this kind of patient. Yet, impaired liver function due to extensive hepatic metastases and/or intra- or extrahepatic cholestasis may occur in GIST patients for whom no reasonable alternative may exist besides a probatory treatment with imatinib. We here report on two patients with GIST and markedly elevated liver enzymes who were treated with imatinib and followed-up for 3–4 months.

Correspondence to S Bauer/J Schütte, Innere Klinik und Poliklinik (Tumorforschung), Universitätsklinikum Essen, Westdeutsches Tumorzentrum, Hufelandstrasse 55, 45122 Essen, Germany.
Tel: (+49) 201723 2024; Fax: (+49) 201723 5925;
E-mail: sebastianbauer@uni-essen.de/jochen.schuette@uni-essen.de

Case report

The first patient is a 58-year-old male with a GIST of the small bowel. Following previous treatments with small bowel resection, hemihepatectomy, and local hepatic procedures including laser-induced thermotherapy, embolizations and doxorubicin therapy, he presented at our institution with multiple hepatic and i.p. tumor manifestations, a dilation of intrahepatic bile ducts and a congestion of the portal and splenic veins. Serum chemistry analysis showed bilirubin 6.6 mg/dl, γ-glutamyltransferase (GGT) 779 U/l, alkaline phosphatase (AP) 1321 U/l, AST 40 U/l, ALT 41 U/l and cholinesterase 2210 U/l. Imatinib was started on 7 November 2001, beginning with a dose of 100 mg b.i.d. for 3 days and continued with a daily oral dose of 400 mg. Repeated positron emission tomography (PET) and/or computed tomography (CT) scans after 4 and 8 weeks showed loss of all pathologically increased glucose utilization and a regression of almost every tumor manifestation while leaving markedly dilated intrahepatic bile ducts. After 6–8 weeks of imatinib therapy, serum chemistry showed minimum values of bilirubin (2.6 mg/dl), GGT (444 U/l) and

AP (981 U/l) which subsequently increased again in the following 8 weeks. Imatinib therapy was paused on 6 March 2002, when bilirubin was 6.5 mg/dl, GGT 492 U/l, AP 1559 U/l, and fever and upper abdominal pain occurred. The CT scan at this time showed a cystic, non-contrast-enhancing lesion between the pancreas and the stomach with a diameter of 16 cm, which was shown to represent encapsulated ascites at laparotomy.

Hematological side effects in this patient consisted of thrombocytopenia and neutropenia grade $\leqslant$II (NCI-CTC). After 3 months of therapy fever (with proven bacteremia) occurred during a transient grade II leukocytopenia. Neutropenic fever (grade II) recurred again on 6 March 2002 in association with the afore-mentioned findings. Except the encapsulated ascites, other non-hematological or hematological toxicities grade $>$II were not encountered.

The second patient is a 70-year-old female with a newly diagnosed unresectable GIST involving the pancreatic head with concomitant intra- and extrahepatic cholestasis, and a cranial metastasis in the right temporal lobe with perifocal edema. She received cranial irradiation plus dexamethasone from 7 to 23 January 2002. Imatinib was given from 25 December 2001 to March 2002. Serum chemistry at treatment start showed AP 2805 U/l, GGT 700 U/l, AST 28 U/l, ALT 102 U/l and bilirubin 2.28 mg/dl. Imatinib was initiated at a dose of 100 mg q.d. for 4 days and increased to a maximum dose of 600 mg q.d. over the next 4 days. Treatment was paused after 21 days of treatment for 3 days due to thrombocytopenia grade III and was continued with reconstituted thrombocytes at a daily dose of 400 mg for the rest of the treatment. Abdominal CT scan 6 weeks after treatment start showed a minor response of the abdominal tumor. AST, ALT and bilirubin normalized within the first 2 weeks after treatment start, while AP and GGT levels decreased to 427 U/l and 155 U/l, respectively, at last follow-up.

In addition to the afore-mentioned transient thrombocytopenia grade III, neutropenia grade II and a consecutive single episode of fever with bacteremia (*Enterococcus faecalis* and *Escherichia coli*) which was successfully treated with piperacillin/tazobactam was observed. Following a reduction of the daily dexamethasone dose with completion of the cranial radiotherapy, the patient developed some weakness of her right arm along with an increasing perifocal edema as shown in the cranial CT scan. Neurological symptoms resolved after a few days of an escalated dexamethasone dose. Other side effects have not occurred.

Discussion

Liver metastases represent the most frequent metastatic site in patients with gastrointestinal stromal tumors.[5] Thus, elevated liver enzymes and/or impaired liver function may be a common finding in these patients, raising questions as to the pharmacokinetics and the tolerability of imatinib. However, since patients with markedly increased liver enzymes as the two patients described in this report have been excluded from clinical trials of imatinib and pharmacokinetic data are not yet available, there is (to our knowledge) a current paucity of experience with imatinib in patients with this pattern of laboratory parameters. Given the lack of treatment alternatives and the inherent ethical concerns, both of our patients who showed a markedly elevated serum bilirubin and/or increased cholestasis parameters received imatinib under close surveillance. With a follow-up duration of up to 4 months, no unexpected and/or serious toxicities were observed. Both the myelosuppression and the fluid retention which required a surgical intervention in one patient were in the range of already known side effects of imatinib.

Conclusion

Given the lack of treatment alternatives and pharmacokinetic data which may guide the treatment with imatinib in patients with GIST and compromised liver function, our observations may aid in the decision of imatinib being administered to this kind of patient under close surveillance.

References

1. Talpaz M, Silver RT, Druker BJ, *et al.* Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood* 2002; **99**: 1928–37.
2. Joensuu H, Roberts PJ, Sarlomo-Rikala M, *et al.* Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001; **344**: 1052–6.
3. van Oosterom AT, Judson I, Verweij J, *et al.* Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumors: a phase I study. *Lancet* 2001; **358**: 1421–3.

4. von Mehren M, Blanke C, Joensuu H, *et al.* High incidence of durable responses induced by imatinib mesylate (Gleevec) in patients with unresectable and metastatic gastrointestinal stromal tumors. *Proc Am Soc Clin Oncol* 2002; **21**: 403a.

5. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg* 2000; **231**: 51–8.

(Received 16 May 2002; accepted 17 June 2002)