Case report

Limited administration of the tyrosine kinase inhibitor, imatinib mesylate, in a case of intra-abdominal recurrence of gastrointestinal stromal tumors

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We report the case of a 62-year-old woman with a gastrointestinal stromal tumor of the stomach. The patient underwent resection of the tumor, but an intra-abdominal recurrence was discovered 2 months after the operation. Because the recurring tumors gradually grew in size and number, the patient received treatment with *imatinib mesylate*; however, the treatment lasted only 7 weeks due to severe cutaneous adverse reactions to the *imatinib mesylate*. After treatment with *imatinib mesylate*, a marked reduction of the intra-abdominal lesions was observed. The skin rash was improved by treatment with a topical steroid and an antihistamine medication. This report showed that seven-week administration of *imatinib mesylate* led a partial response for ten months in spite of *imatinib mesylate* discontinuance.

(Key words : gastrointestinal stromal tumor, *imatinib mesylate*, adverse reaction, limited administration)

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors and arise from precursors of the connective tissue cells of the gastrointestinal tract.[1] These tumors recur in 30-40% of patients with GISTs after completely resection.[2,3] The treatment options for the intra-abdominal recurrence of GIST are limited. The recurrent lesions are rarely responsive to chemotherapy or radiotherapy. Moreover, historical data show a median survival of only 9 months for patients with metastatic disease and local recurrence.[2]

The c-Kit receptor tyrosine kinase protein appears to be a major factor in the molecular pathogenesis of GISTs. The specific tyrosine kinase inhibitor, *imatinib mesylate*, acts directly against the c-KIT receptor tyrosine kinase protein. The first effective outcome following treatment with *imatinib mesylate* was reported by Joensuu et al. in 2001.[4] Other reported cases had successful outcomes after long-term administration of *imatinib mesylate*.[4,5] However, in the case reported here, treatment with *imatinib mesylate* was discontinued after short-term administration because adverse cutaneous reactions developed. However, the patient continued to show

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a partial response for many months afterwards.

Case report

A 62-year-old woman was found to have a left upper abdominal mass on July 10, 2002. The patient had a medical history of hypertension and diabetes mellitus. The family history was unremarkable. An upper gastrointestinal study series showed a protruding tumor in the upper portion of the stomach. The endoscopic finding showed a large gastric tumor with ulceration in the upper region. Computed tomography showed a large tumor that occupied the left upper intraperitoneal space and had an irregular borderline with adjacent organs (Fig.1). Two days after the esophagogastroduodenoscopy, the patient was admitted to the hospital because of wheezing and high-grade fever. Laboratory studies at the time of admission showed leukocytosis and a high C-reactive protein level. Angiography was performed to investigate the origin of the tumor and the results revealed that the tumor was fed by the splenic and middle colic arteries. We estimated that the origin of the tumor was either the stomach or the mesocolon of the transverse colon. To ameliorate the patient's condition, an emergent resection of the tumor with a partial gastrectomy and transverse colectomy was performed on July 26, 2002. The size of the resected specimen was 18 cm×16 cm and it weighed 930 g. Histologic examination of the specimen revealed fewer than four cells undergoing mitosis in ten high-power fields and identified the mass as a gastrointestinal stromal tumor (Fig.2). The diagnosis was confirmed by immunostaining for the c-KIT protein. Eleven days after the operation, the patient had a high-grade fever and wound infection. Computed tomography the next day revealed an intra-abdominal abscess that required drainage. The patient resumed a liquid diet 30 days after surgery and was discharged from the hospital 64 days after surgery.

A follow-up computed tomography study 2 months after the operation showed peritoneal seedings near the caudate lobe and in the pelvic cavity (Fig.3). The patient agreed to receive *imatinib mesylate* and gave informed consent. Treatment with four 100-mg capsules of *imatinib mesylate* once daily was started in December 2002. After 2 weeks of *imatinib mesylate* treatment, the patient experienced a pruritic, erythematous rash predominantly on the trunk and

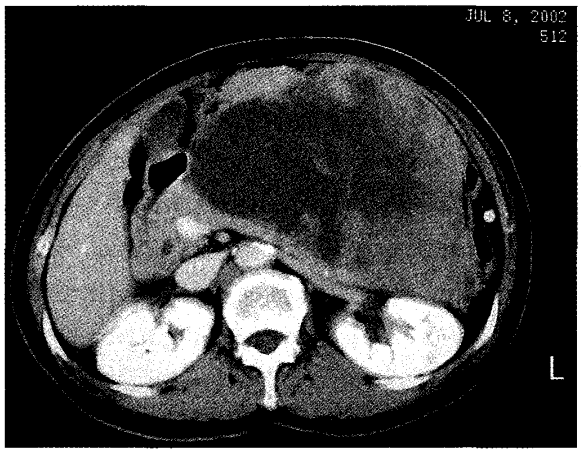

Fig.1 An enhanced CT of the abdomen at the time of admission demonstrated a giant heterogeneous tumor.

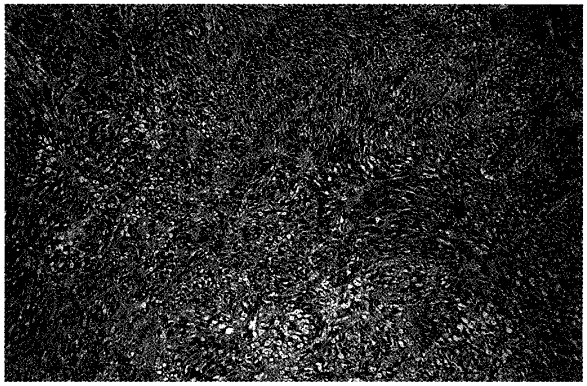

Fig.2 Histological findings. The tumor was composed of spindle-shaped cells with an interlacing bundle pattern. Hematoxylin and eosin stain, ×200

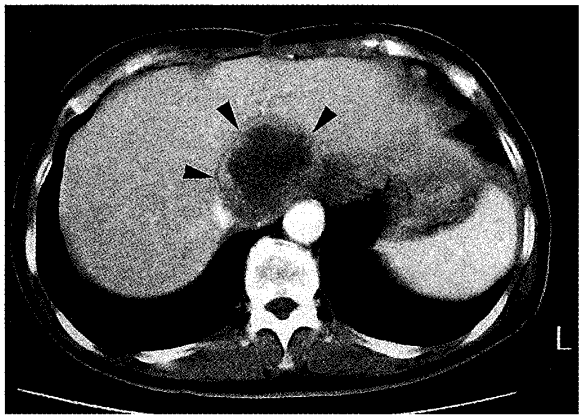

Fig.3 An abdominal CT showed disseminated tumor near the caudate lobe

spreading to the upper and lower extremities. The *imatinib mesylate* treatment was therefore stopped until the cutaneous lesions had nearly disappeared. Despite the reintroduction of *imatinib mesylate* in a reduced dose (300 mg), widespread, scaling, brawny erythema and desquamation occurred (Fig.4). The *imatinib mesylate* treatment was again discontinued and the rash was improved by the 1-month administration of an antihistamine and topical steroids (Fig.5).

The two lesions found by computed tomography in September, were reduced to 26% and 44% of their original sizes by January 2003, and no new lesion was found. Moreover, the lesions had almost completely disappeared by June 2003 (Fig.6). However, on the seventeenth postoperative month, an abdominal CT scan showed multifocal lesions compatible with metastatic tumor. These lesions resected at another hospital on January 13, 2004. Five months after the second laparotomy, new lesions showed. The patient has been treated for abdominal pain with narcotic as an outpatient.

Discussion

Treatment with *imatinib mesylate* is recommended to be continued as long as there is no evidence of progressive disease or unacceptable toxicity[6,7]. Furthermore adverse events with *imatinib mesylate* can usually be managed with either a reduction of the dose or an interruption of treatment[8]. Therefore our case requiring permanent discontinuation of treatment with

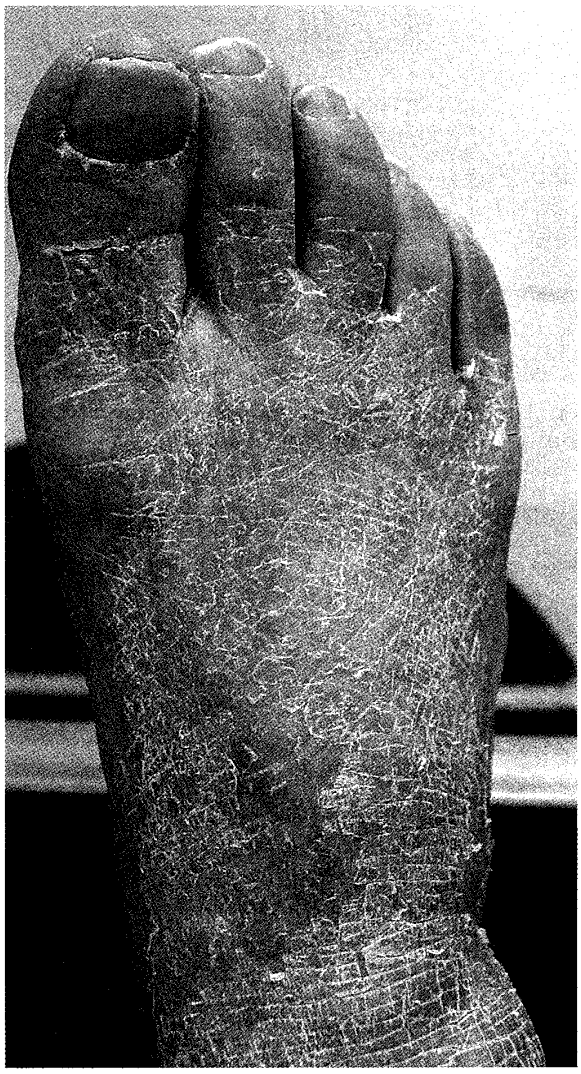

Fig.4 Exfoliative dermatitis appeared over the trunk and upper and lower extremities.

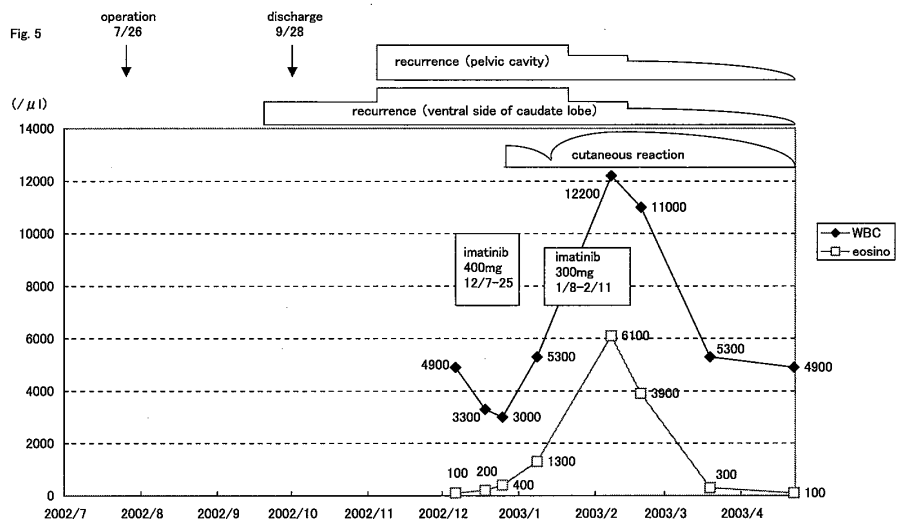

Fig.5 Clinical course. Extremely high eosinophil counts and developing exfoliative dermatitis were observed after the second administration of *imatinib mesylate*. This high eosinophil counts normalized along with the resolution of the dermatitis.

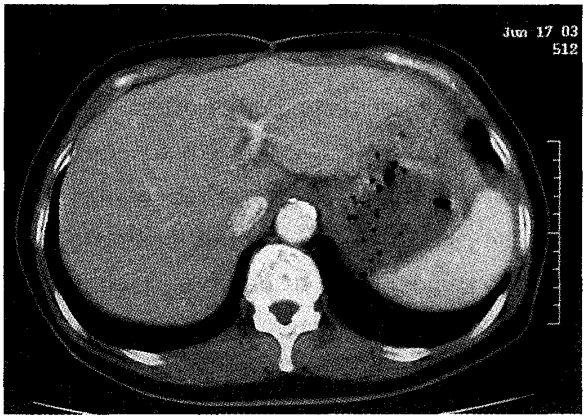

Fig.6 After 7 weeks of treatment, the disseminated tumor near the caudate lobe was dramatically reduced.

imatinib mesylate is rare and the clinical course like our case is not well described yet.

Treatment with *imatinib mesylate* is generally well tolerated, although virtually every patient has had at least some mild or moderate adverse events (grade 1 or 2) that might have been related to therapy.[8] The most common adverse event is edema (in 74.1% of patients), which is most frequently periorbital. Dermatitis or rash is reported in 30.6% of patients. On the other hand, in 7% to 21% of patients treated with the specific tyrosine kinase inhibitor, *imatinib mesylate*, adverse cutaneous reactions of mild to moderate severity have developed.[9,10]

Of the *imatinib mesylate*-induced skin rashes, the most common is a maculopapular rash that is most prominent over the forearms and trunk and occasionally occurs on the face.[11] In most cases, the rash is mild and easily manageable with antihistamines and/or topical steroids. In more severe cases, a short course of oral steroids may be required. A few patients develop a severe, desquamative rash that mandates immediate discontinuation of *imatinib mesylate* and institution of steroid therapy.[11] Depending on the clinical situation, treatment with *imatinib mesylate* may be resumed with a gradual dose escalation after the rash has resolved.[12]

In these cases, prednisone has typically been given at 1 mg/kg and tapered to 20 mg over several weeks. As the steroids are being tapered, the *imatinib mesylate* treatment has been restarted at 100 mg per day and the dose increased by 100 mg per week as long as the rash does not recur. This approach should only be considered in patients for whom no treatment option exists other than *imatinib mesylate*.[11]

Long-term follow-up data from patients with GIST treated with *imatinib mesylate* do not yet exist, and no information regarding the likelihood of an initially responsive tumor later developing *imatinib mesylate* resistance is available. Therefore, an optimal length of treatment is currently unknown.[6,7] The pharmacologic rationale for the use of *imatinib mesylate* is clear because this compound potently inhibits KIT activity in vitro. However, KIT signaling pathways are known to regulate many aspects of cellular behavior, including proliferation, apoptosis, adhesion, and differentiation. At present, which pathways determine the clinical responses to *imatinib mesylate* are unclear. Nonetheless, *imatinib mesylate* can reduce GIST tumor size, suggesting that the response of GIST to *imatinib mesylate* is not merely cytostatic. Within 8 hours of *imatinib mesylate* therapy, changes in tumors can be seen on a positron

emission tomography scan, suggesting that *imatinib mesylate* therapy induces rapid metabolic changes in tumor cells.[13]

We gave the patient in this case report three drugs other than *imatinib mesylate* (nifedipine, trichlormethiazide, and glibenclamide) that are known to cause adverse cutaneous reactions; however, two pieces of evidence strongly suggest that *imatinib mesylate* was the causative agent. First, reintroduction of the *imatinib mesylate* induced a flare of the skin reaction. Second, the patient's history of long-term exposure to nifedipine, trichlormethiazide, and glibenclamide (more than 10 years) reduces the likelihood that these drugs caused the cutaneous reaction.[12]

From the case reported here, we showed that seven-week administration of *imatinib mesylate* reduced the recurrence of lesions and the patient maintained a partial response for ten months in spite of *imatinib mesylate* discontinuance.

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腹腔内再発したgastrointestinal stromal tumor（GIST）の1症例におけるチロシンキナーゼ阻害剤（メシル酸イマチニブ）の短期投与

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星　永進

要　約

患者は62歳，女性。2002年7月左上腹部の腫瘤を主訴に当センターを受診した。18cm大の腹腔内腫瘍に対し，胃，横行結腸合併腫瘍切除術を施行。胃GIST（c-kit陽性）と診断された。2002年9月に腹腔内再発巣が出現，増悪し，2002年12月 *imatinib mesylate* を400mg/日で開始。投与2週間後より発熱，体幹四肢の広範囲に掻痒を伴う斑状疹，眼周囲，口唇の浮腫が出現。2週間休薬後300mg/日で再開したが，同様の症状が出現し再開後5週間で中止した。2003年2月再発巣の著明な縮小（縮小率74%）を確認した。その後腫瘍の増大を認めなかったが，2003年12月再発巣が増悪し，2004年1月腫瘍切除術を施行。2004年6月他部位に再発が確認され，現在はsupportive careの状態である。今回の我々の報告のような *imatinib mesylate* 短期間投与後の投与再開不可能な症例の臨床経過は報告されていない。

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