Metastatic gastrointestinal stromal tumor with long-term response after treatment with concomitant radiotherapy and imatinib mesylate

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Total surgical excision of the tumor is considered to be the only hope in treatment of malignant mesenchymal tumors. The roles of radiotherapy and/or chemotherapy have not yet been established. We report here a case of metastatic gastrointestinal stromal tumors with a dramatic long duration of response after treatment with concurrent radiotherapy and imatinib mesylate. The patient had a long-term complete response at the radiotherapy region with concomitant imatinib therapy although previous metastatic sides persisted with partial response. ***Anti-Cancer Drugs*** **18:969–972 © 2007 Lippincott Williams & Wilkins.**

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Introduction

According to the ultrastructural and immunohistological features, the majority of soft tissue sarcomas in the gastrointestinal system have their origin in the pacemaker cells of Cajal and are now named as gastrointestinal stromal tumors (GISTs) [1,2]. A new point of view to the pathogenesis of these tumors is giving new hope for improving their prognosis. GIST is characterized by the expression of c-kit, a tyrosine-kinase receptor, which is known to have regulatory functions on cell growth. The mutations of c-kit play a key role in the pathogenesis of GIST. A tyrosine kinase inhibitor imatinib (imatinib mesylate, ST1571, Novartis Pharma AG for Novartis Pharmaceuticals Corporation, Switzerland), initially used in treatment of myeloid leukemia, has proven to mediate tumor regression in patients with GIST and has become a part of GIST treatment [3,4]. A recent randomized phase III study by Verweij *et al.* [11] demonstrated that there is significant disease free survival (progression free survival) benefit for advanced GIST patients treated with imatinib [5]. Total surgical excision of the tumor is generally considered to be the only curative treatment option for the malignant mesenchymal tumors and the roles of radiotherapy or chemotherapy have not been established yet.

Case

A 55-year-old male patient with a gluteal mass with draining abscess formation was referred. The computed tomography (CT) of the abdomen revealed a pelvic mass of 15×10 cm diameter, located anterior of the sacrum and coccyx which invaded and narrowed the rectum. In addition, there were multiple metastatic solid lesions in the liver with the diameter of the largest being 5 cm. The mass adjacent to the sacrum was resected incompletely and the abscess was drained. Histopathological examination and the immunohistochemistry of the resected specimen were compatible with GIST, with expression of c-kit and CD34 (Fig. 1). Radiotherapy with an energy level of 6 MV in 200-cGy fractions from the anterior and posterior ports (total 5400 cGy in 27 fractions) by linear accelerator was applied to the residual tumor for the palliation of symptoms. Imatinib mesilate 400 mg/day was administered concomitantly with radiotherapy. The lesions at the perineum and gluteal region regressed dramatically and analgesics were stopped. The CT scan performed after 2 months of treatment showed partial remission of the residual mass adjacent to the sacrum, whereas the lesions in the liver were stable in number and size. A minimal decrease, however, was observed in tumor density compared with the preoperative evaluation. On the psychical examination, there was a remarkable recovery in the draining perineal lesions. Four months after radiotherapy, the liver lesions were stable in size and further regression of the pelvic lesion was observed. The pelvic lesions completely disappeared 27 months after radiotherapy, whereas treatment with imatinib was continued (Fig. 2). After 33 months, liver lesions regressed (the diameter of the largest was 3×2 cm). After 37-month imatinib therapy, progression in liver lesions was seen on CT scans of the abdomen (Fig. 3), but there were no gluteal or pelvic recurrences. The dose of imatinib was increased to 600 mg/day, but as the liver lesions progressed with this maximum tolerated dose, the patient was given sunitinib. The patient is still alive with liver metastases on sunitinib and there is no recurrence at the radiotherapy region.

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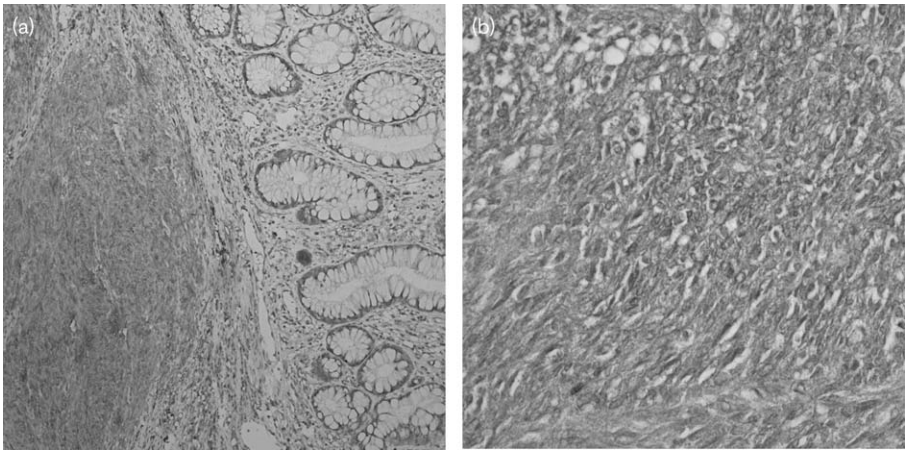
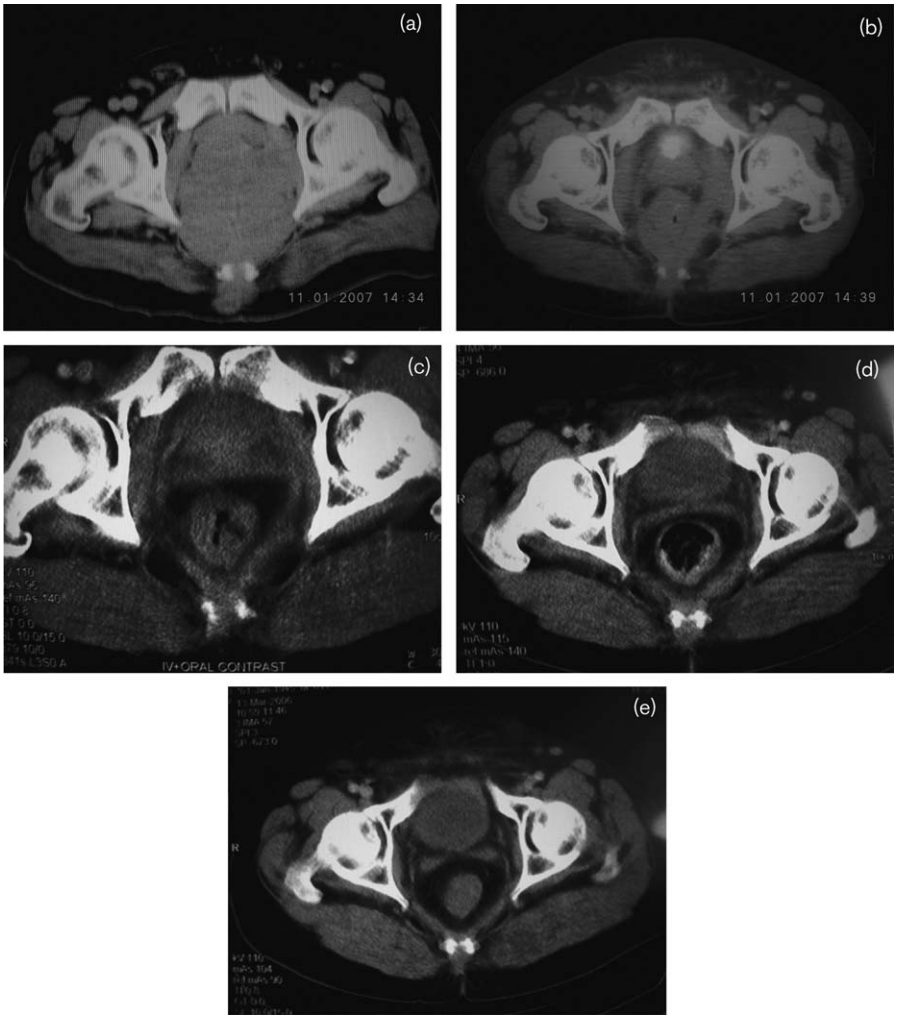
Fig. 1



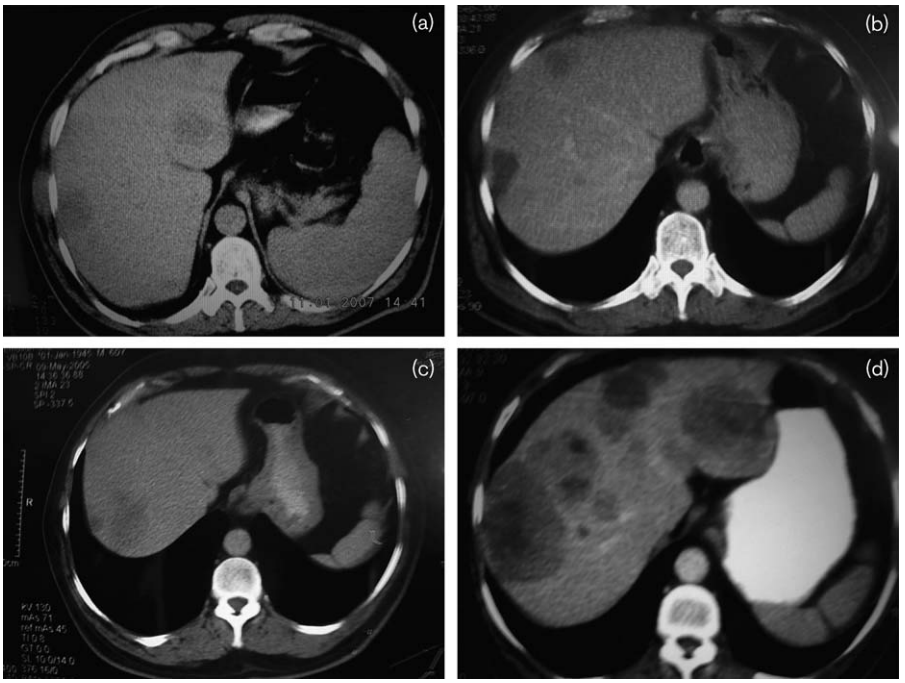
Pathology and immunohistochemistry of the tumor: (a) immunohistochemistry staining with CD117 (× 10) and (b) immunohistochemistry staining with CD34 (× 40).

Fig. 2



Regression of pelvic lesion: (a) before chemoradiotherapy, and (b) 2, (c) 17, (d) 27 and (e) 37 months after chemoradiotherapy.

Fig. 3



Regression and progression of liver lesions: (a) before imatinib treatment, and after (b) 17, (c) 33 and (d) 37 months treatment with imatinib.

Discussion

Imatinib exerts a synergism with chemotherapy, and when combined with chemotherapy, has an enhanced antitumor activity [6]. The interaction, however, between imatinib and radiotherapy is unknown, and should be investigated. Holdhoff *et al.* [7] reported that pretreatment of a glioblastoma (GM) cell line with imitanib significantly enhanced the cytotoxic effect of ionizing radiation; however, this effect was not seen in breast cancer and colon cancer cell lines. They suggested that imitanib possibly disrupted the autocrine platelet-derived growth factor (PDGF)/PDGF receptor (PDGFR) loop. This loop was highly activated only in the GM cell line, whereas c-abl and c-kit were expressed equally in GM, breast and colon cancer cells.

Russel *et al.* [8] reported that expression of Rad51, which is an essential component of the homologous DNA repair pathway, was reduced when glioma cells were pretreated with imatinib, which is a relatively specific inhibitor of c-abl, a tyrosine kinase that can play a role in the regulation of Rad51. They concluded that Rad51 might be an appropriate target for selectively enhancing the radiosensitivity of brain tumor cells [8]. Taking together these data, one may conclude that PDGF/PDGFR loop disruption and reduced expression of Rad51 may be related to the enhanced effect of the concomitant use of imatinib and radiotherapy [9]. Changes in these two targets with imatinib therapy may be responsible for the long-term response in our patient. Shioyama *et al.* [10] reported a case of unresectable retroperitoneal GIST metastasis, which was controlled long term by radiotherapy combined with arterial chemotherapy and immunotherapy. They administered arterial carboplatin and epirubicin chemotherapy and radiotherapy concurrently. Carboplatin and epirubicin were infused from the right infraphrenic artery and lumbar arteries. The total radiation dose was 51 Gy and they also administered four doses of intratumoral injections of a biological response modifier, OK432 (5 KE), given percutaneously at 1-week intervals on an outpatient basis at the hospital. Follow-up CT carried out for 6 years after the treatment revealed that the tumor markedly decreased in size to a small low-density structure of 20 mm in diameter.

No report exists in the English literature reporting the concurrent use of radiotherapy and imatinib in patients with GIST. The interaction between radiotherapy and imatinib in this case may be defined as synergy. Therefore, it might be concluded that the long-term local control of the pelvic lesion is a result of the use of concurrent radiotherapy and imatinib. The persistence and then progression of liver lesions support this comment. Further investigation of concurrent radiotherapy and imatinib is warranted.

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