Neoadjuvant imatinib for unresectable gastrointestinal stromal tumor

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We have evaluated the feasibility of the use of neoadjuvant imatinib mesylate in the management of unresectable localized gastrointestinal stromal tumors. In a pilot experience, two patients with unresectable gastrointestinal tumors were treated with neoadjuvant imatinib. Their treatment course and surgical outcomes are described. In both cases, the patient attained sufficient tumor regression to enable complete resection of tumor. We conclude that in the management of unresectable gastrointestinal stromal tumors, neoadjuvant administration of imatinib may facilitate sufficient tumor regression to facilitate subsequent tumor resection with curative intent. *Anti-Cancer Drugs* 15:599–602

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Introduction

Gastrointestinal stromal tumors (GIST) are non-epithelial mesenchymal chemotherapy-resistant tumors that occur predominantly in the gastrointestinal tract [1]. GIST tumors are defined histologically as highly cellular spindle cell or epithelioid mesenchymal tumors with positive immunocytochemical staining for CD117 antigen [2]. KIT oncoprotein, detected by CD117 antigen, is a receptor tyrosine kinase encoded by c-*kit* proto-oncogene. Constitutive activation of KIT is most commonly the result of activating mutations in the c-*kit* gene, but abnormal constitutive KIT activation may be present even in the absence of mutations and results in persistent uncontrolled cellular proliferation [3,4].

Imatinib (commercial name Glivec; Novartis), a specific tyrosine kinase inhibitor which targets the Bcr–Abl fusion protein, has induced dramatic therapeutic responses in chronic myeloid leukemia patients [5,6]. Imatinib was also found to inhibit the mutated KIT receptor tyrosine kinase, found in nearly all cases of GIST [3]. This led to preclinical evaluation of imatinib in GIST cell lines [7,8].

Following a report of an excellent response to imatinib in a patient with metastatic GIST [9], 36 patients with non-resectable or metastatic GIST were treated in an EORTC phase I study [10]. Sixty-nine percent of patients achieved a partial response and disease stabilization was accomplished in a further 19% [10]. A larger phase II study in 147 patients [11] confirmed these results. Although treatment was well tolerated overall, mild-to-moderate edema, diarrhea and fatigue were common, and in 5% of patients, gastrointestinal or intra-abdominal hemorrhage occurred. In patients with GIST tumors which respond to imatinib, serial positron emission tomography (PET) scans demonstrate diminished ^{18}FDG uptake compared to baseline studies [12]. Indeed, this can be an early indicator of tumor response.

Whereas, many patients with GIST present with metastatic disease that is not amenable to cure, some patients do present with localized disease [13]. Resection of localized disease results in long-term disease-free survival in 54% of patients [14]. In some patients, however, GIST presents as localized disease, albeit non-resectable. Curing such patients has heretofore not been possible.

We describe two cases of advanced unresectable GIST. Both were treated with imatinib (neoadjuvant), with the intention making complete surgical resection possible.

Case 1

A 52-year-old white male was admitted to the surgery department in July 2002 complaining of weakness and melena during the preceding 3 weeks. There were no other gastrointestinal complaints. Physical examination and laboratory results were unremarkable except for a Hb level of 6.7 mg/dl. After transfusion, he underwent gastroscopy which demonstrated a polypoid lesion with central ulceration in the gastric fundus. Biopsy confirmed GIST, staining positive for CD34 and KIT, and negative for S100. A total body computed tomography (CT) scan revealed a 12-cm mass along the greater curvature of the stomach (Fig. 1a). The mass was adherent to the hilum of the spleen. There were two suspicious lesions in the liver. A PET scan demonstrated increased accumulation of

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^{18}FDG in the left upper quadrant as well as in one of the hepatic lesions. The patient was thus considered inoperable and was started on imatinib 400 mg/day. Clinically, the patient responded rapidly. This response was confirmed objectively by CT scan (Fig. 1b) and PET-CT (46% reduction in the long axis on a two-dimension CT scan). By January 2003, there was no abnormal uptake of ^{18}FDG on PET-CT.

Repeat gastroscopy demonstrated the presence only of a 10-mm polyp in the gastric fundus. In March 2003, the patient underwent partial gastrectomy, splenectomy along with resection of the suspected hepatic lesions. On pathology, the tumor was $6.5 \times 4.5 \times 4\,cm^3$ in size and composed mainly of necrotic material. No tumor cells were observed in the omental fat, spleen or liver. The hepatic lesions were bile duct cystadenomas. The patient had an uneventful post-operative course. After 6 months of follow-up the patient remains in remission under ongoing treatment with imatinib.

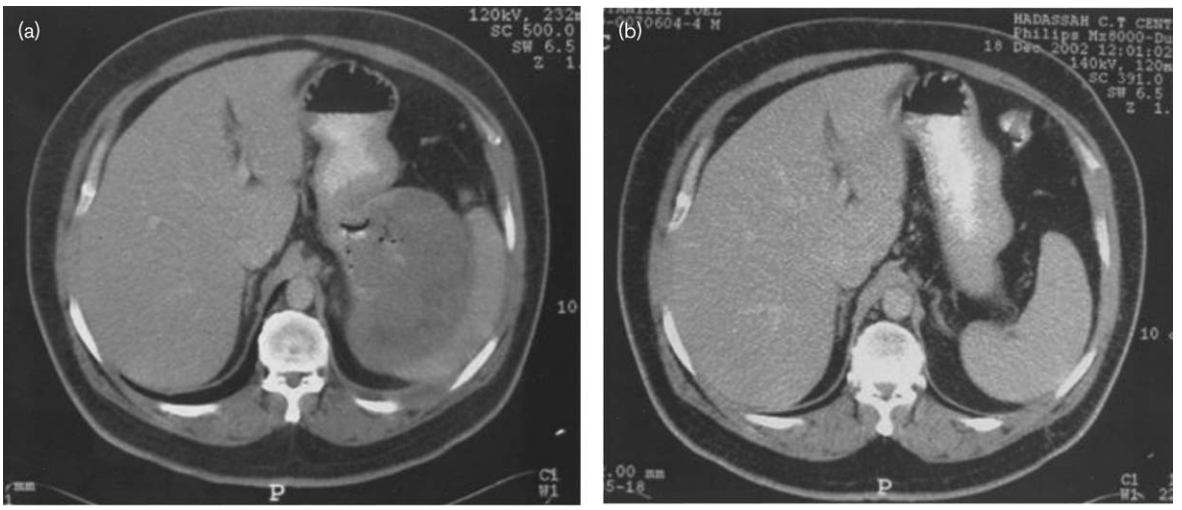
Case 2

A 52-year-old, previously well man was admitted to the surgery department in June 2002 with 1 month of diffuse abdominal and back pain and weight loss. A large mass was palpable in the mid abdomen with the rest of the examination being uneventful. Laboratory results showed an elevated LDH (908 U/l, normal range 315–615) and a high platelet count (792 000/mm^3, normal range 130 000–400 000/mm^3). A CT scan of the abdomen and pelvis (Fig. 2a) revealed a 28-cm left abdominal mass, which extended to the pelvis, and crossed the midline displacing the stomach, the right colon and the left adrenal and kidney.

An ultrasound guided core biopsy was consistent with GIST. An attempt to excise the mass on July 2002 failed, because the disease extended throughout the upper part of the abdomen, and penetrated the left diaphragm, the stomach, the pancreatic tail, the splenic hilum and the retroperitoneum. Therapy with imatinib, 400 mg/day, was started in August 2002. The patient experienced rapid symptomatic relief, and reduction in tumor size was confirmed by physical examination and sequential CT scans performed at 3, 5 and 8 months (53% reduction in the long axis on two-dimension CT scan) (Fig. 2b).

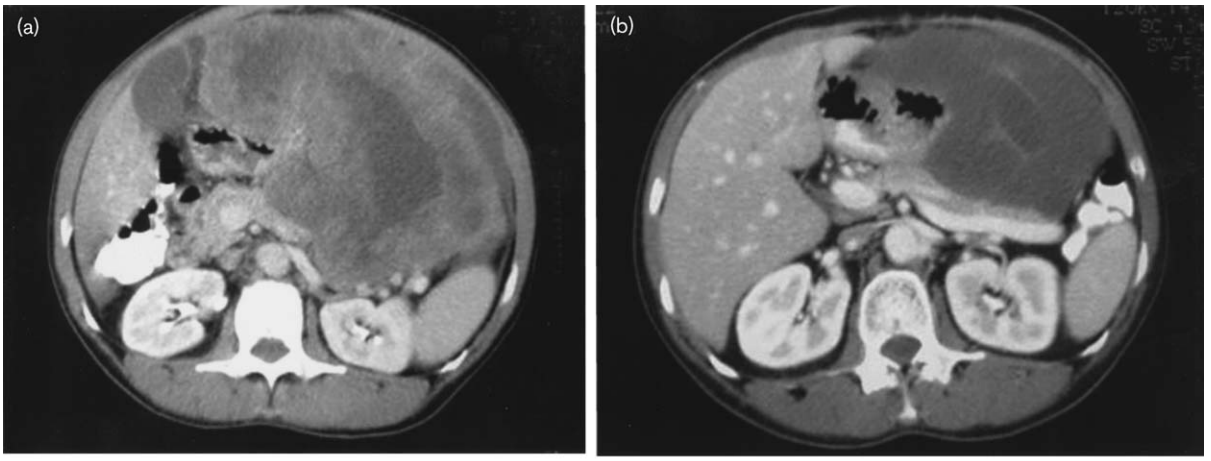
In view of the clinical and radiological response, the patient was re-operated in March 2003. He underwent partial gastrectomy, splenectomy, resection of small segment of the left diaphragm and excision of a 2-cm gastric antral mass. No other disease was seen in the abdomen. The pathology revealed a tumor mass of $17 \times 9 \times 10\,cm^3$ in size with free margins, decrease in tumor cellularity and significant tumor cell degeneration on microscopy. The 2-cm antral mass was a focus of GIST and was fully resected. The post-operative course was uneventful. The Ki-67 labeling index of the resected tumor was 10% that of the initial pre-treatment biopsy sample. After 6 months, repeat CT scan demonstrated a small, localized recurrence in the region of the gastric bed and this has been resected. At laparotomy, no other evidence of disease was identified.

Fig. 1



Pre- and post-therapy CT scans of unresectable GIST (Case 1).

Fig. 2



Pre- and post-therapy CT scans of initially unresectable GIST (Case 2).

The patient is now being maintained on ongoing therapy with imatinib.

Discussion

The mainstay of curative therapy for GIST is complete surgical resection [13]. Until now, unresectable or metastatic GIST tumors have been associated with a poor prognosis, since there were no known effective anti-tumor agents. Imatinib was approved by the US Food and Drug Administration for the treatment of KIT-expressing GIST in February 2002 [14], but its role as neoadjuvant or adjuvant therapy has not yet been evaluated.

There are very few recent reports on imatinib as neoadjuvant treatment in GIST. There is a recent report of a patient with a 35-cm GIST tumor and multiple liver metastases that was treated with imatinib to the point of resectability. After 7 months follow-up this patient had no evidence of disease [15]. A German group has described eight patients operated for responding residual tumor. Seven out of the eight patients achieved complete resection of tumor following a median duration of 57 weeks (range 36–90 weeks) of imatinib treatment [16].

In this paper we describe two cases of unresectable GIST in whom treatment with imatinib resulted in dramatic tumor response rendering complete surgical resection feasible. The first patient had a major response as shown by CT scan (46% decrease in the two-dimensional long axis) PET scan and pathologic examination of the surgical specimen. The second patient had a 53% reduction in the long axis detected by CT scan.

In both cases resection with clear margins was made possible as a consequence of 8 months of imatinib therapy. The post-operative follow-up for these patients has been short (6 and 4 months, respectively) and therefore it is premature to assess the curative potential of such an approach. Despite this, our experience suggests that imatinib may be an effective neoadjuvant therapy, able to convert non-resectable tumors to resectability.

The survival benefit of this approach must await long-term follow-up of index cases and confirmation by clinical trials. This approach is currently being evaluated in a phase II trial of neoadjuvant imatinib for patients with marginally resectable primary or recurrent/metastatic GIST which is being organized by the Radiation Therapy Oncology Group in collaboration with the American Collage of Radiology Imaging Network (RTOG S-0132/ ACRIN 6665).

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