

Brief Report

**EFFECT OF THE TYROSINE
KINASE INHIBITOR STI571
IN A PATIENT WITH A METASTATIC
GASTROINTESTINAL STROMAL TUMOR**

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GASTROINTESTINAL stromal tumors are a group of mesenchymal neoplasms that arise from precursors of the connective-tissue cells of the gastrointestinal tract.¹ They occur predominantly in middle-aged and older persons, and approximately 70 percent of the tumors are found in the stomach, 20 to 30 percent are found in the small intestine, and less than 10 percent are found elsewhere in the gastrointestinal tract.¹ Recent studies have shown that cells in gastrointestinal stromal tumors express a growth factor receptor with tyrosine kinase activity termed *c-kit*. This receptor, the product of the proto-oncogene *c-kit*, can be detected by immunohistochemical staining for CD117, which appears to be the most specific diagnostic criterion for the diagnosis of gastrointestinal stromal tumors.² The ligand for the *c-kit* receptor is stem-cell factor, also known as steel factor or *c-kit* ligand.³ Mutations of *c-kit* that cause constitutive activation of the tyrosine kinase function of *c-kit* are detectable in most gastrointestinal stromal tumors and appear to play a central part in the pathogenesis of these tumors.^{4,5} These mutations result in ligand-independent tyrosine kinase activity, autophosphorylation of *c-kit*, uncontrolled cell proliferation, and stimulation of downstream signaling pathways, including those involving

phosphatidylinositol 3-kinase and mitogen-activated protein kinases. Gastrointestinal stromal tumors are notoriously unresponsive to cancer chemotherapy, and there is no effective therapy for advanced, metastatic disease.⁶

We used STI571 (Glivec, Novartis, Basel, Switzerland),⁷ an inhibitor of the tyrosine kinase activity of *c-kit*, in a patient with a gastrointestinal stromal tumor.

CASE REPORT

In October 1996, a 50-year-old, previously healthy woman presented with mild abdominal discomfort and a large mass in the upper abdomen. Two tumors, 6.5 and 10 cm in diameter, were removed from the stomach by proximal gastric resection, and the greater omentum and mesocolic peritoneum were removed because of the presence of multiple metastatic nodules 1 to 2 mm in diameter. Histologic examination of the specimens revealed more than 20 cells undergoing mitosis per 10 high-power fields and identified the masses as a gastrointestinal stromal tumor. The diagnosis was confirmed by immunostaining for CD117, and a *c-kit* mutation consisting of a deletion of 15 bp from exon 11 was detected in tumor DNA amplified by the polymerase chain reaction.⁸

Recurrent tumors in the left upper abdomen, two liver metastases, and multiple small intra-abdominal metastases were excised in February 1998, and in September 1998 six more liver metastases and an ovarian metastasis were removed. Seven cycles of chemotherapy with mesna, doxorubicin, ifosfamide, and dacarbazine were given from November 1998 to March 1999 for additional liver metastases, but there was no clinical response. In March 1999, progression of the disease prompted removal of a metastasis that was obstructing the large bowel and 45 smaller metastases by laparotomy. The patient was treated between April 1999 and February 2000 with 400 mg of thalidomide once daily and 900,000 U of subcutaneous interferon alfa three times a day, but by February 2000 the liver metastases were progressing in size and number, and several new intra-abdominal and mesenteric metastases were documented by magnetic resonance imaging (MRI).

The patient then agreed to participate in this study of STI571. The institutional review board of Helsinki University Central Hospital approved the study, and the patient gave written informed consent. Treatment with four 100-mg capsules of STI571 once daily was started in March 2000. This dose was based on evaluations of the safety and tolerability of STI571 in patients with chronic myeloid leukemia.⁹ Toxicity was assessed at follow-up visits every two to four weeks, and blood-cell counts and blood chemical values were analyzed every one to two weeks. The response to treatment was assessed with dynamic MRI, positron-emission tomography (PET) with [¹⁸F]fluorodeoxyglucose as a tracer, and serial needle biopsies of a liver metastasis.

METHODS

Immunostaining for CD117 was performed with a polyclonal rabbit antibody (sc-168, Santa Cruz Biotechnology, Santa Cruz, Calif.) diluted 1:200 and for Ki-67 antigen, a marker of cell proliferation, with another polyclonal rabbit antibody (A0047, Dako, Glostrup, Denmark) diluted 1:150. Staining was analyzed with a detection kit (ChemMate Peroxidase/DAB, Dako) designed to be used with an automated immunostaining system (TechMate 500 Medical Systems, Ventana, Tucson, Ariz.).

RESULTS

Evaluation of the Response by MRI

When measured as the sum of the products of two perpendicular axes of each of eight large liver metastases, the size of the tumor one day before the start of treatment with STI571 was 112.5 cm². On subsequent MRI scans, the size of the tumor was as fol-

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lows: 67 cm² (after 2 weeks of treatment), 54 cm² (at 1 month), 42 cm² (at 2 months), 36 cm² (at 4 months), 33 cm² (at 5.5 months), and 28 cm² (at 8 months). No new lesions appeared, and 6 of the 28 liver metastases disappeared. At the peripheral rim of the hepatic metastases, the considerable contrast enhancement that had been seen on the dynamic MRI scans (a finding consistent with the presence of viable tumor) before the beginning of STI571 treatment was dramatically reduced; indeed, no enhancement was seen on dynamic MRI scans obtained during treatment. In addition, many of the metastases became hypodense (Fig. 1). As of February 2001, the tumor at

all sites continued to respond to treatment, and the patient remained clinically well.

Evaluation by PET Scanning with [¹⁸F]Fluorodeoxyglucose

Multiple liver metastases and increased accumulation of [¹⁸F]fluorodeoxyglucose in the right renal pelvis and ureter, a finding indicative of hydronephrosis, were seen on a PET scan obtained four days before treatment with STI571 was started (Fig. 2A). On a PET scan obtained one month after STI571 was started, no abnormal uptake of [¹⁸F]fluorodeoxyglucose was seen in the liver or right kidney (Fig. 2B). In a finding consistent with the changed, hypodense ap-

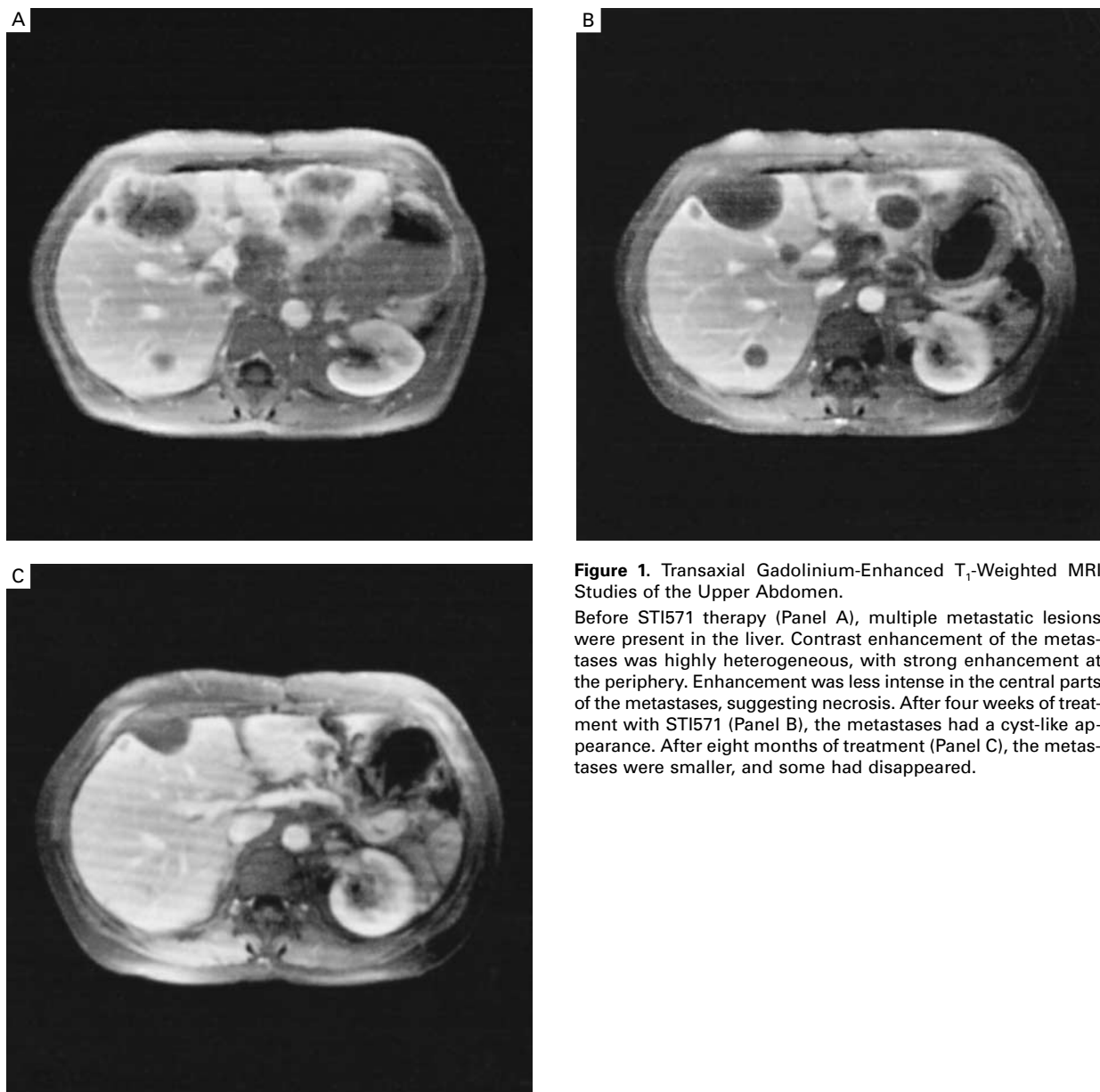


Figure 1. Transaxial Gadolinium-Enhanced T₁-Weighted MRI Studies of the Upper Abdomen.

Before STI571 therapy (Panel A), multiple metastatic lesions were present in the liver. Contrast enhancement of the metastases was highly heterogeneous, with strong enhancement at the periphery. Enhancement was less intense in the central parts of the metastases, suggesting necrosis. After four weeks of treatment with STI571 (Panel B), the metastases had a cyst-like appearance. After eight months of treatment (Panel C), the metastases were smaller, and some had disappeared.

pearance of metastases on MRI, “cold” areas, with less uptake of [^{18}F]fluorodeoxyglucose than in the surrounding liver parenchyma, were seen at the sites of liver metastases on a PET scan obtained two months after STI571 was started.

Histologic Findings

Serial needle-biopsy specimens of a ventrally located liver metastasis obtained one and two months after STI571 treatment was started showed a marked decrease in the density of the tumor cells, as well as myxoid degeneration and scarring, with no signs of an inflammatory reaction or necrosis (Fig. 3). The few remaining cells in the myxoid background were probably pyknotic tumor cells and not mast cells, according to their immunohistochemical characteristics (positive for CD117 and negative for CD45 and Giemsa stain). These cells did not stain for the cell-proliferation marker Ki-67, suggesting that they were not actively dividing. Endothelial cells within the lesion were histologically normal, with no suggestion of cytotoxic effects.

Side Effects of STI571

STI571 was well tolerated, with only mild, transient nausea related to the swallowing of the capsules; this minor symptom improved when the drug was taken with food. No clinically significant changes were noted in the peripheral blood-cell counts or blood chemi-

cal values. No drug-related adverse effects on the liver, kidneys, or heart were observed. All of the main subjective adverse effects were mild (grade 1 according to version 2.0 of the Common Toxicity Criteria of the National Cancer Institute¹⁰) and consisted of an increased frequency of bowel movements (two to four a day), occasional muscle cramps in the legs, and slight, transient ankle edema. The World Health Organization performance status improved from 1 (indicating the presence of cancer-related symptoms) to 0 (normal) during STI571 therapy.

DISCUSSION

There is no effective therapy for unresectable or metastatic gastrointestinal stromal tumor, which is invariably fatal. STI571, a phenylaminopyrimidine derivative, is a small molecule that selectively inhibits the enzymatic activity of several tyrosine kinases, including ABL and the BCR-ABL fusion protein of chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia; platelet-derived growth factor receptor; and the product of the *c-kit* gene. This selective activity of STI571 suggests that it has a relatively narrow spectrum of anticancer activity. Our results indicate that inhibition by STI571 of the constitutively active mutant *c-kit* tyrosine kinase of gastrointestinal stromal tumors is an effective therapy for these tumors.

Our patient had a rapidly progressive metastatic gas-

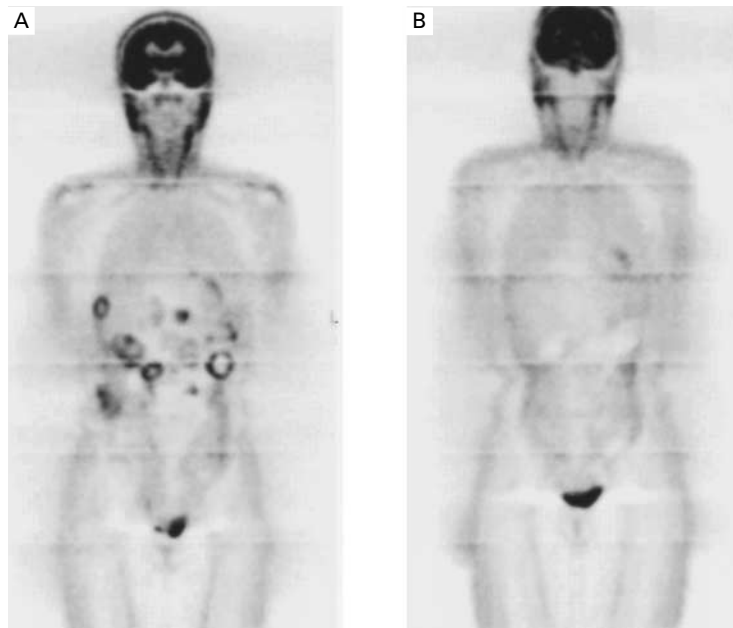


Figure 2. PET Studies with [^{18}F]Fluorodeoxyglucose as the Tracer.

Before STI571 therapy (Panel A), there were multiple metastases in the liver and upper abdomen. There was also marked retention of [^{18}F]fluorodeoxyglucose in the right renal pelvis and ureter, a finding indicative of hydronephrosis. After four weeks of treatment (Panel B), there was no abnormal uptake of tracer in the liver or right kidney.

gastrointestinal stromal tumor that was resistant to chemotherapy. She had a complete metabolic response within one month after the start of STI571 treatment, as shown by negative findings on PET and the 52 percent decrease in tumor volume on MRI. Many of the liver metastases became hypodense, and the tumor enhancement on dynamic MRI was markedly reduced, suggesting decreased viability. Histopathological evaluation of serial needle-biopsy specimens of a liver

metastasis confirmed the anticancer activity of this treatment. With treatment, extensive fibrosis, myxoid degeneration, and a few scattered, nonproliferating CD117-positive cells replaced the abundant, frequently mitotic, Ki-67-positive gastrointestinal stromal-tumor cells. The absence of visible damage to the vascular endothelial cells in the biopsy specimens indicated the selective action of STI571 in this patient. These responses have now continued during more

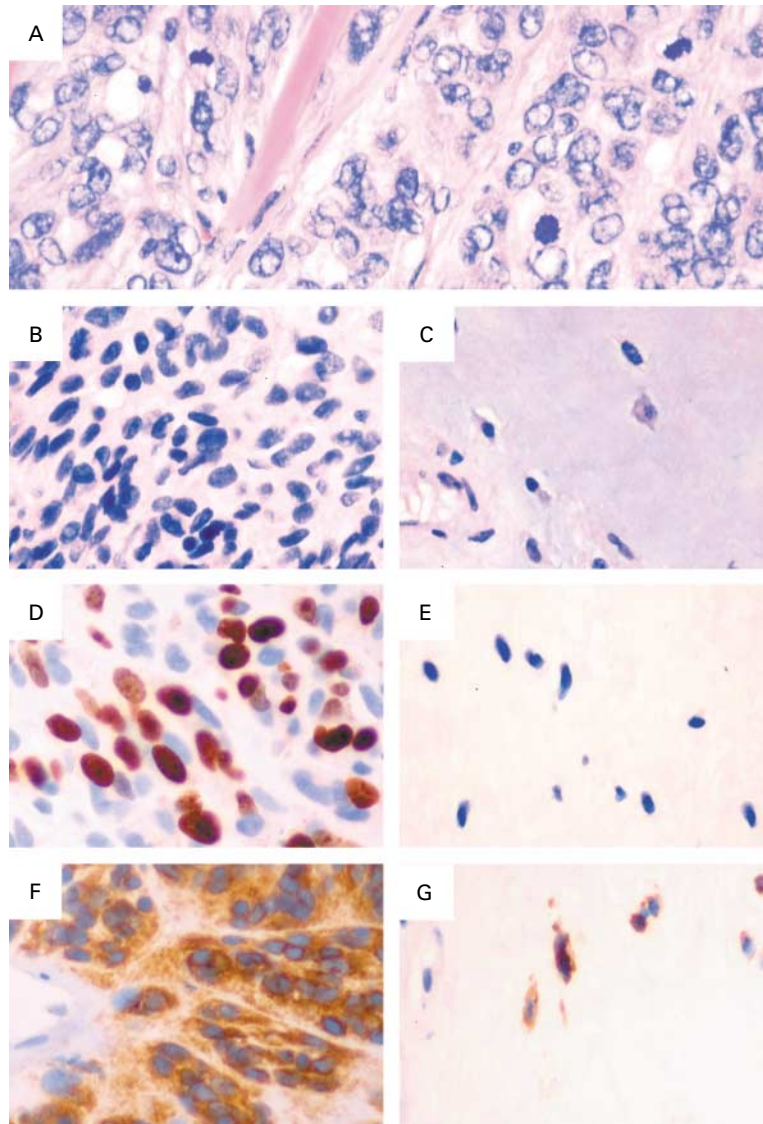


Figure 3. Histologic Appearance of the Primary Gastrointestinal Stromal Tumor (Hematoxylin and Eosin [Panels A, B, and C] and Immunostaining for Ki-67 [Panels D and E] and CD117 [Panels F and G]). In 1996, frequent mitotic figures were present (Panel A, $\times 400$). In 2000, a pretreatment biopsy specimen from a cellular liver metastasis (Panel B, $\times 200$) had a high frequency of Ki-67-positive nuclei (Panel D, $\times 200$) and staining for CD117 (Panel F, $\times 200$). After three weeks of STI571 treatment, histologic examination of the liver metastasis showed myxoid degeneration and a few pyknotic cells (Panel C; hematoxylin and eosin, $\times 200$), no staining for Ki-67 (Panel E, $\times 200$), and only a few, scattered CD117-positive cells (Panel G, $\times 200$).

than 11 months of treatment. In addition, the toxicity of STI571 therapy was minimal and consisted mainly of mild dyspepsia and a slightly increased frequency of bowel movements.

In addition to its activity in BCR-ABL-positive leukemias, STI571 may be active in solid tumors that rely on the expression of c-kit, ABL, or platelet-derived growth factor receptor. Among the solid tumors, gastrointestinal stromal tumors may be especially responsive to STI571 because they uniformly express c-kit and because a tumor-specific *c-kit* mutation appears to be the chief cause of this neoplasm. Our patient's favorable response to STI571 supports the concept that specific inhibition of tyrosine kinase is a clinically useful therapeutic intervention for tumors in which aberrant tyrosine kinase signaling is critical.

We are indebted to J. Lasota and M. Miettinen (Department of Soft Tissue Pathology, Armed Forces Institute of Pathology, Washington, D.C.) for allowing us to refer to the results of c-kit mutation analysis in this patient; to H. Minn (Turku PET Center, University of Turku, Turku, Finland) for skillful analyses of PET images; to Christopher Fletcher, Jonathan Fletcher, and Samuel Singer (Departments of Pathology and Surgical Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston); and to Charles D. Blanke and Michael C.

Heinrich (Department of Medical Oncology, Oregon Health Sciences University, Portland) for helpful discussions.

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