Abstract

We describe a patient who had a metastatic gastrointestinal stromal tumor (GIST) after previous failed extensive therapy, including multiple surgeries and hepatic artery embolization. Within a few months of starting administration of imatinib mesylate, the patient exhibited a clinical response with grade 3 neutropenia, when pulmonary tuberculosis developed. A c-kit mutation in exon 11 was detected only in metastatic liver specimens. It is unclear whether or not pulmonary tuberculosis may be induced by imatinib mesylate treatment, but caution is warranted in immunocompromised GIST patients. This is the first report of tuberculosis associated with neutropenia during imatinib mesylate treatment. (Internal Medicine 44: 114–119, 2005)

Key words: c-kit proto-oncogene, tyrosine kinase inhibitor, adjuvant treatment, drug toxicity

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. These tumors span a wide clinical spectrum from low-grade to high-grade malignancy and have long been recognized for their nearly absolute resistance to chemotherapy and radiation treatment (1–4). Surgery is the primary treatment modality for GISTs, but GISTs represent an incurable malignancy for patients with metastatic or unresectable disease. Until the year 2000, the prognosis for patients with metastatic GISTs was very poor, but the advent of imatinib mesylate (formerly STI571, [Glivec]; Novartis, Basel, Switzerland) has dramatically changed this perception (5–7). By analogy to its inhibitory effect on the BCR-ABL tyrosine kinase in CML, it was postulated that imatinib mesylate would selectively inhibit the constitutive activity of c-kit proto-oncogene which encodes the receptor (KIT) tyrosine kinase in GISTs (8–11). Here, we report a case of malignant GIST of the small intestine complicated with pulmonary tuberculosis during treatment with imatinib mesylate.

Case Report

In June 1995, a 64-year-old, previously healthy man presented with low grade fever and abdominal discomfort in the upper abdomen. Computed tomography (CT) scan revealed a large mass (7×5×10 cm) in contact with the left lateral segment of the liver, which seemed to be connected with the proximal jejunum. Laparotomy was subsequently performed with the putative diagnosis of abdominal abscess or small intestinal tumor. A large tumor, located in the proximal jejunum, approximately 8 cm distal to the ligament of Treitz, was resected. Histologic examination of the specimens revealed clusters of spindle-shaped cells and identified the tumor as a leiomyosarcoma because mitotic activity over 8 cell mitoses per 50 high-power fields (HPF), high cellularity, and paucity of stroma strongly suggested high-grade malignancy (Fig. 1A). Immunohistochemistry for expression of the KIT receptor tyrosine kinase (detected as CD117 antigen) was not performed at that time. In November 1998, progressive anemia developed and the tumor recurred. A large tumor (19×16×12 cm) was removed from the jejunum with a large segment of transverse colon. Multiple small liver me-
tastases as well as multiple tiny metastatic nodules on the peritoneum were found at the time of surgery. On immunohistochemistry, the tumor was positive for CD117 and CD34, (Fig. 1B, C) and negative for $\alpha$ smooth-muscle actin and desmin. The tumor was typical for gastrointestinal stromal tumors. By May 1999, the liver metastases were progressing in size and number. Five cycles of transhepatic artery embolization (TAE) were given from May 1999 to March 2001 for multiple liver metastases, but there was no clinical response. In September 2001, abdominal pain and distension in the lower abdomen developed. CT scans revealed a large tumor in the peritoneal cavity. Emergency laparotomy was performed with a suspicious diagnosis of the tumor rupture. A large tumor (20×16×10 cm) was resected with a segment of ileum. On histologic examination, the tumor had been largely replaced by necrotizing tissues. We had no other therapeutic measures available for progressive, widely metastatic disease other than imatinib mesylate. Then, the patient gave written informed consent and agreed to treatment of imatinib mesylate. Imatinib mesylate was initiated at a dose of 400 mg orally twice a day from December 2001. CT scans of the patient treated with imatinib mesylate before and after 3 months of treatment documented rapid regression of metastatic liver disease (Fig. 2A, B). However, the metastases were larger and new lesions developed, suggesting resistance to imatinib after 5 months (Fig. 2C). The patient exhibited a major objective clinical response with the toxicities, including periorbital edema, nausea, and grade 3 neutropenia (868/mm$^3$) until April 2002, when cough producing yellowish sputum with increasing dyspnea and persisting fever developed. Chest radiographs and CT scan revealed well-defined nodules randomly distributed throughout the lungs (Fig. 3A). Microscopical examination of sputum smears showed a few acid-fast bacilli. *Mycobacterium tuberculosis* (*M. tuberculosis*) was detected in sputum by polymerase chain reaction and subsequent sputum culture for *M. tuberculosis* was positive. The patient discontinued imatinib mesylate and was given isoniazid (300 mg/day), rifampicin (450 mg/day), pyrazinamide (1.5 g/day), and streptomycin sulfate (0.5 g×3 times/week). He remained afebrile, and his condition began to improve slightly, with a diminished cough, after the initiation of tuberculosis treatment. However, he was gradually cachectic and weak because of progressing liver, intra-abdominal, and mesenteric metastases and he died in February 2003. Specimen of the lung obtained from autopsy revealed that giant necrotizing granulomas were present in the parenchyma (Fig. 3B).

Figure 1. Microscopic findings of the resected tumor revealed clusters of spindle-shaped cells, high cellularity, and paucity of stroma (Panel A, HE stain, ×200). On immunohistochemistry, the tumor was positive for CD117 (Panel B) and CD34 (Panel C). On histologic examination, the metastatic liver specimens obtained from the autopsy revealed had been largely replaced by necrotizing tissues (Panel D, arrows).
Figure 2. Pre- and post-treatment CT scans. Before imatinib mesylate therapy (Panel A), multiple large metastatic lesions were present in the liver. After 3 months (Panel B) of treatment with imatinib mesylate, the metastases were smaller and enhancement was less intense in the central parts of the metastases on contrast CT scans, suggesting necrosis. However, after 5 months (Panel C) the metastases were larger and new lesions developed, suggesting resistance to imatinib mesylate.

Figure 3. CT scans of the middle lung zones revealed well-defined nodules randomly distributed throughout the lungs (Panel A). Specimen of the lung obtained from autopsy revealed that giant necrotizing granulomas were present in the parenchyma (Panel B, arrows, HE stain, ×100).
Tumor size, mitotic rate, and c-kit mutation

We retrospectively investigated tumor size, mitotic rate, and c-kit mutation in the three primary tumor specimens from surgical resection and metastatic liver specimens from autopsy (Table 1). Tumor size of more than 10 cm, high mitotic index over 5 or more mitoses/50 HPF, and high MIB-1 index of approximately 10% suggested high-grade malignancy. A c-kit mutation consisting of codon 558 (AAG \(\rightarrow\) AAC) and codon 559 (GTT \(\rightarrow\) GCT) in exon 11 was detected (Fig. 4), while mutations in exon 9, 13, and 17 were not found in fresh frozen liver specimens. Moreover, c-kit mutations in three specimens from surgical resection were not found.

Discussion

This case casts doubt on 1) when GISTs acquire a gain-of-function mutation in the c-kit proto-oncogene, 2) how to predict the malignant potential and treat with imatinib mesylate in adjuvant settings 3) toxicities of imatinib mesylate.

In 1998, Hirota and colleagues (12) reported that some GISTs contain an exon 11 mutation in the c-kit proto-oncogene. The presence of a gain-of-function c-kit mutation provides a constitutive stimulus for tumor cell growth and an uncontrolled antiapoptotic signal that favors the malignant clone. The prevalence of c-kit mutation in GIST is as high as 90%. The majority of GISTs have c-kit mutation mainly in exon 11 (highly conserved juxtamembrane region) which is true of the present case (1, 2, 4). However, we could not detect c-kit mutations in three primary specimens from surgical resection. One plausible explanation was that the type of tissue for DNA extraction (archival paraffin material vs. frozen tissue) might have affected the sensitivity of mutation detection. Another possibility was that it is likely that GISTs acquire additional c-kit mutations in tumor progression and metastases. It is currently recognized that even small tumors that appear to be low-grade malignancy by conventional histopathologic criteria can potentially recur (often many years after the initial diagnosis) and metastasize, documenting the malignant potential of even the most histologically low-grade malignancy (13). Cytogenetic mechanisms in the progression from low-grade to high-grade malignancy GISTs also remain to be elucidated (14).

Imatinib mesylate is a landmark development in cancer therapy (5, 7). The application of imatinib mesylate represents a major paradigm shift in cancer therapy, targeting specific molecular abnormalities crucial in the etiology of cancer. The initial evaluation of primary GISTs is important. However, one of the most difficult issues in the diagnosis of GISTs is the discrimination of high-grade malignant tumors from low-grade malignant growths, suggesting a better definition of primary GISTs with favorable characteristics would be a tumor with uncertain malignant potential. Predicting the clinical behavior of GISTs based on clinical, pathologic, and histopathologic findings has been attempted but no definite criteria have been established (15, 16). In general, a high likelihood of malignant behavior in GISTs is identified by increased mitotic activity and larger tumor size. Taniguchi et al (17) reported that exon 11 mutation was found to be an independent adverse prognostic factor in patients treated without imatinib mesylate. However, Heinrich et al (18) reported that the presence of mutations in exon 11 predicted both significantly higher rates of response to imatinib mesylate and a longer time to treatment failure. Observations from this case suggest that GIST patients with adverse characteristics such as large tumor size and high mitotic rate have an exceedingly poor prognosis even after complete resection and should be candidates for adjuvant treatment of imatinib mesylate in GIST patients with exon 11 mutation. Because

<table>
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<th>Type of tissue used for DNA extraction</th>
<th>1995, Jun</th>
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<th>2003, Feb</th>
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<td>Peritoneum</td>
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<td>18</td>
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The size of the resected tumor was measured along its greatest axis. The mitotic index (MI) is measured by counting the number of mitotic figures in 50 high-powered fields (HPF) and expressing the result as the number of mitoses per 50 HPF. Immunostaining for Ki-67 antigen (MIB-1), a marker of cell proliferation, with mouse monoclonal antibody diluted 1:50 was performed. MIB-1 index is measured by counting the number of positive cells per 100 cells and expressing the result as a percentage. N.E.: not examined.
imatinib mesylate may possibly have its greatest impact on recurrence and survival when there is minimal disease, as in the present case after complete gross tumor resection when only residual microscopic disease may exist (11, 19), trials of adjuvant therapy with imatinib mesylate are ongoing. However, many questions including the optimal doses or duration of administration applies to the use of imatinib mesylate in adjuvant settings.

Drug-related adverse events observed to date include edema (periorbital or lower), nausea, diarrhea, intermittent muscle cramps, fatigue, rash, headache, and abdominal pain. The most medically serious side effects are GI or intratumor hemorrhage, and are postulated to be associated with massive tumor necrosis induced by imatinib mesylate, but to date it is unclear whether or not this may be exacerbated by treatment. Occasional severe side effects (toxicity grade 3/4) have been reported in approximately 5% of GIST patients (6). Indeed, grade 3 neutropenia (868/mm³) developed in this case. The patient had no tuberculosis history. Thus, it is not plausible that imatinib mesylate causes a reactivation of tuberculosis. It is unclear whether or not pulmonary tuberculosis may be induced by imatinib mesylate treatment, but caution is warranted in immunocompromised GIST patients. In general, myelotoxicity was less frequent in patients with GISTs, suggesting that the myelosuppression associated with imatinib mesylate in hematologic cancers may be related to the pathophysiology of the leukemic bone marrow. However, because follow-up of GIST patients treated with imatinib mesylate has been relatively short, long-term safety data are currently unavailable, so cumulative toxicity and long-term toxicity cannot yet be fully excluded.

In conclusion, observations from this case suggest that 1) GISTs may acquire additional c-kit mutations in the progression of the disease, 2) standard methods and criteria for providing consistent prognostic classification including analysis of KIT mutations should be established to ensure appropriate treatment, and 3) GIST patients with adverse characteristics such as a large tumor size and a high mitotic rate may be candidates for adjuvant treatment of imatinib mesylate with attention to toxicity, such as tuberculosis, especially in the immunocompromised hosts.

References