—Report on Experiments and Clinical Cases—

High Efficacy of Imatinib for Recurrent Gastrointestinal Stromal Tumor in the Jejunum: A Case Report

Kimiyoshi Yokoi¹, Noritake Tanaka¹, Shoji Kyouno¹, Noriyuki Ishikawa¹,
Tomoko Seya¹, Takashi Shirakawa¹, Yoshiyuki Takahashi¹,
Yoshiharu Ohaki¹, Kiyohiko Yamashita¹ and Takashi Tajiri³

¹Department of Surgery, Chiba-Hokusoh Hospital, Nippon Medical School
²Department of Pathology, Chiba-Hokusoh Hospital, Nippon Medical School
³The First Department of Surgery, Nippon Medical School

Abstract

Gastrointestinal stromal tumor is a mesenchymal tumor of the digestive tract. Although there used to be no effective therapy for the tumor, there have been many recent reports on the efficacy of imatinib. We report on a 53-year-old female patient with a primary tumor of the jejunum who underwent 3 operations. As the tumor could not be removed at the 3rd operation, she was given imatinib orally. Results showed significant reduction ratios of the tumor area (83.0%) and volume (92.2%) at 18 months after starting imatinib administration. Also, the mean reduction ratios of the tumor area and volume per month (%/M) after starting imatinib treatment showed remarkable results, especially during the initial 3 weeks: 53.9%/M and 49.5%/M, respectively.

Whether imatinib is the first choice of treatment for GIST or not, and what is the appropriate dose and period should be resolved.

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Key words: GIST, STI571, imatinib, recommended dosage, c-kit

Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the digestive tract¹. Most GISTs were previously diagnosed as leiomyomas, leiomyosarcomas, leiomyoblastomas and Schwannomas, even when immunohistochemical examination failed to show myogenic or neurogenic differentiation². The concept of GIST is newly advocated³. Further, in line with the advancement of detection methods using immunohistochemical⁴ or genetic technology, the relationship between c-kit expression and interstitial cells of Cajal (ICC) has been elucidated. As a result, attention has been directed to the finding that the cell origin of GIST is ICC⁵.

It has also been reported that GIST is generally resistant to chemotherapy and that there is no treatment choice other than surgery. though the molecular targeting drug imatinib (STI571, Novartis, Basel, Switzerland) developed for treating chronic myeloid leukemia (CML) has been proven effective⁶ by many reports for c-kit (CD117, KIT tyrosine

Correspondence to Kimiyoshi Yokoi, MD, Department of Surgery, Chiba-Hokusoh Hospital, Nippon Medical School, 1715 Kamagari, Inba-mura, Inba-gun, Chiba 270-1694, Japan
E-mail: kimiyoko@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)
kinase) positive GIST. We experienced a patient with c-kit positive recurrent GIST in the small intestine that responded to imatinib. The results, together with a literature survey, are reported.

Case Report

On June 4, 1999, a 50-year-old Japanese woman was admitted to Chiba-Hokusoh Hospital, Nippon Medical School with chief complaints of lower abdominal pain, pain on urination and fever. Past history was remarkable only for an appendectomy at age 20; family history was non-contributory. On June 10, 1999, the first operation was conducted following a diagnosis of pelvic tumor. The tumor, measuring approximately 9 cm in diameter, was a pedunculated exoluminal type of the jejunum that invaded the pelvis and showed massive adhesions to both the pelvic viscera and peritoneum. Because the intraoperative pathological diagnosis showed a malignancy, we conducted procedures including jejunectomy together with a total hysterectomy, bilateral oophorectomy, partial cystectomy, and peritonectomy (Fig. 1).

Pathohistological findings showed solid proliferation of spindle cells, partial fascicular or interlacing arrangement, moderate levels of cellularity and nuclear atypia, and 3 mitosis per 50 high-power field (Fig. 2a). Immunohistochemical examination showed negative findings for α-SMA, S-100 protein and CD 34; and positive findings of vimentine as well as c-kit (Fig. 2b). No lymph node metastasis was found. Tumor cells were not seen in the uterus, ovary, urinary bladder or pelvic peritoneum. Follow-up examination under CT, conducted at about 6-month intervals, showed a tumor recurrence, measuring approximately 8 cm in diameter, in the right pelvis in June 2001. The patient underwent the second operation on July 9, 2001. The tumor was in the right pelvic cavity with peritoneal dissemination in the mesentery composed of 21 nodes up to one cm in diameter. The tumor and all nodes were resected. Pathological findings were similar to the primary tumor’s histology. On October 9, 2001, CT revealed rapid growth of the tumor, approximately 9 cm in diameter, in the right pelvis (Fig. 3a). The third operation was performed
on November 26, 2001, but the tumor could not be removed.

Since in Japan, imatinib is only approved by the National Health Insurance Reimbursement System for CML, but not for GIST, we had to obtain approval from the hospital’s Ethical Committee to use imatinib for her GIST; the patient and her family had to pay approximately $3,500 a month for the drug; and we had to obtain informed consent from the patient, especially regarding possible adverse reactions. On December 25, 2001, oral administration of imatinib was started at a daily dose of 400 mg. But, owing to the financial burden on the patient and her family, the daily dose was decreased to 200 mg in the 7th month of treatment. And the daily dose was increased to 400 mg again in the 19th month, because imatinib was approved by the National Health Insurance Reimbursement System.
for GIST on July 17, 2003.

Her physical findings before starting imatinib administration were height, 153 cm; weight, 64 kg; blood pressure, 126/76 mm Hg; pulse, 68/minute; general state was good; no nodes were palpable; there was no edema of the extremities and no anemia. A tumor mass was palpable in the right lower abdominal region. Blood examination before starting imatinib administration showed: white blood cell count, 5,740/μL; red blood cell count, 425×10^9/μL; hemoglobin, 129 g/dL; hematocrit, 39.4%; and platelets, 23.7×10^9/μL. Blood chemistries were within normal limits. Tumor markers were within normal ranges including CEA, 1.0 ng/mL; CA19-9, 6.0 u/mL; CA125, 14 u/mL; and CA72-4, 3.0 u/mL. CT examination showed no metastasis to other organs such as the liver, lung, or spleen.

Although tumor response to treatments has generally been judged according to the Response Evaluation Criteria in Solid Tumors (RECIST)\(^6\), we employed WHO criteria\(^5\) in the present study. We measured the maximum long diameter and the corresponding vertical long diameter using CT to obtain tumor area, which was applied for judging the response. We also measured tumor volume as a reference point. Further, we defined the mean tumor reduction ratio per month (%/M) as another reference criterion for tumor response to our treatment. As for evaluating adverse reactions, we used the Common Toxicity Criteria Manual\(^11\).

CT examinations were conducted regularly from December 25, 2001, when imatinib administration was started, and tumor areas and volumes were obtained (Fig. 3). On October 9, 2001, before staring imatinib administration, CT calculation showed a tumor area of 50.8 cm\(^2\) and a volume of 161.8 cm\(^3\), and, using on those values as the standards, each reduction ratio was obtained. The tumor area (2D), volume (3D) and the reduction ratio of 2D and 3D, respectively, were as follows: 30.3 cm\(^2\), 101.7 cm\(^2\), 40.4% and 37.1% (at 3 weeks after starting imatinib administration); 24.3 cm\(^2\), 57.0 cm\(^2\), 52.1% and 64.8% (at 2 months); 16.1 cm\(^2\), 31.0 cm\(^2\), 68.3% and 80.9% (at 4 months); 14.7 cm\(^2\), 22.4 cm\(^2\), 71.0% and 86.2% (at 6 months); and 8.6 cm\(^2\), 12.6 cm\(^2\), 83.0% and 92.2% (at 18 months) (Fig. 4). At two months after starting imatinib, a partial response (PR) was judged. Also, the mean reduction ratios of tumor area (Fig. 5a) and volume (Fig. 5b) per month included: during the initial 3 weeks, respectively, 53.9%/M and 49.5%/M; from 3 weeks to 2 months, 9.4%/M and 22.2%/M; from 2 to 4 months, 8.1%/M and 8.1%/M; from 4 to 6 months, 1.8%/M and 2.7%/M; and from 6 to 18 months, 1.0%/M and 0.9%/M. These findings showed a higher reduction ratio effect in the initial periods.

Adverse reactions due to imatinib included nausea, edema and leukocytopenia, all of which were grade 1. Nausea appeared on imatinib administration day 4, and domperidone was given for approximately 3 weeks resulting in disappearance of nausea. Edema developed on imatinib administration day 10 in her face and lower extremities; the former disappeared 8 months after its appearance and the latter decreased during the 5 months after its development, whereas edema around her eyes remained. No drug was used to treat the edema. Blood cell counts showed reductions from 6 to 8 weeks after starting imatinib administration, the
tumors. Thereafter, the actual meaning of GIST has gradually changed, and, at present, we use the term when a tumor shows positive immunostaining of either CD34 or c-kit (regardless of developing either myogenic or neurogenic marker). During these years, there have been 2 notable reports. The first was a communication by Hirota et al. in 1998 stating that GIST shows a high incidence of gain-of-function mutation of c-kit gene and that, since c-kit develops in the interstitial cells of Cajal (ICC), a pacemaker cell in the digestive tract, the cell origin of GIST is ICC. The second was on the relationship between imatinib and GIST. In particular, imatinib was originally developed in 1996 to treat CML, and is a molecular targeting drug that selectively inhibits activity of Bcr-Abl fusion protein (Bcr-Abl tyrosine kinase), a genetic product of the Philadelphia (Ph) chromosome and a pathogenic substance that causes CML. It has been also clarified that imatinib inhibits both platelet-derived growth factor (PDGF) receptor and c-kit tyrosine kinase activity. The best treatment for GIST is surgical resection, since chemotherapy and radiotherapy are ineffective. As a result, patients showing metastasis or recurrence with unresectable GIST have had no treatment options. In 2001, Joensuu et al. focused attention on imatinib to inhibit c-kit tyrosine kinase activity and they used imatinib at a dose of 400 mg/day to treat a 50-year-old woman with recurrent GIST of the stomach and reported a significant effect in this patient. van Oosterom et al. reported 40 patients showing the effects of imatinib in metastatic GIST. Demetri et al. conducted a multicenter cooperative study with 147 patients and reported the following results: complete response, none; partial response, 79 patients (53.7%); stable disease, 41 patients (27.9%); and progressive disease, 20 patients (13.6%), and adverse reactions of the patients were mostly grades 1 and 2, indicating imatinib is well tolerated. We also used imatinib to treat a GIST patient who showed a significant response at 3 weeks after starting imatinib administration. Due to the financial burden on the patient, the daily dose was reduced from 400 mg to 200 mg at 7th month after starting imatinib administration. Based on a fact that the mean tumor reduction ratio was same

Fig. 5 The mean tumor reduction rate (%/M): 2D during 3 weeks after starting imatinib administration shows 53.9% and 3D during the same periods shows 49.5%, indicating a significant reduction rate in the initial periods. (a) Results obtained by 2D. (b) Results obtained by 3D.

lowest levels of which were: leukocytes, 3,480/μL; erythrocytes, 327×10⁶/μL; hemoglobin, 9.7 g/dL; hematocrit, 30.7%; and platelets, 14.5×10⁹/μL. No abnormality was observed in other laboratory examination values.

The patient continues to be treated on an outpatient basis.

Discussion

The concept of GIST has been widely recognized since 1996 when Rosai reported GIST as a collective diagnostic name for digestive mesenchymal system
degree during the latest 12 months, a daily dose of 200 mg was effective enough to reduce the tumor size. In most studies, on the other hand, imatinib is used at a daily dose of 300 to 800 mg\(^{12,13}\). Our present case is the first report that a low dose (200 mg) administration for 13 months showed high efficacy in a GIST patient. At present, the daily dose is increased to 400 mg, which is the recommended dosage generally, because the financial burden became light and it expects further effect.

Imatinib is an extremely effective drug in c-kit positive GIST patients with recurrence and metastasis, and such patients can benefit from outpatient treatment with less adverse reactions. In regard to imatinib, remaining issues include whether imatinib is the first choice of treatment for GIST or not, and what is the appropriate dose and period. These issues require urgent resolution.

References


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