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Case Report

Benefit of Continuation of Low-Dose Imatinib for Gastrointestinal Stromal Tumors despite Adverse Events with Regular-Dose Imatinib

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Keywords
Gastrointestinal stromal tumors · Imatinib · Exon 11 *KIT* mutation · Tyrosine kinase inhibitor

Abstract
Tyrosine kinase inhibitors (TKIs) such as imatinib improve the prognosis of patients with gastrointestinal stromal tumors (GISTs). However, treatment options for GISTs are still limited, and the continuation of TKIs is difficult due to adverse events in some cases. The effectiveness of low-dose imatinib is unclear. We report 2 cases to show effectiveness of low-dose imatinib in patients with adverse events. The first case is a male in his early 60s with a history of intestinal GIST resection who was diagnosed with recurrent GIST with peritoneal dissemination. He was started on low-dose imatinib (300 mg) because of a history of subconjunctival hemorrhage after receiving postoperative imatinib. Follow-up contrast-enhanced ultrasonography revealed that the tumors had shrunk in size and number after 2 months of treatment with 300-mg imatinib. He continued this treatment and showed partial response for 8 months. The second case is a female in her late 70s with rectal GIST who was treated with imatinib 400 mg. Due to a severe skin lesion, she changed her treatment to sunitinib 2 months after initiation. However, new metastasis in the liver was confirmed after 4 months of administration of sunitinib. She underwent surgical esection of the rectal tumor to reduce the volume. After the surgery, low-dose imatinib (300 mg)

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with oral steroids was adopted. Follow-up confirmed the absence of recurrence at the rectum and no increase in hepatic tumor size for 18 months. Aggressive treatment with low-dose imatinib instead of discontinuation or alteration of treatment may benefit patients with unresectable and postoperative GISTs with sensible mutation to imatinib.

Introduction

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors arising from intestinal cells of Cajal in the gastrointestinal (GI) tract [1]. More than 90% of GISTs are associated with *KIT* (*CD117*) or platelet-derived growth factor receptor A (*PDGFRA*) mutation, and less than 10% of GISTs have no identified tyrosine kinase mutations [2]. The prognosis of GISTs differs depending on several factors such as tumor size, tumor site, mitotic status, and gene mutations [3]. According to Asian and worldwide consensus, localized and resectable GISTs are first surgically resected, and adjuvant therapy is adopted according to the risk of recurrence [4]. When unresectable or metastatic, or after curable resection, molecular targeted therapy can be initiated because GIST is insensitive to conventional chemotherapy [5], and the introduction of imatinib, a selective tyrosine kinase inhibitor (TKI) of BCR-ABL, KIT, PDGFRA, is initially considered.

Imatinib mesylate is an oral multiple TKI that has been shown to improve tumor response in GISTs using the response evaluation criteria in solid tumors (RECIST) [6, 7] and is considered the first-line drug option for GISTs. The recommended starting dose of imatinib is 400 mg/day for both adjuvant therapy and unresectable cases, and adverse events, such as rash, GI symptoms, pulmonary disease, fatigue, and subconjunctival hemorrhage, should be closely monitored [4].

Here, we present 2 cases of patients with metastatic GISTs who received low-dose imatinib (300 mg/day) and showed favorable clinical courses. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000529002).

Case Report

Case 1

A male in his early 60s underwent MRI for further inspection for elevated serum prostate-specific antigen level (7.74 ng/mL) in our institution, and a 3-cm peritoneal tumor in the lower abdomen was coincidentally confirmed as peritoneal metastasis, prompting further examination at the digestive surgery department. He was a nonsmoker and mild drinker. His body mass index was 18.05 kg/m^2. He had an allergy to iodine-based contrast. He had a history of intestinal GIST and had undergone surgical treatment and retinal detachment. He had undergone surgical resection of a 5-cm ruptured GIST containing c-kit-positive cells 8 years prior that was classified as high risk according to the modified Fletcher classification (Fig. 1a–d). Genetic mutation in exon 11 (555–572 deletion) was confirmed. After surgical resection, he initiated imatinib 400 mg and experienced a subconjunctival hemorrhage. The dose of imatinib was, thus, reduced to 300 mg. After 3 years without recurrence, imatinib was discontinued.

18-fluorodeoxyglucose positron emission tomography (PET)-CT showed increased 18-fluorodeoxyglucose uptake of the suspected tumor and other small lesions in the lower

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Fig. 1. Gross findings (**a**, **b**) and pathological findings of a resected intestinal specimen including H&E staining (**c**: ×40) and positive immunohistochemistry findings of c-kit (**d**: ×100) in case 1. Lower gastroendoscopic findings revealed a 5-cm elastic hard submucosal tumor at the anterior rectal wall (**e**). Gross findings (**f**) and pathological findings of a resected intestinal specimen, including H&E staining (**g**: ×20) and positive immunohistochemistry findings of c-kit (**h**: ×100) in case 2.

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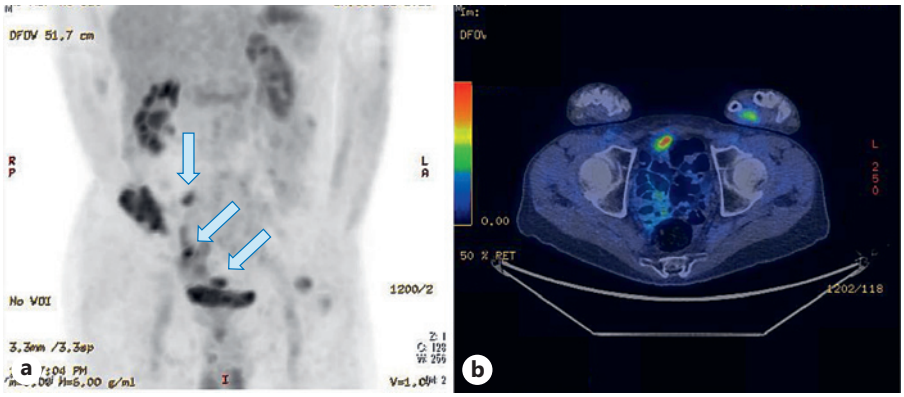

Fig. 2. a, b. 18-fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT revealed increased FDG uptake at the lesions in the lower intraperitoneal cavity.

intraperitoneal cavity (Fig. 2a, b). Contrast-enhanced ultrasonography revealed a 28 × 20-mm low echoic tumor with basket pattern blood flow signals (surrounding blood flow and fine flowing within the tumor) by peritoneum in the lower abdomen. Seven additional tumors with similar echo levels and vascular patterns ranging from 10 to 20 mm were detected in the lower peritoneal cavity. We diagnosed the tumors as recurrent GIST with peritoneal dissemination based on the imaging findings. Despite adverse events, readministration of imatinib was considered based on the diagnosis of recurrent GISTs and the past efficacy of imatinib. To reduce the adverse event risk, a reduced dose of imatinib was initiated (300 mg). Follow-up contrast-enhanced ultrasonography revealed that the lesions were reduced in size and number after 2 months of low-dose imatinib administration without severe adverse events: a 15 × 9-mm large tumor and two other tumors of 9-mm size. After 6 more months of imatinib, only one tumor (7 mm) was detected on follow-up contrast-enhanced ultrasonography, and he has still continued 300 mg imatinib without adverse events.

Case 2

A female in her late 70s was referred to our hospital after being diagnosed with rectal GIST 2 years ago. She was a nondrinker and a former smoker (40 cigarettes/day for 40 years). Her body mass index was 23.55 kg/m^2. She had no known allergy. She had a history of pulmonary tuberculosis and breast cancer, curatively resected 6 years ago, and regularly took an H2 blocker.

Lower gastroendoscopy revealed a 5-cm elastic hard submucosal tumor at the anterior rectal wall (Fig. 1e), and endoscopic ultrasonography revealed low-echoic contents with small cystic lesions. A fine needle biopsy was performed, and GIST was diagnosed with characteristic findings, including spindle-shaped cells and positive immunohistochemistry for GISTs (c-kit, CD34, DOG-1, S-100). Further, genetic mutation in exon 11 (557–558 deletion) was confirmed. Imatinib 400 mg was initiated based on the diagnosis. However, due to severe systemic rash and edema, she discontinued imatinib after 2 months from initiation. Her skin biopsy revealed interface dermatitis with eosinophils, and her rash and edema completely disappeared after the discontinuation of imatinib. She started sunitinib 37.5 mg as second-line therapy. Four months after initiation of sunitinib, PET-CT, MRI, and contrast-enhanced CT revealed a newly detected metastatic hepatic tumor (Fig. 3a, b) with no change in the primary rectal tumor. After a multidisciplinary expert team meeting, she underwent surgical resection of the 4-cm rectal tumor to reduce the volume. Pathological findings confirmed the diagnosis of GIST, and mitotic index was >5/50 HPF (Fig. 1f–h), classified as high risk according to the modified Fletcher classification. No metastasis was confirmed in dissected lymph nodes. She

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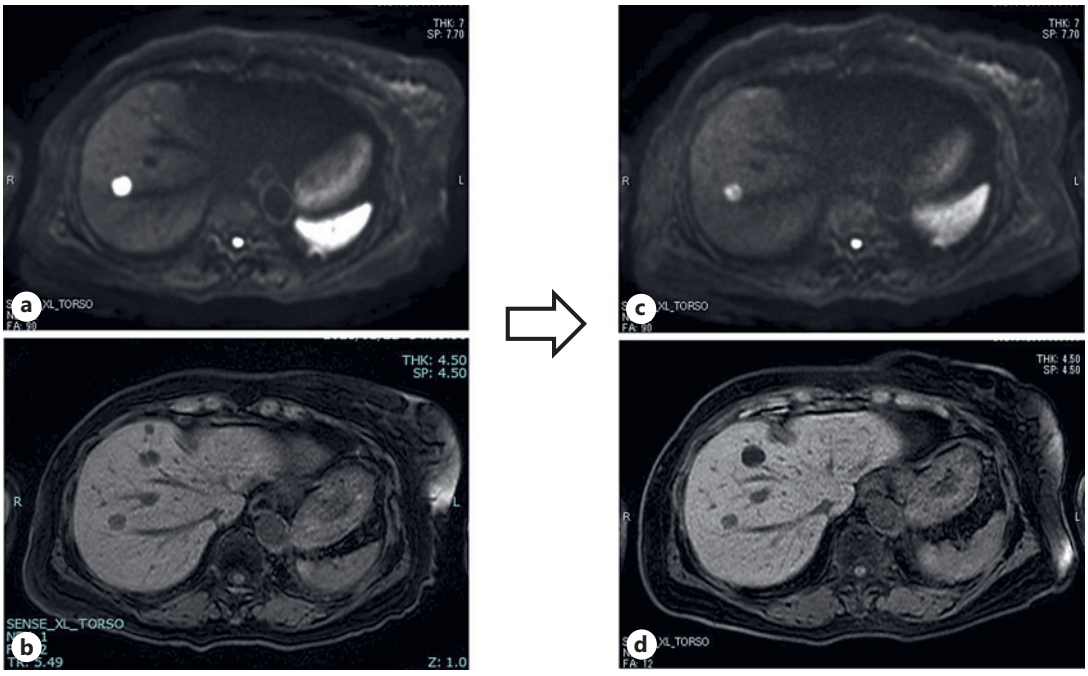

Fig. 3. a, b. Magnetic resonance image (MRI) revealed a newly detected metastatic hepatic tumor. **c**, **d** Follow-up MRI after 300 mg imatinib/day for 18 months following surgical treatment of rectal GIST led to metastatic hepatic tumor size reduction.

was administered 200 mg imatinib with oral steroids again after the surgical resection, leading to no adverse events. Finally, 300 mg was administered, and she has continued the treatment for 18 months without severe adverse events. Follow-up MRI showed no recurrence in the colon and reduced size of the metastatic hepatic tumor (from 17 mm × 15 mm × 14 mm to 12 mm × 10 mm × 8 mm) (Fig. 3c, d).

Discussion

We reported 2 cases of GISTs treated with low-dose imatinib, despite mild side effects, that showed favorable treatment response. Imatinib continuation was possible due to dose reduction and concomitant steroid administration to manage side effects. Therefore, even in patients who experience severe side effects, with dose reduction, imatinib can be beneficial compared to drug switching or discontinuation of imatinib.

Adverse events, treatment failure, poor adherence, and completion of recommended periods are all causes for the discontinuation of imatinib and other TKIs. The major causes of discontinuation were skin reactions, hepatotoxicity, neutropenia, GI bleeding, and cardiac events [7]. In our cases, managing adverse events was critical to the continued use of imatinib. Adverse drug reactions occur in a dose-dependent manner, implying that the events are caused by the pharmacologic effect rather than hypersensitivity [8]. Thus, we reduced the dose of imatinib to control adverse events. A previous case report showed that reducing imatinib to 200 mg/day allowed patients with metastatic GIST suffering from severe adverse events, such as skin rash, tremor, and alopecia, to continue treatment with tolerable side effects (rash) [9]. In case 2, we combined systemic steroids for skin rash. Topical and systemic corticosteroids have been found to be effective against imatinib-induced skin reactions [10].

Low-dose imatinib was sufficiently effective in our two reported cases as well as in past case reports [9]. However, it is still unknown whether reduced-dose imatinib is also effective for GISTs. Further follow-up and case accumulation are necessary to clarify this.

Treatment failure is another reason for imatinib discontinuation. Patients with GISTs, like those with other malignant diseases, have few therapeutic alternatives. TKIs such as sunitinib and regorafenib can be used to treat GISTs, but no other drugs are available. The discontinuation of imatinib or switching to other TKIs like sunitinib leads to tumor recurrence. While several clinical studies confirmed that imatinib improved patients' prognosis [6] when compared to patients with GIST stage IV without imatinib administration [11], patients treated with sunitinib after progression had a median PFS of only 6 months [12]. Given that imatinib has far superior therapeutic benefits than other TKIs, imatinib rechallenge is being considered even after patients have previously received imatinib, sunitinib, and regorafenib. It was proved that imatinib rechallenge, which is defined as readministration of imatinib after treatment failure of imatinib and sunitinib, showed better outcomes compared to patients without imatinib (improvement of overall survival in patients with unresectable GISTs) [13] In case 2, the patient discontinued imatinib at first due to adverse events; however, after treatment failure with sunitinib, imatinib was reintroduced, leading to a favorable outcome.

The genetic mutations of GIST should be precisely evaluated for two reasons. First, genetic profiles provide information about the prognosis of patients with GISTs. Patients with exon 11 deletion have a larger tumor size, higher mitotic status, and poorer survival, compared to those without KIT exon 11 deletions [14]. Genetic analysis also helps in treatment response prediction. Recent research has confirmed that GISTs with exon 11 mutations are more sensitive to imatinib than those with other alterations (exons 13, 14, and 17) [4]. Sunitinib is more effective for KIT exon 13 and exon 14 mutations and less so in KIT exon 17 and exon 18 mutations [15]. Patients with PDGFRA exon 14 and 18 mutations are sensitive to imatinib and have better clinical outcomes than those with KIT mutations [3]. Both of our cases had an exon 11 deletion mutation, and case 2 showed tumor progression after the initiation of sunitinib. Both cases also showed the efficacy of imatinib. Imatinib administration is a key strategy for improving patient outcomes based on genetic status, particularly in patients with exon 11 mutations.

A limitation of this case series is nonuniformity of imaging modality before and after imatinib treatment. In addition, due to cost limitations, we did not perform PET-CT examination as a follow-up. Instead, contrast-enhanced ultrasonography was adopted in case 1 and MRI was adopted in case 2 for metastatic tumor follow-up. Further, we provide a small number of cases from single institution and different duration of administration of low-dose imatinib. Further accumulation of cases from multiple centers and prospective study protocol are required to elucidate the effectiveness of low-dose imatinib for GISTs.

Conclusion

Aggressive treatment, including continuation with decreased dose and readministration of imatinib, may benefit patients with GISTs. Careful management of adverse events due to TKIs and genetic mutation analysis is crucial for improving the outcomes of patients with unresectable or metastatic GISTs.

Acknowledgment

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Statement of Ethics

We reported this case in compliance with the principles of the Declaration of Helsinki. The cases were reviewed and approved by the Institutional Ethics Committee of Kawasaki Medical School. The approval number is 5750-00. Written informed consents were provided by the patients for publication of this case report and any accompanying images.

Conflict of Interest Statement

All authors have no competing interests.

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Author Contributions

Ryo Katsumata contributed to the literature review, manuscript writing, visualization, and project administration. Yasumasa Monobe and Hideyo Fujiwara contributed to pathological evaluation and data collection. Yosuke Katata contributed to conceptualization, data collection, and supervision. Takashi Urano, Akihisa Akagi, Kotone Tsujimoto, and Takako Konishi contributed to the data analysis and treatment of the patients. Noriaki Manabe contributed to data collection. Tomoari Kamada contributed to data collection and supervision. Hirofumi Kawamoto contributed to data collection and diagnosis of the patients. Tomoari Kamada contributed to data collection and literature review. Tomoki Yamatsuji contributed to surgical treatment, supervision, and visualization. Yoshio Naomoto contributed to the conceptualization, treatment of the patients, and supervision. Ryo Katsumata, Yasumasa Monobe, Yosuke Katata, Hideyo Fujiwara, Takashi Urano, Akihisa Akagi, Kotone Tsujimoto, Takako Konishi, Noriaki Manabe, Tomoari Kamada, Hirofumi Kawamoto, Tomoki Yamatsuji, and Yoshio Naomoto read and approved the final manuscript.

Data Availability Statement

All data generated during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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