

Complete response to second-line chemotherapy with sunitinib in a patient with high-risk gastrointestinal stromal tumor: A case report

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Abstract. Gastrointestinal stromal tumors (GISTs) are a type of sarcoma and the most common mesenchymal tumor of the gastrointestinal tract. Systemic chemotherapy is recommended for unresectable or metastatic GISTs. Imatinib, an oral multi-targeted receptor tyrosine kinase inhibitor, is an effective adjuvant chemotherapy for primary high-risk cases and palliative chemotherapy for unresectable or metastatic cases. For imatinib-resistant cases, second-line chemotherapy with sunitinib is recommended, as it has been demonstrated to result in a significantly longer median progression-free survival time and produce a higher response rate compared with placebo treatment. The current report describes the case of a 54-year-old woman who initially presented with persistent upper abdominal pain and anorexia. Upper gastrointestinal endoscopy and computed tomography revealed a submucosal tumor of the stomach with no apparent metastases. The patient underwent total radical gastrectomy and was diagnosed histologically with GIST with a high-risk of recurrence; therefore, adjuvant chemotherapy with imatinib was administered. However, multiple liver and lymph node metastases were subsequently detected, and the patient therefore received second-line sunitinib therapy. Following two cycles of sunitinib, the liver and lymph node metastases disappeared, and a complete response (CR) was achieved and sustained for at least 9 months. To the best of our knowledge, there have been no such cases of CR in previous prospective clinical trials examining the effects of sunitinib, and no other case reports of this worldwide. Thus, this study reports an extremely rare

case of a patient with metastatic GIST who achieved CR with sunitinib as second-line chemotherapy.

Introduction

Gastrointestinal stromal tumors (GISTs) are a type of sarcoma and the most common mesenchymal tumor of the gastrointestinal tract. They arise from the interstitial cells of Cajal, typically occur in older individuals, and are most common in the stomach, followed by the small intestine (1). In Japan, GIST arises most frequently from the stomach, with a prevalence of 1-2 per 100,000 people (2). The majority of GISTs express the protein product of the KIT proto-oncogene, a transmembrane receptor tyrosine kinase (RTK), the activity of which would normally be regulated by the binding of its ligand (stem cell factor). KIT is positively expressed in ~95% of GISTs; therefore, if a tumor is positive for KIT on immunohistochemistry and its cells are morphologically consistent with GIST on hematoxylin and eosin staining, a diagnosis of GIST can be determined (3). CD34 is positively expressed in 70-80% of GIST cases, and CD34-positive staining can thus indicate a diagnosis of GIST, unless KIT expression is absent (4).

As >40% of GISTs are clinically malignant and considered to be metastatic (1,5-7), systemic chemotherapy is indicated in a substantial proportion of GIST cases. Imatinib mesylate is an oral multi-targeted RTK inhibitor that is effective as adjuvant chemotherapy for primary high-risk cases (8,9) and as palliative chemotherapy for unresectable or metastatic cases (10,11).

For imatinib-resistant GIST in unresectable or metastatic cases, second-line chemotherapy is recommended. Sunitinib mesylate is an oral multi-targeted RTK inhibitor whose effects are associated with the blockade of RTK signaling by KIT, platelet-derived growth factor receptors (PDGFRs), vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, and Fms-like tyrosine kinase-3 receptor (12). In patients with GIST, sunitinib treatment has been shown to lead to a significantly longer median progression-free survival (mPFS) time and a higher response rate (RR) compared with a placebo (12). Continuous daily dosing of sunitinib in GIST patients was also reported to be effective for disease control (13). However, to the best of our knowledge,

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there have been no cases showing complete response (CR) in prospective clinical trials examining the effects of sunitinib for GIST or in case reports worldwide.

The present report describes an extremely rare case involving a patient with metastatic GIST who achieved a CR with sunitinib as second-line chemotherapy. To our knowledge, this is the first case report to describe this outcome.

Case report

A 54-year-old woman presented with persistent upper abdominal pain and anorexia, and visited a local doctor in March 2015. The patient had a history of surgeries for a myoma of the uterus, and no history of smoking or alcohol consumption. Her family history included no cancers. Abdominal ultrasound revealed a subcutaneous mass of the upper abdomen, and upper gastrointestinal endoscopy showed a submucosal tumor of the posterior wall of the stomach. As GIST of the stomach was suspected, the patient was referred to the Department of Surgery of Miyazaki Prefectural Miyazaki Hospital (Miyazaki, Japan) in April 2015. Abdominal ultrasound demonstrated free space inside the tumor. As the patient's systolic blood pressure was 80 mmHg (normal range, 90-130 mmHg) and her hemoglobin level was 8.0 g/dl (normal range, 12.0-15.0 g/dl), she was diagnosed with hypovolemic shock due to tumor hemorrhage. Since no distant metastases were observed on computed tomography (CT) (Fig. 1), the patient underwent total gastrectomy and distal pancreatectomy with splenectomy for an advanced invasive tumor. Histological examination of the resected specimen revealed rupture and hemorrhage of the tumor, which was >15 cm in maximum diameter (Fig. 2A). The tumor consisted of spindle-shaped or polygonal cells with enlarged nuclei (Fig. 2B). Immunohistochemically, the cells were positive for KIT and CD34, and partially positive for smooth muscle actin and p53 (Fig. 2C-E). Staining for S100 and desmin was negative, and the MIB-1 positive rate was 10.07% (288/2859 cells; Fig. 2F and G). The tumor was resected completely. Since the patient was diagnosed with a high-risk GIST using the modified Fletcher classification (rupture, size >10 cm, and >10 mitoses per 50 high-power fields) (14), adjuvant chemotherapy with imatinib for 3 years was indicated.

The patient was referred to the Department of Oncology of Miyazaki Prefectural Miyazaki Hospital in May 2015. Her general condition was good and organ functions were well-preserved. Therefore, systemic chemotherapy with imatinib at 400 mg/day was initiated. In June 2015, the dose of imatinib was reduced to 300 mg/day due to diarrhea of grade 2 according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (15).

However, in November 2015, multiple metastases in the liver and a metastatic lymph node near the celiac artery were detected on CT (Fig. 3A and B). The patient's Eastern Cooperative Oncology Group performance status was 0, and her vital signs were within normal ranges. Blood testing revealed a decreased red blood cell count of $329 \times 10^4/\mu\text{l}$ (normal range, $380\text{--}500 \times 10^4/\mu\text{l}$) and a decreased hemoglobin level of 10.8 g/dl (normal range, 12.0-15.0 g/dl); however, the patient's general condition remained good, and organ functions were preserved. Second-line chemotherapy with sunitinib (50 mg/day;

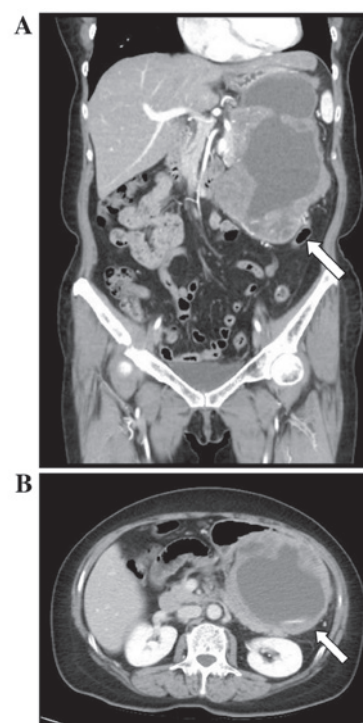


Figure 1. Computed tomography at initial diagnosis revealed (A) a submucosal tumor of the stomach (arrow) with no metastases and (B) tumor hemorrhage (arrow).

days 1-28 per 6-week cycle) was initiated. From the second cycle of chemotherapy, the dose of sunitinib was reduced to 37.5 mg/day due to CTCAE v4.0 grade 1 fatigue. CTCAE v4.0 grade 1 diarrhea and grade 1 proteinuria were also observed, but no other severe adverse events occurred. After two cycles of sunitinib chemotherapy, the liver and lymph node metastases had disappeared, and a partial response, as defined by Response Evaluation Criteria In Solid Tumors version 1.1 (16), was achieved in February 2016. The patient received two additional cycles of sunitinib, and CR was indicated by CT in May 2016 (Fig. 3C and D). The patient then demanded that chemotherapy be discontinued, despite our recommendation that it be continued. The patient has maintained a CR for 6 months. The most recent follow-up was in March 2017.

Discussion

In the present case, the patient could be diagnosed with GIST histologically due to the presence of CD34 and KIT immunoreactivity (3). Risk classification is used for GIST cases with no metastases. Historically, the Fletcher classification, which considers tumor size and mitoses, was the first to be used (17). However, it has also been reported that the MIB-1 labeling index and the existence of tumor necrosis are useful as indicators of tumor proliferation (18-20). In addition, since the prognosis of GIST was observed to be dependent on the site of the tumor, the Miettinen classification has been used as a standard for predicting tumor recurrence (21). Furthermore, the modified Fletcher classification, which takes account of tumor size, mitoses, tumor site and tumor rupture, was reported to be more useful for the selection of high-risk recurrent cases compared with the original Fletcher classification (14). The

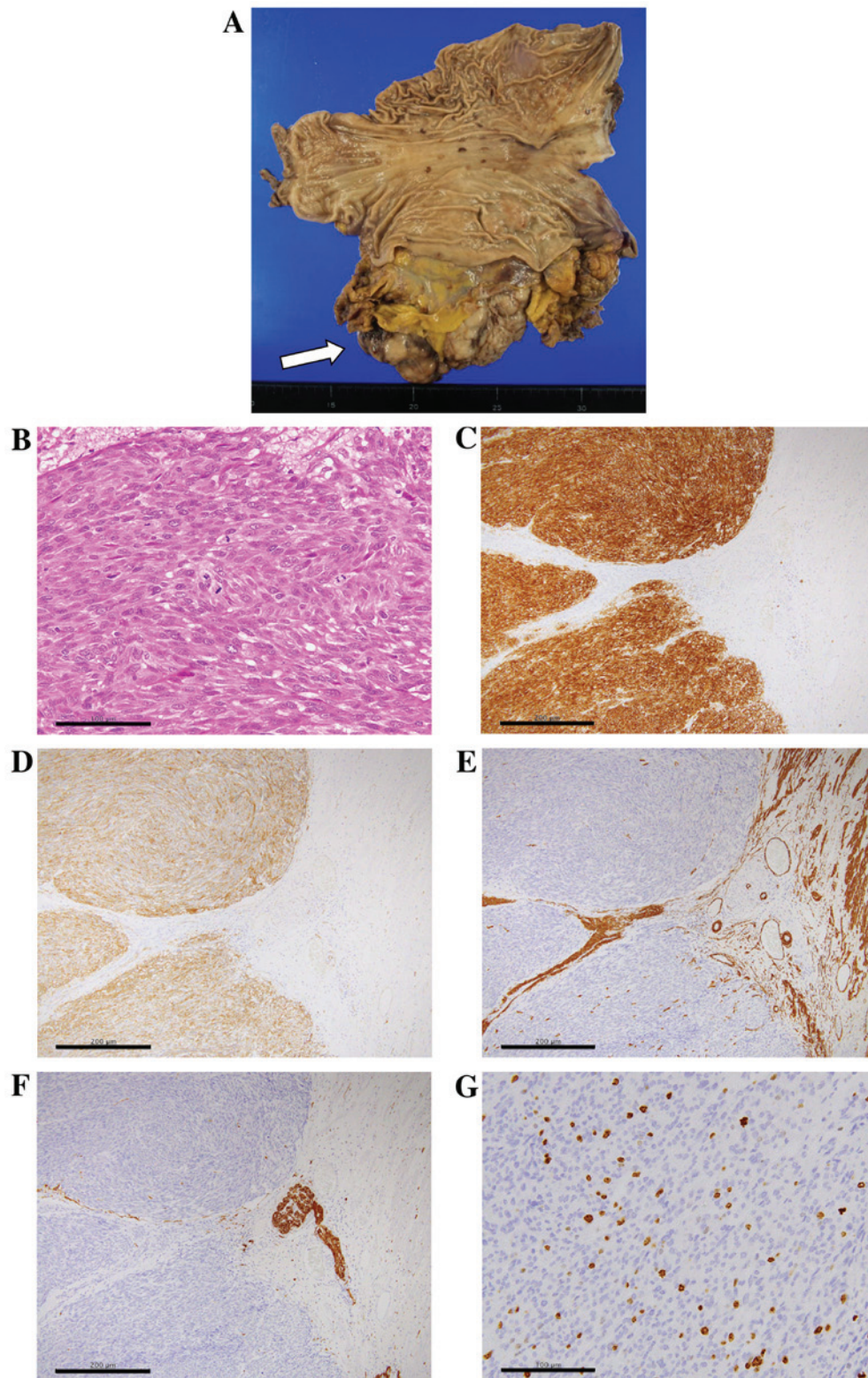


Figure 2. Macroscopic and histological examination of the resected specimen. (A) Macroscopically, the resected tumor was >15 cm in maximum diameter. (B) On hematoxylin and eosin staining, the tumor consisted of spindle-shaped or polygonal cells with enlarged nuclei (scale bar, 100 μ m). (C-F) Immunohistochemically, the cells were positive for (C) KIT and (D) CD34, (E) partially positive for smooth muscle actin, and (F) negative for S100 (scale bar, 200 μ m). (G) The MIB-1 positive rate was 10.07% (288/2859 cells; scale bar, 100 μ m).

present case was diagnosed as high-risk GIST according to the modified Fletcher classification. Although the modified Fletcher classification is a discontinuous indicator for risk assessment, Contour maps are considered to be continuous and

useful for the diagnosis of tumor recurrence (14). In the present case, the probability of tumor recurrence was within 80-90% according to contour maps. Therefore, adjuvant chemotherapy with imatinib was indicated for this case.

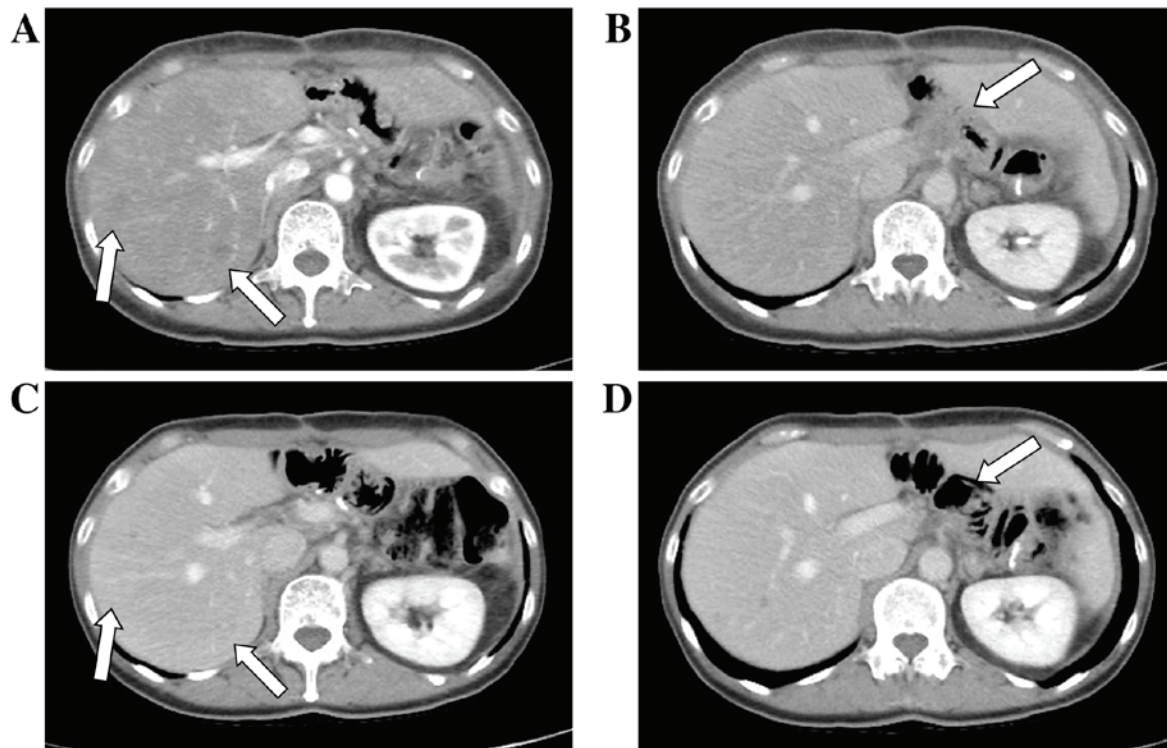


Figure 3. Computed tomography images. In November 2015, following imatinib treatment, (A) multiple metastases (arrows) in the liver and (B) a metastatic lymph node (arrow) near the celiac artery were detected. In May 2016, after 4 cycles of sunitinib, disappearance of (C) the liver metastases (arrows) and (D) the lymph node metastasis (arrow) was observed.

For GIST patients whose tumors are totally resected, imatinib is an effective adjuvant chemotherapy in primary high-risk cases in order to improve the recurrence-free survival time (8,9). For cases of progressive disease in patients receiving 400 mg/day of imatinib therapy, dose escalation to 800 mg/day was reported to be effective in the EORTC62005 trial (22) and the S0033 trial (23). Imatinib dose escalation may have been effective for the current patient; however, 800 mg/day of imatinib is not permitted by the medical insurance system of Japan.

Sunitinib is recommended for imatinib-resistant GIST that is unresectable or metastatic, and significantly longer mPFS times and higher RRs have been observed (12). A previous study conducted a clinical evaluation of continuous daily dosing of sunitinib in patients with advanced GIST following imatinib failure (13). In that study, the disease control rate of sunitinib was 53%, the RR was 13%, the mPFS time was 34 weeks, and the median overall survival (OS) time was 107 weeks. Sahu *et al* (24) reported no CRs among 15 Indian patients prospectively treated with sunitinib as second-line chemotherapy. Thus, in the prospective clinical trials examining the effects of sunitinib, no cases have achieved CR, to our knowledge.

Retrospective studies reporting CR with second-line chemotherapy involving sunitinib have also been few. Dudeck *et al* (25) reported no CRs among 51 German patients with GIST. To the best of our knowledge, there have been three cases of CR following sunitinib as second-line chemotherapy for GIST in retrospective studies: 2/199 patients (1.0%) achieved CR in a Taiwanese study (26), and 1/48 patients (2.1%) achieved CR in a Chinese study (27). However, to

our knowledge, there have been no individual case reports published anywhere worldwide; thus, the present study is the first case report showing CR following second-line sunitinib treatment for GIST.

This case report has several limitations. For example, fluoro-deoxyglucose-positron emission tomography (FDG-PET) was not performed. This modality can detect metastatic lesions that are negative on other modalities, and the patient may therefore have had other metastases prior to commencing sunitinib. However, FDG-PET-negative GIST cases can also occur, and FDG-PET is therefore not considered a substitute for CT (28). Furthermore, in the present study, detection of KIT mutation was not performed. Imatinib has a lower reductive effect for GIST cases with a PDGFRA exon 18 D842V mutation (22), and decreased plasma levels of soluble KIT, (compared with the baseline levels) at 20 and 24 weeks after imatinib administration are associated with a prolonged OS time (13). As the four instances of CR were all observed in Asian patients, it is possible that Asian patients may have certain characteristics associated with the effect of sunitinib; however, this requires investigation.

In conclusion, the present case of GIST in which CR was achieved with second-line sunitinib is extremely rare. This information is of importance for the treatment of GIST and also for clinical research.

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