

[CASE REPORT]

Reduction and Escalation in the Dose of Sunitinib Were Adequately Effective against Gastrointestinal Stromal Tumor of the Small Intestine

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Abstract:

We herein report the first case in which an escalated dose of sunitinib was effective, even after dose reduction. A 64-year-old man with gastrointestinal stromal tumor of the small intestine discontinued adjuvant imatinib because of interstitial pneumonia. After two years, peritoneal recurrence was detected. Sunitinib was started at 50 mg/day for 4 weeks every 6 weeks, after which the dosage was reduced to 37.5 mg/day because of grade 1 gastritis, stomatitis, and a fever. Four months later, computed tomography showed progressive disease. As the adverse events were well-controlled by medication, we escalated the dose to 50 mg/day and achieved a partial response.

Key words: gastrointestinal stromal tumor, sunitinib, dose modification

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Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. Surgical resection is the first recommended therapy, and systemic chemotherapy is administered for unresectable tumors, as they are resistant to radiotherapy. However, conventional chemotherapies are not applicable, and tyrosine kinase inhibitors (TKIs) show efficacy on GISTs according to the tumor molecular pathogenesis.

Imatinib mesylate, a small molecule that inhibits the activation of KIT and platelet-derived growth factor receptor (PDGFR) α proteins, is the first choice of treatment for GISTs (1, 2). Sunitinib has significant clinical benefits in patients with imatinib-resistant GISTs. It is approved at a dose of 50 mg/day for 4 weeks followed by a 2-week off period (2, 3), but in a clinical setting, it is usually intolerable due to adverse events. Therefore, dose modification is usually required.

We herein report the first case in which escalating the dose of sunitinib was effective, even after dose reduction. We also show the effectiveness of modifying the sunitinib-administration schedule.

Case Report

A 64-year-old man visited our hospital with complaints of anorectal pain and incomplete stool evacuation. Computed tomography (CT) and magnetic resonance imaging showed a mass in the left lower quadrant of the abdomen (Fig. 1). As colonoscopy revealed no lesions, a submucosal tumor was suspected. Laparotomy was performed for diagnostic treatment, and the tumor turned out to be a 7.5-cm GIST of the small intestine with a mitotic rate of 23 mitoses per 50 high-power fields (HPF). It harbored a mutation in *KIT* exon 11 (Fig. 2). The tumor was classified as having a high risk of recurrence using the modified-Fletcher classification, and adjuvant therapy with imatinib was planned. Due to interstitial pneumonia, imatinib was discontinued after eight

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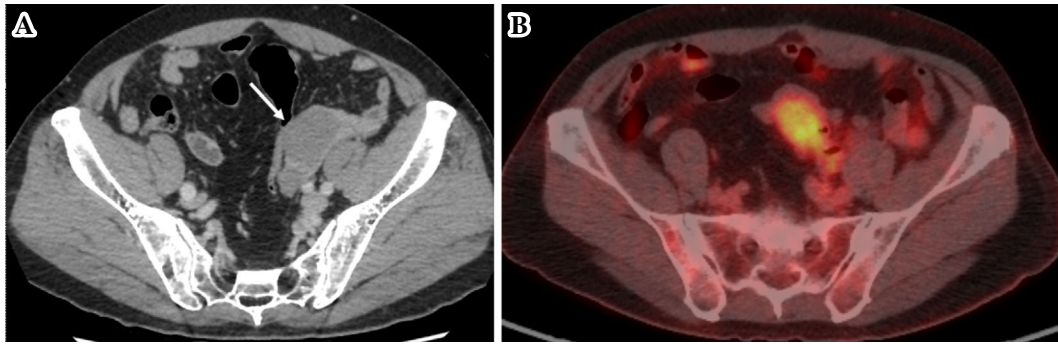


Figure 3. Intrapelvic recurrence lesions revealed by CT (A, indicated with white arrow) and positron emission tomography (PET, B).

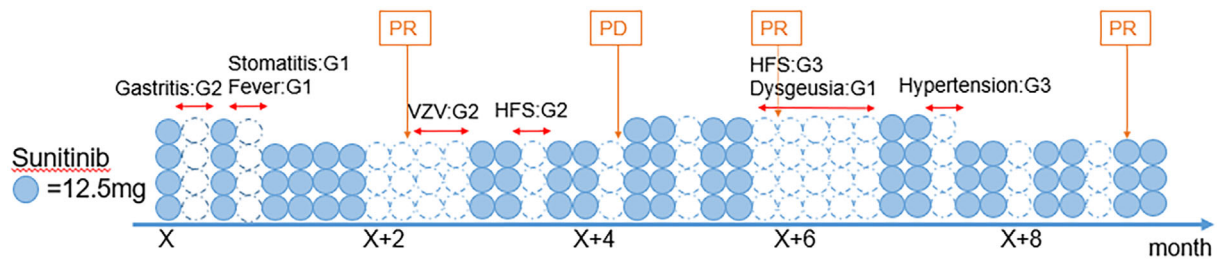


Figure 4. Treatment progress chart.



Figure 5. Latest CT image taken 17 months after starting the administration of sunitinib. The intrapelvic lesions indicated with a white arrow decreased in size, and the lesions around the rectum diminished as well.

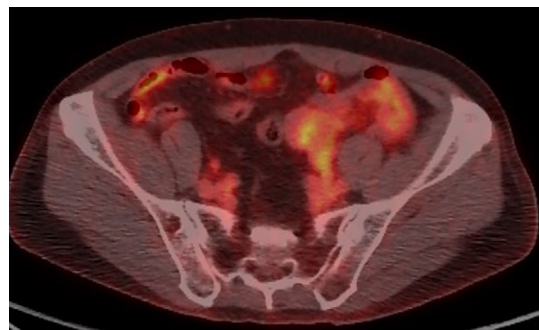


Figure 6. Latest PET image taken 18 months after starting the administration of sunitinib. The FDG uptake in the tumor decreased.

sent study, can also be treated with sunitinib.

Sunitinib is recommended to be used at a dose of 50 mg/day for 4 weeks followed by a 2-week off period according to a phase I trial (8). However, Japanese post-marketing surveillance has reported that as many as 60% of patients with GIST require dose reduction (9), so modification of the drug dose and treatment schedule is usually needed. To our knowledge, the present case is the first to show the effectiveness and safety of escalating the sunitinib dose even after a previous dose reduction. In addition to escalation, modifying the treatment schedule might also be effective. Preclinical data have reported tumor growth during the off-dosing period, suggesting that sunitinib might be effective when used continuously (10). Furthermore, a phase II trial

showed that the concentration of sunitinib decreased to pre-dose levels during a 14-day rest period (11). Based on these reports, various modifications of sunitinib administration have been considered. For example, a phase I trial of sunitinib for two weeks followed by a one-week off period (2/1 schedule) has shown tolerability among patients. This 2/1 schedule kept the sunitinib concentration detectable even on day 1 of course 2, while no significant drug accumulation between courses was detected. This indicates that the 2/1 schedule can prolong sunitinib exposure without inducing intolerance (12).

Kinase genotype has also been shown to influence the clinical activity of sunitinib. In detail, the progression-free survival (PFS) is known to be shorter (5.1 to 7.0 months) for patients with primary *KIT* exon 11 mutations than for those with *KIT* exon 9 mutations or with a wild-type geno-

type (13, 14). It is difficult to compare the PFS of the present case with the values in other cases because our patient used sunitinib as the first-line treatment due to intolerance of imatinib. However, we can safely say that sunitinib was effective in our case.

Supplying sufficient medication is also believed to be important, as demonstrated in this case; whereby a proton pump inhibitor against gastritis, topical steroids against stomatitis and hand-foot syndrome, and an Angiotensin Converting Enzyme inhibitor and calcium channel blocker against hypertension were administered.

In conclusion, the present findings suggest that escalation of sunitinib can be considered after reducing the dose due to adverse events and that the treatment schedule can be modified when required.

The authors state that they have no Conflict of Interest (COI).

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