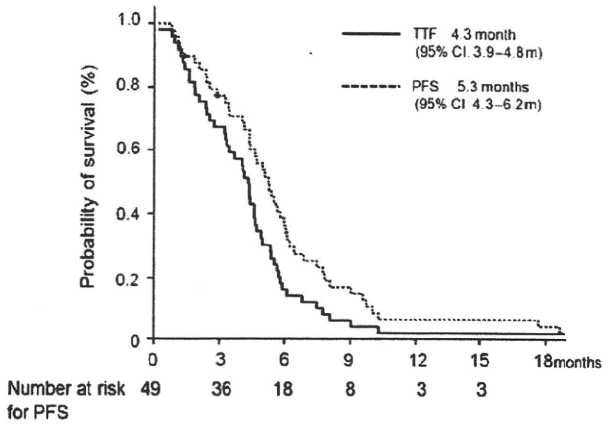

Figure 1. Progression-free survival (PFS) and time to treatment failure (TTF).

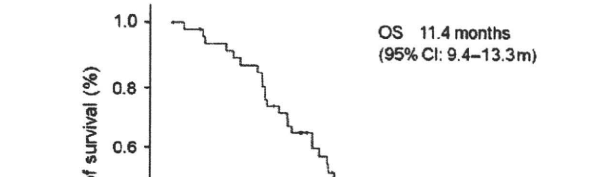

Figure 2. Overall survival.

One patient died within 28 days of the last dose of study medication due to liver failure caused by rapid tumour progression.

All patients ($n = 51$) experienced at least one adverse event during the study, most of which were mild to moderate in severity (Table 3). The most common adverse events with FOLFOX6 were peripheral sensory neuropathy (82%), anorexia (78%), leukopoenia (75%), neutropenia (73%), thrombocytopenia (69%), nausea (61%) and stomatitis (31%). The most common grade 3/4 adverse events were neutropenia (43%) and leukopoenia (12%).

DISCUSSION

FOLFOX4 was the gold standard regimen for colorectal cancer in first- and second-line therapy, but the frequent hospital visits were problematic. FOLFOX6 uses the new, simplified, biweekly LV + 5-FU regimen, with a disposable pump for outpatient therapy (8). An oxaliplatin dose of 100 mg/m^2 was chosen because the results obtained in previous studies suggest a possible dose intensity effect on the

Table 3. Toxicity ($n = 51$)

Adverse event CTC-AE v.3.0	Grade 1–4		Grade 3–4	
	No.	%	No.	%
Neutropenia	37	72.5	22	43.1
Leukopoenia	38	74.5	6	11.8
Anaemia	22	43.1	4	7.8
Thrombocytopenia	35	68.6	2	3.9
Anorexia	40	78.4	2	3.9
Nausea	31	60.8	2	3.9
Stomatitis	16	31.4	0	0
Febrile neutropenia	2	3.9	2	3.9
Hand–foot syndrome	7	13.7	1	2.0
Pigmentation	10	19.6	–	–
Sensory neuropathy[a]	42	82.4	2	3.9

[a]Sensory neuropathy was evaluated by Debiopharm neurotoxicity criteria.

RR and because the toxicity profile was very similar except for a higher neutropenia occurrence with FOLFOX4. FOLFOX4 showed an RR of 21.2% and OS of 11.5 months in 5-FU refractory patients (7). An RR of 9.9% and TTF of 4.6 months was observed in patients who failed to respond to irinotecan-based therapy (5). On the other hand, FOLFOX6 showed an RR of 27% in 5-FU pretreated colorectal cancer patients and 15% in patients who failed to respond to FOLFIRI therapy (8,9). Our results were almost the same, with an RR of 12.9% for irinotecan pretreated patients and 20% for no-irinotecan patients.

In this prospective trial, we evaluated the efficacy and safety of FOLFOX6 in Japanese patients with metastatic colorectal cancer (MCRC). The administration schedule and doses selected for our study were identical to those used in the Tournigand study (7). The major common grade 3/4 adverse events evident in our patient population were neutropenia (43.1%), leukocytopenia (11.8%) and anaemia (7.8%). All other grade 3/4 adverse events occurred in 5% of patients or less. It is notable that the rate of grade 3 sensory neuropathy was only 3.9% in our study population, which is considerably lower than the rates reported with FOLFOX in other Phase-III studies (9.2–20%) (5,7,9,12). This may be due to the short duration of treatment. In the second line, many patients failed to respond to treatment before cumulative toxicity developed. Moreover, there were many criteria for evaluating sensory neuropathy. Some studies used the Debiopharm criteria, while others used CTC-AE v.3.0, so it was difficult to compare sensory neuropathy between studies in detail. Nevertheless, FOLFOX6 demonstrated a predictable and manageable safety profile in Japanese patients.

The recent use of five active drugs, such as 5-FU, irinotecan, oxaliplatin, bevacizumab and cetuximab, appears

to be of major importance in prolonging the survival of MCRC patients (13). Sensory neuropathy can be treatment-limiting with oxaliplatin-based regimens. In our study, three patients discontinued treatment due to neuropathy. In such cases, oxaliplatin discontinuation and reintroduction using the OPTIMOX (stop-and-go) strategy (14) proves useful. The aim of chemotherapy for metastatic cancer is not to cure the disease, but to prolong the patient's survival and to continue the treatment as long as possible. From this viewpoint, the oxaliplatin starting dose has been decreased to 85 mg/m^2, which is the so-called modified FOLFOX6 regimen. The modified FOLFOX6 has not been directly compared with FOLFOX6, but its efficacy and safety profile is similar to that of FOLFOX6. It showed an RR of 41%, PFS of 8.7 months and low peripheral neuropathy (18%: Grade 3) among first-line colorectal cancer patients (15). In another retrospective study, the RR of mFOLFOX6 was reported to be 8.7% for irinotecan pretreated patients (16). Our results seemed to be slightly better (12.8%), but the number of patients was too small to compare the efficacy between FOLFOX6 and mFOLFOX6. In this study, the dose of oxaliplatin needed to be reduced in 20 patients (40%) and the relative dose intensity for oxaliplatin was 0.845. It was considered that the total dose of oxaliplatin was not significantly different between the starting dose of 100 mg/m^2 or 85 mg/m^2. The modified FOLFOX6 is becoming the community standard for FOLFOX.

Molecular-targeted drugs, such as bevacizumab or cetuximab, have an added effect on cytotoxic agents (12,17,18), and are built in as standard treatment in all lines. However, quite a few patients are unable to use bevacizumab or cetuximab due to complications or efficacy. Hypertension or thrombotic events were limiting the toxicity for bevacizumab treatment (19), and KRAS mutation, which occurs in about 40% of the patients, was a negative predictive factor for cetuximab treatment (20). Thus, it remains important to evaluate the regimen of cytotoxic agents and to manage them in our clinical practice.

In conclusion, this study suggests that FOLFOX6 had an acceptable profile in terms of both efficacy and safety in previously treated Japanese colorectal cancer patients. The efficacy and safety profile of FOLFOX6 in this study was consistent with that observed in Western patients. The FOLFOX6 regimen can therefore be considered as one of the standard treatments for Japanese patients with MCRC.

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Conflict of interest statement

None declared.

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Vesicocutaneous fistula formation during treatment with sunitinib malate: Case report

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Abstract

Background: The oral multi-kinase inhibitor sunitinib malate improves the survival of patients with gastrointestinal stromal tumors (GIST) after the disease progresses or intolerance to imatinib mesylate develops. Urinary fistulae arising during treatment with sunitinib for GIST have not been described.

Case presentation: We describe a 62-year-old female patient diagnosed with unresectable GIST that involved the abdominal wall, urinary bladder wall, bowel, mesentery and peritoneum in the pelvic cavity. Intestinocutaneous fistulae developed on a surgical lesion after orally administered imatinib was supplemented by an arterial infusion of 5-flurouracil. Sunitinib was started after the patient developed resistance to imatinib. On day 4 of the fourth course of sunitinib, a widely dilated cutaneous fistula discharged large amounts of fluid accompanied by severe abdominal pain. Urinary communication was indicated based on the results of an intravenous injection of indigo carmine. Computed tomography findings suggested a small opening on the anterior urinary bladder wall and fistulous communication between the bladder and abdominal walls bridged by a subcutaneous cavity. The fistula closed and the amount of discharge

decreased when sunitinib was discontinued. Therefore, sunitinib might have been associated with the development of the vesicocutaneous fistula in our patient.

Conclusion: This is the first description of a vesicocutaneous fistula forming while under sunitinib treatment. Clinicians should be aware of the possible complication of vesicocutaneous fistula formation during treatment with molecular targeting agents in patients with extravesical invasion and peritoneal dissemination of GIST.

Background

Sunitinib malate is a multi-kinase inhibitor of platelet-derived growth factor receptors (PDGFRα, PDGRFβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2, VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony-stimulating factor receptor Type 1 (CSR-1R), and the neurotrophic factor receptor (RET) derivative of a glial cell line [1]. Sunitinib has improved clinical outcomes for patients with progressive unresectable gastrointestinal stromal tumors (GIST) or who develop intolerance to imatinib mesylate and it is reasonably well tolerated [1] [2] [3] [4] [5]. A Phase III GIST study found objective response rates in sunitinib and placebo groups of 7% and 0%, respectively ($p = 0.006$) [6]. Only 9% of patients discontinued sunitinib therapy due to adverse events compared with 8% in the control group. The most common adverse reactions that occurred in over 20% of patients were fatigue (34%), diarrhea (29%), skin discoloration (25%), nausea (24%) and anorexia (19%), and all were typically of mild to moderate intensity.

An adjacent organ is usually displaced by GIST. Fistula formation is rare in patients with untreated GIST and in those treated with sunitinib for intra-abdominal malignancies [7].

We describe the clinical aspects of a rare vesicocutaneous fistula that was associated with sunitinib therapy.

Case presentation

A 62-year-old woman was diagnosed with c-kit-positive GIST of the ascending colon with a single hepatic lesion. She was surgically treated by right hemicolectomy and partial hepatectomy. A histological assessment of a specimen of the hepatic lesion revealed GIST metastasis. Therefore, imatinib mesylate (400 mg/day) was started. After 2 years of imatinib treatment, the disease recurred in the liver, mesentery and peritoneum. Increasing the dose of imatinib to 600 mg/day did not prevent disease progression, so an arterial infusion of 5-fluorouracil (5-FU) was added to the imatinib treatment for 3 months. Thereafter, intestinocutaneous fistulae developed on the previous surgical wound and she was referred to our hospital for further treatment for recurrence.

Her baseline performance status was excellent. A physical examination revealed right-sided abdominal tenderness. A small amount of a fetid discharge exuded from the cutaneous fistulae, suggesting communication with the intestine. An ostomy bag was

therefore placed around the fistulae. Contrast-enhanced computed tomography (CT) images revealed that an abdominal mass involved the abdominal wall, urinary bladder wall, bowel, mesentery and peritoneum in the pelvic cavity (Fig. 1A and E) and that a 1.3-cm low-density lesion was located in the right lobe of the liver. Signs of active infection had been absent.

Sunitinib was initiated as a standard regimen (50 mg/day for 4 weeks, every 6 weeks) for the peritoneal and liver metastases. The patient developed mild diarrhea (NCI Common Terminology Criteria for Adverse Events; grade 2) accompanied by mild abdominal pain, fever and leukocytosis on day 11 of the first course of sunitinib. No obvious signs of infection sign were evident on CT images or in culture samples of urine, stool, blood and sputum. Sunitinib was re-administered at a dose of 37.5 mg/day. The patient developed grade 2 hypothyroidism on day 8 and grade 3 vomiting with severe dehydration on the day 18 of the second course. Therefore, sunitinib was discontinued until recovery. During the third course of sunitinib, the patient tolerated a reduced dose of 25 mg/day, despite the presence of grade 1 non-hematological toxicities such as hand-foot syndrome, nausea and diarrhea. At the end of the third course, she had frequent urination with micro-hematuria.

Leukocytopenia and elevated C-reactive protein were not found. The symptoms disappeared during antibiotic therapy.

On day 4 of the fourth course of sunitinib, the abdominal mass was reduced on CT images (Fig. 1B and F) and the hepatic mass decreased in density but not in size. Immediately after this CT examination, the patient developed severe abdominal pain with moderate muscle defense. A large amount of fluid material was concomitantly discharged from the cutaneous fistulae. Urinary communication was indicated from the results of an intravenous indigo carmine injection. The fistula orifice was markedly dilated on CT images (Fig. 1C and Fig. 2A) and a small opening in the anterior bladder wall was evident (Fig. 1G). Urinary leakage was localized in the subcutaneous cavity and pan-peritonitis was not evident. The abdominal symptoms gradually improved with decreased fluid drainage after sunitinib was discontinued. One month later, the size of the fistula had also obviously decreased (Fig. 1D and H) and the fistula orifice was closed (Fig. 2B). The clinical course indicated that sunitinib might have been associated with formation of the vesicocutaneous fistula in our patient.

Discussion

Sunitinib is reasonably well tolerated and patients with GIST seldom develop fistulae while under treatment with this drug [3] [6]. The GIST in our patient involved a cutaneous fistula on a previous surgical wound and another on the urinary bladder wall. Vesicocutaneous fistulae developed while she was under treatment with sunitinib, and healed upon discontinuing the drug. These findings indicated that sunitinib might be associated with the fistula formation.

Sunitinib reduced the tumor at the onset of vesicocutaneous fistula formation (Fig. 1B and 1F). A multi-centre phase II study (NCIC CTG Trial IND.184) evaluated the activity of sunitinib in 19 women with locally advanced or metastatic cervical carcinoma [8]. The patients enrolled in that study, including four who developed fistulae, did not achieve objective responses. On the other hand, notable tumor shrinkage resulted in the complete healing of a fistula in a patient with GIST under imatinib therapy [9]. Taken together, tumor reduction alone might not be sufficient for fistula formation and other mechanisms are suggested.

Sunitinib has potent anti-angiogenic effects and it exerts anti-tumor activities by

inhibiting blood vessel growth via inhibition of the VEGF-VEGFR pathway [5] [6]. These anti-angiogenic properties play a critical role in impaired mucosal homeostasis and wound healing. Sunitinib causes tumors to shrink and tumor cell necrosis results as a consequence of a decrease in the number of vessels and reduced blood flow in the center of tumors [6] [10]. Urinary leakage in our patient was localized to the cavity that formed between a potentially fragile urinary bladder wall and the part of the abdominal wall that involved GIST. Rapid degradation in the center of a tumor contrasting with a sustained rim of well-vascularized tumor tissue in the surrounding area can form a pseudo-capsule at the interface between a tumor and normal tissue [6].

Conclusions

This is the first description of a vesicocutaneous fistula forming while under sunitinib treatment in a patient with GIST. The anti-tumor effect of the drug might be associated in part with the development of vesicocutaneous fistulae. The tumor involved the abdominal wall, urinary bladder wall, bowel, mesentery and peritoneum in the pelvic cavity. Clinicians should be aware of the possibility of vesicocutaneous fistula formation in

patients with peritoneal metastasis of GIST during treatment with molecular targeting agents.

Consent

Written informed consent was obtained from the patient to publish this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations

CT: computed tomography

NCIC CTG: National Cancer Institute of Canada Clinical Trials Group

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KW was involved in writing, reviewing, editing and finalizing the manuscript. SO and RM were involved in writing, editing and reviewing the manuscript. SK, YH and HS participated in the care of the patient and assisted in drafting the manuscript. KS was the chief oncologist involved with the case and also reviewed, edited and finalized the manuscript. All authors have read and approved the final version.

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2003, **13:**1669-1678.

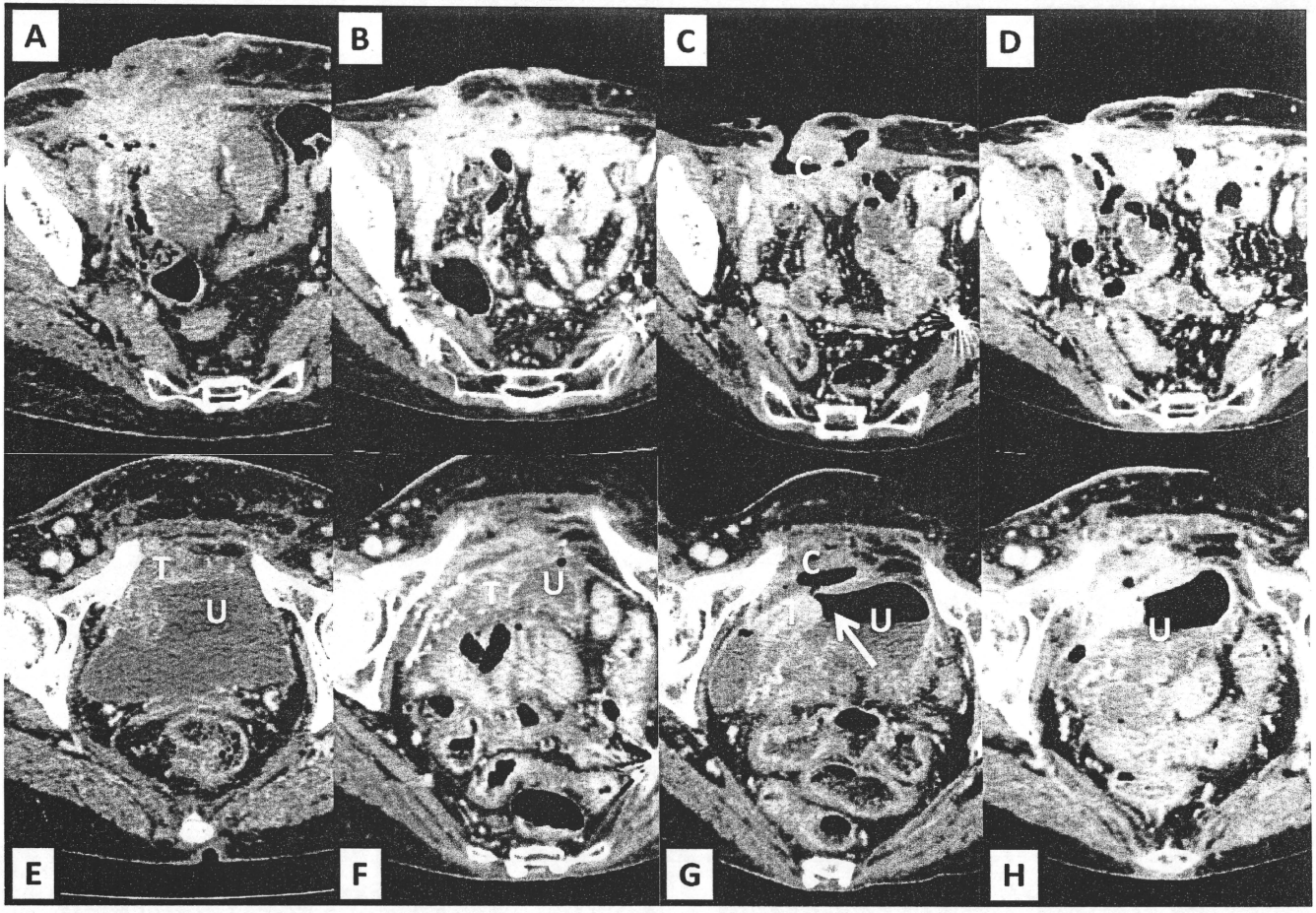
Figure Legends

Figure 1. CT findings.

U, urinary bladder; T, tumor (GIST); C, subcutaneous cavity. Tumor was located between abdominal wall (A) and urinary bladder (E) before sunitinib therapy. Abdominal tumor was smaller on day 4 of fourth course of sunitinib (B and F). Vesicocutaneous fistula bridged by subcutaneous cavity at onset of abdominal pain (C and G). Small opening (arrow) at anterior bladder wall. Air collected in urinary bladder. Fistula healed after sunitinib discontinuation (D and H) and subcutaneous cavity became smaller.

Figure 2. Gross findings on day 4 of fourth course of sunitinib (A) and after its discontinuation (B).

Cutaneous fistula orifice closed after sunitinib discontinuation.



Prior to sunitinib treatment | Before the onset of abdominal pain | After the onset of abdominal pain | After discontinuation of sunitinib treatment

Figure 1