A Case of Pancreatic Side Effects Resulting from Sorafenib and Axitinib Treatment of Stage IV Renal Cell Carcinoma

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Tyrosine kinase inhibitors such as sorafenib and axitinib were developed to treat malignancies, including stage IV renal cell carcinoma. Recently, we experienced a patient with pancreatic side effects from both sorafenib and axitinib. We report this case and include a discussion of the literature. 

Keywords: renal cell carcinoma, sorafenib, axitinib, pancreatitis, side effects

Introduction

The 5-year survival rate of patients with stage IV renal cell carcinoma (RCC) was reported to be less than 20%.1 Recently, several molecular-targeted agents, including sorafenib (BAY 43–9006) and axitinib (AG-013736), have been developed and have significantly improved the survival of stage IV RCC patients.2,3 Sorafenib is a multi-targeted tyrosine kinase inhibitor (TKI) that targets several tyrosine kinases, including vascular endothelial growth factor (VEGF) receptors 2 (also known as kinase insert domain receptor) and 3 (also known as fms-related tyrosine kinase 4: FRT4).4 Axitinib is a potent and selective inhibitor of VEGF receptors 1 (also known as FRT1), 2, and 3.5 Several side effects, including acute pancreatitis, associated with the use of these agents have been reported. Recently, we experienced a case of severe acute pancreatitis caused by axitinib. Interestingly, the patient had previously stopped sorafenib treatment because of pancreatic enzyme elevation. Here, we describe the course of this case and include a discussion of the literature.

Case

In 2011, a 63-year-old man underwent left radical nephrectomy for RCC. After the operation, he suffered from mild renal involvement (serum creatinine: 1.3 mg/dL). The pathological diagnosis was clear cell carcinoma, including grade 3 components (TNM classification: pT1a [3 cm], cN0, cM0, v1, ly0). One year after the operation, multiple bone metastases appeared, and so sorafenib treatment was initiated (400 mg/day, Fig. 1). After this initiation, splenic, pulmonary, and novel bone metastases gradually appeared and/or progressed. At day 413 of sorafenib treatment, serum pancreatic enzyme levels increased, so the sorafenib treatment was withdrawn (amylose was 295 IU/L [normal range: 43–135 IU/L] and lipase was 329 IU/L [11–59 U/L]: a grade 4 adverse event [AE] in the Common Terminology Criteria for Adverse Events [CTCAE] v4.0, Fig. 1). It should be noted that the patient did not drink alcohol. Because serum pancreatic enzyme levels subsequently normalized, sorafenib treatment was resumed. However, the agent was again withdrawn as a result of amylase re-elevation, which confirmed that sorafenib negatively affected the pancreas in this patient. After 3 months of sorafenib withdrawal, axitinib was...
indicated (10 mg/day). Although pulmonary metastases decreased in size by up to 20%, other metastases gradually progressed. Subsequently, mild and intermittent diarrhea was observed. At day 296 of axitinib treatment, the patient suddenly suffered from severe upper abdominal pain and was hospitalized at the Self-Defense Forces Central Hospital. Although contrast medium was not used because of renal involvement, computed tomography showed no significant findings in the pancreas and no gallstones causing pancreatitis. However, very high serum pancreatic enzyme levels (amylase 925 IU/L [normal range: 43–135 IU/L] and lipase 1201 IU/L [11–59 U/L]), a grade 4 AE in CTCAE v4.0, Fig. 1 and severe upper abdominal pain fulfilled the criteria of acute pancreatitis (see Discussion).6 As a result of axitinib and diet withdrawal as well as appropriate therapy for pancreatitis, the patient promptly recovered within 7 days, suggesting that axitinib had negatively affected the pancreas in this patient, just as sorafenib had done.

### Discussion

This is the first report of a patient suffering from pancreatic side effects caused by both sorafenib and axitinib (and the second case report of acute pancreatitis caused by axitinib).7 Sorafenib and axitinib are tyrosine kinase inhibitors targeting VEGFs.4,5 The side effects in this case may have occurred as a result of common pathophysiological mechanisms associated with sorafenib and axitinib, because both of these agents block VEGF receptors.

Pezzili et al. recently reviewed patients with pancreatic side effects caused by TKIs, although axitinib was not included in that study.8 Sorafenib was shown to be one of the major agents among these TKIs that causes pancreatic side effects: lipase elevation in 41.0% of patients (29.9% in those receiving placebo), amylase elevation in 29.9% of patients (23.1%), and acute pancreatitis in 0.7% of patients (0.2%). Among these side effects, acute pancreatitis is the most severe complication and is associated with high mortality. Acute pancreatitis is diagnosed in patients fulfilling at least two of the following criteria: (i) severe abdominal pain, (ii) serum amylase and lipase elevation to three times greater than the upper limit of normal, and (iii) characteristic findings on contrast-enhanced computed tomography.6 As shown by a search of PubMed in December 2014 using the terms “sorafenib” or “axitinib” and “acute pancreatitis,” only five and one acute pancreatitis cases caused by sorafenib or axitinib, respectively, have been reported (Table 1). In the sorafenib-treated cohort (two women and three men), the average age and duration of treatment prior to acute pancreatitis were 65.2 ± 11.9 years and 0.8 ± 0.3 months, respectively. On the other hand, the only case report of acute pancreatitis caused by axitinib concerns a 29-year-old woman, who was the youngest among all of the patients shown in Table 1. In addition, the duration of axitinib treatment prior to acute pancreatitis in that case was 4 months, which was longer than the average of those with sorafenib. As for our case, although the age of the patient was similar to that of the sorafenib cohort, the duration of axitinib treatment prior to acute pancreatitis was 10 months, which is the longest among the cases shown in Table 1.

Although the mechanisms of pancreatic side effects

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**Fig. 1** Levels of serum pancreatic enzymes. Serum amylase and lipase levels became elevated after a period of sorafenib treatment and a period of axitinib treatment. Enzyme levels decreased on treatment cessation.
caused by TKIs have not been fully elucidated, three hypotheses were proposed by Peron et al.7: (i) pancreatic ischemia caused by targeting VEGF receptors in fenestrated capillaries, which have an important role both in tumor growth and in endocrine tissue functions,9 (ii) loss of VEGF-protective function in several organs,10 and (iii) duodenal influx as a result of suppressed gastrointestinal (GI) motility caused by TKIs.11 This study involved a retrospective approach, and pancreatic blood flow was unfortunately not analyzed. In terms of analyzing VEGF function in the normal pancreas, no suitable markers have been reported. In terms of GI function, the patient suffered from diarrhea, but did not have duodenal symptoms. In the future, further observations of pancreatic blood flow and gastrointestinal symptoms will be needed to address these hypotheses.

In conclusion, we report the first case of pancreatic side effects caused by both sorafenib and axitinib. More case reports and further basic science research will be needed to identify patients who should not use normally beneficial TKIs because of the risk of pancreatic side effects.

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The authors have no conflicts of interest to report.

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References


