Sorafenib-induced Acute Pancreatitis: A Case Report and Review of the Literature

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Abstract

Sorafenib has been approved to increase the survival in patients with advanced hepatocellular carcinoma. Acute pancreatitis is an uncommon complication of sorafenib treatment. Only a few cases of sorafenib-induced acute pancreatitis have been reported in the English literature. We herein present the case of a 56-year-old man with hepatocellular carcinoma treated with sorafenib at 200 mg once daily. After six days of treatment, he suffered epigastric pain. Laboratory tests showed markedly elevated serum amylase and lipase levels. Imaging studies demonstrated negative findings. Sorafenib-induced acute pancreatitis was diagnosed after reviewing his history. The sorafenib treatment was discontinued, and his symptoms were resolved seven days later. To date, this case had the shortest duration and the lowest dosage of sorafenib to have induced acute pancreatitis.

Key words: sorafenib, acute pancreatitis, multikinase inhibitor, hepatocellular carcinoma, hyperamylasemia, hyperlipasemia


Introduction

Since its U.S. Food and Drug Administration (FDA) approval in December 2005, sorafenib has been used for the treatment of metastatic renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC). The most common side effects of sorafenib treatment are endocrine and laboratory toxicity (hypophosphatemia, hyperlipasemia, hyperamylasemia), cardiovascular and respiratory toxicity (hypertension, bleeding, dyspnea), bone marrow toxicity (lymphopenia, anemia), gastrointestinal (GI), hepatic, and renal toxicity (anorexia, nausea, vomiting, diarrhea) and dermatological toxicity (mucositis, rash and hand-foot skin reaction) (1). The incidence rates of hyperamylasemia and hyperlipasemia were 20-38.2% and 27-55.7%, respectively, depending on the dosage of sorafenib (2-4). Elevations of the serum amylase and lipase levels occur about four to seven days after starting the administration of sorafenib (4). However, acute pancreatitis has rarely been reported. We herein present the case of a 56-year-old man with HCC who suffered acute pancreatitis after six days of treatment with 200 mg once daily sorafenib. To date, this case of acute pancreatitis caused by sorafenib occurred after the lowest dose and the shortest treatment duration.

Case Report

A 56-year-old man presented to our emergency department because of a one-day history of abdominal pain. The patient had a decades-long history of chronic hepatitis B (CHB)-related liver cirrhosis and type 2 diabetes mellitus (DM). He had been diagnosed with intermediate-stage HCC four years prior. To treat his HCC, he underwent transcatheter arterial chemoembolization (TACE) seven times. Two years prior to his presentation to our emergency department, follow-up abdominal computed tomography (CT) showed main portal vein invasion by HCC. Thus, under a diagnosis of advance stage HCC with Child-Pugh class B (CP-B) [no encephalopathy, no obvious ascites, alanine aminotransferase...
ALT: 49 IU/L, aspartate aminotransferase (AST): 75 IU/L, total bilirubin: 2.1 mg/dL, albumin: 2.7 g/dL, prothrombin time (PT): 11.4 seconds, he started to receive sorafenib at 200 mg once daily. Six days after taking sorafenib, he developed acute epigastric pain that led him to visit our emergency department. There was no fever, chest pain, dyspnea, or diarrhea. He denied any recent history of alcohol consumption or cholelithiasis. The last TACE had been performed five months before his presentation to our hospital.

Upon admission, a physical examination showed that the man had yellowish discoloration of his skin, icteric sclerae of his eyes, superficial venous engorgement on his abdomen, and tenderness at the upper abdomen without rebound. His vital signs showed that his body temperature was 36.5°C, blood pressure was 100/64 mm-Hg, pulse rate was 90 beats/min regularly and respiratory rate was 18 times/min without distress. The laboratory tests showed the following: serum total bilirubin 2.3 mg/dL (normal, 0.2-1.3 mg/dL), ALT 49 IU/L (normal, <40 U/L), AST 76 IU/L (normal, <35 U/L), PT 12.4 seconds (normal, 9.5-11.7 seconds), albumin 2.5 g/dL (normal, 3.7-5.3 g/dL), amylase 1,388 U/L (normal, 28-100 U/L), and lipase 3,685 U/L (normal, 8-58 U/L). The results of other laboratory tests were normal. A chest X-ray showed no perforation of hollow organs (Fig. 1). On the basis of the clinical symptoms and elevation of the pancreatic enzyme levels, a diagnosis of acute pancreatitis was made.

After admission, abdominal ultrasound and CT showed no obvious pancreatic tumors (Fig. 2). Endoscopic retrograde cholangiopancreatography demonstrated a normal biliary tract and mild dilatation of the pancreatic duct without stones or neoplasms. Based on the negative finding of imaging studies, we reviewed his drug history. He had taken propranolol, telbivudine, furosemide, sorafenib, repaglinide, and rabeprazole to control his liver disease, DM, and a gastric ulcer. Among these drugs, we considered that sorafenib and repaglinide were possible causes of his conditions, because he had been taking the other agents for several years without side effects before the administration of repaglinide. Because nateglinide and repaglinide are the same type of drug, repaglinide was not considered to be the cause of the acute pancreatitis. Therefore, sorafenib was highly suspected to have caused the acute pancreatitis. We decided to discontinue the use of sorafenib by the patient. Seven days after the discontinuation of sorafenib, his symptoms resolved and the pancreatic enzyme levels had recovered to the normal range. We did not rechallenge the patient with sorafenib treatment, and he died of disease progression four months later.

**Discussion**

Sorafenib is a small-molecule inhibitor that binds to the serine/threonine Raf-1 kinase and multiple classes of receptor tyrosine kinases (RTKs). These RTKs include vascular endothelial growth factor receptor (VEGFR)-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR), Fms-like tyrosine kinase-3 (FLT-3), and c-kit (5). The Ras/Raf/MEK/ERK pathway plays central roles in cell proliferation and apoptosis, and the VEGFR-2/PDGFR-beta signaling cascade is involved in vasculogenesis, tumor cell motility and metastasis (6).

The most frequently described side effects of sorafenib treatment are usually reversible, including skin rashes (in 40% of patients), hand-foot skin reactions (30%), diarrhea (43%) and hypertension (17%) (7). Hyperamylasemia and hyperlipasemia are also common side effects of sorafenib treatment. The incidence rates of hyperamylasemia and hyperlipasemia were 20-38.2% and 27-55.7% respectively, depending on the dosage of sorafenib (2-4).

In a phase I clinical trial of sorafenib in 69 patients, three cases of grade 3 pancreatitis were observed (2). These three patients experienced dose-independent pancreatitis: two patients on the 100 mg twice daily regimen developed pancreatitis three weeks and six weeks after starting treatment, respectively, and the other patient experienced pancreatitis after receiving 400 mg of sorafenib twice daily for eight months. Upon the withdrawal of sorafenib, all three patients...
recovered within 10 to 14 days (2). In another phase I study of sorafenib in 31 Japanese patients with advanced refractory solid tumors, the patients were divided into four treatment groups: three patients were treated with sorafenib at 100 mg twice daily, 15 patients were treated with sorafenib at 200 mg twice daily, six patients received 400 mg twice daily and seven patients received 600 mg twice daily. In the group that received 100 mg twice daily, elevation of the serum lipase and amylase levels was not observed. In the 200 mg twice daily group, there were four patients who showed elevation of lipase levels (27%) and three who showed elevated amylase levels (20%). In the group that received 400 mg twice daily, three patients (50%) had elevation of both the lipase and amylase levels. In the group that received 600 mg twice daily, there were four patients (57%) and two patients (29%) who showed elevated lipase and amylase levels, respectively. In that trial, the serum amylase and lipase levels began increasing from four to seven days after starting the sorafenib treatment (4). After the discontinuation of sorafenib treatment, the serum pancreatic enzymes returned to the normal levels within three to 10 days.

In a phase II clinical trial of sorafenib treatment in 129 patients, hyperamylasemia and hyperlipasemia were observed in 38.2% and 55.7% of all patients, respectively (3). In that trial, the serum pancreatic enzymes returned to the normal levels within three to 10 days.

Sorafenib may also lead to the reflux of duodenal contents into the pancreatic duct because it causes GI motility abnormalities (8). The reflux of duodenal contents induces the premature activation of zymogens within pancreatic acinar cells, resulting in the autodigestion of pancreatic tissue. To date, there have been only seven case reports of sorafenib-induced acute pancreatitis, including six cases in the English literature and our present case (11-16). These cases are summarized in Table 1. The patients who suffered from sorafenib-induced pancreatitis included four men and three women, whose ages ranged from 53 to 80 years old (mean age: 65.4 years); four patients had received sorafenib for metastatic RCC and three had received it for HCC. In a previous study, it was revealed that elevations in hepatic transaminases and pancreatic amylase developed more frequently in patients with RCC than in those with HCC (17). This was consistent with the patients listed in Table 1. The duration of sorafenib treatment prior to the onset of acute pancreatitis ranged from six days to six weeks. Four cases developed acute pancreatitis from 10 days to four weeks following the start of sorafenib treatment (11). In another case, the serum lipase and amylase levels did not return to normal until seven weeks after discontinuing sorafenib treatment (12).

Table 1. Previous Case Reports of Sorafenib-induced Pancreatitis Compared with Our Case Report.

<table>
<thead>
<tr>
<th>References</th>
<th>Gender and age</th>
<th>Malignancy</th>
<th>Treatment</th>
<th>Duration of treatment prior to development of pancreatitis</th>
<th>Amylase / Lipase (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[12]</td>
<td>53/F</td>
<td>Metastatic RCC</td>
<td>Sorafenib 400 mg b.i.d.</td>
<td>3 weeks</td>
<td>1,361/99</td>
</tr>
<tr>
<td>[13]</td>
<td>80/M</td>
<td>Metastatic RCC</td>
<td>Sorafenib 400 mg b.i.d.</td>
<td>4 weeks</td>
<td>156/&gt;200</td>
</tr>
<tr>
<td>[14]</td>
<td>53/M</td>
<td>HCC</td>
<td>Sorafenib unknown dose</td>
<td>4 weeks</td>
<td>118/484</td>
</tr>
<tr>
<td>[15]</td>
<td>71/M</td>
<td>Metastatic RCC</td>
<td>Sorafenib 400 mg b.i.d.</td>
<td>2 weeks</td>
<td>973/2,733</td>
</tr>
<tr>
<td>[16]</td>
<td>69/F</td>
<td>Metastatic RCC</td>
<td>Sorafenib 400 mg b.i.d.</td>
<td>10 days</td>
<td>244/1,014</td>
</tr>
<tr>
<td>[17]</td>
<td>76/F</td>
<td>HCC</td>
<td>Sorafenib 400 mg q.d.</td>
<td>6 weeks</td>
<td>124/&gt;3,000</td>
</tr>
<tr>
<td><strong>Our case</strong></td>
<td>56/M</td>
<td>HCC</td>
<td>Sorafenib 200 mg q.d.</td>
<td>6 days</td>
<td>1,388/3,685</td>
</tr>
</tbody>
</table>

RCC: renal cell carcinoma, HCC: hepatocellular carcinoma

Sorafenib may also lead to the release of autodigestive enzymes. However, elevations of the pancreatic enzyme levels have not been observed following treatment with anti-VEGFR monoclonal antibodies (e.g., bevacizumab), anti-EGFR therapies or other oral antiangiogenic compounds. Of note, sorafenib and sunitinib inhibit multiple tyrosine kinase receptors (including PDGFR, VEGFR, and FLT-3) and all can induce hyperlipasemia and hyperamylasemia (8). Thus, it is unknown whether the combined inhibition of VEGFR, PDGFR and FLT-3 leads to the elevation of pancreatic enzyme levels or whether there is another cause (9). However, there was one case report about axitinib-induced acute pancreatitis. Axitinib is a selective tyrosine kinase inhibitor of VEGFR. Thus, VEGFR inhibition may be more important than PDGFR or FLT-3 inhibition with regard to inducing hyperlipasemia and hyperamylasemia (10).

Sorafenib may also lead to the reflux of duodenal contents into the pancreatic duct because it causes GI motility abnormalities (8). The reflux of duodenal contents induces the premature activation of zymogens within pancreatic acinar cells, resulting in the autodigestion of pancreatic tissue. To date, there have been only seven case reports of sorafenib-induced acute pancreatitis, including six cases in the English literature and our present case (11-16). These seven cases are summarized in Table 1. The patients who suffered from sorafenib-induced pancreatitis included four men and three women, whose ages ranged from 53 to 80 years old (mean age: 65.4 years); four patients had received sorafenib for metastatic RCC and three had received it for HCC. In a previous study, it was revealed that elevations in hepatic transaminases and pancreatic amylase developed more frequently in patients with RCC than in those with HCC (17). This was consistent with the patients listed in Table 1. The duration of sorafenib treatment prior to the onset of acute pancreatitis ranged from six days to six weeks. Four cases developed acute pancreatitis from 10 days to four weeks following the start of sorafenib treatment (11). In another case, the serum lipase and amylase levels did not return to normal until seven weeks after discontinuing sorafenib treatment (12).
weeks after taking 800 mg of sorafenib daily. Our case had the shortest duration of treatment of only six days, and the patient had received only 200 mg/day. Therefore, it appears that the sorafenib-induced pancreatitis can occur relatively independent of the treatment duration and dose.

As mentioned above, the serum amylase and lipase levels began increasing after four to seven days of treatment with sorafenib (4). In most case reports, the duration of the sorafenib treatment prior to the onset of pancreatitis was beyond this range. This suggests that it may be possible to follow the serum pancreatic enzyme levels to prevent the occurrence of acute pancreatitis. Moreover, one of the previous patients with CHB-related liver cirrhosis and HCC (CP-B) was treated with TACE three years earlier. That patient took sorafenib 400 mg once daily for six weeks, and then she suffered acute pancreatitis. In our present case, the patient also had CHB-related liver cirrhosis and HCC (CP-B) and underwent TACE seven times. Acute pancreatitis developed six days after he had started to receive 200 mg of sorafenib once daily. We consider that the liver function of the patient and the number of TACE treatments may affect the sorafenib metabolism.

Although it is commonly used in HCC patients with CP-A, the use of sorafenib for HCC patients with CP-B is controversial. Although it is not contraindicated, the use of sorafenib in CP-B cases is not considered appropriate in some countries’ guidelines. In our present patient, the acute pancreatitis occurred within a short duration of starting to use sorafenib in a CP-B patient, despite the fact that it was given at a low dose. Table 1 does not allow any generalizations to be made that the sorafenib-induced pancreatitis is related to the treatment duration or dosage, or to the patient age or gender. Therefore, we consider that the incidence of pancreatitis is most likely affected by the inter-individual variations in sorafenib pharmacokinetics.

These variations in the metabolism of sorafenib may arise due to differences in the genetic backgrounds and patients’ characteristics (18). There were nine polymorphisms in four genes (CYP3A5, UGT1A9, ABCB1, and ABCG2) that have been considered to be potentially involved in the pharmacokinetics of sorafenib (19, 20). The active metabolite of sorafenib, pyridine N-oxide (M-2), is metabolized primarily by cytochrome P450 (CYP) 3A4 in the liver and by uridine diphosphate glucuronyl transferase (UGT) 1A9 to sorafenib glucuronide (21-23). However, the ratio of M-2 to the sum of sorafenib (uncharged form) and three other metabolites (M-3, M-4, and M-5) was only 9-16% (24). Thus, M-2 may make only a minor contribution to the toxicity of sorafenib.

Genetic variations of CYP3A4/3A5 and UGT1A1/1A9 may influence the metabolic variability, but do not seem to have a significant effect on the sorafenib exposure (20, 25). The inter-individual variability, including factors such as gender, diet and albuminemia, may also influence the exposure to sorafenib (2, 19, 20, 26). The greater exposure of females to sorafenib may be related to females’ lower lean body mass (LBM) compared to males (20). Several previous studies have shown a positive relationship between the LBM and total clearance of other anticancer drugs, such as epirubicin and carboplatin (27). With regard to individual variations in the diet and albuminemia, these might influence the use of sorafenib and cause large intra- and inter-patient variability in bioavailability due to the low solubility of sorafenib in the GI tract (28). Therefore, many factors can influence the sorafenib-induced toxicity. However, data regarding the determinants of sorafenib-induced toxicity still remain scarce.

We also reviewed the outcomes of the rechallenge with sorafenib. These results are shown in Table 2. In most cases, sorafenib treatment was discontinued after acute pancreatitis; in one case, the treatment was changed to sunitinib. Two pa-

<table>
<thead>
<tr>
<th>References</th>
<th>Gender and age</th>
<th>Malignancy</th>
<th>Treatment</th>
<th>Treatment after pancreatitis recovery</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>[12]</td>
<td>53/F</td>
<td>Metastatic RCC</td>
<td>Sorafenib 400 mg b.i.d.</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>[13]</td>
<td>80/M</td>
<td>Metastatic RCC</td>
<td>Sorafenib 400 mg b.i.d.</td>
<td>Sorafenib 400 mg q.d.</td>
<td>Acute pancreatitis with increased lipase (87 U/L)</td>
</tr>
<tr>
<td>[14]</td>
<td>53/M</td>
<td>HCC</td>
<td>Sorafenib unknown dose</td>
<td>No resumption</td>
<td>Hematocrit drop from progression of HCC</td>
</tr>
<tr>
<td>[15]</td>
<td>71/M</td>
<td>Metastatic RCC</td>
<td>Sorafenib 400 mg b.i.d.</td>
<td>No resumption</td>
<td>No recurrence of pancreatitis</td>
</tr>
<tr>
<td>[16]</td>
<td>69/F</td>
<td>Metastatic RCC</td>
<td>Sorafenib 400 mg b.i.d.</td>
<td>Sunitinib 37.5 mg q.d. for 4 weeks on and 2 weeks off</td>
<td>Recurrence of pancreatitis</td>
</tr>
<tr>
<td>Our case</td>
<td>56/M</td>
<td>HCC</td>
<td>Sorafenib 200 mg q.d.</td>
<td>No resumption</td>
<td>No recurrence of pancreatitis</td>
</tr>
</tbody>
</table>

RCC: renal cell carcinoma, HCC: hepatocellular carcinoma, q.d.: once daily, b.i.d.: twice daily
tients who restarted taking sorafenib developed acute pancreatitis again. Only one case showed no recurrence of pancreatitis after resuming treatment with sorafenib 200 mg once daily. Hence, the author of that study concluded that the resumption of sorafenib treatment appeared to be safe with an initial low-dose drug administration (24). However, based on our experience and our review of the previous studies, acute pancreatitis may occur after restarting sorafenib treatment even at a low dose (200 mg once daily).

In conclusion, although the incidence of hyperamylasemia and hyperlipasemia is high in patients treated with sorafenib, the incidence of acute pancreatitis is low. The hyperamylasemia and hyperlipasemia are usually dependent on the dose of sorafenib, and typically occur within a short duration of time after starting sorafenib treatment. In contrast, acute pancreatitis may occur independently of the dose of sorafenib and can occur at any time after sorafenib treatment. Therefore, acute pancreatitis should be suspected by clinicians when patients treated with sorafenib present with an acute abdomen, even if they are receiving a low dose and have a short duration of treatment. Moreover, clinicians should perform more careful follow-up examinations when prescribing sorafenib to HCC patients with CP-B. Early discontinuation of sorafenib treatment is important to avoid the progression of acute pancreatitis.

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

References