LETTER

Sorafenib-Induced Acute Pancreatitis

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Dear Sir:

Sorafenib is an oral inhibitor of multi-kinase proteins approved in 2005 for treatment of metastatic renal cell carcinoma. It has also been approved for treatment of advanced hepatocellular carcinoma as it has been shown to increase median survival by 3 months in such patients [1]. These receptor trypsin kinase inhibitors include platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR)-2, VEGFR-3, Fms-like tyrosine kinase-3 (FLT-3) and c-kit [2]. Side effects associated with sorafenib include diarrhea, hypertension, hand-foot skin reaction, and fatigue [2]. Previously, there were at least two case reports of sorafenib-associated pancreatitis in the literature [3, 4]. We present another case of a patient on sorafenib presenting with abdominal pain that was found to have acute pancreatitis.

A 53-year-old male with past medical history of human immunodeficiency virus off highly active antiretroviral therapy (HAART) medications, hepatitis C (model for end-stage liver disease, MELD 14; Child B), decompensated liver cirrhosis with ascites, portal vein thrombosis and hepatocellular carcinoma on palliative sorafenib who presented to the hospital with increased abdominal girth and pain one month after initiation of sorafenib. Of note, his only medication at the time of presentation was oxycodone. His white blood cell count was normal and his hematocrit (29%; reference range: 42-50%) and platelet count were at baseline (99,000 mm-3; reference range: 150-350 mm-3). His creatinine was at its baseline of 1.3 mg/dL (reference range: 0.6-1.2 mg/dL) and his lactic acid was normal at 0.9 mmol/L (reference range: 0.4-2.2 mmol/L). His liver function tests were elevated however they were at his baseline. His lipase and amylase, however, were elevated at 484 U/L (reference range: 0-60 U/L) and 118 U/L (reference range: 28-100 U/L), respectively. Clinically his pancreatitis was mild according to the Atlanta criteria [5]. Right upper quadrant showed gallstones but no evidence of cholecystitis or choledocholithiasis. Hepatobiliary iminodiacetic acid (HIDA) scan was negative for gallstones. CT scan of abdomen and pelvis revealed multifocal hepatoma with background of cirrhosis and portal hypertension with large ascites and non-occlusive main portal vein thrombosis not significantly changed. Additionally, patient was not consuming alcohol and his calcium and triglyceride levels were within normal limits. Patient was made nihil per os and started on intravenous fluids and as needed pain medication. After his sorafenib was held, his abdominal pain resolved completely. After discharge from the hospitalization there was no rechallenge with sorafenib. Unfortunately, shortly after this hospitalization, patient presented to the hospital with shock secondary to significant hematocrit drop from hemoperitoneum from progression of his hepatocellular carcinoma (hematocrit of 14.7%) requiring multiple rounds of blood products. He was eventually transferred to hospice given his poor prognosis. In the case of this patient, the casual relationship between sorafenib and the acute onset of pancreatitis is probable [6, 7, 8].

Sorafenib is a multi-kinase inhibitor with anti-proliferative and anti-angiogenic activity. As far as we know, there have been two case reports of sorafenib-induced pancreatitis in the literature (Table 1). There have been reports of clinical pancreatitis in 3 of 451 patients treated with sorafenib [9]. The explanation for mechanism of sorafenib-induced pancreatitis includes pancreatic ischemia from the anti-angiogenic effect of the medication (anti-VEGF) [2]. The protective effect of VEGF and PDGF may also be impaired by sorafenib causing increased severity of pancreatitis [2]. Sorafenib may also cause pancreatitis and may also be responsible for reflux of duodenal contents into the pancreatic duct given the fact that it causes gastrointestinal motility abnormalities.
induces the premature activation of zymogens within pancreatic acinar cells resulting in autodigestion of pancreatic tissue [3]. By exclusion, the case of pancreatitis presented here was most likely caused by sorafenib although other factors or medications could be not completely ruled out. Sorafenib should be included in the list of anti-neoplastic drugs that can potentially cause pancreatitis. The anti-neoplastic agents that can cause pancreatitis include alemtuzumab, cyclophosphamide, capcitabine, doxorubicin, estramustine, ifosfamide, imatinib, methotrexate, oxaliplatin, paclitaxel, tamoxifen, thalidomide, trastuzumab, vinblastine, and vinorelbine. Pancreatitis should be a strong consideration for patients on sorafenib who present with abdominal pain. Patients should be made aware of this rare side effect before initiation of treatment and prompt discontinuation of this agent is of paramount importance once pancreatitis is diagnosed.

Table 1. Previous case reports of sorafenib-induced pancreatitis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Gender and age</th>
<th>Malignancy</th>
<th>Treatment</th>
<th>Duration of treatment prior to development of pancreatitis</th>
<th>Lipase and amylase (reference range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amar et al., 2007 [3]</td>
<td>Female 53 years</td>
<td>Metastatic renal cell carcinoma</td>
<td>Sorafenib 400mg po twice daily</td>
<td>3 weeks</td>
<td>99 U/L (10-73 U/L) 1,361 U/L (26-102 U/L)</td>
</tr>
<tr>
<td>Li and Srinivas, 2007 [4]</td>
<td>Male 80 years</td>
<td>Metastatic renal cell carcinoma</td>
<td>Sorafenib 400 mg po twice daily</td>
<td>4 weeks</td>
<td>&gt;200 U/L (0-50 U/L) 156 U/L (0-140 U/L)</td>
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References

Conflict of interest The authors have no potential conflicts of interest