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CASE REPORT

Sorafenib-induced Acute Pancreatitis

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Sorafenib was approved in 2005 for the treatment of metastatic renal cell carcinoma and advanced hepatocellular carcinoma (HCC). Acute pancreatitis is a side-effect of sorafenib usage. We present a patient with advanced HCC who presented with acute Grade D pancreatitis caused by sorafenib administration. Following the discontinuation of sorafenib, fasting, and fluid replacement, the patient's clinical manifestation of Grade D pancreatitis subsided in a short time. One month after discharge, she resumed sorafenib treatment (200 mg/day) due to disease progression. Based on this experience, resumption of sorafenib treatment appears to be safe.

Key words: Sorafenib, pancreatitis, hepatocellular carcinoma

INTRODUCTION

Sorafenib is an oral inhibitor of multi-kinase proteins and possesses anti-proliferative and anti-angiogenic activity. This drug was approved in 2005 for the treatment of metastatic renal cell carcinoma and advanced hepatocellular carcinoma (HCC) and has been shown to increase the median survival time by 3 months.[1] Hypertension and hand or foot dermal reactions are some of the common side-effects of sorafenib administration, whereas acute pancreatitis is more rare with an incidence rate of <1%.[2] We present a patient with advanced HCC who presented with acute Grade D pancreatitis following a 6-week course of sorafenib.

CASE REPORT

A 76-year-old woman, with a history of hepatitis B-related liver cirrhosis (child Class B), complicated with HCC (American Joint Committee on Cancer Stage II [cT2N0M0]; Barcelona Clinic Liver Cancer Stage B), was treated with transarterial chemoembolization 3 years previously. Six weeks prior to admission, she was advised additional treatment with sorafenib (400 mg, daily) for extrahepatic lymph node metastasis. Her model for end-stage liver disease score was measured at approximately 15 points. Upon admission, the afebrile patient presented with severe epigastric pain radiating to her back, tarry stools, and a yellowish skin discoloration that had persisted for 2 days. The patient did not have a history of gallstones, dyslipidemia, pancreatitis, alcohol consumption, or exposure to potentially causative agents.

A physical examination revealed local epigastric tenderness with no peritonitis or Cullen or Grey-Turner signs. The baseline laboratory tests (normal values in parentheses) yielded the following results: White blood cell count: 10,280 cells/mm^3 (<10,000); aspartate aminotransferase/alanine aminotransferase: 91/48 IU/L; total bilirubin: 1.4 mg/dL (<1.2); amylase: 124 U/L (<100); lipase: >3,000 U/L (<60); creatinine: 1.3 mg/dL (<1.2); lactic acid: 0.9 mmol/L (<2.2); alkaline phosphate: 95 U/L (<104); α-fetoprotein: 26 ng/mL (<20); total calcium: 7.5 mg/dL (>8.0); and Ca 19-9: 301 U/mL (<37). Computed tomography (CT) of the patient's abdomen showed edematous pancreatitis with stranding of the surrounding fat and fluid accumulation over the bilateral anterior pararenal space [Figure 1].

Following the treatments of stopping sorafenib, fasting, and fluid replacement, the patient's clinical manifestation of Grade D pancreatitis (definition:exudative pancreatitis: Balthazar D, without pancreatic necrosis; peripancreatic collections are due to extrapancreatic necrosis)[3] and serum lipase levels normalized over a 5 days hospitalization period. One month after discharge, she resumed sorafenib treatment (200 mg/day) due to disease progression. Her dosage was increased to 400 mg/day and maintained at that level. Since resuming sorafenib therapy, the patient has not experienced any abdominal discomfort or abnormal pancreatic enzyme levels after a follow-up of 40 days following the restart of sorafenib;

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the advanced HCC has also remained under control with the sorafenib therapy. Two months after diascharge, CT image of abdomen showing regression compared with previous Grade D pancreatitis [Figure 2].

DISCUSSION

The probable mechanism underlying the development of sorafenib-related pancreatitis is pancreatic ischemia due to the impairment of vascular endothelial growth factor and platelet-derived growth factor activity.[2] Female gender, and elevated cumulative doses of sorafenib, and UGT1A9 polymorphism are the factors that predispose patients to develop sorafenib-induced pancreatitis.[4]

Until date, there have been reports of seven cases of sorafenib-related pancreatitis, including five metastatic renal cell carcinoma and two HCC. Inclusive of the present case, these patients were middle-aged (individual age range: 50-80 years; men: 4, women: 3), all of who experienced an abrupt attack after sorafenib exposure. Acute pancreatitis is a complication during sorafenib treatment and immediate discontinuation of the drug is critical to prevent a lethal outcome. Thus, acute pancreatitis should be suspected in patients presenting with clinical symptoms who have recently initiated sorafenib treatment.

As shown in Table 1, the patients described in the previously published case reports did not undergo an additional challenge with sorafenib after they were discharged. Our patient

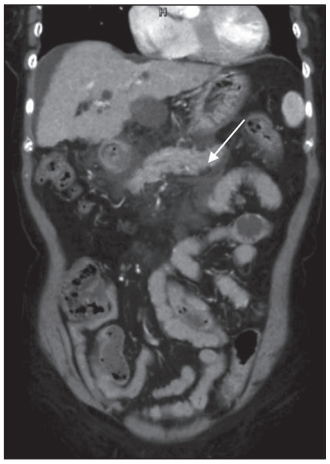

Figure 1. Computed tomography image of abdomen: grade D pancreatitis with fluid accumulation in the bilateral anterior pararenal space (white arrow). Hepatocellular carcinoma lesion over lateral segment is not significant in this figure

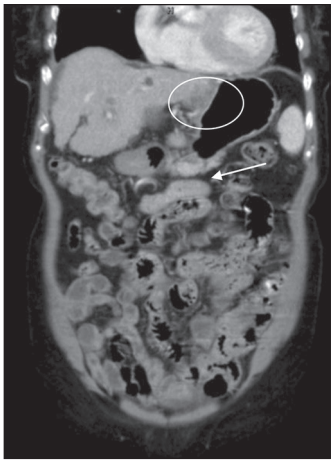

Figure 2. Computed tomography image of abdomen showing regression compared to previous Grade D pancreatitis. No fluid accumulation in the bilateral anterior pararenal space (white arrow) was noted. Hepatocellular carcinoma lesion (white circle)

Table 1. Comparison of all case reports with regard to sorafenib-related acute pancreatitis

References	Malignancy	Gender	Age	Treatment	Duration	Ranson's criteria	Treatment
Amar *et al*., 2007[5]	Metastatic renal cell carcinoma	Female	53	Sorafenib	800 mg, daily; 3-week	Unknown	Stopped sorafenib
Li and Srinivas, 2007	Metastatic renal cell carcinoma	Male	80	Sorafenib	800 mg, daily; 4-week	Unknown	Stopped sorafenib
Saadati and Saif, 2010[6]	Child B LC; MELD 14; HCC AJCC Stage II	Male	53	Sorafenib	Dose and duration unknown	Unknown	Stopped sorafenib
Sevin, 2013[7]	Metastatic renal cell carcinoma	Female	69	Sorafenib	400 mg, twice daily; 10 days	Unknown	Stopped sorafenib
Sevin, 2013[7]	Metastatic renal cell carcinoma	Male	59	Sunitinib	37.5 mg, daily; 4 weeks	Unknown	Stopped sunitinib
Kobayashi *et al*., 2011[8]	Metastatic renal cell carcinoma	Male	71	Sorafenib	400 mg, twice daily; 14 days	Ranson's criteria: 3	Stopped sorafenib
Our case 2012	Child B LC; MELD 15; HCC AJCC Stage II	Female	76	Sorafenib	400 mg, daily; 6 weeks	Ranson's criteria: 2	Stopped sorafenib temporarily, then resume treatment at 200 mg, daily 1-month later

LC = liver cirrhosis; MELD = model for end-stage liver disease; AJCC = american joint committee on cancer; HCC = hepatocellular carcinoma

recovered quickly after discontinuing sorafenib and did not experience additional symptoms following re-initiation of therapy 1 month later after discontinuing sorafenib.

CONCLUSION

Based on this experience, resumption of sorafenib treatment appears to be safe, provided that a low-dose of drug is initially administered and the dose is gradually increased to the original dose. Although more experience is necessary to provide conclusive information, we suggest that patients who suffer from severe sorafenib-induced pancreatitis may not need to permanently discontinue therapy.

DISCLOSURE

All authors declare no competing financial interests.

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